TITLE PAGE

PROTOCOL TITLE

Managing Fatigue Using Virtual Reality for Post-Operative Lung Cancer Patients: Understanding the Post-Surgical Non-Small Cell Lung Cancer Patient's Symptom Experience
National Cancer Institute, National Institutes of Health Grant Award # (R01 CA 205025)

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Team Science Multi-Institutional Study

Historical Introduction of the Study: Managing Fatigue Using Virtual Reality for Post-Operative Lung Cancer Patients

Historically, the Lead Site for this National Cancer Institute (NCI), National Institutes of Health (NIH) R01 3-arm randomized controlled trial (RCT) was Michigan State University. The NCI sponsored grant was officially awarded to Dr. Amy Jude Hoffman, PhD, RN, at Michigan State University on April 1, 2018. Dr. Hoffman, the Principal Investigator, received Michigan State University Institutional Review Board (IRB) approval to initiate the grant on September 21, 2017. Please see the attached 45 CFR 46.118 Designation Determination IRB approval letter that was sent to NCI with Dr. Hoffman's NCI "Just In Time" request.

The NCI honored Michigan State University (MSU) IRB's approval via the 45 CFR 46.118 Designation Determination mechanism for the R01 which allows the researcher to open up a Contracts and Grants Account to spend funds immediately while doing the prep work to include an IRB, as well as completing the Clinical Trials Gov applications, hiring personnel, and preparing to initiate the grant. Note that approaching human subjects is only commenced after an IRB application is approved. Likewise, Dr. Hoffman's prior NCI R21 2-arm RCT grant award (CA164515) received a 45 CFR 46.118 Designation Determination, and NCI provided an immediate Notice of Award for the grant funds to be accessed to allow for the preparatory work for the grant to be implemented and funded right away. Again, human subject activity is only commenced after an IRB application is approved.

A mechanism such as the 45 CRF 46.118 Designation Determination approval by MSU IRB consequently allowed for the issuance of a Notice of Award by the NCI ensuring the award of the grant and its optimal initiation and implementation prior to approaching human subjects. Again, human subject activity would commence only after the initial approvals were received, again in this case, an IRB application and review at Michigan State University.

Last, note that Dr. Hoffman's NCI-NIH Grant (R01 CA205025) was relinquished from Michigan State University and is being transferred from Michigan State University to the University of Nebraska Medical Center with subsequent official paperwork sent to NCI to transfer the grant to the UNMC in June 2018. The NCI is ready to transfer and provide a Notice of Award (R01 CA205025) for the grant pending IRB approval and the NCI is requesting a September 1, 2018, start date.

Dr. Hoffman was honored and grateful to join UNMC July 1, 2018, and at that time was completing the processes for the institutional grant transfer and was grateful for the support by the UNMC Sponsored Programs Administration, the UNMC IRB, and the UNMC College of Nursing. Currently, Dr. Hoffman is completing an IRB application to be submitted soon to UNMC IRB. NCI is requesting a September 1, 2018, start date to release this grant. Dr. Hoffman will provide a copy of the UNMC IRB to the Scientific Review Committee at UNMC and the Fred and Pamela Buffet Cancer Center as well

Lead Institution: The University of Nebraska Medical Center

Five Performance Sites to Include:
McLaren Greater Lansing Hospital, Lansing, MI
Munson Medical Center, Cardiothoracic Surgeons of Grand Traverse, Traverse City, MI
Nebraska Medicine, Omaha, NE
Spectrum Health, Grand Rapids, MI
Sparrow Hospital, Lansing, MI

Historical Background of the Michigan Performance Sites

Historical Background: McLaren Greater Lansing Hospital, Sparrow Hospital, and Spectrum Health are the founding institutions that started the Team Science with Dr. Hoffman. These three institutions started and completed the NCI-NIH feasibility and pilot 2-arm RCT (R21 CA164515) work. Additionally, these three performance sites worked collaboratively to streamline IRB processes and resources while ensuring protection of human subjects. The NCI-NIH is most excited about these performance sites [McLaren Greater Lansing Hospital, Spectrum Health, and Sparrow Hospital] during their feasibility and pilot work (RCT R21 CA164515) and this was well noted by comments made by the R01 Scientific Review Panel and NCI Program Officer, Dr. Ann O'Mara, PhD, RN. In addition, Dr. O'Mara would consult with Dr. Hoffman to learn from her team's success in the recruitment of participants from a very complex patient population, the post-surgical non-small cell lung cancer population. This consultation was requested by Dr. O'Mara since other institutions with NCI grant awards could learn from our success in recruitment since Team Science proved difficult in processes to support participant recruitment in other institutions. Dr. Hoffman also was contacted by clinical researchers from various institutions such as Cleveland Clinic, Harvard School of Medicine, Duke University Medical Center, and Memorial Sloan Kettering to consult on optimization of Team Science to ensure the success of their study.

Consequently, the R01 RCT application submitted to NCI supported by the feasibility and pilot work was well received and this enthusiasm for these performance sites led to the awarding of this current NCI-NIH award April 1, 2018. Cardiothoracic Surgeons of Grand Traverse at Munson Medical Center was added in the original R01 RCT submission and was also excited to collaborate in Team Science through a streamlined IRB approach. We are excited about adding Nebraska Medicine with Dr. Karin Trujillo, MD, to this important program of research since Dr. Hoffman with great enthusiasm joined The University of Nebraska Medical Center July 1, 2018.

Brief Introduction of the Michigan Performance Sites

McLaren Greater Lansing Hospital – Lansing, MI: A founding institution of this program of research led by Dr. Hoffman, McLaren is an award winning 389-bed hospital part of the McLaren Health Care network serving the greater Lansing area for over 100 years. McLaren was one of our primary recruiting sites for our recently completed **RCT (R21 CA164515)** and both McLaren and our team are looking forward to working together in research again. McLaren Lung Cancer Institute at McLaren Greater Lansing Hospital provides a multidisciplinary, patient centric approach with the goal to reduce "door to therapy" time via a team of experts including a dedicated Patient Navigator Program to ensure seamless, coordinated care, along with any necessary resources. In 2014, McLaren Health Care completed the acquisition of the Barbara Ann Karmanos Cancer Institute, a designated comprehensive cancer center by the National Cancer Institute. McLaren Health Care, a fully integrated health care network of 12 hospitals and 350+ facilities serving the state of Michigan, including the merged acquisition of the Barbara Ann Karmonos Cancer Institute (NCI-designated comprehensive cancer centers), elected Dr. Hoffman to serve on the McLaren's Executive Leadership Research Advisory Board to fully engage all disciplines to advance research in their organization.

Munson Medical Center (MMC) and Cardiothoracic Surgeons of Grand Traverse —Traverse City, MI: MMC is a 391-bed nonprofit hospital serving as northern Michigan's regional referral center. Cardiothoracic Surgeons of Grand Traverse is affiliated with MMC supplying cardiothoracic surgery expertise to MMC and supporting the proposed study as the participant recruitment site. Three thoracic surgeons from this practice will be supporting the study. Relative to MMC, it is the largest of the nine Munson Health Care system hospitals located throughout northern Michigan with 510 physicians and 3,700 employees. Munson Medical Center was ranked 62nd nationally among 4,667 hospitals, was one of just two percent of hospitals in the country.

Sparrow Hospital – Lansing, MI: A founding institution of this program of research led by Dr. Hoffman, Sparrow is an award winning 676-bed hospital serving as mid-Michigan's only level 1 trauma center and Michigan's only member of the Mayo Clinic Care Network. Sparrow served as one of our primary recruiting sites for our **two-arm RCT (R21 CA164515)** and we are planning to continue the proposed study seamlessly initiating the previously established working relationship. Sparrow Cancer Center is expanding and will be opening a new state-of-the-art Cancer Center in 2017, the Herbert-Herman Cancer Center, to play an expanded role with Sparrow's continuing relationship with the Mayo Clinic Care Network. In addition, Sparrow Hospital achieved Magnet designation via the American Nurses Credentialing Center in 2014. Sparrow incorporates a multidisciplinary approach in their lung and chest clinic reducing the time from diagnosis to treatment and improving the quality of care for patients.

Spectrum Health – Grand Rapids, MI: A founding institution of this program of research led by Dr. Hoffman, Spectrum Health was recognized among American's 50 Best Hospitals for two years consecutively from 2015-2016. Spectrum was one of our primary recruiting sites for our recently completed **RCT (R21 CA164515)** and we are looking forward to working together in research again. Spectrum Health Cardiothoracic Surgery located in the Fred and Lena Meijer Heart Center opened in 2004 at Spectrum Health. The Fred and Lena Meijer Heart Center has become a leader in heart care and lung care in the region, state and nation and remains the only hospital in Grand Rapids that provides open-heart surgery and heart and lung transplant. The Fred and Lena Meijer Heart Center covers eight stories and 330,000 square feet, has 164 patient beds, has a medical staff of more than 50 specialists, and serves more than 8,500 inpatients each year. Spectrum Health hosts the Lemmen-Holton Cancer Pavilion that provides a full range of comprehensive oncology services for a variety of cancer diagnoses. Opened at Spectrum Health in 2008, the six-story, 284,000 square-foot pavilion provides outpatient cancer services treating more than 70% of all new adult cancer cases within the Kent County region of western Michigan alone. Integrated within the Lemmen-Holton Cancer Pavilion is the Lung Mass and Cancer Multispecialty Team Clinic. The Lung Mass and Cancer Multispecialty Team is comprised of diverse certified oncology providers to provide a faster path to diagnosis and treatment. Spectrum Health is also recognized for Magnet Status by the American Nurses Credentialing Center.

ABSTRACT

Persons with non-small cell lung cancer (NSCLC) report significantly more unmet supportive care needs than other cancer populations, yet they are among the most vulnerable and least studied. Two of the most prevalent unmet supportive care needs include overcoming fatigue and attaining adequate exercise to meet physical demands of daily living. Cancer-related fatigue (CRF) is a prevalent, persistent, and distressing symptom in the NSCLC population. CRF correlates with greater severity of 15 other symptoms, leading to lower physical function for persons with NSCLC. Among 13 core symptoms across 3,106 breast, colorectal, prostate, and lung cancer patients, persons with lung cancer were the most symptomatic, with moderate to severe fatigue being reported with the greatest prevalence. While surgery is the standard curative treatment for NSCLC, no formal guidelines exist for post-surgical rehabilitation. **We propose** a randomized controlled trial (RCT) of a novel rehabilitative intervention for persons with NSCLC after surgery. Our intervention promotes self-management of CRF and tests the intervention's impact on CRF severity and fatigability with analysis by age. Our **preliminary data** included a two-arm RCT (R21 CA164515) incorporating the proposed intervention, where we exceeded goals for recruitment (67%), retention (97%), adherence (93%), and acceptability. Our 6-wk exercise intervention demonstrated preliminary efficacy in significantly reducing CRF severity and fatigability as compared to usual care, with mean CRF levels restored to levels *lower* than pre-surgery. The exercise group's functional performance exceeded usual care. No adverse events were reported; participants had a mean age of 67 with a mean of 8 comorbid conditions. Our **long-term goal** is to develop interventions to increase perceived self-efficacy for CRF self-management in order to improve CRF, symptom status, functional status, and quality of life (QOL) for persons with NSCLC. Our **objective** in this application is to determine the efficacy, optimal timing, and sustainability of our innovative home-based exercise intervention. This study has the potential to **transform** the current standard by providing a rehabilitative exercise intervention after surgery. The intervention is home-based, self-paced, and builds in duration upon discharge from the hospital after

surgery. **Aim 1:** Determine efficacy by comparing the immediate intervention group with wait-list control (usual care) and attention control by age. **Aim 2:** Determine efficacy of initiating the exercise intervention 6 wks post-discharge and compare results with the immediate intervention group for all ages. **Aim 3:** Determine the immediate intervention's sustainability by analyzing 3a) rates of extension, adherence, and retention; 3b) acceptability; and 3c) efficacy of primary and secondary outcomes. **IMPACT**: Our results will provide a novel exercise intervention, and its optimal timing, and fills the gap for a vulnerable population by providing a practical, portable, and low-cost means of reducing CRF severity and fatigability that is enjoyable and applicable to nearly all post-thoracotomy lung cancer patients.

Section 1.0 Objectives

Persons with non-small cell lung cancer (NSCLC) report significantly more unmet supportive care needs than other cancer populations, yet they are among the most vulnerable and least studied.[1,2] Two of the most prevalent unmet supportive care needs include overcoming fatigue and attaining adequate exercise to meet physical demands of daily living.[1-6] Cancer-related fatigue (CRF) is a prevalent, persistent, and distressing symptom in the NSCLC population.[7-16] The Principal Investigator has identified CRF as a priority symptom that correlates with greater severity of 15 other symptoms, leading to lower physical function and quality of life (QOL) for persons with NSCLC.[17] Likewise, among 13 core symptoms across 3,106 breast, colorectal, prostate, and lung cancer patients, Cleeland et al. found that persons with lung cancer were the most symptomatic, with moderate to severe fatigue being reported with the greatest prevalence.[18] To compound this problem, while surgery is the standard curative treatment for NSCLC, no formal guidelines exist for post-surgical rehabilitation.[8,19-21]

To address this need, **we propose** a novel rehabilitative exercise intervention for persons with NSCLC after surgery. Our intervention promotes self-management of CRF to reduce CRF severity and fatigability (fatigue associated with activity, an indicator of functional capacity) with analysis by age. This randomized controlled trial (RCT) addresses the NCI Clinical Trials Planning Meeting priority need for longitudinal studies of exercise interventions that address CRF that are practical, portable, safe, and independent of climate, and that use motivation for intervention uptake.[22] In support of this application, we conducted a **two-arm RCT (R21 CA164515)** incorporating the proposed intervention and exceeded goals for recruitment (67%), retention (97%), adherence (93%), and acceptability.[23,24] Our 6-wk exercise intervention demonstrated preliminary efficacy in significantly reducing CRF severity and fatigability, compared to usual care, restoring mean CRF to levels lower than pre-surgery. The exercise group's mental and physical functional performance exceeded usual care with no adverse events. Participants had a mean age of 67 and mean of 8 comorbid conditions.

Our **long-term goal** is to develop interventions to increase perceived self-efficacy (PSE), perception of ability, for CRF self-management as a means of improving functional status and quality of life for persons with NSCLC.[25] Our **objective** in this application is to determine the efficacy, optimal timing of initiation, and sustainability of our 6-wk home-based exercise intervention. The **significance** of this study is that it targets two of the most troublesome unmet needs, fatigue and lack of exercise, in an understudied, vulnerable population with the potential to **transform** the current standard of care by providing a rehabilitative exercise intervention after surgery. The proposed research advances the field by providing both an intervention for CRF self-management and evidence for its optimal initiation and sustainability, which currently does not exist for the post-thoracotomy NSCLC population. Our exercise intervention is guided by a theoretical approach (tested by the PI) incorporating self-efficacy theory to strengthen a person's ability to manage their CRF and walking ability.[17,26] The exercise intervention is **innovative** in its timing and approach in providing self-paced exercise to a vulnerable post-surgical NSCLC population upon discharge from the hospital. The Nintendo's Wii Fit Plus is used to provide light-intensity, virtual reality walking and balance exercise that departs from the status quo and transcends barriers to exercise, as demonstrated by our R21 RCT retention and adherence outcomes.

This study employs a three-arm RCT for persons undergoing NSCLC surgery with participants being randomly assigned to an immediate (post-hospital discharge) exercise intervention group, a wait-list control group (6 wks usual care [wks 1-6] and 6 wks exercise [wks 7-12]), or a 6 wk attention control group (wks 1-6).

Primary Outcome: Cancer-Related Fatigue (Severity and Fatigability).

Secondary Outcomes: Severity of Other Symptoms; PSE for CRF Self-Management, Walking, and Balance; Functional Performance; and Quality of Life (QOL).

Aim 1: Determine efficacy of three groups by comparing: 1) immediate exercise intervention group; 2) a wait-list control group; 3) an attention control group by age. Hypothesis 1: The exercise intervention group will outperform wait-list and attention control on all primary and secondary outcomes at wk 6 for all ages.

Aim 2: Determine efficacy of initiating the exercise intervention 6 wks post-discharge and compare results with the immediate intervention group by age. Hypothesis 2*:* The immediate exercise intervention group will improve for all ages at a greater rate and magnitude than the wait-list group for all outcomes.

Aim 3: Determine the immediate exercise intervention's sustainability by analyzing a) rates of extension, adherence, and retention; b) acceptability; and c) efficacy of primary and secondary outcomes. Hypothesis 3: The exercise intervention will be acceptable with >50% extending at wk 6 and >70% adherence and retention at wk 12, with improved primary and secondary outcomes at wk 12.

IMPACT: Our results will provide a novel, practical, portable, low-cost, and enjoyable exercise intervention with important information on its optimal timing and sustainability to fill the gap regarding approaches that are applicable to nearly all post-thoracotomy lung cancer patients for reducing CRF severity and fatigability.[20,22,27-32]

Section 2.0 Introduction

Significance

2A) OVERALL SCIENTIFIC PREMISE

Fatigue remains a prevalent and distressing symptom in post-surgical NSCLC patients.[15,16,33] Exercise has been shown to be effective in treating CRF.[20,34] However, research investigating the effect of exercise on CRF is limited in the post-surgical NSCLC population as these patients are excluded from studies due to complex medical issues.[27-29,32,35] To date, while surgery is a standard curative treatment for NSCLC, no guidelines exist for post-surgical rehabilitation.[8,36-38] The results of our two-arm RCT (R21 CA164515) targeting CRF severity and fatigability via exercise for patients transitioning from hospital to home **sets the premise** for the proposed research, which holds considerable promise to improve post-surgical management of CRF.[23] Our two-arm R21 RCT exceeded goals for retention (97%), adherence (93%), and acceptability with no adverse effects despite participants having a mean age of 67 and a mean of 8 co-morbid conditions.[23,24] Our 6-wk exercise intervention demonstrated preliminary efficacy in significantly reducing CRF severity and fatigability as compared with usual care, with mean CRF levels restored to levels lower than pre-surgery.[23] Limited evidence exists on the optimal timing and sustainability of an exercise intervention targeting CRF for the post-surgical NSCLC population.[30,31] The proposed RCT investigates efficacy, optimal timing, and sustainability to provide an effective exercise intervention for rehabilitation of the post-surgical NSCLC population.

2B) CRITICAL NEED

Adults with multiple comorbid conditions and complex treatment plans, such as those with NSCLC, are vulnerable during the transition from hospital to home.[39-42] In a study of 888 persons with varied cancer diagnoses from initial diagnosis to two years after diagnosis, having a lung cancer diagnosis was found to be a strong independent predictor of reporting a higher number of unmet needs *as compared to all other cancer diagnoses combined*.[2] The most frequently unmet supportive care needs are managing fatigue and physical deterioration, performing activities of daily living, and receiving support to exercise.[1-6,43] Likewise, greater levels of supportive care needs are associated with greater symptom distress and worse physical functioning.[1]

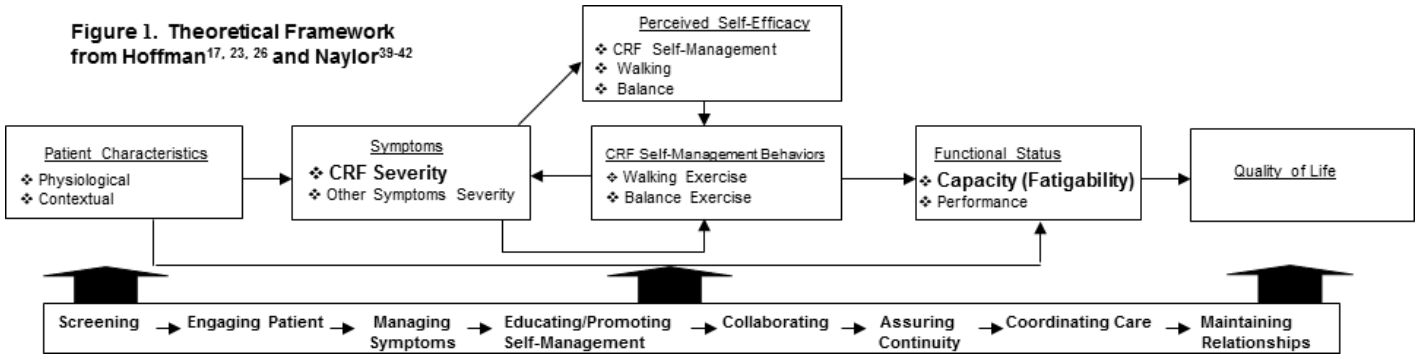
Fatigue is a prevalent, severe, and debilitating cancer symptom in persons with lung cancer. Fatigue is the most common distressing and unmanaged symptom in persons with cancer.[13,44-50] In a 2013 study among

3,106 ambulatory patients with breast, prostate, colorectal, or lung cancer with nearly 75% receiving treatment, fatigue was the most prevalent and severe symptom in each group.[18] Persons with lung cancer were most symptomatic, with nearly 30% rating 5 of 13 symptoms' severity as moderate or severe. Moderate or severe fatigue was more prevalent in persons with lung cancer than in persons with breast, prostate, or colorectal cancer.[18] In 2014, Wang and colleagues reported that among persons with solid tumors receiving cancer treatment, having lung cancer was one of the most important contributors to moderate to severe fatigue.[10] As shown in a 2011 national study of 4,512 cancer survivors, fatigue is persistent even one year post-diagnosis and after treatment.[51] Also, > 25% of the participants reported having high symptom burden more than one year after diagnosis, with persons with lung cancer reporting high symptom burden with fatigue having the greatest impact on health-related QOL.[51] Longitudinal studies of post-surgical NSCLC patients also report persistent and/or worsening of CRF, other symptoms, physical functional status, and QOL.[8,11,14,21,52,53]

An intervention must be applicable to patients of all ages. Oksholm et al. report few age-related differences among 270 persons undergoing surgery for lung cancer, noting that fatigue and multiple symptoms are highly prevalent in both younger (< 65) and older (> 65) patients.[54] While fatigue is a major issue among all ages, fatigue is prevalent in older adults (> 65) and interferes with activity, leading to loss of independence.[55] Among older adults void of mobility limitations or disability, fatigue when performing activities such as walking (fatigability) is predictive of activity limitations, functional decline, and disability.[56-59] In persons 75-80 yrs old, sustained fatigue was found to be a strong predictor of mortality.[60] With 67% of persons diagnosed with lung cancer aged 65+ at time of diagnosis,[61] and fatigue identified as a priority symptom, it is critical to have an intervention that is effective and applicable to lung cancer patients of all ages.[15,16,20] Results of our R21 RCT indicate the exercise intervention was beneficial for both younger (<65) and older (> 65) patients with CRF severity of both groups improving by a mean of 3.3 (scale 0-10, 10 = most severe) over their corresponding control groups post-intervention.

2C). SIGNIFICANT CONTRIBUTION

Our study incorporates a transdisciplinary, novel exercise intervention relevant for all ages that addresses CRF self-management to improve CRF severity and fatigability for a vulnerable population during a critical transition in their treatment.[22] This study proposes a highly accessible solution to meet the unmet rehabilitative support needs[62] targeting CRF via a PSE-enhancing exercise intervention to improve CRF severity and fatigability, other symptoms' severity, and functional performance. This study helps meet the priority need identified in the NCI Clinical Trials Planning Meeting[22] and 2014-2018 Oncology Nursing Society Research Agenda[63] for implementation of longitudinal exercise trials for safe interventions that are practical, portable, independent of climate, and using motivation as a key factor for uptake. The proposed research is based on Principles of the Transitional Care Model,[40-42,64] which underpins the approach to the implementation of the proposed intervention. The Transitional Care Model provides a continuum of care including pre- and post-surgical screening and engagement, management of symptoms using education for the promotion of self-management, health care team and patient collaboration, continuity of care from hospital to home, and postsurgical coordination of care while maintaining relationships in a transdisciplinary approach. A tested theoretical framework from the synthesis of the Theory of Unpleasant Symptoms[65,66] and Bandura's Self-efficacy Theory[67] guides the intervention's design and testing (**Fig 1**)[17,23,26] and provides insight into how a person's PSE for self-managing symptoms influences performance of those behaviors. Hoffman and colleagues[17] found that for persons with cancer, including lung cancer, targeting CRF severity directly and indirectly through PSE for CRF self-management is important to functional status. Thus, we hypothesize that patient characteristics are influencing factors of symptoms and functional status.



A key characteristic is age and its influence on CRF severity and fatigability. Symptoms affect PSE. Symptoms and PSE affect CRF self-management behaviors. The performance of CRF self-management behaviors affects symptoms and functional status.[68] Two dimensions of functional status are functional capacity (one's maximum potential to perform activities) and functional performance (daily activities in the normal course of their lives).[68] This study investigates effects of an exercise intervention on CRF severity and fatigability, with fatigability indicated by a person's functional capacity that enables or restricts functional performance.[68] The effect of CRF self-management behaviors on CRF severity and fatigability ultimately affect quality of life, a "person's sense of well-being that stems from satisfaction or dissatisfaction with the areas of life that are important to him/her." **The results of our two-arm R21 RCT indicate that our exercise intervention is feasible, acceptable, safe, and enjoyable, while providing significant improvements in CRF severity and fatigability** for the intervention group versus the control group.[23,24] Likewise, our home-based intervention removes barriers to exercise for a patient population that has significant health and logistical barriers to exercise.[24,30,69] Our participants confirmed that the exercise intervention fills the gap in post-thoracotomy rehabilitation and meets their needs by providing a means to overcome the barriers to exercise they experience.[35]

2D) EXPECTED BENEFITS

Lung cancer is the most common cancer worldwide (1.8 million cases/year, NSCLC accounting for ~85% of cases).[70] The 5-year survival rate for lung cancer is 55% for cases detected early[70] with surgery being the best curative treatment; CRF is reported as the most prevalent and distressing symptom in this population.[35,52,71] This research addresses a glaring knowledge gap in how to rehabilitate and treat CRF in this sizeable, high acuity cancer population.[8,35] Based on existing evidence, [72-75] results of our single-arm pilot (no control group)[76,77] and two-arm R21 RCT,[23] we expect the benefits of this study to confirm that post-surgical NSCLC patients will find the exercise intervention effective in reducing CRF severity and fatigability (functional capacity). Further, we expect the exercise intervention group will outperform the attention control and wait-list control groups by age for other symptoms' severity; PSE for CRF self-management; PSE for walking; PSE for balance; functional performance; and QOL. We expect the wait-list exercise intervention group's CRF severity and fatigability to improve, but not as significantly as the immediate exercise intervention group. We also expect >50% of the immediate exercise intervention group to extend 6 more wks, with adherence and retention rates of >70% at wk 12, with improved primary and secondary outcomes at wk 12. Once this exercise intervention's effectiveness is further demonstrated, the intervention will provide a practical and portable means to treat CRF severity and fatigability for NSCLC and other vulnerable populations transitioning from hospital to home.

Innovation

2E) TRANSFORMING THE STATUS QUO

This study is the first extensive study to target and analyze by age a priority symptom, fatigue and its associated fatigability, in a vulnerable, underserved post-thoracotomy NSCLC population during their transition from hospital to home. Our proposed research builds on the results of our single-arm pilot and

two-arm RCT. The approach executes transitional care principles to address a high-risk, high-cost, high-volume patient population and their most critical reported unmet needs. We will assess the timing and the corresponding sustaining effects of the exercise intervention in order to help define its optimal delivery.

This is also the first large-scale RCT of post-surgical NSCLC patients to test a highly accessible, home-based, light-intensity exercise intervention that incorporates PSE-enhancing strategies. It utilizes an enjoyable approach through virtual reality (using the Nintendo Wii Fit Plus), which may offset the effects of unpleasant symptoms to facilitate exercise. By using an entertaining light-intensity exercise intervention, in the home, with a PSE-enhancing approach, we expect to transcend exercise barriers and provide a safe, practical, inexpensive, and portable means to effective CRF self-management and improved CRF severity and fatigability. No exercise intervention studies for the post-surgical NSCLC population have utilized fatigability to measure effectiveness of a fatigue intervention. This is important, given that fatigability is the degree of fatigue associated with activity of any kind and is a measure of the impact fatigue has on functional capacity that influences functional performance. Thus, without a fatigability measure, it is difficult to determine the effectiveness of an intervention for fatigue.[68,78]

2F) LIMITATIONS & BARRIERS OF STATUS QUO ADDRESSED

Studies on exercise interventions for post-surgical NSCLC patients are very limited. Currently, there are no guidelines for routine rehabilitative support for persons with NSCLC after surgery.[8,19,21,38] The optimal exercise program for persons with NSCLC recovering from surgery is not known.[37,79-83] In 2012, three systematic Cochrane reviews of the general cancer population indicated that exercise can be beneficial for the management of CRF and health-related QOL. This benefit was seen from cancer diagnosis, through active treatment, and post-treatment, with treatment including surgery, chemotherapy, radiation therapy, and/or hormone therapy.[27-29] However, all three reviews recommended caution when interpreting these positive results because the majority of the studies were conducted on the breast cancer population, who are typically less vulnerable, younger, and have minimal comorbid conditions.

2G) Our pilot data suggest that our exercise intervention is effective in removing the post-surgical NSCLC population's significant barriers to exercise while the exercise intervention's minimal exclusion criteria maximize its applicability. To date, the eligibility criteria for exercise interventions in post-surgical NSCLC patients have excluded much of the post-surgical NSCLC population: These criteria eliminate patients with common comorbid conditions; require moderate-to-vigorous exercise intensity; have been structured, and inpatient or facility-based; have not reported adherence rates while exhibiting poor rates of retention.[30,31,69,72,84-87] In our R21 RCT, the proposed intervention showed preliminary efficacy in improving fatigue severity and fatigability while removing the barriers to exercise through light-intensity, home-based, self-paced, self-efficacy enhancing attributes that were highly acceptable, resulting in high retention rates.[23,24] Our research addresses NCI recommendations for high-priority research focused on overcoming barriers to implementation and strategies to increase uptake and effect size of interventions like exercise, to promote CRF management.[22]

2H) TRANSFORMING POST-THORACOTOMY REHABILITATION THROUGH INNOVATION

It is difficult to determine how to exercise vulnerable, post-thoracotomy NSCLC patients and keep them exercising.[29-31] The latest Cochrane reviews on exercise interventions on health-related QOL, including fatigue during/after active cancer treatment, recommend research investigating how to sustain positive effects of exercise over time. These reviews recommend research to determine the central attributes of exercise (mode, intensity, frequency, duration, timing) for cancer patients other than breast cancer.[27-29] The Cochrane review of non-invasive interventions for improving well-being and QOL in lung cancer patients recommends the development of interventions focused on symptom self-management to promote functional ability.[88] Recommendations were made to test the feasibility and effectiveness of non-invasive interventions for the lung cancer population "within real life settings as opposed to the sometimes artificial setting of a research study."[88]

- Our proposed study couples self-efficacy theory[67,89] with an innovative approach using virtual reality gaming technology, implemented in the comfort of the patient's home to help sustain exercise by providing a

convenient and enjoyable means of exercise.[29] We learned in our single-arm pilot, which was corroborated in our follow-up two-arm RCT that participants found the proposed exercise program enjoyable and "the right type of exercise at the right time" for their body and mind to recover.[76,77]

The challenge has been to determine how to exercise a post-thoracotomy patient who is typically deconditioned, as demonstrated by reduced exercise capacity related to a sedentary lifestyle, the surgery itself, and multiple comorbid conditions.[75,90] This deconditioning is exacerbated by the debilitating effects of the thoracotomy procedure and its sedentary recovery, with further reductions in exercise capacity upon initiation of adjuvant chemotherapy and/or radiation therapy.[90] In our RCT, 21 of 37 exercise intervention participants were prescribed walkers on discharge. After 6 wks, all exercise participants, including those who required a walker pre-surgery, no longer needed walkers. Conversely, 6 of 35 control group participants were prescribed walkers at discharge, with 4 needing their walker at the end of the study. Also, 9 of 37 intervention participants were discharged with oxygen therapy. After 6 wks of exercise, only 4 required minimal oxygen for vigorous activities. Conversely, 6 of 35 in the control group required oxygen at discharge with 3 requiring oxygen for activities of daily living post study. Our team developed a prospective approach by incorporating an innovative exercise intervention that disrupts the debilitating deconditioning spiral by providing vulnerable patients a means to safely exercise after the transition from hospital to home.[76,91,92]

2I) Introduction to the Approach

By designing services for the hospital-to-home transition, we provide health care continuity and avoid preventable poor outcomes among high-risk patient groups. To date, exercise interventions for post-surgical NSCLC patients have been facility-based, utilizing conventional equipment with moderate- to high-intensity exercise.[72,81,84,85] Studies have not addressed the critical post-surgical hospital-to-home transition, leaving patients without a plan to address symptoms such as CRF severity and associated fatigability.[8] Naylor's[39,42] work demonstrates that adults with multiple comorbid conditions and complex treatment plans are vulnerable during the hospital-to-home transition. Naylor also demonstrated that designing services for this transition provides health care continuity and prevents poor outcomes among high-risk patient groups.[93]

2J) Research suggests that light-intensity exercise may improve functioning and QOL and may be an alternative to higher-intensity exercise programs for deconditioned populations with comorbid conditions.[94,95] In our R21 RCT, we found that light-intensity (<3.0 METs) was practical, as the intensity falls within their current prescribed physical activity level; it reduced CRF severity and fatigability as compared to the usual care group; and it was safe, with no adverse events reported.

2K) Given that CRF is a multiple determinant construct,[96] research suggests that integrating *self-efficacy* with physical exercise may be beneficial in ameliorating fatigue.[97] To date, there have been no intervention studies dedicated to persons with NSCLC after surgery that have incorporated self-efficacy enhancing processes and light-intensity exercise to target CRF. According to Bandura,[67(p.411)] successful adoption and adherence to exercise even in healthy populations requires PSE to engage in exercise. Structuring an environment that can reduce exercise barriers with motivational supports is essential for the post-surgical NSCLC population. Bandura[67 (407-421)] states that before building a person's PSE to exercise, barriers to exercise need to be removed. Exercise barriers include travel, timing, weather, and the belief that exercise is onerous, monotonous, and strenuous. Additional barriers include lack of knowledge, skills, and abilities to implement an exercise program. NSCLC patients have added barriers of symptoms such as CRF that prevent daily activities. Bandura[67 (p.147)] states that a change in environment can instantly alter what preoccupies one's thinking. Studies show that unpleasant sensations are offset by competing pleasant sensations, hypothesizing that the brain is limited to how many sources of information it can process at one time.[98-101] Researchers hypothesize that while a patient is engaged in a pleasant activity, there is less attention available to process unpleasant sensations, providing relief of the unpleasant sensation and augmenting the pleasant sensation.[98,102] The proposed intervention virtually transports the patient to enjoyable environments

overcoming barriers to exercise by introducing an attention strategy to self-attract pleasant thoughts, relieving the unpleasantness of unwanted symptoms.[67 (p.147)]

2L) Generating evidence to determine key exercise intervention attributes and optimal timing is critical. Exercise is an effective means for treating CRF.[20,29,32,71,82] However, research investigating exercise in the lung cancer population following surgery is limited, with heterogeneity of exercise programs.[27,29] Limited evidence can be found showing the most essential attributes to making exercise effective (mode, intensity, frequency, duration, timing).[27,29] We expect that light-intensity exercise initiated immediately after hospital discharge will positively affect CRF severity and fatigability, but the optimal timing of exercise initiation is not known.[27,29] Generating evidence to determine optimal intervention timing is critical, given that the post-surgical lung cancer population experiences significant symptom burden decreased functional status, and QOL.[8,10,15,16,18,52,54,103] Consequently, obtaining symptom data from participants who initiate the exercise intervention: a) immediately upon returning home after surgery and b) 6 weeks after returning home will provide insight into the recovery process and the importance of exercise timing on CRF severity and fatigability.[76,77] With diminishing health care resources, it is important to understand how and when to apply resources to optimize outcomes.[22]

Fig 2: RCT Participant Demographics
Mean age = 67 yrs (range 32-89 yrs)
56% female
74% married
56% retired
29% employed outside home
89% White
7% Black (n = 5)
4% American Indian (n=3)
19% did not complete HS
43% completed HS only
28% some college or post-HS training
10% college and/or post-grad

2M) Exercise interventions must be sustainable to ensure continued use/effectiveness throughout the post-thoracotomy NSCLC population's survivorship trajectory.[104] Sustainability is defined as the continued use beyond the initial implementation of the intervention for the continued achievement of desirable outcomes for the intended population.[104-106] Little research has been conducted with the post-thoracotomy lung cancer population on how to *sustain* changes in exercise behaviors and their associated effects over time for CRF, functional status, and QOL.[27-29,69] Cochrane reviews[27-29] state that research is required to investigate how to sustain these positive effects and determine the attributes that lead to success—a key goal of intervention science—to understand if investments are leading to longer-term beneficial outcomes.[104] The design of the proposed exercise intervention combines recommended attributes identified as potential motivators to promote a sustained exercise intervention in the cancer population. These exercise motivators include but are not limited to: use of self-efficacy theory to create intrinsic demand for the intervention;[29,89] use of a home-based approach[30] with service delivery, including face-to-face contact followed up with phone contact;[107] use of informational motivators such as activity logs; portable heart rate monitors and pedometers; and expert consultation provided by qualified health care providers.[82]

PRELIMINARY WORK

2N) Two-Arm R21 RCT Pilot Published 2017[23,24]

Purpose. Examine feasibility, acceptability, and preliminary efficacy of a rehabilitative intervention for CRF severity, fatigability, PSE for fatigue self-management, other symptoms' severity, PSE for walking & balance, and functional performance for post-surgical NSCLC patients.

Methods. Participants (**Figs 2, 3**) were randomly assigned prior to surgery to intervention group (IG) (n = 37) or usual care group (UCG) (n = 35). The IG performed prescription-based virtual reality walking and balance exercise using the Nintendo Wii in their home. The 6-wk light-intensity exercise intervention was self-paced, gradually building in duration upon hospital discharge after NSCLC surgery. A nurse called the participant within 24 hrs post-surgical hospital discharge to screen for readiness to start the intervention. A home visit to start exercise was scheduled within 4 days of discharge. The nurse made a second home visit at the start of wk 2 and phone visits at the start of wks 3-6, with additional visits on participant request. Both home and phone visits supported participants by providing PSE-enhancing CRF self-management interventions to support exercise and adjust the exercise prescription

.

Aim 1 Results (feasibility, acceptability, safety) Recruitment. We recruited 67% of eligible participants, exceeding our goal of 50%. Also, recruiting goals of N=64 were exceeded: 72 participants completed the study, recruited from one hospital site in west Michigan and two hospitals in mid-Michigan. Retention, adherence, acceptability, & adverse events: Retention was assessed by measuring percentage completing the program from first phone visit after surgery to final data collection at wk 6. Even though this vulnerable population had a mean of 8 comorbid conditions, the goal of 70% retention was exceeded: 97% of participants completed the intervention. Adherence was measured by computing percentage participating in the intervention that adhered to the recommended intervention. The goal of 70% adherence was exceeded, as 37 participants adhered to their prescribed exercise at a rate of 93%. Acceptability was assessed via a 15-item questionnaire providing feedback in multiple areas. The 37 participants gave a mean rank of 5.6 (scale 0-6, 6 = highest acceptability) exceeding our goal of a mean positive acceptability score of 4. Participants stated that the intervention was enjoyable and effective in helping control their fatigue. A proposed improvement was after 10 mins of walking with the Wii, participants wanted the option to walk outside or in another venue; this is now incorporated in our proposed intervention. No adverse events were reported.

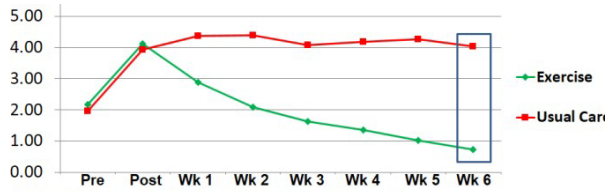


Figure 4. Cancer Related Fatigue Severity Mean Scores (0-10, 10 – Most Severe)

4% bi-lobectomy resection
5% pneumonectomy resection
5% other resections.
Cell type following resection

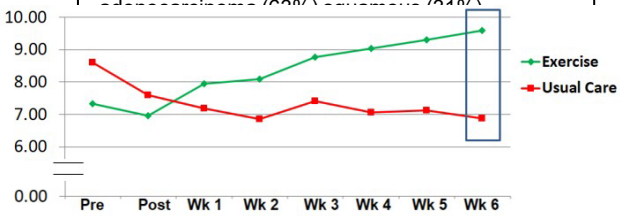


Figure 5. Perceived Self-Efficacy for Fatigue Self-Management Mean Scores (0-10, 10 = Greatest Self-efficacy for Fatigue Self-management)

Aim 2 Results (preliminary efficacy of exercise intervention) Preliminary efficacy was assessed by comparing results of the IG (N=37) with the UCG (N=35). Primary outcomes were CRF severity, fatigability, and PSE for CRF self-management. Effect sizes were calculated using Cohen's *d* mean difference methods by calculating the mean difference between IG and UCG divided by SD of the UCG (more conservative).

Cancer-related Fatigue Severity was measured using the Brief Fatigue Inventory[108] with data collected pre- and post-surgery, upon return home from hospital, and at the end of each wk for 6 wks. Results (**Fig 4**) indicate on a scale of 0-10 (10 = most severe), IG and UCG pre-/post-surgery values show no significant difference. At wk 6, a significant difference was found between the IG (M=0.7, SD 0.7) and UCG (M=4.0, SD 2.0) [t (42) = -9.3, p<.001; 95% CI -4.0 to -2.6; *d* = 1.7]. The IG's wk 6 CRF severity (M=0.7, SD 0.7) showed significant recovery from post-surgery (M=4.1, SD1.9) [t (36) = 9.9, p <.001; 95% CI 2.7 to 4.1; *d* = 1.8], restoring to a CRF severity *lower* than pre-surgery levels (M=2.2, SD 2.0)
[t (36) = 4.4, p<.001; 95% CI 0.8 to 2.1; *d* = 0.7].

PSE for CRF Self-Management measured by the PSE for Fatigue Self-Management Instrument[109] shows (**Fig 5**) on a scale of 0-10 (10 = greatest PSE) the IG's PSE for CRF self-management improves from post-surgery (M=7.0, SD 2.0) to wk 6 (M=9.6, SD 0.7), while the UCG's PSE decreased from post-surgery (M=7.6,

SD 2.6) to wk 6 (M=6.9, SD 2.1) resulting in a significant difference at wk 6 [t (41.8) = 7.4, p<.001; 95% CI 2.0 to 3.5; *d* = 1.3].

Fatigability (fatigue with activity, indicator of functional capacity) was measured by the 6-min walk test (6MWT) pre-surgery and post-study, by assessing fatigue reported during the 6MWT and distance walked in 6 mins.[110] The IG's wk 6, post-study fatigability decreased from pre-surgery while the UCG's *increased*. IG's fatigue during 6MWT (0-10, 10= most severe) decreased from pre-surgery (M=2.0, SD 1.7) to post-intervention (M=0.4, SD 0.8) while their distance walked increased by a mean of 15% (SD 15). Conversely, the UCG's fatigability *increased* as their 6MWT fatigue increased from pre-surgery (M=1.5, SD 1.8) to post 6 wks (M=3.1, SD 1.5) while their distance walked decreased by a mean of 21% (SD 19). The difference between the IG and UCGs' fatigue during the post-study 6MWT was significant [t (50.9) = -9.3, p<.001; 95% CI -3.3 to -2.1; *d* = 1.8) as was % change in distance walked post-study vs. pre-surgery 6MWT [t (70) = 9.0, p < .001; 95% CI 28 to 44; *d* = 1.9].

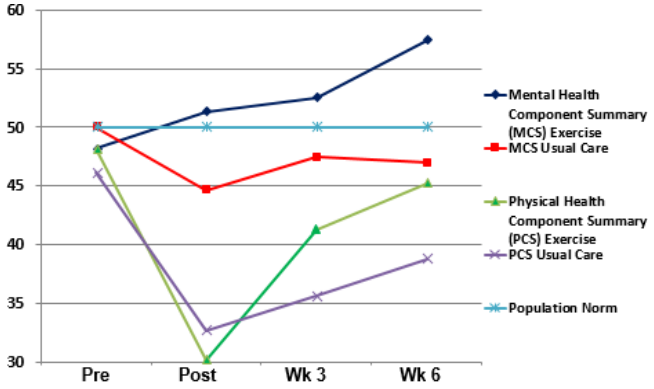


Figure 7. Physical and Mental Health Component Summary SF-36 (60 = Greater Mental/Physical Health)

15 Other symptoms' (not including fatigue) frequency, severity, and interference levels were measured using the M.D. Anderson Symptom Inventory.[111] **Fig 6** shows number, severity, and interference from pre-surgery to wk 6, post-study for IG and UCGs. **Mean # symptoms** reported by the IG decreased from 8.4 (SD 2.4) post-surgery to 4.6 (SD 3.2) at wk 6 post-study, while the UCG reported a mean of 6.6 (SD 3.3) post-surgery and increased to 7.4 (SD 3.3) at wk 6, post-study, a significant difference between groups at wk 6 [t (70) = -3.7; p<.001; 95% CI -4.4 to -1.3; *d* = 0.9]. Likewise, **mean symptom severity** of the IG was 4.7 (SD 1.5) post-surgery and decreased to 2.1 (SD 1.0) at wk 6, while the UCG started equivalent to the IG post-surgery at a mean severity of 4.9 (SD 1.6) and only reduced to a mean level of 3.8 (SD 1.5) by wk 6, a significant difference between groups at wk 6 [t (61.2) = -5.6; p<.001; 95% CI -2.3 to -1.1; *d* = 1.1]. For **mean symptom interference**, the IG reported post-surgery mean interference of 3.3 (SD 2.1) decreasing to a level of 0.5 (SD 0.8) at wk 6, while the UCG reported a post-surgery mean interference of 4.5 (SD 2.8) and improved to an interference level of 2.9 (SD 2.3) at wk 6, a significant difference between groups at wk 6 [t (41.8) = -6.0; p< .001; 95% CI -3.2 to -1.6; *d* = 1.1].

Functional Performance was measured using the Medical Outcomes Short-Form-36 (SF-36)[112] pre-/post-surgery and after wks 3 & 6. SF-36 uses norm-based scoring with physical and mental health components of the SF-36 scored to have the same mean (50) and SD (10) in the general U.S. population, with component scores ranging from 20 to 70. The Mental Health component of the IG (**Fig 7**) consistently improved from a mean pre-surgery level of 48.2 to 57.5 at wk 6 (exceeding national norm of 50). Conversely, the UCG's mean Mental Health component scores *dropped* after surgery and stayed relatively flat for wks 3 & 6 (47.4 and 47 respectively). Physical Health component scores dropped for both groups post-surgery, with IG's improving from post-surgery 30.2 to a wk 6 of 45.2. The UCG improved at a much slower rate, starting at post-surgery level of 32.7 and improving to 38.8 at wk 6 post-study.

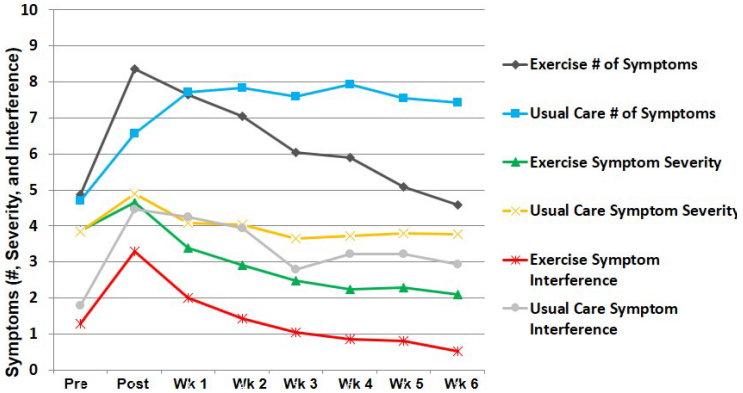


Figure 6. Other Symptom Mean Scores (Number, Severity, Interference (0-10, 10 = Most Severe and Most Interference)

Implications of Preliminary Work. Results justify efficacy testing with a larger sample, attention control group, and focus on optimal timing and sustainability of the exercise intervention. The proposed intervention retains all pilot components, incorporating participant feedback to add exercise flexibility with/without the Wii after achieving 10 mins/day of continuous walking for 5 days/wk.

Section 3.0 Eligibility Criteria

The research proposed for this application is a randomized controlled trial (RCT) to determine the efficacy, optimal timing, and sustainability of an innovative home-based exercise intervention for post-surgical non-small cell lung cancer (NSCLC) patients after discharge from the hospital. This exercise intervention is designed to enhance perceived self-efficacy (PSE) for cancer-related fatigue (CRF) self-management to improve CRF severity and fatigability (fatigue associated with activity, an indicator of functional capacity) to augment the rehabilitation of persons of all ages with NSCLC after surgery.

No special vulnerable populations will be studied.

Eligibility. Based on results of our R21 RCT, we will use criteria shown for participation in this study:

Inclusion Criteria. 1) Women and men at least 18 years of age with suspected NSCLC to be confirmed after surgery; 2) Karnofsky Performance Status score of at least 70%, which provides functional impairment classification, universally used in oncology, and is scored from 0% (dead) to 100% (no complaints); 3) Thoracic surgeon approval pre- and post-surgery; 4) Medically stable comorbid conditions allowing for NSCLC surgery clearance; 5) Has phone access capability; 6) Able to speak and write English; 7) Able to hear and speak for phone interviews; 8) Owns a television; and, 9) Lives within 2 hours driving distance of recruitment site. This study includes both men and women since lung cancer remains the second most common, newly diagnosed solid tumor and accounts for more deaths than any other cancer regardless of gender.[61] While the average age of persons with lung cancer at diagnosis is 70 years, age alone is not a reason to deny persons with NSCLC access to curative-intent surgical intervention since lung resection remains the best treatment option.[114] Consequently, persons 18 years of age and older and diagnosed with lung cancer will be eligible to participate. While 99.8% of persons diagnosed with lung cancer are at least 35 years of age upon diagnosis,[155] those younger than 35 years of age will also need to recover from surgery, including meeting the needs of managing CRF and exercise.[16] In addition, most exercise interventions conducted in the cancer population have excluded persons with comorbid conditions.[29] Since the lung cancer population commonly has comorbid conditions, our research team included participants with medically stable comorbid conditions allowing the participant to be cleared for NSCLC surgery. The mean age was 67 (SD 9.9) years with a range in age from 32 to 89 years in our **NCI-NIH two-arm RCT (R21 CA164515)**, with both the youngest and oldest participants completing the intervention. In addition the mean number of comorbid conditions upon entry into our two-arm RCT was 8 (SD 3.9) with a range of 0 to 17 co-morbid conditions. Despite participants' diverse ages from 32 to 89 years and having a mean of 8 comorbid conditions, there were no reported adverse events. Moreover, since cancer survivors are recommended to return to normal daily activities as quickly as possible after surgery,[82] and the light-intensity exercise intervention mimics normal daily activities,[118] persons with NSCLC with medically stable comorbid conditions are included to participate in the study. The proposed RCT in this application addresses the NCI Clinical Trials Planning Meeting priority need for longitudinal studies of exercise interventions that address CRF that are practical, portable, safe, independent of climate, and use motivation for intervention uptake.[22]

Exclusion Criteria. 1) Severe impairment of sight, hearing, speaking; 2) Active treatment for malignancy within past 3 months (other than non-melanoma skin cancer or long-term hormonal treatment for common cancers such as breast and prostate if disease is stable; 3) Weight greater than 330 pound (weight capacity of the Wii balance board); 4) History of photosensitive seizures; 5) Any condition or disorder that would impede safe participation as directed; and 6) Plans to relocate outside the area during the study period or unable to fully participate.

Section 4.0 Registration Procedure

Random Assignment. Randomization will be implemented after consent and before surgery. A random number table generated by our statistician will assign the participant to the IIG, WCG, *or ACG*. Blocking factors in the randomization scheme include participant's age (< 65 or ≥ 65 years) and functional capacity level (6MWT distance ≥ 452 meters).

Blocking Factors in the Randomization Scheme. Randomization will be implemented after consent and participants will be assigned to IIG, ACG, or WCG. This gives all participants an equal chance of being assigned to one of the three study groups. Blocking factors used successfully in the randomization scheme of our two-arm RCT (R21 CA164515) include the participant's age (≤ 64 years or ≥ 65 years) and functional capacity level (those that achieve six minute walk test [6MWT] distance ≥ 452 meters). This is based upon the work of our oncology exercise consultant, Dr. Lee Jones, who found for persons with NSCLC that the 6MW distance provides important objective prognostic information relative to survival in that 452 meters was found to be the minimum distance achieved for those in the high capacity functioning group.

Figure 8. Study Design (N=180)		Pre-surgery	Surgery	Post-surgery	Weeks 1-6		Weeks 7-12	
R	Immediate Intervention Group (IIG n=60)	B, S	H	D, V	D, V, ⟶	S	D, ⟶	S
R	Wait-list Control Group (WCG n=60)	B, S	H	D	D, Usual Care	S, V, D	D, V, ⟶	S
R	Attention Control Group (ACG n=60)	B, S	H	D	D, Attention Control	S		
R=random assignment, B=baseline data collection, S=six-minute walk test administered, H= hospital visit, V = home visit, ⟶ = exercising, D=data collection								

Screening and Registering Participants. For prospective participants scheduled to undergo surgery for suspected NSCLC, the cardiothoracic surgeon's office will: 1) Inform prospective participants about the availability of the study. 2) Provide prospective participants with an approved informed consent document and brochure that provides information about the study. 3) Provide prospective participants with information about contacting Dr. Hoffman for further information about the study and enrollment. 4) Obtain permission from the prospective participant for Dr. Hoffman to contact them if they wish for more information about the study. If the participant is eligible to participate in the study, the Dr. Hoffman or the nurse recruiter will give a copy of the informed consent form and an approved recruitment brochure providing an overview of the study. Potential participants will be given the opportunity to enroll when meeting with Dr. Hoffman or the nurse recruiter after given time to go through the consenting process and know they want to participate or they may elect to take the information home and decide at a later time. The consenting process includes time for patients to read over the consent document and ask questions prior to making any decision about participation. Contact information for the nurse recruiter will be provided as well. This will give the potential participant the ability to consider participation in the study out of the clinical environment. The nurse recruiter will call the potential participant at home to answer any questions and assess interest in participation after time is given to the potential participant to read and review material provided. If the potential participant expresses interest in participation either when initially presented the opportunity or after they have gone home, the nurse recruiter, will either begin the consenting process and enrollment or schedule a meeting to begin the enrollment process with both occurring in a designated private conference room at the participant's convenience. Potential participants will be informed both verbally and in writing that participation is entirely voluntary and they may refuse to participate and withdraw from the study at any time. Potential participants will be assured that refusal to participate will in no way alter the quality of usual health care they receive. The patient will receive a copy of the consent with their signature. The study brochure provides the participant with the ability to contact the Principal Investigator to discuss participation in the study and to let the study team know that they are not interested in participating.

Section 5.0 Research Design

5A) Introduction to the Research Design of Proposed Project

We propose a three-arm, repeated measures RCT for persons undergoing NSCLC surgery as shown in **Fig 8**. The design provides for **efficacy** comparisons of outcome measures among the immediate (exercise) intervention group (IIG), the wait-list control group (WCG) usual care, and the attention control group (ACG) by age after 6 wks (**Aim 1**) through the measurement of primary and secondary outcomes. The design also provides for evaluation of the timing of the intervention (**Aim 2**) by comparing study outcomes of the IIG's wks 1-6 with those of the WCG's wks 7-12 by age to account for time since surgery. Note that the timing of the data collection occurs near the time of the assessment during the week when the assessment is conducted. For example, if a participant has an unexpected visitor at their home and would like to have the data collector call the next day, then the data collector may call the next day. Unlike mice or non-human studies, we need to balance absolute timing against the needs of our human participants so we incorporate some flexibility required of our human participants when collecting data. Determining optimal timing to initiate an exercise program for post-surgical NSCLC patients is needed. We chose to start the WCG intervention at 6-wks post-hospital discharge based on Leach et al.'s[113] findings that 43% of the 66 postsurgical NSCLC patients in their study preferred to start an exercise program during adjuvant treatment. Also,
adjuvant treatment (radiation and/or chemotherapy) commonly begins 4-10 wks after surgery, with nearly 30% of patients undergoing adjuvant treatment.[114] Sustainability of the intervention (**Aim 3**) can be determined by offering the IIG the option to extend their exercise to 12 wks and calculating the percent that elect to extend, assessing acceptability, adherence, and retention while measuring primary and secondary outcomes for efficacy. Adverse events will be monitored to provide for safety (R21 RCT reported no adverse events).

5B) Setting & Sample. The target sample will be recruited in **5 sites**. We will continue the working relationships we built while conducting our R21 RCT with Spectrum Health, McLaren, and Sparrow Health. We will add Munson Healthcare and Nebraska Medicine Campus. Results from our R21 RCT show very large effect sizes between the exercise and usual care groups that are not expected to hold in this proposed study as we have additional sites with more diverse populations and two new study arms (ACG and WCG). Our sample size assessment for primary Aim 1 uses the expected CRF severity scores by age group shown in **Table 1 (below)** with CRF estimates from our R21 RCT for comparison. An exemplar multiple regression model was run with age distribution approximating the NSCLC population with 33% < 65 yrs and 67% $\geq$ 65 yrs, model error standard deviation (SD) = 2.0. Comparable R21 results suggest a SD between 0.7 and 2.6 in these two age groups. With overall significance level at 5%, we computed the total sample size N to ensure at least 80% power in 4 pre-specified comparisons between IIG and ACG for ages <65 and $\geq$ 65. With N = 180 (60/group, 20 <65 yrs and 40 $\geq$ 65 yrs) power to detect the expected CRF is shown in **Table 2 (below)** with the minimum sample size for each comparison. Based on our R21 RCT and previous cancer work,[115] we will over-recruit to account for a conservative attrition rate of 20% (N = 225 = 180/0.8), and under plausible assumptions,[116,117] conservatively provide for 90% compliance increasing for a total of N = 279 $\approx$ 225/(0.9)(0.9)[117] patients.

Table 1: Expected mean CRF Severity scores at 6 weeks post-surgery by age

Group	Age	CRF-Expected	CRF-from R21
IIG	<65	2.5	0.81
IIG	65+	2.0	0.68
WCG	<65	4.5	4.12
WCG	65+	4.2	3.99
ACG	<65	4.3	4.12
ACG	65+	4.0	3.99

Table 2: Power to detect expected differences in mean CRF Severity scores between groups by age

Comparison	Age	Power (N=180)	N for 80% power
IIG vs ACG	<65	0.81	180
IIG vs WCG	<65	0.88	144
IIG vs ACG	65+	0.94	81
IIG vs WCG	65+	>0.99	63

5C) Study Protocol

The following protocol was used successfully in our R21 RCT with the addition of the WCG and ACG in the proposed study. Participants scheduled for NSCLC surgery will be identified by the surgeon's office prior to surgery, recruited, and enrolled by the nurse recruiter.

5C1) Study Interventions.

5C1a) The exercise intervention is designed to promote regular, light-intensity walking and balance exercise < 3.0 metabolic equivalents (METs), which corresponds to usual activities of daily living.[118] Combining walking with balance exercises has been found to have a positive effect on balance, and walking confidence and speed.[119,120] Participants will perform warm-up exercises designed for this patient population. Walking should be comfortable and self-paced (e.g., they can stop instantly at any time unlike a treadmill). The Wii Fit Plus provides a virtual environment where the participant sees themselves, friends, and even their dog walking on a sunny day next to a stream, through a village with happy, familiar faces offering encouragement. As they walk in place in their home, they will see themselves taking a corresponding step in the virtual environment. We followed the American College of Sports Medicine (ACSM),[37,80,82,121] American Heart Association (AHA),[122] and American Cancer Society (ACS)[79,83] principles of exercise prescription for duration (6 wks) and dosage (5 min increase per wk) for safe exercise prescription. Duration of walking will start at 5 mins/day, 5 days during wk 1, and will build by 5 mins/day each week with the goal of walking 30 mins per day during wk 6 (Appendix A1). Increase in walking duration will be assessed by the exercise nurse intervener at the start of each week. Duration will be increased 5 mins each week if participant's PSE for attaining that duration is $\geq$70% on a 0-100% scale (100% = high PSE).[121] Gradually increasing walking duration promotes achievement of exercise goals, building PSE for CRF self-management and walking. Incorporating feedback from our R21 RCT, participants who can achieve a minimum of 10 mins continuous walking will be given the option to use the Wii or walk outside or at a place of their choice (mall, gym) to achieve their walking prescription. Participants will also perform Wii Fit-Plus balance exercises 5 days/wk for wks 1-6 (Appendix A1). Participants will self-select from a menu of predetermined Wii balance exercises, with each exercise taking less than 3 mins to complete. Balance exercises use a gaming format and scoring systems as motivation to improve performance. Exercises include downhill skiing, soccer, golf, and video game activities. Exercises use competitive and engaging formats, keeping users captivated so they forget they are exercising. Exercises provide encouragement that participants can partake in hobbies in which they may have thought they could never participate again. Participants will wear a pedometer to record their total steps/day. Pedometers will not be worn during exercise so non-intervention activity can be compared with the activity of the ACG and wks 1-6 of the WCG. Data are recorded in participant's Daily Diary (Appendix A2). IIG participants receive the exercise intervention during wks 1-12 post-surgery and WCG participants will receive usual care, which is standard medical care from health providers for 6 wks after hospital discharge followed by the exercise intervention during wks 7-12. Safety: Inclusion criteria require that participants have phone access while exercising, should participant need assistance. Participants are provided safety criteria in the Daily Diary prior to start of each exercise intervention. Participants are taught to maintain a light-intensity dose of exercise by: 1) using portable pulse oximeter to ensure heart rate $\leq$ 60% of heart rate reserve;[37,80] 2) ensuring perceived level of exertion is <3 on a scale of 0-10;[37,79,80] and 3) ensuring they can talk and sing while exercising (Talk Test).[37,80,121,123] Participants will document any symptoms/problems that occur during exercise intervention and any action taken in Daily Diary, for review by nurse. Nurse will be available by phone and can make a home visit to ensure participant safety. Note that no safety issues were reported in either the single-arm or the R21 RCT.

5C1b) The attention control intervention is designed to provide general supportive cancer-related education that is not directly related to treating CRF. The following booklets published by the NCI will guide the delivery of planned, educational content, delivered weekly by the ACG nurse intervener as prescribed using the protocol in Appendix A3: 1) What You Need to Know About Lung Cancer; 2) Taking Time: Support for People with Cancer; and 3) Care for the Caregiver. The ACG participants will be matched to the IIG participants in the

exercise intervention in terms of frequency of visits (1 visit per wk); duration of visit (about 10 mins); and social interaction (one-on-one instruction from a nurse). Each booklet will be used over a 2-wk period with calls about 10 mins. Nurse and patient will be given copies of each NCI booklet and phone scripts for each visit (Appendix A3)**.** Highlights of each booklet will be pointed out following the script. While there is a sentence recommending exercise as a way to treat fatigue, and discussion on general nutrition provided in the "Taking Time: Support for

People with Cancer" brochure, fatigue and general nutrition will not be reviewed in the ACG intervention. Reading this recommendation is equivalent to what many health care providers tell their patients to do providing a systematic suggestion while our intervention is being tested over and above this suggestion.

5C2) Study Procedures. IIG participants will have baseline data collected by the nurse recruiter. Following principles of transitional care,[124] the exercise nurse intervener will engage the participant using protocol in Appendix A4 in the hospital post-surgery to review the exercise intervention and teach PSE-enhancing CRF self-management education (Appendix A5) that uses National Comprehensive Cancer Network Guidelines.[125] To ensure continuity, a primary nurse will be assigned to each participant. Data collectors will contact IIG by phone within approximately 24 hrs of discharge to collect data (if too ill, re-scheduled within approximately 3 days of discharge) and at approximately the end of each week for 6 wks. The nurse will make a phone visit within approximately 24 hrs of post-surgical discharge to screen participant's readiness to start exercise. Participants will be deemed ready to start if usual level of severity for key symptoms of pain, nausea, and dyspnea are rated $\leq$ 4 on an 11-point scale (0-10, 10 = most severe). If participant is ready to exercise, a home visit will be scheduled to start exercise within approximately 4 days of discharge.
When severity of a key symptom is rated > 4, nurse will intervene and contact participant's surgeon's office for recommendations. The nurse will repeat this step each day until participant is ready to start exercising. Once participant is ready, nurse will arrange home visit within approximately 3 days. The initial home visit will include connecting Wii to pariticipant's TV, setting up Wii FitPlus log on password, teaching exercise intervention, and reinforcing CRF self-management education and exercise safety precautions. The nurse will follow-up with phone visit within approximately 24 hrs to answer questions and concerns, make a follow-up home visit at approximately the start of wk 2 of exercise, phone visits at approximately the start of wks 3-6, and additional visits per participant request. During visits, nurse will review IIG participant's Daily Diary (Appendix A2) with participant and provide PSE-enhancing CRF self-management interventions (Appendix A6). These PSE-enhancing interventions include providing mastery and/or vicarious experiences; social encouragement; and reinterpretation of physical and psychological symptoms to support exercise program to adjust exercise prescription per guidelines. Participant uses Daily Diary to record weekly exercise activity and exercise-related symptoms or issues. IIG participants will be given the option to extend exercise for another 6 wks to study wk 12. Data collection will continue on a weekly basis, culminating with a 6MWT at end of approximately wk 12. Nurse calls will continue weekly to prescribe balance exercises and advance walking prescription 5 mins each week, with goal of achieving minimum 30 min/day. Participants may extend beyond 30 min/day with rate of increase no more than 5 min/day each wk, with participants' PSE for attaining that duration $\geq$ 70% on a 0-100% scale (100%=high PSE) (Appendix A1).

5C2a) WCG participants will have baseline data collected pre-surgery by the nurse recruiter and receive a pedometer and instructions for recording total steps/day in Daily Diary (Appendix A7). The WCG nurse intervener (nurse) will visit in the hospital post-surgery to review study trajectory. Research staff will contact WCG by phone within approximately 24 hrs of discharge to collect post-surgery data (if too ill, data collection rescheduled within 3 days of discharge). Research staff will perform phone visits using protocol in Appendix A8 at the approximate end of wks 1-6 to control for staff interaction and data collection. During wk 6, an exercise nurse intervener will make a phone visit to screen participant's readiness to start intervention as described for IIG participants. Once participant is ready to start, nurse will arrange home visit within approximately 3 days. The exercise intervention and procedures will be identical to those received by the IIG group during wks 1-6. Staff contact WCG by phone (if too ill, data collection re-scheduled within approximately 3 days) to collect data at the end of approximately wks 7-12.

5C2b) ACG participants will have baseline data collected pre-surgery by a nurse recruiter and receive a pedometer and instructions for recording total steps/day in Daily Diary (Appendix A7). The ACG nurse intervener will visit in the hospital post-surgery to review study trajectory, make a phone visit within approximately 4 days of post-surgical discharge to initiate the ACG intervention (Appendix A3), and make phone visits at the start of approximately wks 2-6. During visits, the nurse will deliver the ACG intervention. Data collectors will contact ACG by phone within approximately 24 hrs of hospital discharge (if too ill, re-scheduled within approximately 3 days of discharge) and at the approximate end of each week for 6 wks to

obtain outcome measures.

5C3) Protocol Fidelity. Protocol fidelity will ensure consistency in design, dose, training, delivery, receipt, and enactment of the intervention (detailed procedural protocols in Appendix A3, A4).126,127 Design Fidelity. The intervention was designed based on tested Principles of the Transitional Care Model,[40-42,64] and a tested theoretical framework, the Theory of Symptom Self-Management. Adherence to the theoretical underpinning will be evaluated by the PI through monthly team meetings and the use of intervention guidelines and protocols to include: Efficacy-Enhancing CRF Self-Management Intervention Guidelines (Appendix A6); Nurse Intervener Study Protocol for the IIG, ACG and WCG (Appendix A3, A4); and their respective Daily Diaries (Appendix A2, A7). A monthly team meeting will be held by the PI on use of these guidelines and protocols. Dose Fidelity. Dose of the intervention was designed following the principles of exercise prescription via the ACSM,[37,80,82,121] AHA,[122] and ACS.[79,83] Dose of the intervention for the IIG and WCG is defined in the Exercise Prescription Guidelines (Appendix A1). Likewise, dose of the ACG will be matched to the IIG in frequency, duration, and social interaction. The PI will train the interventionist on dosage and the IIG and WCG Daily Diaries and ACG Telephone Script Logs (Appendix A3) will be evaluated on a monthly basis. Training Fidelity. Initial orientation with standardized training manuals will be used to ensure the required skill level of the interventionists. Quarterly meetings will be led by the PI to maintain knowledge and prevent drift from original protocol. Delivery Fidelity. Weekly interventionists' IIG and WCG logs and ACG logs documenting intervention delivery will be peer reviewed to standardize delivery and ensure protocol adherence. Logs and corresponding audio tapes will be randomly selected on a quarterly basis to ensure adherence with feedback provided regarding performance. Logs and tapes will be used to generate case studies for review in monthly team meetings. Receipt Fidelity. Daily Diaries for the IIG and WCG will be used to assess participant's completion and understanding of the intervention as intended (Appendix A2). The script checklist documenting date, time, and minutes spent by the nurse with the ACG participant will document receipt of the intervention as intended (Appendix A3). Interventionist will review Daily Diaries and recorded prescriptions weekly (via a checklist) with the participant to ensure that the participant was able to understand the prescribed treatment activities. Enactment Fidelity. Interventionists will assess the level of intervention achieved on a weekly basis by the participant through the review of the participant's Daily Diary that documents exercise completed to ensure the participant performed the intervention per prescription.

Section 6.0 Measurement of Effect

As earlier stated following our Specific Aims and Hypothesis, based on existing evidence,[72-75] results of our single-arm pilot (no control group)[76,77] and two-arm R21 RCT,[23] we expect the benefits of this study to confirm that post-surgical NSCLC patients will find the exercise intervention effective in reducing CRF severity and fatigability (functional capacity). Further, we expect the exercise intervention group will outperform the attention control and wait-list control groups by age for other symptoms' severity; PSE for CRF self-management; PSE for walking; PSE for balance; functional performance; and QOL. We expect the wait-list exercise intervention group's CRF severity and fatigability to improve, but not as significantly as the immediate exercise intervention group. We also expect >50% of the immediate exercise intervention group to extend 6 more wks, with adherence and retention rates of >70% at wk 12, with improved primary and secondary outcomes at wk 12.

Section 7.0 Study Parameters

Measures for Aims 1-3. Aim 1 - Measurement IIG v. ACG and IIG v. WCG Comparisons. Table 3 depicts main study variables and corresponding measures embedded in the concepts of the theoretical framework in Fig 1 (see measures Appendix B1-B9). All measures are administered to all participants using the schedule in Table 3. Participant characteristics as depicted in Table 3 describe the sample. Age is a key biological variable. Given that lung cancer and CRF are significant problems for persons of all ages, and an exercise intervention must be applicable to patients of all ages, study variables will be analyzed for participants by age (< 65 and $\geq$ 65). Also, this study includes men and women as lung cancer is the second most common diagnosed solid tumor with CRF a common symptom for both.[128] All primary and secondary outcome measures have well established psychometrics, both validity and reliability, with internal consistency scores reported in Table 3 for the cancer

population including use in post-surgical NSCLC.23-24 All measures were used successfully in the R21 RCT without participant complaint about burden. The Karnofsky Performance Scale provides functional impairment classification, universally used in oncology, and is scored from 0% (dead) to 100% (no complaints).[129]

Primary outcome measures include the **Brief Fatigue Inventory (BFI) and Fatigability as shown in Table 3 (below)**. **The BFI** measures CRF severity and its impact on daily life on an 11-pt scale (0-10, 10=most severe).[23,76,108] **Fatigability** will be measured using the 6-min walk test (6MWT), which is a measure of sub-maximal functional capacity. It has been used successfully in persons before/after lung resection for cancer.[23,75,76,130] Following the American Thoracic Society Guidelines,[131] the 6MWT is relevant to measuring functional capacity to perform everyday activities.[132,133] After completing the 6MWT, participants will be asked their average fatigue level during 6MWT using the Borg Scale.[131] Fatigability will be calculated by dividing average level of fatigue by average 6MWT walking velocity measuring degree of fatigue associated with performing everyday activity.

Secondary outcome measures are described in **Table 3 (below)** and include the following: **M.D. Anderson Symptom Inventory Lung Cancer Module** measures severity of 16 symptoms and symptoms interference on daily life on an 11-pt scale (0-10, 10= most severe and most interference).[92,111] **Perceived Self-Efficacy for Fatigue Self-Management Instrument** (developed/tested by Principal Investigator) measures perception of ability to manage fatigue on an 11-pt scale (0-10, 10 = very certain).[23,109] **Self-Efficacy for Walking Duration** measures a person's perception to complete incremental 5-min periods of walking;[23,134] and the **Activities-Specific Balance Confidence Scale** measures a person's perception of balance during every day activities,[23,135,136] using an 11-pt scale (0-100%, 100%= very confident). **Daily Diary** is a weekly diary that provides a structured design for participants to record their weekly exercise prescription and daily performance. All 72 two-arm R21 RCT participants used the Daily Diary to record their daily study-related physical activity including number of steps recorded (pedometer).[23,137-140] Pedometers are valid and reliable measures of functional performance.[141,142] **Medical Outcomes Short Form-36 version 2.0** is a widely used measure with eight subscales that focus on physical and mental health components of functional performance. Subscale scores are linearly transformed, producing normative scores (0-100, 100 = higher functional status).[23,112] **Quality of Life Index Cancer** version III measures level of satisfaction and importance of aspects of a person's life producing an overall QOL score, with four domains: health and functioning; family; socioeconomic; and psychological and spiritual. Uses a 6-pt rating scale (1-6, 6 = very satisfied and very important).[92,143]

Revision is underlined added on May 19, 2019: This includes the addition of three tools as follows in order. A revised Cover Page of the evaluations [Measurement Material] for the study is included to reflect this change.

1) Added the Appendix 14: PROMIS Item Bank v 1.0 Sleep-Related Impairment-Short Form 8a.

Justification: To assess sleep related-impairment since sleep disturbance is a frequent and severe symptom in the lung cancer population, found in the NIH, NCI R21 student that led to this current NIH, NCI R01study. For the duration of study participation, measurement will occur with participants pre-surgery, post-surgery, weeks 3, 6, 9, and 12. A summed score is calculated on 8 items taking 2 minutes to complete. The Sleep-Related Impairment-Short Form 8a has been psychometrically tested with internal consistency reliability at 0.90 upwards. A copy of the tool is provided in this revision.

2) Added the Appendix 15: Brief Pain Inventory (BPI).

Justification: To assess pain since pain is highly correlated with cancer-related fatigue. The Brief Pain Inventory is a companion to the Brief Fatigue Inventory Tool and was used in the parent National Institutes of Health (NIH), National Cancer Institute (NCI) R21 study conducted by the Principal Investigator, Dr. Amy Jude Hoffman, that led to this current NIH, NCI R01 study. The BPI is brief as the title indicates, taking 5 minutes to complete, focusing on the severity of pain, impact of pain on daily living, sources of pain, pain

treatments/medications and amount of pain relief in the past 24 hours. For the duration of study participation, measurement will occur with participants pre-surgery, post-surgery, weeks 3, 6, 9, and 12. The tool has been psychometrically tested with internal consistency scores ranging from 0.77 to 0.91. A copy of the tool is provided in this revision.

3) Added the Appendix 16: Perceived Self-Efficacy for Pain Self-Management Inventory (PSEPSM).

Justification: To assess the certainty in performing pain-managing behaviors. The PSEPSM was used in the parent NIH, NCI R21 study that led to this current NIH, NCI R01 study. The PSEPSM Instrument is a self-report measure containing 6 items related to the certainty in performing pain-managing behaviors that takes 3 minutes to complete. On an 11-point scale (0-10, 10 = very certain), respondents rate their certainty in performing pain-managing behaviors. For the duration of study participation, measurement will occur with participants pre-surgery, post-surgery, weeks 3, 6, 9, and 12. The PSEPSM has been psychometrically tested developed by the Principal Investigator, Dr. Amy Jude Hoffman, based on the Perceived Self-Efficacy for Fatigue Self-Management Tool with internal consistency of 0.92 in the surgical lung cancer population. A copy of the tool is provided in this revision.

Note: In Table 3, a schedule is provided for collection of data. All time points such as Pre- & Post-surgery and Weeks 1 – 12 are collected approximately at this time point.

Table 3. Main Concepts, Variable, Measures, Collection Schedule, and Measurement Objective

Concept	Variable	Measure (# of items)	Schedule	Measurement Description and (Cronbach's alpha):
Patient Characteristics	Physiological	Demographic Questionnaire; Medical Record; Karnofsky Performance Scale.	Pre & Post-Surgery Weeks 1-12	Pre-Surgery: Age; Sex; Race; Co-morbid Conditions; Smoking History; Body Mass Index (BMI); Medications. Post-Sx Treatments (walker, oxygen, adjuvant therapy); Functional Impairment. Post-Surgery: Stage of Cancer; Type of and Extent of Lung Resection; BMI; Medications; Post-Sx Treatments. Weeks 1-12: Medications; Post-Sx Treatment. Wk 6, 12: BMI.
Patient Characteristics	Contextual	Demographic Questionnaire	Pre-Surgery	Education Level; Employment Data; Health Insurance Status; Income Level; and Marital Status.
Symptoms	CRF Severity	Brief Fatigue Inventory (9 items)	Pre & Post-Surgery Weeks 1-12	Severity of CRF and impact of CRF on daily living (.82-.97).
Symptoms	Other Symptom Severity	M.D. Anderson Symptom Inventory Lung Cancer Module (22 items)	Pre & Post-Surgery Weeks 1-12	Severity of pain, nausea, disturbed sleep, distress, dyspnea, difficulty remembering, decreased appetite, drowsiness, dry mouth, fatigue, sadness, numbness/tingling, vomiting, sore throat, cough, constipation and impact on daily living (.82-.94).
Perceived Self-Efficacy	CRF and Walking Self-management	PSE for Fatigue Self-Management (6 items), Walking Duration (12 items)	Pre & Post-Surgery Weeks 1-12	PSE for CRF self-management (.92) and PSE for walking duration (.95).
Perceived Self-Efficacy	Balance	Activities-specific Balance Confidence (16 items)	Pre & Post-Surgery Weeks 3, 6, 9, 12	PSE for balance for increasingly challenging activities (.82-.90).
CRF Self-Management Behaviors	Walking Exercise	Recorded in Daily Diary and electronically in the Wii Fit Plus	Weeks 1-12	Total number of minutes walked with the Wii per week.
CRF Self-Management Behaviors	Balance Exercise	Recorded in Daily Diary and electronically in the Wii Fit Plus	Weeks 1-12	Total number of balance exercises completed with the Wii per week.
Functional Status	Capacity	Fatigability; Six-minute Walk Test	Pre-Surgery, Prior to Chemo/Week 6, & 12	Degree of fatigue associated with walking during the six-minute walk test. Distance walked in six minutes.
Functional Status	Performance	SF-36 v2 – 8 subscales accounting for two components, physical and mental health (36 items)	Pre & Post-Surgery Weeks 3, 6, 9, 12	Performance of daily mental and physical activities that people do in the normal course of their lives (.78-.92)
Functional Status	Performance	Pedometer Daily Diary	Weeks 1-12	Performance in average number of steps taken per day per week
Quality of Life	Quality of Life	QOL Index: Overall QOL, Family, Health/Function, Socioeconomic, Psych/Spiritual (66 items)	Pre & Post Surgery Weeks 3, 6, 9, 12	Satisfaction with various aspects of life and the importance of each aspect of life to the person (.73-.99)
Legend: Surgery = Sx; CRF = Cancer-Related Fatigue. PSE = Perceived Self-Efficacy. Medical Outcomes Short Form-36 v2 = SF-36 v2.. QOL = Quality of Life				

Revision 5/19/2019. Updated Table with the following 3 measures added.

Table 3. Main Concepts, Variable, Measures, Collection Schedule, and Measurement Objective

Concept	Variable	Measure # Items	Schedule	Measurement Description (Cronbach's alpha)
Symptoms	Sleep Impairment	PROMIS v 1.0 Sleep-Related Impairment Short-Form 8a (8 Items)	Pre & Post-Surgery Weeks 3, 6, 9, 12	Degree of sleep-related impairment. (0.90)
Symptoms	Pain Source, Pain Treatment, Severity and Interference Information	The Brief Pain Inventory (4 Severity Items; 7 Interference items; 4 Source Items)	Pre & Post-Surgery Weeks 3, 6, 9, 12	Degree of pain severity and impact of pain on every day. living. (0.77 to 0.91)
Perceived Self-Efficacy	Pain Self-Management	The Perceived Self-Efficacy for Pain Self-Management Inventory (6 Items)	Pre & Post-Surgery Weeks 3, 6, 9, 12	Degree of pain self-management. (0.90)

Aim 2 – Measures – WCG Delayed Intervention. At the start of wk 7, WCG will begin the intervention, concluding at wk 12. Aim 1 study variables and measures (Table 3) will be analyzed for Aim 2 for wks 7-12 to compare with the IIG wks 1-6 outcomes.

Aim 3 – Measures – IIG Intervention Sustainability. At the start of wk 7, IIG participants will be given the option to extend the intervention an additional 6 wks. We will measure the extension rate as % participants who elect to extend. Adherence to the intervention will be measured as % participating in the intervention who adhered to prescribed intervention. Weekly adherence will be calculated by taking number of times prescribed intervention was completed divided by total number of interventions prescribed for week. These data are recorded in the Daily Diary and will be confirmed by research staff reviewing recorded data in Wii Fit-Plus. Retention, measured as part of sustainment, will be calculated as % who elected to extend 6 wks who completed final data collection at wk 12. Based on our conceptual definition of sustainability, we will measure the extent to which components of the intervention were rated acceptable for continued use by participant. Acceptability will be measured at end of wk 6 and 12 using a 15-item Acceptability Questionnaire (Appendix B1) using a numeric scale (1 to 6: 6 = agrees strongly) with higher scores indicating greater acceptability of the exercise program. The Questionnaire has a Flesch-Kinkaid 6th grade reading level and was successfully used in our R21 RCT and allows participants to rate how well barriers and facilitators to exercise are addressed. Open-ended questions provide further input.23,24 Efficacy will be measured using the same study variables and measures analyzed in Aim 1 (Table 3) for wks 7-12.

Section 8.0 Drug Formulation and Procurement

Not applicable. This study is not a pharmaceutical trial.

Section 9.0 Toxicity and Adverse Event Reporting Guidelines

Study Monitoring

The Principal Investigator of the study will monitor for all potential unanticipated problems that may involve risk to participants and will report adverse events (unanticipated problems), including serious adverse events in accordance to institutional policy. Continuous, close monitoring will occur in several ways. First, adverse events identified during implementation of the intervention are monitored through the nurse who assesses the participant on a weekly basis either by home and/or phone visit utilizing the Daily Diary. The nurse documents any adverse event reported by the participant and immediately reports the occurrence to the Principal Investigator. In addition, the Principal Investigator will monitor participants' Daily Diaries for adverse events and specifically, as it relates to Section 9.0 of this application, any and all adverse events will be reviewed, evaluated, and documented. Using a consultative approach, Dr. Hoffman, the Principal Investigator, will ensure reporting of results from the data and safety review to the transdisciplinary team of Co-Investigators and Key Consultants occurring two times a year and more frequently when deemed necessary for the health and safety of participants.

Note: All 72 two-arm R21 RCT participants used the Daily Diary to record their daily study-related physical activity including number of steps recorded (pedometer).[23,137-140] used successfully in the R21 RCT without participant complaint about burden. **Note**: In the R21 RCT, no adverse events were reported; participants had a mean age of 67 with a mean of 8 comorbid conditions. The Daily Diary is structured with an area for participants to report experiences related to problems or symptoms during or after exercising. This format of reporting adverse events is supported in the literature and discussed in the Study Protocol in the Research Design Section (Section 5.0) and Study Parameters Section (Section 7.0).[139] The nurse will review the Daily Diary once a week with the participant and more if necessary to evaluate for potential adverse events. Providing the participant with a means to record problems/symptoms (possible adverse events) will help the participant to develop skills to recognize CRF and other symptoms and effectively develop skills to interpret changes in symptoms and physical functioning.[67] Likewise, as the participant records the solution to the problems or symptoms (possible adverse events), the participant is building a personal database of health problems and solutions to draw from in the future which enhances their PSE for CRF self-management.[67] DeNijs and colleagues[138] reported in a systematic review of the general cancer population that persons with CRF did not adhere to an exercise regimen since they no longer felt certain about their bodies and needed support in order to self-manage fatigue. Thus, the nurse can enhance PSE to self-manage CRF through means of monitoring and interpreting symptoms using the diary to problem solve to make decisions regarding the effect of exercise on CRF and other outcomes. In addition, the Daily Diary outlines the safety procedures for the participant to follow before each exercise session. Moreover, the participant will have phone access seven days a week to contact the nurse should the participant identify or need support in managing problems or symptoms during or after exercising.

Auditing
Auditing is a systematic and independent examination of trial-related activities and documents to determine:

- whether the evaluated trial-related activities were conducted
- the data were recorded, analyzed, and accurately reported, according to the protocol, to the sponsor's SOPs, GCP, and applicable regulatory requirement(s).

Auditing is a Quality Assurance, one point snapshot of one subject.

This study will undergo audit on at least a quarterly basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

Detailed policy and procedures for this section may be reviewed at:
https://www.unmc.edu/cancercenter/clinical/prms.html

FRED & PAMELA BUFFETT CANCER CENTER DATA AND SAFETY MONITORING COMMITTEE (DSMC) REPORTING

In its initial review, the DSMC will make a recommendation for the frequency of DSMC monitoring based on an assessment of risk associated with study-associated therapy, per the DSMC policy.

All adverse events grade three or higher (expected or unexpected, regardless of attribution) will be reported to the University of Nebraska Medical Center, Fred & Pamela Buffett Cancer Center DSMC in accordance with DSMC guidelines.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject participating in a clinical trial, which does not necessarily have a causal relationship with protocol specified therapy. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of any investigational therapy/device or intervention, whether or not the event is considered causally related to the use of the product.

Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria and/or if the investigator considers them to be adverse events. In general, if a laboratory abnormality or change in vital sign is associated with a specific diagnosis that is being reported concurrently as an adverse event the findings that support the diagnosis do not need to be reported as separate adverse events unless the investigator feels it is appropriate.

Treatment-emergent Adverse Event: Treatment-emergent adverse event is defined as any adverse event with onset or worsening from the time of trial intervention until 30 days after the final protocol specified intervention.

Serious Adverse Event: A serious adverse event is one that at any dose (including overdose) and regardless of causality that:

- Results in death
- Is life-threatening 1
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity 2
- Is a congenital anomaly or birth defect
- Is an important medical event 3

1. “Life-threatening” means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe. **2**. “Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions. **3**. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred.

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious.

Attribution of AE/SAE: The investigator will determine the likelihood of relationship of the AE to the study based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause is obvious.
Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study.
Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.
Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.
Definitely related: The occurrence and timing of the AE are clearly attributable to the study treatment.

AEs will be collected from the time the subject signs the consent form until 30 days after the final protocol specified intervention. All AEs will be followed until resolution or a cause is identified. AEs judged by the investigator as not related or probably not related to the treatment will NOT be followed beyond the end of the study.

Section 10.0 Statistical Considerations

Statistical Analysis. All tests of hypotheses will be two-tailed at alpha=0.05. We compare groups at baseline using parametric and non-parametric tests to assess equivalence of confounding physiological and contextual patient characteristics, and pre-surgical outcome variables. If substantive differences exist, they will be controlled for in subsequent analyses by regression techniques, guided by the degree of dissimilarity rather than strict statistical significance.[144]

Primary analysis (Aim 1) is the comparison among study groups of the primary outcome CRF severity and fatigability assessed at approximately 6 wks post-surgery. Analysis is based on a regression model for both CRF scores with the following variables in the regression equation: baseline CRF, study group, age, and (if appropriate) plausible interaction between these variables. We test association of study group with outcomes.

In Aim 2 our hypothesis comparing outcomes in IIG and WCG by age group will be addressed in the context of a longitudinal analysis. There are 6 time-ordered differences between IIG and WCG. We use generalized linear (mixed) models to allow flexible correlation structures in the repeated measures.[145,146] Our regression equation has in addition to the aforementioned variables: time (week) of assessment, and critically, study group with time interactions. The model allows us to test if group effects are changing over time – referred to as a “parallel” profile analysis.[147] If the hypothesis is supported, we test whether that average profiles (over time) in

the two groups are the same. Aim 3 concerns three binary responses in the IIG group at 6 wks: extension, retention, and adherence. Logistic regression models will be used to assess the influence of explanatory variables on the likelihood of outcome.[147-149]

Secondary Outcomes: An analogous strategy is applicable to continuous outcomes assessed at 12 wks. We will use linear models with the caveat that models are conditional on electing to extend participation. Statistical analysis will include intent-to-treat (ITT) analysis and per protocol analysis.[150,151] ITT principle calls for making inference on the whole sample, with patients as randomized to their study group.[152] To address missingness in our response data we will explore strategies for imputation.[153] The techniques described above allow missing at random (MAR). Inverse-probability weighting[154] will be investigated to accommodate missing data patterns that are not MAR. Assurance of analysis robustness and minimization of bias: We use a range of outcome measures based on the patient-centered principle to ensure the relevance of the study both biologically and practically. To enhance reproducibility, we will ensure protocol fidelity and follow our analytic plans, including addressing missing data in outcomes. To minimize analysis bias, we will adjust for factors such as potential between group unbalance and examine the robustness of our conclusions under deviations of model assumptions.

Note: Determination of Sample Size is discussed under the Research Design (Section 5, specifically, Section 5B)

TIMELINE. The research timeline is shown in Table 4.

POTENTIAL PROBLEMS AND ALTERNATIVE STRATEGIES. We acknowledge that NSCLC patients after surgery may be subject to complications requiring a break from the intervention. Should participants report unmanaged symptoms or clinical problems, they will be referred to their health care provider per protocol. Should the participant become ill, causing them to miss three consecutive exercise interventions, the participant will be instructed to call their nurse, who will reevaluate and adjust the exercise prescription per protocol. Should the primary nurse intervener become ill or unable to meet with participant, a pre-assigned secondary nurse intervener will step in. There could be diffusion of treatment effects between IIG, WCG, and ACG as well as confounding effects if a disproportionate number of physically active participants are assigned to the IIG, WCG, or ACG. We will assess functional capacity levels and use block randomization to minimize these effects.

Table 4. Research Timeline	Year 1				Year 2				Year 3				Year 4				Year 5			
Activities	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Intervention Materials Development	X																			
Order Supplies; Computers	X																			
Hiring and Training of Research Staff	X	X																		
Recruitment and Study Performance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Data Analysis															X	X	X	X	X	X
Dissemination of Results																	X	X	X	X

Section 11.0 Records to be Kept

The records described in "**Table 3. Main Concepts, Variable, Measures, Collection Schedule, and Measurement Objective**" will be kept. Likewise, data from the forms will be entered electronically into a study database and secured according to Institutional Review Board standards at the University of Nebraska Medical Center.

Section 12.0 Patient Consent

The consent form adheres to the guidelines established by the Institutional Review Board of the University of Nebraska Medical Center and is pending for IRB Review.

Section 13 References

1. Sanders S, Bantum E, Owen J, Thornton A, Stanton A. Supportive care needs in patients with lung cancer. *Psychooncology.* 2010;10:480-489.

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Section 14.0 Data Collection Forms

Submitted as a separate document.

Revision: 5/19/2019:

The following three forms are submitted as the added Data Collection Forms. These forms are added to the Appendices Cover Page:

1) Appendix B14: Sleep Related Impairment – Short Form 8a
2) Appendix 15: Brief Pain Inventory
3) Appendix B16: Perceived Self-Efficacy for Pain Self-Management Instrument