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The Relationship Of Physical Activity And Perceived Fatigue In Men Receiving External Beam Radiation Therapy For Non-Metastatic Prostate Cancer

Timothy Charles Flory Fuss

THE RELATIONSHIP OF PHYSICAL ACTIVITY AND PERCEIVED FATIGUE IN MEN RECEIVING EXTERNAL BEAM RADIATION THERAPY FOR NON-METASTATIC PROSTATE CANCER

by

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Timothy Charles Flory Fuss

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ABSTRACT

Nature of the Problem/Study

Prostate cancer is the second most common cancer in men in the United States, with 2.9 million men diagnosed with prostate cancer alive today (American Cancer Society, 2017). Given the rate of survival and substantial number of men living with prostate cancer, addressing symptoms and quality of life in these men is increasingly important.

Fatigue is reported to be the most distressing side effect of radiation therapy (RT), negatively effecting physical function and quality of life (Minton et al., 2013). Finding measures to predict, treat and help prevent fatigue can improve long term outcomes in cancer treatment.

The primary aim of this study is to explore the relationship between physical activity count (accelerometry) and perceived fatigue in men with non-metastatic prostate cancer (NMPC) receiving EBRT at beginning, midpoint and at end of therapy.

Methodology

An observational, correlational study examined the relationship between physical activity level (activity counts) and perceived fatigue at three time points, baseline (prior to EBRT), midpoint (Day 19-21) and post-therapy (Day 38-42).

Free living physical activity was measured with an accelerometer and through daily logs. Perceived fatigue was measured with the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) at the beginning, midpoint and conclusion of EBRT in men with prostate cancer. Statistical analysis was conducted to determine correlations between physical activity count and

fatigue scores. Pearson correlation was conducted at the three time points. Linear regression analysis investigated if there is a relationship between perceived fatigue scores and activity counts at the three time points, while adjusting for baseline score.

Results

Physical activity and fatigue were not correlated at any time points, however, total physical activity counts were predictive of fatigue at completion of therapy. Lower hemoglobin, baseline fatigue and total physical activity counts were predictive of fatigue at completion of therapy. These men may have continued their usual activities despite fatigue during therapy or may have been sedentary prior to therapy. Physical activity level should be monitored and, as decreasing physical activity is predictive of fatigue at completion of therapy.

CHAPTER I

INTRODUCTION

Fatigue is reported to be the most distressing side effect of radiation therapy (RT), negatively effecting physical function and quality of life (Minton et al., 2013). It may be related to both cancer itself and treatment; and is known to worsen over time during external beam radiation therapy (EBRT) (Hsiao, Wang, Kaushal, Chen, & Saligan, 2014). Finding measures to predict, treat and prevent fatigue can improve long term outcomes in cancer treatment (e.g., identify individuals most likely to experience debilitating fatigue, reduce perceived fatigue, and improve quality of life).

Primary Aim of This Study

The primary aim of this study is to explore the relationship between physical activity (accelerometry) and perceived fatigue in men with non-metastatic prostate cancer (NMPC) receiving EBRT at beginning, midpoint and at end of therapy.

Research Questions

1. Is there a relationship between physical activity and fatigue at baseline, midpoint and conclusion of EBRT therapy?
2. Does physical activity predict fatigue at midpoint and completion of EBRT?

Research Strategy

Significance

Prostate cancer is the second most common cancer and is the third leading cause of death in men in the United States. In 2019, 174,650 new cases are estimated to occur, with 31,620 deaths estimated (American Cancer Society, 2019). Prostate cancer makes up 27% of new cancer

cases and 10% of cancer-related deaths (Woolen, Holzmeyer, Nesbitt & Siami, 2014). Despite these statistics, 2.9 million men diagnosed with prostate cancer are alive today with a 15-year survival rate of 96% (American Cancer Society, 2019). Given the rate of survival and substantial number of men living with prostate cancer, addressing symptoms and quality of life in these men is increasingly important. Minton et al. (2013) point out that "as cancer has evolved into a chronic disease, the focus has been extended to improving functional status and quality of life for survivors" (p. 2125).

The general aim of this study is to enhance scientific knowledge in cancer-related fatigue by providing insight into physical activity, a key piece of the symptom, which has been largely unexplored in men receiving radiation therapy for prostate cancer. Symptom science requires synthesis of many factors and understanding the relationship between physical activity and fatigue is an important piece of that endeavor. This approach is very much in line with the goals of nursing and more specifically the research goals of the National Institute of Nursing Research (NINR), which include identifying "biological and behavioral dynamics of symptoms" and "clinical factors that can be used to stratify groups of patients with different patterns of symptoms" (NINR, 2016, p. 48).

Understanding the relationship of physical activity and perceived fatigue may help predict fatigue trajectory based on knowledge of baseline physical activity. Predicting those at risk for worsening fatigue or worse treatment outcomes could lead to patient education regarding when to expect fatigue and possible ways to mitigate it. This study is also expected to contribute to the body of knowledge used to inform future intervention studies evaluating various types of physical activities and timing relative to treatment outcomes. Predictive modeling could be carried out, using variables including physical activity. Such a program of individually tailored

physical activity fits with the NIH "precision health" initiative (NINR, 2016) and may improve fatigue levels and quality of life. Objectively measured physical activity using accelerometers needs further investigation, particularly in this population of men receiving EBRT who frequently report symptoms of fatigue.

Theoretical Framework

The National Institutes of Health Symptom Science Model (NIH-SSM), serves as the theoretical framework for this study (Cashion & Grady, 2015). The model arose from the work of the Division of Intramural Research of the National Institutes for Nursing Research (NINR) where early connections were being made between symptoms, symptom clusters and emerging "omics" methods for biomarker discovery. Biomarkers are molecules that correlate with risk of disease or disease severity and possible response to treatment (Hasin, Seldin, & Lusis, 2017). "Omics" is a field of study in biological sciences that investigates potential biomarkers of health conditions, using genomics, transcriptomics, proteomics, metabolomics and microbiomics among others. The NIH-SSM incorporates these innovative "omics" methods with the goal to draw on nursing's "consistent commitment to prevent and eliminate symptoms" (Cashion, Gill, Hawes, Henderon, & Saligan, 2016, p. 499), and the nurses' central role to conduct symptom research because of their clinical and research expertise.

The basic premise of the NIH-SSM is that complex symptoms can be classified into various phenotypes, which then have associated biomarkers and which can lead to clinical applications. The model is represented as a circle rather than a linear trajectory to demonstrate continued discovery in each interconnected area (Cashion et al., 2016).

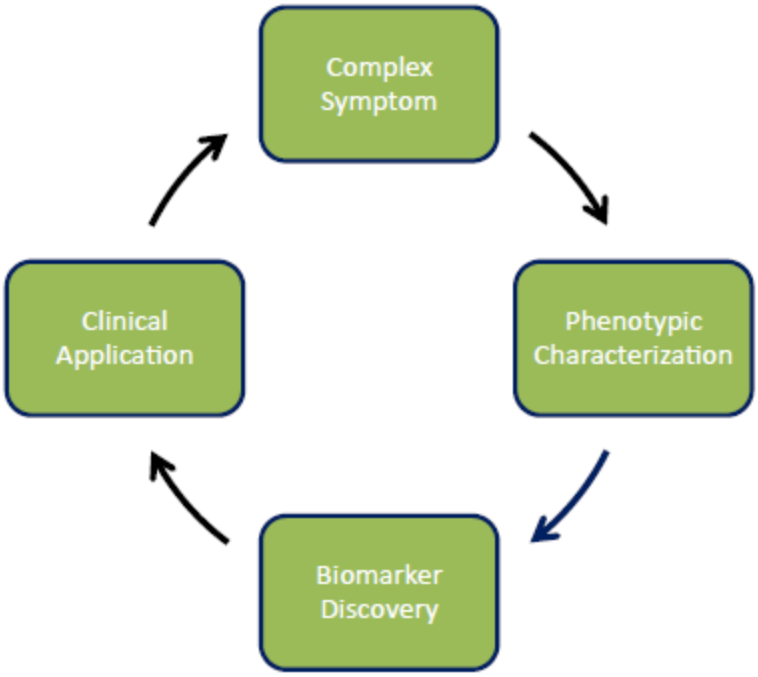

Figure 1: The National Institutes of Health-Symptom Science Model (NIH-SSM). (From Cashion, Gill, Hawes, Henderson & Saligan (2016). Used with permission.)

The NIH-SSM, explained in detail above, represents a paradigm shift in nursing research, as it is based on the work done at the NINR intramural program to "use emerging 'omics' methods to study symptoms experienced by the individual" (Cashion et al., 2016, p. 500). This dissertation study, conducted at the NINR in collaboration with some of the original authors, can serve as an important step to advance further research. While not moving on to the "omics" portion of the model, the focus on real-world, observable characteristics emphasizes the importance of developing clear characterization of symptom phenotypes prior to and alongside "omics" research investigating biomarkers.

The NIH-SSM has also been applied to cancer-related fatigue as depicted below. Physical activity may be a factor in high versus low fatigue phenotypes and is a potential behavioral intervention as noted in the diagram.

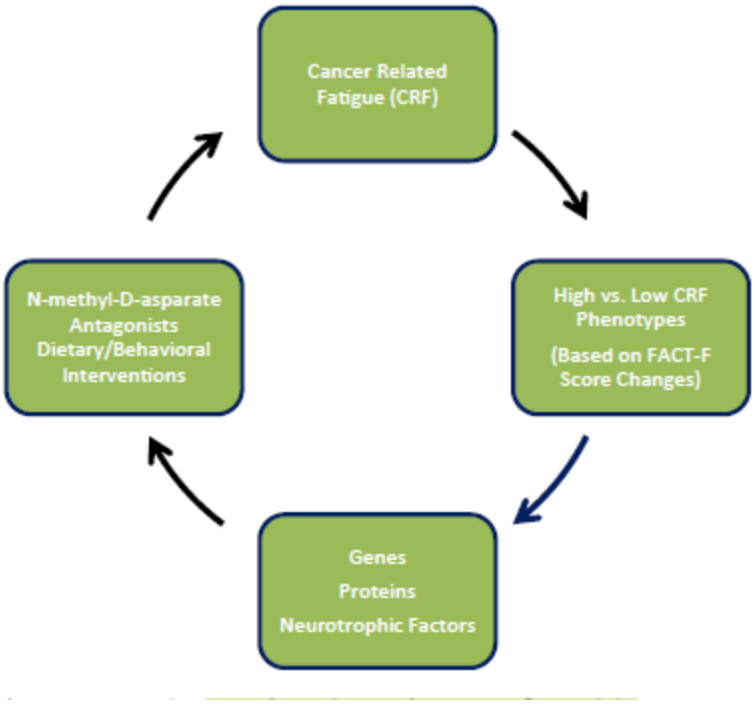

Figure 2: NIH-SSM specific to Cancer-Related Fatigue.
(From Cashion et al., 2016. Used with permission.)

Innovation.

While the use of accelerometry or the use of fatigue scales, such as the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) are not new or novel, the use of these two validated tools together in this population has seldom occurred. Many studies have relied on self-report alone for one or both measures. Accelerometry data in this population will be very useful in determining cut-points for determining sedentary activity in cancer fatigue, which will be useful in guiding further research.

The NIH-SSM may come to be viewed as a new paradigm for nursing research. Reynolds (2007) describes four criteria that determine a paradigm, each being demonstrated in this model. The first characteristic of a paradigm is "a unique description of the phenomena" (p. 25). This model certainly does offer a unique description, by examining symptoms which make up

phenotypes from multiple angles and how those relate to biomarkers. This relationship leads to Reynolds' second characteristic, new research strategies, namely the development of symptom phenotypes and then the association with biomarkers. A new paradigm should generate new research questions, such as the one posed in this study, born from the focus on symptom description. Further research questions will certainly be generated searching to link established fatigue phenotypes with biomarkers. Finally, Reynolds (2007) requires a paradigm to "explain events previously unexplained" (p. 25). This model clearly provides a path for new explanations since symptoms to date have not been examined closely in relation to other symptom clusters or biomarkers.

The NIH-SSM is composed of definitional, existence and associative statements. Symptoms are defined "as the self-reported perception of an individual's experience of disease or physical disturbance and can include experiences such as fatigue, pain and cognitive dysfunction" (Cashion et al., 2016, p. 500). Another key definitional statement in the model is symptom clustering, which "occurs when patients experience multiple symptoms concurrently" (p. 500). The model relies on the existence statement that phenotypes for various symptoms do exist, based on "observable characteristics and traits" from "behavioral, biological and clinical" data (p. 500). This fits with Reynolds' (2007) description of existence statements as "providing typology, a classification of objects or phenomena" (p. 69). For example, patients can be classified into high fatigue and low fatigue groups with associated behaviors and biomarkers (Feng, Suy, Collins & Saligan, 2017). While causation is difficult to prove, the model is based on the associative statement that symptoms are the most common motivator for seeking health care (Cashion et al., 2016). At the core of the model are the associative statements that complex

symptoms have particular phenotypes. Phenotypes are associated with specific biomarkers, and biomarkers may lead to clinical applications (Cashion et al., 2016).

Assumptions.

Associative statement #1. The primary associative statement addressed in this study is that a complex symptom (fatigue) has a clinically relevant phenotype, which can be refined over time, through further research. Although assumptions for the NIH-SSM are not overtly stated, assumptions for the Symptom Management Model (Dodd et al., 2001), which influenced the development of the NIH-SSM are very applicable to the association of complex symptoms with phenotypes. The first assumption is that symptoms are based on the perception of the individual and the self-reporting of that individual. This assumption is important because while seemingly obvious that symptoms are individualized, the reporting of those symptoms could vary dramatically from the actual perception of the symptom.

The next assumption is that symptoms are dynamic, depending on the individual and outcomes related to the person, health, and environment (Dodd et al., 2001). This assumption holds true and may be the most important because of the multifactorial nature of symptoms. Biological, social, emotional, geographical, and other considerations all contribute to the development, perception, and expression of symptoms.

The associative statement linking complex symptoms to phenotype is appropriate and relevant to direct the development of nursing knowledge. The authors of the NIH-SSM point out that nurses have unique knowledge and skills to address symptoms because of their close involvement with the patient as well as an understanding of biological mechanisms (Cashion & Grady, 2015). Nurses are most likely to see how an individual patient expresses symptoms. Cashion et al. (2016) point out that the association of complex symptoms with phenotypes

parallels the goals of the NIH Precision Medicine Initiative to develop a personalized approach to advancing science and improving the lives of patients. While "omics" play an increasing role in nursing research (Wright, Ralph, Ohm & Anderson, 2013), this focus on symptoms and their characteristics point out the importance of the person and what is observed outwardly. This helps maintain the focus of research, keeping it relevant and in the realm of nursing.

Associative statement # 2. The second relevant associative statement is that accurately identified phenotypes lead to biomarker discovery (Cashion & Grady, 2015). Several key assumptions from Dodd et al. (2001) also apply here. The first assumption is that symptoms may not yet be experienced but can be predicted, and thus interventions planned. Predicting symptoms is a major focus of biomarker discovery, particularly in the cancer fatigue population. With strong phenotype-biomarker association, fatigue can be predicted, patients educated on its likelihood, and therapeutic interventions planned.

A final assumption is that biomarkers can be identified and will be useful in the future. While biomarker research is increasing dramatically and becoming more accessible to a variety of researchers (Anderson, 2015), the sheer number of possibilities is daunting. Years of research may go into the investigation of biomarkers that ultimately have little clinical utility. The extreme volume of possibilities and data available in this era of "big data" warrant consideration and prioritization of phenotype-biomarker combinations that show promise.

Implications of the model. The phenotype-biomarker connection has clear implications for directing nursing research. In fact, it may appear that it is the primary driver of research promoted by the NINR as it has been a major focus of the NINR research agenda and educational offerings (Cashion, 2017). The focus on the phenotype-biomarker association has resulted in increased collaboration across disciplines at the NIH Intramural research program,

including nursing, the National Cancer Institute (Hsiao et al., 2014), mental health (Saligan, Luckenbaugh, Slonena, Machado-Vieira & Zarate, 2016), and others (Cashion et al., 2016). Gaining an understanding of physical activity as it relates to fatigue may aid in developing an accurate phenotype, the visible characteristics of interaction between the genotype, and the environment. The scope of this dissertation study may be a first step to advancing phenotype and biomarker discovery. The results will be interfaced with the phenotype and biomarker research within the larger NIH study protocol on this population of men.

One criticism of the NIH-SSM and the phenotype-biomarker connection in particular is that the arrow connecting the two does not go in both directions. Phenotype development is necessary for biomarker discovery, but the model does not focus on returning to phenotype refinement, based on biomarkers. The model is circular, but interventions lie between biomarkers and a return to phenotypes. One does not need to wait for interventions to re-examine phenotypes, based on biomarkers. Feng, Dickinson, Kline and Saligan (2016) found that biomarkers differed greatly, based on methods used to phenotype fatigue, thus the idea of phenotype should be revisited, based on biomarker evidence. While the model is new, there seem to be fewer studies on interventions, which if following the model exclusively could result in a bottleneck for further discovery.

Delimitations

This study examines data that has been collected as part of an ongoing NINR study since 2014. Data was collected until December 2018. Participants were men receiving EBRT for NMPC at the NIH Clinical Center, Bethesda, Maryland and were also enrolled in one treatment study with the National Cancer Institute. Fatigue level, measured with FACT-F, and physical activity, measured with an accelerometer, were measured at baseline, midpoint of therapy, and

post-EBRT. Specific exclusion criteria and operational definitions are discussed in detail in chapter three.

The Researcher

While enrolled in the PhD program at the University of North Dakota, the researcher became affiliated with the NINR as a special volunteer with the Symptoms Biology Unit, part of the Symptom Management Branch of the NINR Division of Intramural Research. The current focus of the Symptoms Biology Unit is understanding the biobehavioral correlates of Cancer-Related Fatigue. A summer internship and research practicums were completed under Dr. Leorey Saligan, one of NINR's tenure track investigators. The researcher was mentored and participated in many facets of the work of the Symptoms Biology Unit. These areas included conducting data collection with the research nurse, orientation to working with samples in the laboratory, observing and monitoring patients during exercise interventions, using study forms to gather data, reviewing procedures for storing of data, and reviewing data from physical activity monitors and logs. Attendance at unit meetings and other activities at NIH provided mentoring and networking with members of the Symptoms Biology Unit, which includes interprofessional doctorally-prepared researchers in laboratory, clinical, and animal research areas. Team members cited in this dissertation include L. Saligan, R. Feng, B. Wolff, K. Dickinson (Filler) and A. Ross. The researcher has attended numerous lectures and discussions offered on the NIH campus. The researcher also completed required NIH trainings in classroom and online formats including modules on Human Subjects Research, Laboratory Safety, Genetic Research, Social and Behavioral Research, and Shipping of Biological Materials.

In collaboration with mentors in the Symptoms Biology Unit, this researcher began a pilot study, investigating the relationship of objective and subjective physical activity data in a

cancer fatigue study. A poster presentation with initial data was made at the NIH in August 2016. In early 2017, additional data was gathered and refined with further findings presented at the Midwest Nursing Research Society conference in March of 2017. The researcher has written multiple academic papers on the topic of cancer-related fatigue in men with prostate cancer throughout the PhD program at the University of North Dakota and was a co-author of a publication with the NINR team (Feng, Fuss, Dickinson, Ross & Saligan, 2019).

Conclusion

This chapter has described the problem of cancer-related fatigue, how it may affect men with prostate cancer, and outlines the importance of examining physical activity in this population. The purpose of the study, primary aim. and research questions were described. The theoretical framework used, the NIH-SSM, was discussed in reference to this particular research problem. Assumptions and delimitations of the study were explained. An in-depth literature review is provided in Chapter Two and the specific methodology used in this study is explained in Chapter Three.

CHAPTER II

REVIEW OF THE LITERATURE

Cancer-related fatigue is the longest lasting and most disruptive symptom in men with prostate cancer (Husson et al., 2015; Weis, 2011) with some men noting fatigue more than one year after treatment (Feng, Wolff, Lukkahatai, Espina & Saligan, 2016). Cancer-related fatigue is defined as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (National Comprehensive Cancer Network, 2017, p. PFT 1).

Fatigue occurs mostly with treatment but can persist and prevent men from working or resuming normal activity for up to a year (National Comprehensive Cancer Care Network, 2017). Persistent fatigue was present at one year in 22% of cancer survivors in a group with mixed cancers (Goedendorp, Gielissen, Verhagen & Bleijenberg, 2013). Specifically, radiation therapy (RT) is a significant cause of fatigue with the incidence of fatigue related to RT reported to affect 71% (Langston, Armes, Levy, Tidey, & Ream, 2013), up to approximately 80% of patients (Miaskowki et al., 2011). Approximately a third of patients will have fatigue one year post treatment, ranging from 24% (Langston et al., 2013), up to 41% (Feng, Wolff, et al., 2016). These late onset symptoms are postulated to occur due to release of reactive oxygen species and persistent inflammation induced by radiation and can be present even at two years post RT (Feng, Suy, Collins, & Saligan, 2017).

Mechanisms of Fatigue

Physiologic pathways leading to cancer-related fatigue continue to be explored in the literature. The National Comprehensive Cancer Network (NCCN) (2017) suggests multiple mechanisms causing cancer-related fatigue including "pro-inflammatory cytokines, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, circadian rhythm desynchronization, skeletal muscle wasting, and genetic dysregulation" (p. MS-2) but notes limited evidence for these various mechanisms. In addition to these factors, an expert panel review cited metabolic/endocrine disruption and abnormalities of neuromuscular function (Saligan et al., 2015). There may also be a "deficient adaptive response to insults from cancer therapies" (Gonzalez, Abbas-Aghababazadeh, Fridley, Ghansah & Saligan, 2018, p. 3). Production of reactive oxygen species was associated with fatigue developed during RT (Hsiao, Wang, Kaushal, Chen & Saligan, 2014). Sestrins, genes activated by stress, may also play a role, as downregulation of a particular sestrin was recently associated with worsening of fatigue in men with prostate cancer treated with RT. This may have therapeutic implications for antioxidant supplementation or exercise (Gonzalez et al., 2018), given that exercise was found to positively effect sestrin regulation in a mouse model (Lenhare et al., 2017). A specific genomic profile and phenotype may also be responsible for the experience of fatigue (Feng et al. 2015).

A "vicious cycle" of fatigue has been noted, with fatigue leading to reduced physical activity, which then worsens fatigue, leading to further deconditioning and increased morbidity and mortality (Nail, 2002; Siegel, Lekas & Maheshwari, 2012; Vermaete, Wolter, Veerhoef & Gosselink, 2014). An increase in sedentary behavior may worsen fatigue and functional decline from cancer treatments (Phillips et al., 2015). Sedentary behavior, measured as time with counts < 100 cpm, increased significantly among breast cancer survivors in relation to fatigue, among

other factors (Phillips, Lloyd, Awick & McAuley, 2016). Variations in physical activity have been associated with cancer-related fatigue (Yennurajalingam et al., 2016). Physical inactivity has known consequences including decreased quality of life and physical functioning among cancer survivors (Blair, Robien, Inoue-Choi, Rahn & Lazovich, 2016; Vallance et al., 2014) and is associated with increased mortality (Canniotto et al., 2016; Krane et al., 2018)

Consequences of Fatigue

Persistent fatigue can have a profound impact on function and quality of life, possibly even years after cancer treatment (Goedendorp et al., 2013). Consequences include interference with ability to work, economic hardships, unemployment, increased hospitalization, disruption in treatment, and decreased survival (Larkin, Lopez & Aromataris, 2014; Gonzalez et al., 2018). Personal consequences can also affect work, family and social lives, which can be "accompanied by guilt, anger, boredom and loss of self-esteem" (Larkin et al., 2014, p. 550).

It is important to understand subsets of physical activities, including exercise, Activities of Daily Living (ADLs), Instrumental Activities of Daily living (IADLS), other "lifestyle activities," and how they may affect fatigue and change over time as a result of fatigue. Table 1 defines terms of varied activity.

"Lifestyle activities," activities carried out during the normal course of a day, may differ among individuals and groups and may not be accurately captured through self-report. Some groups may be more active based on geography, occupation, and other factors. Objective measurement of physical activity would be useful in detecting these differences and quantifying all daily activities, including ADLs, IADLs and other activities, not just planned exercise.

Table 1. Variations in Activity

Term	Definition
Physical activity	Bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level. It can be categorized according to mode, intensity and purpose (Physical Activity Guidelines Advisory Committee, 2008).
Activities of Daily Living (ADLs)	"Activities required for everyday living including eating, bathing, toileting, dressing, getting into or out of bed or a chair, and basic mobility" (Physical Activity Guidelines Advisory Committee, 2008, p. C-2).
Instrumental Activities of Daily Living (IADL)	"Activities related to independent living including preparing meals, managing money, shopping for groceries or personal items, performing housework and using a telephone" (Physical Activity Guidelines Advisory Committee, 2008, p. C-2)
Lifestyle activities	"Actions that one carries out in the course of one's daily life that can contribute to a sizeable energy expenditure such as taking the stairs instead of the elevator, walking to do errands instead of driving, getting off the bus one stop earlier or parking further away than usual" (Physical Activity Guidelines Advisory Committee, 2008, p. C-2).
Exercise	"A sub-category of physical activity that is planned, structured and repetitive and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective (Physical Activity Guidelines Advisory Committee, 2008 p. C-1)

Exercise as Intervention for CRF

While this study is not an intervention study, it is important to be aware of the current state of the science regarding interventions for CRF. Monitoring for CRF is recommended by the NCCN, and exercise is recommended as a strategy to reduce it (NCCN, 2017). Physical activity,

measured in a free-living setting differs from structured exercise, but increased physical exercise outside of an exercise program may have similar benefits. Other interventions recommended for fatigue include energy conservation, physical activity, psychosocial support, sleep, and nutritional interventions. Pharmacologic interventions are limited but may include treating pain and the possible use of methylphenidate to relieve fatigue. While sleep and depression are often associated with fatigue, the use of antidepressants or medications to aid sleep are not currently recommended for fatigue. Pain, anemia, depression, sleep, and nutritional problems may be treated as necessary (NCCN, 2017).

Mustian and colleagues (2017) found that exercise and psychological interventions, which included group or individual therapy and cognitive behavioral therapy among others, together and individually improved CRF, where pharmacologic interventions did not, thus recommending exercise and psychological intervention as first line treatment for CRF. The Oncology Nursing Society has recommended physical activity to help reduce CRF as a priority (Choosing Wisely, 2015; Huether, Abbott, Cullen, Cullen, & Gaarde, 2016).

Improvement in CRF with exercise has been noted in women (Cho, Dodd, Cooper, & Miaskowski, 2012; Spahn et al., 2013) and in mixed gender groups (Cramp & Byron-Daniels, 2012; Huether et al., 2016; Kummer, Catuogno, Persues, Bloch & Baumann, 2013). In other studies, exercise did not affect CRF (Coleman et al., 2012; Ergun, Eyigor, Karaca, Kisim & Uslu, 2013). In a systematic review, Cramp and Byron-Daniel (2012) found aerobic exercise, but not resistance or other exercise, reduced CRF in breast and prostate cancers, while Keough and Macleod's review (2012) found reduction in CRF with both aerobic and resistance exercises. In two reviews involving participants with multiple cancer types, Mishra and colleagues (2014, 2015) found reductions in fatigue and anxiety with improvements in health-related quality of life

(HRQOL) from exercise interventions, leading them to recommend exercise as part of the treatment plan for those scheduled for or actively receiving cancer treatment.

Exercise in prostate cancer. The majority of studies conducted have been in women with breast cancer or mixed gender and mixed cancer groups with relatively few in men with prostate cancer and RT. Supervised exercise programs have shown benefits in men with prostate cancer (Hojan, Kwiatkowska-Borowczyk, Leporowska & Milecki, 2016; Ross, Dickinson, Nguyen & Saligan, 2017). Moderate intensity exercise was found to improve fatigue, increase functional capacity and decrease pro-inflammatory cytokines in men with prostate cancer (Hojan et al., 2017). Resistance and aerobic exercises both decreased fatigue initially with longer term anti-fatigue effects seen from resistance exercise (Segal et al., 2009). A structured aerobic exercise program in men receiving RT for prostate cancer showed no worsening of fatigue during treatment, improved depressive symptoms, mitigation of urinary symptoms, and improved sleep when compared to a group with no exercise (Ross, Nguyen, Dickinson & Saligan, 2017).

Physical Activity in Cancer Related Fatigue

While exercise interventions have been examined as a treatment for CRF, there is a difference between structured exercise and everyday level of physical activity (Wolvers et al., 2018). Studies examining everyday activity, which include lifestyle activities, are not as prevalent as those examining exercise. Many studies do not use objective measures of physical activity or use specific fatigue scales when investigating for correlations between fatigue and physical activity. Many studies on physical activity in CRF were either not conducted in the U.S. in men with prostate cancer or have small sample size.

In patients undergoing chemotherapy, higher symptom burden was associated with less objectively measured overall physical activity and increased sedentary time (Low et al., 2017). Increasing the amount of time spent in moderate to vigorous physical activity (MVPA) is associated with a decrease in fatigue in several studies carried out predominantly in women with breast cancer (Ehlers et al., 2017; Wolvers et al., 2018), colon cancer (Vallance Terry, Courneya, & Lynch, 2014), and lymphoma (Vermaete et al., 2014). A study in cancer survivors found no difference in mean daily physical activity between cancer survivors and participants in the control group but did find physical activity decreasing significantly as the day went on and an association of decreased physical activity with fatigue (Timmerman, Weering, Tönis, Hermens & Vollenbroek-Hutten, 2015).

In the Netherlands, Wolvers et al. (2018) explored physical activity, using accelerometry and fatigue in patients with mixed types of cancer with the majority of the participants being women with breast cancer. They found physical inactivity to be both due to and a cause of fatigue. In their study, active participants had less improvement in fatigue with increased physical activity when compared to sedentary or average activity groups, leading the authors to suggest that these patients may actually benefit from a decrease in physical activity with a decrease in overall sedentary time by making changes to their daily routine. Use of objective measures, as specified in the Wolvers et al. (2018) study, is warranted to examine the potential associations between physical activity and fatigue in a variety of populations, including men in the U.S. with prostate cancer.

Lower levels of physical activity prior to therapy were associated with fatigue at baseline and post therapy in breast cancer, using a self-report of physical activity (Goedendorp, Gielissen, Verhagen & Bleijenberg, 2013; Goedendorp, Gielissen, Verhagen, Peters & Bleijenberg, 2008).

Self-reported physical activity level was not associated with level of perceived fatigue before or after chemotherapy in another study (Neil, Gotay & Campbell, 2014). Research employing objective measurement of physical activity in diverse groups of cancers is needed.

Decreased physical activity, measured with accelerometers, was associated with increased fatigue in patients with breast cancer receiving chemotherapy (Jim et al., 2011) and after completion of treatment (Minton & Stone, 2012). Cancer patients with fatigue specifically demonstrated less total physical activity measured in cpm by accelerometry and less time spent in light physical activity than a non-fatigued group (Minton & Stone, 2012), which underlines the importance in focusing on routine daily physical activity, not solely on structured exercise.

Physical Activity in Prostate Cancer

Physical activity research specific to prostate cancer is sparse in comparison with breast cancer and other cancers. Gaskin and colleagues (2016) found improvement in quality of life scales with increased physical activity and decreased sedentary time which they deemed clinically significant, while not statistically significant, in a group of men with prostate cancer. Goedendorp et al. (2013) conducted a study in a variety of cancers but found that prostate cancer participants had less persistent fatigue than other participants. Research focusing on physical activity specific to men receiving RT for prostate cancer is even more rare. Bohn and colleagues (2019) found no difference in self-reported physical activity between various prostate cancer therapies. In a small study, Drouin et al. (2012), measured physical activity and fatigue at weeks 1, 4 and 6 of therapy, finding that higher levels of physical activity prior to RT may lead to improvements in fatigue, sleep and physical functioning at the conclusion of therapy.

Use of Objective Measures of Physical Activity

Physical activity can be measured by duration, frequency and intensity for a period of time and can be classified as types of behavior, such as activity, sedentary time and sleep (Ainsworth, Cahalin, Buman & Ross, 2015). Self-reporting of activity levels is frequently used in physical activity research; however, self-reported physical activity was not consistently found to correlate with objective measures such as overall accelerometry physical activity counts. Self-reports of physical activity correlated with high intensity physical activity but not with light to moderate intensity physical activities (Ainsworth et al., 2015; Timmerman et al., 2015). The activities carried out by a fatigued population are likely to be light to moderate; however, accelerometers are known to have difficulty in accurately measuring these lower levels of physical activity (Ainsworth et al., 2015). Commonly used categories for physical activity based on accelerometry are sedentary, light, moderate and vigorous activity (Ainsworth et al., 2015). Specific cpm values used to determine the categories vary somewhat between devices and populations. Cut points for the Actical accelerometer in adults as reported by Colley and Tremblay (2011) are listed below in Table 2.

Table 2. Actical accelerometer cut-points in adults
(Colley &Tremblay, 2011)

Sedentary	< 100 cpm
Light	> 100 cpm-1534 cpm
Moderate	1535 cpm – 3959 cpm
Vigorous	> 3960 cpm

Barriers to Physical Activity

While increased physical activity, either through structured exercise programs or in daily activities has shown to be beneficial in reducing fatigue, barriers exist to increasing physical activity in this population. Men with prostate cancer may not be motivated to engage in

structured exercise (Larkin et al., 2014), which again underscores the importance of increasing physical activity throughout the day to improve treatment outcomes, including fatigue, sleep and quality of life, among others. Men, in particular, may not engage in additional physical activity due to a perception of meeting their physical activity needs through work (Drummond, Elliott, Drummond & Lewis, 2017). Men who were active prior to diagnosis reported decreasing their physical activity after a diagnosis of prostate cancer due to fatigue related to the disruption in routine activities caused by diagnosis and treatment and not being sure if they should exercise following their diagnosis (Sheil, Guinan, Hevey & Hussey, 2017). The men also reported declining mood and confidence related to the effects of androgen deprivation therapy and urinary incontinence as barriers to physical activity. Weather, time of year and availability of facilities for physical activity are also factors that may affect men's decision to engage in physical activity beyond those required as part of their daily routine (Sheil, Guinan, Hevey & Hussey, 2017).

Barriers to Symptom Reporting

Fatigue is a subjective experience, and therefore the individual's self-report of that experience is important to capture. Men, in particular, may have barriers to reporting fatigue, which could affect research in this area. Based on previous research, money, deprivation for benefit of family, and seeing healthy behaviors or seeking help as a feminine trait have been barriers to seeking care for men (Courtenay, 2000; Drummond et al., 2017). It is possible that similar barriers may exist for fatigue reporting. Men may be less likely to share feelings about symptoms, with a possible link between sexual functioning and masculinity in relation to feelings of fatigue as well as genitourinary consequences of prostate cancer and its treatment (Jonsson, Aus & Bertero, 2009). There may be a fear of appearing "weak and vulnerable" (Larkin et al., 2014, p. 550). In a Chinese study, men with higher education were found to report

higher fatigue (Luo et al., 2016). Lack of symptom reporting may also fit in with the importance of work to men in jobs requiring physical labor who live in rural areas (Long & Weinert, 1999).

Men may be less likely to report symptoms than women. In comparing women with breast cancer and men with prostate cancer, Garrett et al. (2011) found that women reported increased fatigue and sleep disturbance compared to men; however, sleep measured with actigraphy showed more sleep disruption in men. This could reflect a broader issue of symptom perception or reporting in men.

Effect of Age on Fatigue

The effect of age on fatigue is less clear than it may seem. Saligan et al. (2015) conducted a review of the literature and found conflicting results. Hamre et al. (2013) found an increase in fatigue with age in a cross-sectional study of childhood leukemia survivors. Fagundes et al. (2011) found no significant difference in fatigue based on age in breast cancer patients; whereas, Banthia, Malcarne, Ko, Varnia and Sadler (2009) and Ehlers et al. (2017) found increased fatigue in younger breast cancer patients. Younger age was also found to be a factor leading to increased fatigue in men with prostate cancer undergoing RT in a descriptive, longitudinal study (Miaskowski et al., 2008). Poirier (2006) also found younger age is associated with increased fatigue in a descriptive study of radiation oncology patients and suggested that greater time demands for younger patients may contribute to an increased sensation of fatigue. Siegel et al. (2012) conducted a qualitative descriptive study, discussing age as a factor that was not often isolated, with previous research yielded differing findings.

Age may have a variable effect on physical activity, depending on the overall health of the participant. Older men with prostate cancer were less likely to exercise (Bohn, Fossa, Wisloff & Thorsen, 2019), and older patients with CRF were more likely to be sedentary (Wolvers et al.,

2017). Age was not associated with physical activity level in cancer survivors (Dennett, Peiris, Shields & Prendergast,2018); however, older individuals in the general population were more likely to adhere to physical activity guidelines for cancer prevention (Kohler et al., 2017).

Body Mass Index (BMI), Anemia, and Sleep

This study examined age, Body Mass Index (BMI), hemoglobin level, and sleep (assessed with the PROMIS-Sleep Disturbance scale). These variables have been used as co-variates in studies closely related to the ongoing NINR protocol (Feng et al., 2018; Feng, Espina & Saligan, 2015; Feng et al., 2015).

BMI is frequently controlled for in CRF studies and failure to do so could lead to erroneous results (Gerber, 2017). Decreased BMI was associated with increased physical activity in breast cancer, but no direct relationship was found between BMI and vitality, used as a measure of fatigue (Kenzik et al., 2018). Conversely, Schmidt and colleagues (2015) found that lower levels of physical activity and increased BMI were associated with long term CRF. In colorectal cancer survivors, BMI was associated with fatigue and physical, emotional and role functioning (Vissers et al., 2017). Recent studies found no difference in age or BMI between fatigued and non-fatigued groups of men one year after EBRT for non-metastatic prostate cancer (Feng et al., 2018), and in stable versus increased fatigue groups (Feng, Espina & Saligan, 2018).

Anemia was associated with radiation-induced fatigue in a literature review by Hsiao, Daly and Saligan (2016). Compared to the general population, those with cancer showed greater fatigue and cancer patients with anemia displayed more fatigue than those without anemia (Cella at al., 2002b). Feng et al. (2015) found that a reduction in a composite variable including red blood cells, hemoglobin and hematocrit was associated with increased fatigue in men receiving

EBRT for prostate cancer. In patients with metastatic disease, anemia due to cancer metastasis may be one pathway to increased fatigue (American Cancer Society, 2018).

Sleep disruption has been found to co-occur with fatigue in cancer and cancer treatment. During chemotherapy, fatigue and insomnia were correlated (Redeker, Lev & Ruggiero, 2000). In breast cancer, fatigue was related to increased number of nighttime awakenings (Berger et al., 2010). Increased fatigue in women with gynecologic cancer was associated with minutes awake at night and regularity of sleep and physical activity patterns (Jim et al., 2011). In men receiving EBRT for prostate cancer, disrupted sleep as a result of urinary symptoms is also associated with fatigue (Feng, Fuss, Dickinson, Ross & Saligan, 2019).

Strategies for data collection and analysis of anemia, BMI and sleep are detailed in Chapter 3.

Fatigue Trajectory Over Time

Reports on the trajectory or change in fatigue over time in patients receiving RT for prostate cancer have varied (Knapp et al., 2012). A longitudinal study found increased fatigue during the course of RT, with a return to baseline following treatment (Geinitz et al., 2010). This lack of energy and drowsiness "steadily improved over the course of the cancer treatment" (Knapp et al., 2012, p. 503). Persistent elevation of fatigue symptoms has been observed twelve months or later following RT in another longitudinal study (Monga, Kerrigan, Thornby, Monga & Zimmermann, 2005). However, a large amount of interindividual variability in fatigue symptoms was observed over the course of RT for prostate cancer (Miaskowski et al., 2008).

While noting the general trajectory of improving fatigue over time, Poirier (2006) noticed an interesting variation with 35% of study participants reporting a dramatic increase in fatigue two weeks following treatment with this fatigue beginning to resolve by one month. Poirier

suggests that a “let down” (p. 598) may occur at the conclusion of treatment when the patient is no longer receiving the support of nurses and radiation therapists, potentially affecting fatigue scores. While not recording fatigue levels beyond completion of therapy, Hsiao et al., (2014) found greater variation in fatigue among participants at completion of RT with some reporting very severe fatigue.

An increase in fatigue following therapy has also been reported. Monga et al. (2005) found fatigue scores were highest one year following therapy. They reported fatigue scores above pre-treatment baseline at the mid-therapy mark, a further increase at completion of therapy, followed by a slight decrease during the 4-8 weeks post therapy. The worst fatigue was 1-year post-treatment with 40% of participants reporting fatigue at that point. In a 5-year prospective study, Fransson (2010) found the highest level of fatigue at the 5-year mark in prostate cancer patients, with 66% of participants reporting fatigue at that time.

Cancer-Related Fatigue Research at NINR

The National Institute for Nursing Research (NINR), the location of the study, has prioritized cancer-related fatigue as a key area of research focus (Cashion, Gill, Hawes, Henderson & Saligan, 2016). NIH recommends examining the problem from a variety of angles. In previous investigations from the parent NINR study on men receiving RT for prostate cancer, scientists at NINR found no fatigue at baseline. However, fatigue increased during RT and was decreasing at completion, but it persisted in a subset of patients for up to two years. This trajectory of fatigue correlated with unique biomarkers for up to the two-year mark (Feng et al., 2017; Feng, Wolff et al., 2016; Filler et al., 2016; Hsiao, Reddy, Chen & Saligan, 2015). Clinical predictors of fatigue were identified, including decreased red blood cells and the use of androgen deprivation therapy (Feng et al., 2015). A symptom cluster, or group of co-occurring symptoms,

was also identified. Anorexia, urinary, depressive and cognitive symptoms all accompanied fatigue in men treated with RT for prostate cancer (Feng et al., 2017; Feng, Wolff et al., 2016; Lynch Kelly et al., 2016).

Determining an accurate phenotype of CRF has been examined at NINR. Phenotype is defined as "the physical, observable properties and characteristics of an organism arising from the interaction of its genetic makeup, or genotype, and the environment" (Funk & Wagnalls New World Encyclopedia, 2017). Various fatigue measurement scales and cut-off points were used to determine clinical meaning. The change of ≥ 3 on the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) delineated the fatigued group from non-fatigued group with associations made with biomarkers found in the fatigued group (Feng, Dickinson, Kline & Saligan, 2016). The authors pointed out that further work is needed to characterize the phenotype of CRF.

Based on findings from previous work, NINR investigators are now examining potential novel interventions, including studies on a thyrotropin releasing hormone analogs (Dougherty, Wolff, Cullen, Saligan & Gershengorn, 2017) and are conducting an ongoing clinical trial on the potential of ketamine to reduce CRF (Cashion, Gill, Hawes, Henderson & Saligan, 2016; Saligan, Luckenbauh, Slonena, Machado-Vieira & Zarate, 2016). A trial examining the potential effect of a structured exercise program on CRF is also currently underway (Ross et al., 2017).

Objective Measurement of Physical Activity

Use of devices to measure physical activity has increased over the past decade (Troiano, McClain, Brychta, & Chen, 2014), and nurses are an important part of that movement, both in the clinical setting and in research (Ainsworth & Buchholz, 2017). A variety of populations have seen benefits from increased regular daily physical activity, apart from structured exercise (Murphy, 2009). Measuring physical activity is not only important for understanding disorders

that directly relate to physical activity, but the relationship between the type, amount, pattern and intensity of physical activity and health benefits in various populations is also extremely valuable (Dowd et al., 2018).

Physical activity research has become more affordable and easier to access since the beginning of this century (Troiano et al., 2014). Multiple generations of devices have been released over the past 30 years (van Hees, Pias, Taherian, Ekelund & Brage, 2010) that have decreased in size and cost with increased capabilities (Troiano et al., 2014). The cost of activity monitors has decreased significantly, allowing their use on a much larger scale, such as in the NHANES study (Troiano et al., 2014) and the UK Biobank study (Ferguson et al., 2018), but this large-scale use is still expensive (Dowd et al., 2018) .

Activity monitors are increasing in complexity, becoming smaller and less intrusive and moving beyond simply examining movement. Sensors are now available in shoes, watches, and of course, have become ubiquitous in mobile phones (Altini, Penders, Vullers, & Amft, 2015; Redmond et al., 2014) . In conjunction with other devices and data, contextual factors, such as location, mode of travel and whom the individual is with can be combined with traditional activity monitor data (Gu, 2016). Data from "smart home" systems with environmental sensors, cameras and motion detectors may also add important context and it may soon be feasible to implant sensors into an individual (Redmond et al., 2014). Methods of interpreting accelerometer data have also evolved with a shift from count-based measurements to estimation of energy expenditure (EE) and characterization of physical activity into categories such as sedentary, light, moderate and vigorous (Troiano et al., 2014).

Despite these advances, existing accelerometer data collected with older devices or methods are likely plentiful and could be used in a broad variety of research. Many current

studies may still be using older equipment and methods for several reasons. Research teams are compelled to get the most use out of devices, given budgetary constraints, and may need to keep methods consistent to allow comparison with data collected earlier in a study (Troiano et al., 2014). For example, a study that collected data over a period of five years would most likely use the same devices and data collection plan for the entire course of the study. If the accelerometers chosen at the outset were not the newest, most expensive model of their time, it is very conceivable that the technology and methods applied more resemble those of the early 2000s than the present day.

The use of devices to monitor physical activity, while widespread, does have inherent problems that must be considered and accounted for when possible. Many older models only store activity "counts" and may have limited battery and storage space, which can result in loss of data (van Hees et al., 2010). Since physical activity research focuses on activity in "free living" or "real world" rather than controlled laboratory settings, a significant amount of noise and artifact can be expected (Haslam, Gordhandas, Ricciardi, Verghese, & Heldt, 2011). Energy expenditure, distance walked, and physical activity classification may be estimated incorrectly (Dowd et al., 2018). Certain activities are often not detected in proportion to the actual effort expended (Altini et al., 2015). Despite these drawbacks, accelerometers have shown a high level of validity for measuring activity "counts" (Dowd et al., 2018) and "moderate to strong test-retest reliability in a free-living environment" (Dowd et al., 2018, p. 20).

The software that derives the data from the device is extremely important. Each device manufacturer creates proprietary software and algorithms to determine "counts" and other measurements, such as energy expenditure, which makes comparison across different devices difficult (Redmond et al., 2014; van Hees et al., 2010; Ward et al., 2005). In addition to

differences in the data itself, multiple approaches to interpreting data are used across researchers (Biobank, 2016).

A variety of factors may cause challenges for researchers who use accelerometers. Researchers must invest time in understanding the operation of the monitor (Ward et al., 2005), and effort is required for realistic and meaningful data (Gu, 2016). Physical activity levels vary from day to day, and missing data is common (Catellier et al., 2005). Patient factors, such as reactivity or wanting to be a "good patient" as well as non-wear of the device can have significant effects (Dowd et al., 2018). Managing the amount of data generated by accelerometers can be overwhelming, given multiple days of data collection divided into very brief segments (Ward et al., 2005).

Conclusion

CRF has many potential implications and is seen as a priority health issue and research problem by prominent organizations, such as NCCN and NINR. Research on physical activity in men with prostate cancer and how it relates to fatigue is lacking in the literature and should be further explored. Chapter 3 describes the methodology for this study, including IRB approval and protection of human subjects, selection of instruments, data collection, and data analysis. Further details are also outlined in Chapter 3 on the decision trail, followed in the NIH protocol for the selection of the type of accelerometer, the determination of what defines a valid day, the number of valid days required for the analysis, and the process used for data cleaning and management.

CHAPTER III

METHODS

This chapter describes the methodology used in this study. The overall research design and strategy, inclusion/exclusion criteria, data collection procedures and protection of human subjects are outlined. Statistical methods and data analysis utilized are explained.

Research Design and Overall Strategy

Research Design

An observational, correlational design was utilized to examine the relationship between physical activity level (activity county) and perceived fatigue at three time points: baseline (prior to EBRT), midpoint (Day 19-21) and post-therapy (Day 38-42). This design was selected because it "examines relationships as they exist in a situation" and "facilitates the identification of interrelationships" (Grove, Burns & Gray, 2013, p. 225), but does not examine causality (Polit & Beck, 2012).

This study assessed physical activity, measured with an accelerometer and through daily logs and perceived fatigue, measured with the FACT-F (Appendix D) at the beginning, midpoint, and conclusion of EBRT in men with prostate cancer. Statistical analysis was conducted to determine correlations between physical activity count and fatigue scores.

This study was carried out at the Hatfield Clinical Research Center of the National Institutes of Health (NIH), NINR where the author is a PhD student special volunteer, and an associate investigator of an existing NIH Institutional Review Board-approved clinical study. Archived data from an ongoing NINR protocol make up the majority of data used with data from new participants added as it became available. Patients receiving EBRT for NMPC were

screened by the research team for inclusion criteria and, if met, approached for participation in the study. Participants at this site receive 38-42 days of EBRT, based on clinical stage of disease (Feng, Fuss, Dickinson, Ross & Saligan, 2019). Previous analysis of the study participants enrolled in this study revealed that 62% of subjects are Caucasians and the mean age is 66.1 years (Feng, Dickinson, et al., 2016). Approximately, 85 patients are treated for prostate cancer at this location each year with nearly half of those treated with EBRT. Attrition rates have traditionally been low at this site (L. Saligan, personal communication, November 11, 2016).

The NINR provides numerous resources to the research team. Collaboration can occur across disciplines, including nursing, neuroscience, and bioinformatics. The team also has access to technical support and computer resources through NIH.

Inclusion Criteria

Inclusion criteria include males 18 years or older diagnosed with non-metastatic prostate cancer scheduled to receive EBRT and able to provide written consent. Exclusion criteria include major depression, history of bipolar disorder, systemic infections, alcohol abuse/dependence, psychosis within the past five years, malignancies other than prostate cancer, uncorrected anemia or hypothyroidism, concurrent chemotherapy or significant fatigue, caused by progressive disease of another body system. Use of androgen deprivation therapy was evaluated but is not an exclusion criterion. These criteria have been used in prior studies at this location (Feng, Dickinson, et al., 2016; Hsiao et al., 2014). Each month, approximately 2-4 patients were enrolled in the research protocol (L. Saligan, personal communication, November 11, 2016). A member of the research team interviewed potential participants and screened for exclusion criteria by verbally administering a survey of the criteria (See Appendix B). Upon obtaining

informed consent, additional information was abstracted from the medical record of the study participant by the research team.

The Hamilton Depression Rating Scale (HAM-D) (Appendix E) was used to screen potential participants for depression with a score greater than 17 indicating depression for this protocol (Feng, Wolff et al., 2016). Presence of depression would be a confounding variable, since it can itself lead to fatigue, so these clients are excluded from the study. The HAM-D consists of 21 items and has good internal reliability (a=.81-.98) (Lydiatt, Denman, McNeily, Puumula & Burke, 2008). Participants scoring 17 or greater after being enrolled in the study would be referred for a mental health consultation as stated in the protocol, however this did not occur in the current study.

Selection of inclusion and exclusion criteria is an important part of designing a research study. Too narrow an approach can be problematic, leading to exclusion of particular populations from research and potential inability to generalize findings (Grove, Burns & Gray, 2013). In this case, however, prostate cancer is a disease, which only affects males, and strict exclusion criteria are necessary to prevent confounders, such as other conditions that may lead to fatigue, strengthening the possibility that fatigue is related to physical activity.

Protection of Human Subjects

As an existing protocol, this study was approved by the NIH Institutional Review Board (IRB). The investigator was approved as an Associate Investigator (AI) on this study, 09-NR-0088. The NIH Primary Investigator (PI), IRB representatives at the University of North Dakota, and NIH were consulted to determine if additional IRB approval was necessary. After discussion and sharing of documentation, it was determined that additional IRB approval was not needed.

The investigator regularly communicated with the PI and research team to ensure adherence to the established protocol.

This study represents minimal risk and burden to participants, mostly concerning time and effort to complete questionnaires and use the accelerometer. Demographic and questionnaire data were collected by the research team during each visit (Appendix B and C).

Risks to Human Subjects.

***Human subjects' involvement, characteristics, and design*.** This study used data from 57 men enrolled in an ongoing NINR study at the Hatfield Clinical Research Center of the NIH, Bethesda, MD. Participants were concurrently recruited for ongoing studies at NIH that have been IRB approved (09-NR-0088, 11-NR-0014, PI: L. Saligan). Members of the research team attended the National Cancer Institute Prostate Multi-Disciplinary Conference each week to identify potential study participants. This recruiting method has been very successful in the past (A. Ross, personal communication, February 27, 2018). Participants for this study were recruited, using the same IRB-approved protocol mentioned above.

Once potential participants were identified, the research team reviewed medical records, and a screening visit was conducted to determine eligibility. Participants must be able to read and understand the written consent form. Informed consent was obtained through a verbal clarification of the purpose, procedure, and potential risks of the study. Participants were informed that they may withdraw from the study at any time, and it will not affect the course of their treatment. If a participant wished not to continue with the study, the participant was not contacted for follow up, and his data and existing forms were destroyed.

***Potential risks*.** The procedures necessary for this study presented minimal risk to participants. The discomfort and inconveniences of this protocol involve the medical history and

questionnaire completion, time and effort associated with use of the accelerometer, and the time required for clinic visits. Study visits occurred along with treatment visits to reduce burden on participants and increase retention. The associated discomforts included the following items:

a. Medical history and questionnaires: There are no known medical risks related to these procedures. Some of the questions may be embarrassing or difficult for the participant to answer.
b. Accelerometer and activity log use: There are no known medical risks related to these procedures. Use of accelerometers requires time, may cause discomfort and embarrassment (O'Brien et al., 2017).

Sources of Materials.

Research materials consisted of demographic, questionnaire, and accelerometer data. Demographic and questionnaire data were collected by the research team at each study visit. A copy of each questionnaire, including FACT-F, PROMIS-SD and HAM-D are found in the Appendix. Participant identities were protected, using identity code numbers, which can only be accessed by the principal investigator of the parent study. Questionnaire data was accessed from a secure NIH database storage network. Output from accelerometers was downloaded and stored on a secure NINR server, approved for data housing purposes by the NIH Office of Information Technology. Participant activity logs were obtained from a secure filing cabinet and scanned to the same secure server.

Data Safety and Monitoring Plan. The office of the NINR Clinical Director and the NIH Combined Neuroscience (CNS) IRB oversaw this study, as part of an ongoing protocol. The IRB-approved NINR Data and Safety Monitoring Plan (DSMP) specifies evaluation of the progress of the study, reviews outcomes and adverse event data, considers ethical issues, and

ensures current state of the science. All reports, produced from the DSMP, were reviewed by the CNS IRB. In addition, all NINR studies undergo regularly required quality assurance monitoring to ensure that human participants are protected. Minimal risk studies such as this one are monitored within 3-6 months of enrolling the first subjects and at least annually after that for the length of the study.

This study used previously collected data from an ongoing trial at this site (NIH Grant # 09-NR-0088) and planned to recruit additional participants from July 2018 to December 2018. Assuming an average of three new participants per month, adding these individuals would have yielded 18 new participants; however, enrollment in this protocol slowed dramatically during this time. The number of patients treated with EBRT at NIH decreased as did the number of patients meeting inclusion criteria. Participants who may have been eligible for this study may also have been recruited for other research protocols.

Power Analysis Power analysis was performed in consultation with the NINR statistician, who was available for consultation on this study. There is no available data for correlation coefficients between fatigue scores and physical activity. Assuming a medium effect size (r=.3) the sample size needed is 112, adjusted for three time point comparisons, with an r=.4, a large effect size, requiring a sample size of 61 (X. Zhang, personal communication, September 7, 2017). Although a large effect was not expected, data is available for 57 participants. This study may serve as a pilot for future studies.

Methods of Measurement and Instruments

Data collection included demographic data, Gleason score, presence of androgen deprivation therapy (ADT), history of prostatectomy, height, weight, hemoglobin level, objective measurement of physical activity using an accelerometer, subjective recording of physical

activity with an activity log, and fatigue scores, using the FACT-F. These variables have been used in previous studies, using members of this cohort (Feng et al., 2015, Feng et al., 2016). Gleason score, ADT, BMI and hemoglobin level are potential confounding variables, therefore, were adjusted for in linear regression.

Participants underwent EBRT at the NIH for non-metastatic prostate cancer. Following consent to participate in the study, at baseline (Day 0), the research team gathered demographic information and administered the FACT-F. At that time participants were instructed in the use of the activity monitor and activity logs. Physical activity was objectively measured with an Actical accelerometer (Mini Mitter, Bend, OR) for four consecutive days including three week-days and one weekend day in their own environment. Participants also recorded an hourly log of their activity for these days, using the NIH activity log form (Appendix A). At the midpoint of therapy (Day 19-21) fatigue scale, activity monitor data and activity logs were again collected. This was repeated at the conclusion of EBRT (Day 38-42). This data collection schedule has been used previously at this site (Feng, Dickinson, et al., 2016; Hsiao et al., 2014).

Table 3. Demographics and Clinical Characteristics

Measurement	Units/Categories/Range
Age	Years
Weight	Kg
Height	Cm
Race	White, African American, Asian, Hispanic, Other
BMI	Kg/m^2
Gleason Score	2-10 (extracted from medical record based on scoring by pathologist)
Androgen deprivation therapy	Yes/No
History of prostatectomy	Yes/No
Hamilton Depression Rating Scale (HAM-D)	0-23

Clinical Characteristics Gleason score, androgen deprivation therapy, and history of prostatectomy are collected as part of the ongoing NINR study. These data were recorded but do not serve as variables or exclusion criteria in this study. Previous studies at this location have included men with and without androgen deprivation therapy and with and without prostatectomy as part of the same cohort (Feng et. al, 2016).

Gleason Score. The Gleason score is assigned by the pathologist examining a prostate biopsy sample. Cells are scored 1-5 with 1 being "low grade" tumor cells and 5 "high grade." The most and second most predominant patterns in the biopsy are assigned scores, which are totaled, resulting in a score of 2-10. Gleason scores of 2-4 tend to be less aggressive tumors with scores of 7-10 being more aggressive (Prostate Cancer Foundation, 2018).

PROMIS-SD. Sleep disturbance was measured with the Patient Reported Outcomes Measurement Information System- Sleep Disturbance (PROMIS-SD) short form. The PROMIS-SD short form is made up of eight items with good validity (0.83) and internal consistency (Cronbach's alpha >0.90) (Mahieu et al., 2016; Yu et al., 2011,). Several participants were missing scores for some items. These values were handled as directed in the PROMIS-SD scoring guide.

FACT-F. The FACT-F has been used for a number of years in cancer settings (Yellen, Cella, Webster, Blendowski & Kaplan, 1997) and at this particular location with men treated with EBRT for prostate cancer (Feng et al., 2016). The scale is made up of 13 items, scored 0-4, with zero being the worst and four the best, with a maximum score of 52. The lower the score, the higher the fatigue intensity (Yellen et al., 1997). The FACT-F has strong test-retest reliability (r=0.90) and internal consistency reliability (a=0.93 and 0.95) on initial and test-retest

administration. Psychometric measures, such as the FACT-F, must be assessed for reliability or accuracy in measuring what it is designed to measure.

Cancer patients with fatigue have been differentiated from the general population with a FACT-F score of 43 (Cella, Eton, Lai, Peterman & Merkel, 2002) and a change of ≥ 3 has been shown to separate fatigued from non-fatigued participants undergoing EBRT for prostate cancer (Feng, Dickinson, et al., 2016). This approach allows comparison with baseline fatigue rather than with a pre-determined threshold, which determines fatigue.

Accelerometer. Accelerometers have been used in multiple cancer studies, including in men with prostate cancer (Gaskin et al., 2016). The Actical accelerometer has been used to differentiate active from sedentary activity with a cut-off of 100 counts per minute as the threshold (Wong, Colley, Gorber & Tramblay, 2011). Its use has been validated in older adults (Hooker et al., 2011), but lower cut points may be needed to differentiate sedentary behavior and light activity due to the general decrease in activity level in this population. Corbett, Valiani, Knaggs and Manini (2016) found that activity counts from accelerometers were associated with Metabolic Equivalent of Task (METs), another measure of activity during rapid, but not usual activity. The cancer fatigue population may be especially difficult to measure, given the possibility of a "flooring effect" in the presence of reduced physical activity level (K. Chen, personal communication, July 6, 2016). Actical accelerometer has shown low to moderate intraclass correlation (.00-.75) and validity could not be established in a fatigued population with multiple sclerosis (Kayes et al., 2009). In a sample of stroke patients, moderate correlations were found between Actical accelerometers and a 6-minute walk test (r=0.6-0.73) (Rand, Eng, Tang, Jeng & Hung, 2009).

The research team has encountered and addressed several specific problems with the Actical accelerometer. The Actical accelerometers available are a combination of older and newer models, but the manufacturer indicates that there is little difference in data provided. The research nurse did note difficulty downloading data from newer models because of data speeds that were too fast for the available equipment. Battery life in older models is only 10 days and could result in lost data due to dead batteries. Participants known to promptly return the accelerometer may be given the older models with shorter battery life, if necessary. This would allow newer models with longer battery life to be used for new participants (A. Ross, personal communication, March 13, 2018).

Newer accelerometers are now available; however, the research team has access to the Actical, and it was used for the earlier participants. At the time the protocol was written and the devices purchased, hip worn accelerometers were the standard. Older models, such as the Actical, were mainly validated in adult patients worn on the hip versus the wrist (Kamada, Shiroma, Harris & Lee, 2017). Hip placed accelerometers had demonstrated much better correlation with energy expenditure but over time, wrist worn devices have begun to catch up and now are used in large studies, such as the National Health and Nutrition Examination Survey (NHANES) (Troiano, McClain, Brytcha & Chen, 2014). Changing the mode of measurement would increase costs and may lead to inconsistencies with data collected previously.

Use of these measurements does represent a time commitment on the part of participants. The FACT-F consists of 13 items and is completed during scheduled clinic visits, so it does not require a great time commitment for the participant. Wearing the activity monitor for four days does take significant effort and attention, given the device needs to be removed for showering

and other activities and then re-applied. The participant is also required to record physical activity hourly while awake, which requires effort and significant attention to detail.

NIH Activity Log. The NIH activity log is used in multiple ongoing studies of cancer fatigue (NIH Protocol 09-NR-0088, 11-NR-0014) (See Appendix A). The log contains a line for each hour of the day. Participants were instructed to record physical activity each hour and to indicate the number of hours spent in a particular activity. Participants were also instructed to report non-wear times for activities, such as showering.

Data Collection and Procedures

Participants for this study were recruited through the Hatfield Clinical Research Center Radiation Oncology Clinic, NIH, Bethesda, MD. The research team met with potential participants and obtained informed consent. The research team met with participants prior to scheduled clinic visits at the three time points (baseline, midpoint of therapy, and conclusion of therapy). At each visit, the FACT-F questionnaires were explained to the participants by the investigator and completed. The participant was provided with an accelerometer and instructed in its use, including proper placement, and was instructed in the use of the activity log. Instructions for returning the accelerometer and log by mail were given at that time, as well.

Potential problems in data collection, using the accelerometers have been identified, including failure to complete activity monitoring over the entire four-day period, improperly placed monitors, and device failure (Wolvers et al., 2018). Participants may fail to complete all survey data for the FACT-F; however, the research team member is present following completion and can follow up with the participant prior to the conclusion of the clinic visit. Accelerometer data is reviewed for completeness after each recording period, which allows for re-instruction in proper use for the two subsequent time points if a problem is discovered during

the first data collection period. It is not possible to recover accelerometer data not properly recorded at the baseline time point, however.

Total physical activity counts were calculated from accelerometer data by taking all valid counts and dividing by the number of valid minutes, yielding average counts per minute (cpm). Afternoon physical activity was also calculated, using the same method, from 2:00-6:00 pm of each valid day.

Increasing fatigue in the afternoon and evening has been reported in patients treated with RT for non-metastatic cancer (Dhruva et al., 2013; Miaskowski & Aouizerat, 2012). This phenomenon was also observed in a mouse model of radiation-induced fatigue. The last four hours of the active cycle (2am-6am) for mice, that are nocturnal, showed greater fatigue than other time periods (Renner et al., 2016). Based on these findings, this study will examine physical activity from 2:00 pm-6:00 pm, separately. In addition to average total daily physical activity counts, average total counts will be calculated for 2:00 pm – 6:00 pm. This period of time is just prior to the wake maintenance zone, a period of increased alertness, several hours prior to bedtime (Shekleton et al., 2018).

Table 4. Variables

Variable	How measured	When measured
Total physical activity counts	Accelerometer- Total counts per day for four consecutive days/ total minutes (continuous variable)	Baseline (prior to EBRT) Midpoint of EBRT Conclusion of EBRT
Afternoon physical activity counts	Accelerometer- total counts from 2:00-6:00 pm on all measurement days/total minutes (continuous variable)	Baseline (prior to EBRT) Midpoint of EBRT Conclusion of EBRT
Fatigue	FACT-F (continuous variable)	Baseline (prior to EBRT) Midpoint of EBRT Conclusion of EBRT
Sleep Disturbance	PROMIS-SD (short form) (continuous variable)	Baseline (prior to EBRT) Midpoint of EBRT Conclusion of EBRT

Data Cleaning

Researchers are faced with a number of important decisions when working with accelerometers and the data they produce. The minimum number of days of accelerometer wear required to answer the specific research question (Ferguson et al., 2018), how many hours will constitute a "day," how non-wear will be determined, and the amount of time that the device was actually worn (Biobank, 2016; Ward et al., 2005). The researcher must also decide on appropriate methods of measurement, such as activity "counts," energy expenditure or classification of physical activity type (Catellier et al., 2005). Data cleaning methods must be employed to find and address missing data (Catellier et al., 2005; Ward et al., 2005), values that are excessively high or low, or seem out of context (Biobank, 2016; Ward, 2005). The researcher also needs to decide what specifics to report, such as average time worn and data cleaning methods so that other researchers may replicate the methods in the future (Ward et al., 2005)

Definition of non-wear. Numerous methods for defining accelerometer non-wear are found in the literature, varying in length of time of no recorded activity and tolerance for single values surrounded by inactivity, or "0" readings from the accelerometer.

One method commonly used is referred to as the Troiano algorithm, adopted by many researchers (see Table 5) but originally demonstrated by Troiano and colleagues (2008). This approach defines non-wear as 60 minutes or greater of consecutive zero values but allowing for up to two minutes of values with counts less than 100. Another commonly used algorithm, (see Table 5) developed by Choi and colleagues (2011) defines non-wear as 90 minutes of 0 counts, allowing for two minutes of non-zero values if there are 30 minutes of zeroes above and below that value. In a large study of women, this algorithm in conjunction with dates from the

participant log was found to be superior to the Troiano algorithm in minimizing missing data (Keadle, Shiroma, Freedson & Lee, 2014).

While many studies have used 60 or 90 minutes to determine non-wear, in a fatigued or older population, allowing for longer periods of inactivity may be necessary to avoid eliminating data, which is actually sedentary time. Unnecessary elimination of data could lead to underestimation of sedentary time and overestimation of activity counts (Hutto et al., 2013). Hutto and colleagues pointed out that older, sedentary individuals can sit for quite some time and not register any accelerometer counts. Their study concluded that at least 120 minutes of consecutive zeroes should be used to determine non-wear in older adults. Subsequent studies allowed 150 minutes of zeroes before removing for non-wear (Hooker et al., 2016).

Initial data cleaning efforts in this study identified non-wear, using the Troiano and Choi algorithms but both resulted in frequent removal of data for non-wear, especially during the evening, a time when the participant was more likely sedentary rather than not wearing the device. Based on these preliminary findings and the rationale above noted by Hutto et al. (2013), a threshold of 120 minutes of continuous zeroes was used to define non-wear. Periods identified as non-wear were removed.

Given the possibility of increased fatigue and decreased physical activity in this population, allowing for even greater than 120 minutes may be appropriate to avoid removing what is actually sedentary activity rather than non-wear. Future studies may address this issue, as it may serve as a limitation of this study.

Determining a Valid Day

In addition to determining non-wear, a valid day of accelerometer wear must also be defined. Many researchers have used 600 or more minutes of valid data to define a valid day of

wear (see Table 5). This method was adopted for this study, given how frequently this approach was used across numerous studies (Compernolle et al., 2017; Deere et al., 2016; Donaldson, Montoye, Tuttle & Kaminsky, 2016; Marmeleira, Laranjo, Marques & Pereira, 2014; Wolf-Hughes, McClain, Dodd, Berrigan & Troiano, 2016). Initial scanning of data showed the clear majority fell into this category and would not result in undue removal of data.

Actical accelerometer data used for this study was obtained from Microsoft Excel files, downloaded from the device at the time of use. These files were created by prior members of the research team, and in some cases, their data management decisions dictated the number of available valid days. Data from earlier participants were already truncated to a period of exactly 72 hours, while data from more recent participants included data from the entire time the device was active, resulting in 3-5 days of valid data. In some cases, whole days of no data were present, and in other cases, there appeared to be activity, but based on the participant log, this movement actually represented transit of the device in the mail. Graphs and participants logs were used to determine start and end times. Since participants were instructed to wear the device at all times, even during sleep, each day of activity was required to have a corresponding night. Determining night time wear versus non-wear was difficult and may be a limitation to this study.

Number of Valid Days Required for Analysis

When creating a research protocol, investigators must decide the number of days to instruct participants to wear the device and how many days must be deemed valid to include their data. Many protocols require participants to wear the accelerometer for seven days with at least four of those days being valid (See table 5). To reduce participant burden, the existing protocol for this study required participants to wear the device for four days. Inclusion or exclusion of weekends also differs with some studies requiring three of seven days to be valid, including one

weekend day (Marmeleira, Laranjo, Marques & Pereira, 2014; Porcellis, Marques & Reichert, 2018) or four weekdays and one weekend day (Westland et al., 2017). The existing protocol directed participants to wear the device for four days, including one weekend day. Given that four days of data were collected, it was not realistic to require four valid days, since many other studies requiring four valid days actually collected seven days of data. For this study, three valid days were required for inclusion.

To help eliminate artifact and varying length of days from beginning and ending wear, Van der Berg and colleagues (2016) excluded the first and last days of data. In many cases, four days of data did not afford this luxury in this study; however, in many cases incomplete "days," such as days with wear starting late in the day or ending early in the day could be removed, still preserving three valid days of measurement.

Determining Accelerometer Wear Versus Non-Wear

Determination of wear versus non-wear of the accelerometer is a key component of data management. Automated algorithms (Chu et al., 2018; Keadle, Shiroma, Freedson, & Lee, 2014), specific software, (Cain & Geremia, 2012; Keadle, Shiroma, Freedson, & Lee, 2014) and manual methods are sometimes used. However, not all researchers have the resources or expertise to utilize software for automated identification of non-wear time. Rillamas-Sun and colleagues (2015) used graphs to identify a clear start of data, and visual inspection of data along with use of participant logs were used by several other research teams (Cain & Geremia, 2012; Joseph et al., 2018). Rillamas-Sun et al. (2015) found similar agreement between the use of logs, visual inspection, and algorithms.

Actical accelerometer data for this study was analyzed, using Microsoft Excel, visual inspection and comparison to participant logs. Activity logs are used to assist with data cleaning

and are useful for identifying time spent in sleep and non-wear time (Wolvers et al., 2018) as well as potentially useful in detecting outliers that should be eliminated from accelerometer data (Fuss et al., 2017). Creating a graph of all four days of data recorded at a specific time point allowed identification of clear start and end times of data in the majority of cases. Graphs also identified "gaps" in data, areas with no counts between areas of activity. These areas were then examined more closely to see if they met the 120-minute criteria for non-wear by manually checking all cells in that time period. Participant logs were reviewed for identified non-wear, such as showering or water sports. If a log noted "nap" or "sleep" during daytime hours, data during that time was not removed, even if it exceeded the 120-minute threshold. Participant logs were used to identify sleep and wake times. These times were correlated with graphed data for consistency. If sleep and wake times were not recorded, obvious sustained spikes in activity in the morning were interpreted as awakening and obvious cessation of sustained activity during night time hours was interpreted as sleep. The 120-minute non-wear algorithm was not applied during nighttime hours of sleep.

Identifying Erroneous Values

Handling values deemed to be erroneous is another task that must be undertaken when using accelerometry. Excessively high values recorded by accelerometers should be evaluated for accuracy and removed, if appropriate. Artifact frequently occurs with placement and removal of the device, so researchers may elect to remove the first and last one minute (Deere et al., 2016) or five minutes (Chen & Bassett, 2005), immediately before placement and removal. Counts deemed excessive may be removed, such as >20,000 counts per minute (Loyen et al., 2017; Vallance et al., 2014), using the Actigraph accelerometer, or for the Actical accelerometer >10,000 cpm (Duncan et al., 2018) or >20,000 cpm (Hooker et al., 2016). Deere and colleagues

(2016) discussed examining and removing excessive acceleration peaks without citing specific count per minute values.

In this study, graphs and individual cells were reviewed for excessive counts surrounding placement and removal of the device. Participants were instructed to wear the device at all times, including sleep, removing the device only for showering or other water activities. Participant logs indicated device placement and removal for these occasions. Data was scanned and compared with participant logs. Determination for removal of data was made by the researcher, based on the data pattern. Typically, activity counts higher than expected were seen for approximately one minute around the time of device placement. These elevations varied from very brief (one 15 second epoch) to longer periods (two minutes). The researcher felt that these peaks obviously represented device placement or removal artifact and decided to remove them rather than always removing data within a set time frame, such as one minute before or after device placement.

Aside from artifact from placement and removal of the device, obviously erroneous activity counts were very uncommon in this study. Activity logs were reviewed and compared with peak activity on graphs and when activity counts seemed above the level typical for a given participant. If an activity, such as exercise, running or other strenuous activity was recorded in the log, this was noted in the spreadsheet and the value left intact. On very rare occasions, a single value >10,000 cpm was identified and removed. These values were deleted with no imputation because they represented a very small percentage of the daily activity (1 minute or less out of 72 hours of data).

Imputation for Missing Data

Various approaches for dealing with missing data exist. Catellier et al. (2005) developed a formula for imputation, based on mean physical activity level, BMI and other factors, while Cain and Geremia (2012) recommended using a mean activity score of valid days without imputation of missing data. Nastasi et al. (2018) discarded days with more than 5% missing data, imputing for missing values with the average over all days at the time point with missing data.

Days with multiple hours of missing data or non-wear may not meet the criteria for valid days as outlined above, and if so, were removed. The most common reason for missing data is removal of data due to non-wear, based on >120 minutes of consecutive zeroes or as noted in the participant log. Even with removal of non-wear time, the clear majority of data remains intact. For example, removal of two hours of non-wear is less than 3% of the total wear time of 72 hours. The counts per minute variable is calculated by taking the total valid counts and dividing by the total minutes for the given measurement period. Thus, eliminating small amounts of data has less effect, since the minutes in the denominator decrease accordingly.

Table 5. Data Management and Cleaning

Determining wear vs. non-wear time	**Defining non-wear**	Troiano algorithm Non-wear = ≥ 60 consecutive minutes of zeroes Allowing for up to 2 minutes of counts < 100 Choi algorithm Non-wear = 90 consecutive minutes of zeroes Allowing 2 minute5s of non-zero if 30 minutes of zeroes above and below that value	Baumann et al., 2018; Compernolle et al., 2017; Garcia-Hermoso et al., 2015; Troiano et al., 2008; Wolf-Hughes, McClain, Dodd, Berrigan & Troiano, 2016 Choi, Liu, Matthews & Buchowski, 2011; Chu et al., 2018; Keadle, Shiroma, Freedson, & Lee, 2014
	Defining valid day	≥ 600 minutes of valid data (10 hours)	Compernolle et al., 2017; Deere et al., 2016; Donaldson, Montoye, Tuttle & Kaminsky, 2016; Marmeleira, Laranjo, Marques & Pereira, 2014; Wolf-Hughes, McClain, Dodd, Berrigan & Troiano, 2016

Table 5. cont.

Determining wear vs. non-wear time	**Number of valid days required for analysis**	4 of 7 valid days	Compernolle et al., 2017; Chu et al., 2018; Henson et al., 2015; Keadle, Shiroma, Freedson, & Lee, 2014; Pozehl et al., 2018
		3 of 7 including one weekend day	Marmeleira, Laranjo, Marques & Pereira, 2014; Porcellis, Marques & Reichert, 2018
Methods to determine non-wear and valid days	**Visual inspection**	Use of graphs to visualize clear start of data	Rillamas-Sun, Buchner, Di, Evenson & LaCroix, 2015
	Combined methods	Non-wear determined with combination of Choi algorithm and logs	Rillamas-Sun, Buchner, Di, Evenson & LaCroix, 2015 Welch, Alexander, Swartz, Miller, Twardzik & Strath, 2017
		Visual inspection and logs	Cain & Geremia, 2012; Joseph, Stromback, Hagstromer & Conraddson, 2018
Identifying erroneous values		Removal of first and last 5 minutes of wear to avoid artifact	Chen, Jerome, LaFerriere, Young & Vollmer, 2009
		Removal of first and last 1 minute after removing or replacing device	Deere et al., 2016
		Excessive counts (Actigraph & Actical) removed >10,000	Duncan et al., 2018
		>20,000	Hooker et al., 2016
		Examination and removal of excessive acceleration peaks	Deere et al., 2016

Statistical Analysis

Accelerometer data were analyzed as total daily physical activity counts in one-minute epochs, as this yields counts per minute. Categorizing physical activity as sedentary, light, moderate, or vigorous is frequently used in physical activity research; however, previous work defining sedentary versus active groups in this population was not found in the literature. This study originally planned to categorize participants as sedentary and non-sedentary, based on

hourly counts per minute (cpm), but due to lack of clear-cut points in the particular monitor used and in a fatigued group, this approach was not utilized. In this population, the small size of a non-sedentary group may prevent data analysis (M. El-Masri, personal communication, April 19, 2018). Future work may focus on categorizing activity as sedentary, light, moderate, and vigorous. These categories with cut points based on cpm are commonly used (Duncan et al., 2018). Frequently used cut points include those created by Colley and Tremblay (2011) and Freedson, Melanson and Sirard, (1998).

Statistical analysis was conducted using SPSS Version for Windows, Version 24. Pearson's correlation was conducted with each variable (fatigue score, physical activity count, age, BMI, and hemoglobin level) at the three time points. The r statistic was calculated with degrees of freedom, based on number of participants in the sample and compared to a table for critical values of r using an α of .05 (Polit, 2010).

FACT-F variables and accelerometer variables had a positive Shapiro-Wilk test ($p < .05$) so were considered not normally distributed. Other variables were examined for skewness and kurtosis, with values < 2, indicating a normal distribution. FACT-F scores were transformed as described in chapter 4.

Accelerometer data were positively skewed, so data transformation was attempted. Square root transformation did not improve normality, but log transformation greatly improved skewness and kurtosis; therefore, the log-transformed variables were used for analysis.

Linear regression analysis was used to investigate if there is a relationship between perceived fatigue scores and physical activity counts at the three study time points, while adjusting for baseline score (M. El-Masri, personal communication, October 16, 2017). Other variables used in the regression analysis include age, BMI, hemoglobin and sleep score, which

are all continuous variables. Necessary assumptions include multivariate normality, the "assumption that each variable and all linear combinations of the variables are normally distributed" (Polit, 2010, p. 245), linearity, the assumption that "there is a straight line relationship between all pairs of variables" (p. 245) and homoscedasticity, "that the variability in scores for one variable is the same at all values of another variable" (p. 246).

Limitations

Patients undergoing treatment and enrolled in studies at NIH are a convenience sample and may not reflect the general population. They may have sought treatment at this location due to specialty referral, patient interest in being treated at a research institution, or other personal or geographic factors. These factors may affect their perception of and willingness to discuss their fatigue symptoms. Fatigue itself may limit energy and/or motivation to participate in completion of surveys and use of the accelerometer. Specific limitations of accelerometers, such as non-wear resulting in missing data, burden to participants, and utility in a fatigued population were discussed above. Potential threats to validity include the potential motivation of physical activity measurement to increase physical activity above usual levels, and a highly motivated population of individuals who self-selected to participate in a research study at the NIH, which introduces the possibility of selection bias (Polit & Beck, 2012). Geographic differences may not be accounted for in this sample drawn mostly from the Washington, DC metropolitan area. Physical activity monitors present risk for error due to potential user and device factors. Participants may forget to wear the device, place it incorrectly, decide not to wear the device due to esthetic objections, or spend time in activities not compatible with accelerometer use, such as swimming. (Wolvers et al., 2018).

The approach used to determine accelerometer non-wear based on 120 minutes of activity counts may have led to unnecessary removal of data and may have increased average hourly activity counts slightly due to not recording sedentary activity. The Actical accelerometer is known to have difficulty measuring very low levels of activity (Duncan et al., 2018; Evenson et al., 2015). This may result in poor recording of movement during sleep, inability to detect wear during sleep from non-wear and could make differentiating daytime sedentary activity from light activity.

Archived accelerometer data was used in this study. Accelerometer data was previously downloaded to Excel files and the raw data was not accessed by the researcher. Data was carefully examined for discrepancies as described in the data cleaning section, but some data files had been edited by previous researchers, limiting the amount of data for review.

This chapter has discussed the research design and strategy, methodology, criteria for inclusion and exclusion, protection of human subjects, and data collection procedures. Methods of measurement and instruments were detailed. Statistical methods for data analysis were explained, and limitations were discussed.

CHAPTER IV

RESULTS

Over the course of the NIH protocol (09-NR-0088), data was collected from 66 participants at baseline (pre-EBRT), at midpoint, and at completion of EBRT. Five participants had missing or invalid physical activity count data at baseline and were excluded. Invalid physical activity count data is defined in this study as < 10 hours of valid data over < 3 measurement days (See chapter 3 for details). Four other participants withdrew before reaching completion of EBRT, bringing the total study sample to N = 57. Three participants had missing or invalid physical activity count data at midpoint and were excluded from analysis at that timepoint only. Pairwise deletion in SPSS was utilized to maintain sample size and remove participants from analysis only for missing variables.

Demographic Characteristics of Sample

The mean age of the sample was 65.51 years (SD ± 6.78; range = 53-84). Mean body mass index (BMI) was 29.88 mg/kg^2 (SD ± 4.52; range = 21.60-43.90). The largest group of participants identified as Whites/Caucasian (n = 33; 57.9%), followed by African Americans/Blacks (n=18; 31.6%), three participants were Asians (5.9%), two were Hispanics (3.5%,) and one identified as "other" (1.8%). The majority of participants did not have a prostatectomy prior to RT (n=42, 73.7%) and had a Gleason score of 7 (n=27, 47.4%). See Table 6 for all demographic information.

Table 6. Demographics

Race	Frequency	Percent
White	33	57.9
African American/Black	18	31.6
Asian	3	5.3
Hispanic	2	3.5
Other	1	1.8
Total	57	100.0
Ethnicity		
Hispanic or Latino	3	5.3
Not Hispanic or Latino	52	91.2
Unknown	2	3.5
Total	57	100.0
Prostatectomy		
No	42	73.7
Yes	15	26.3
Total	57	100.0
Gleason Score		
6	4	7.0
7	27	47.4
8	17	29.8
9	9	15.8
Total	57	100.0

Continuous Variables

Table 7 lists values for the continuous variables at the three study time points. Physical activity counts measured by the Actical accelerometer, expressed as counts per minute (cpm), varied greatly between participants. At baseline the mean was 78.51 cpm (SD ± 49.59; range = 9.97-254.21), the mean at midpoint of EBRT was 75.36 cpm (SD ± 43.53; range = 13.95-259.52), and at completion of therapy was 69.97 cpm (SD ± 53.72, range = 8.92-275.51). Standard deviations for all evening physical activity counts, collected from 1400-1800 were quite large, at baseline (M= 127.4, SD=123.6), midpoint (M = 117.3, SD=89.99) and completion (M = 113.3, SD =102.00), likely due to the variation in physical activity and shorter period of time examined.

Table 7. Continuous Variables

Variable	Mean	Std. Deviation	Min	Max
BMI	29.88	4.52	21.60	43.90
Hgb (baseline)	13.98	.920	12.00	16.60
Hgb (midpoint)	12.96	1.094	10.30	15.40
Hgb (completion)	12.77	1.068	10.80	15.80
FACT-F (baseline)	43.09	9.255	6	52
FACT-F (midpoint)	40.14	10.081	16	52
FACT-F (completion)	39.64	9.734	13	52
PROMIS-SD (baseline)	47.67	9.518	28.90	66.10
PROMIS SD (midpoint)	48.82	9.591	28.90	67.50
PROMIS SD- (completion)	48.88	10.347	28.90	64.90
Total activity cts. (baseline)	78.51	49.593	9.96	254.21
Evening activity cts. (baseline)	127.40	123.658	12.77	750.61
Total activity cts (midpoint)	75.36	43.531	13.95	259.53
Evening activity cts (midpoint)	117.32	89.986	5.44	459.75
Total activity cts (completion)	69.97	53.722	8.92	275.51
Evening activity cts (completion)	113.29	102.00	11.97	458.70

BMI= Body Mass Index; FACT-F= Functional Assessment Cancer Treatment-Fatigue, Hgb= Hemoglobin, PROMIS-SD= Patient Reported Outcomes Measurement Information System-Sleep Disturbance; Total activity counts= Actical accelerometer daily counts per minute; Evening activity counts = 1400-1800 Actical accelerometer counts per minute

Addressing Normality of Data

All variables were examined for normality. In all time points, PROMIS-SD, BMI, age, and Hgb had skewness and kurtosis < 1.96. These values meet the requirement for normality (Ghasemi & Zahediasl, 2012; Laerd Statistics, 2015). All FACT-F and physical activity variables had positive Shapiro-Wilk tests ($p < .05$), which indicates lack of normality. Fatigue scores (FACT-F) were not normally distributed at baseline or completion of therapy (See Table 8). Skewness/standard error at baseline = -5.15, kurtosis/standard error = 5.81. At completion of EBRT, skewness/standard error was -2.10 with a normal kurtosis/standard error of 0.27. At

midpoint, skewness and kurtosis/standard error were both < 2 (-1.97, -1.04, respectively). Based on these values not being normally distributed at two study time points, variable transformation was carried out. FACT-F scores were moderately negatively skewed so were transformed, using the reflect and square root method (Laerd Statistics, 2015). In this method, one is added to the highest recorded value in the data set, which is 52 for FACT-F. The FACT-F score was subtracted from 53, and the square root was taken of that value. This transformation resulted in skewness and kurtosis/ standard error of < 1.96 for all transformed variables (See Table 8).

Of note, the reflect and square root method changed the direction of the fatigue scale, where for the original FACT-F scale, a higher number indicates less fatigue. Once FACT-F scores were transformed, using this method, a lower number means less fatigue. The transformation of FACT-F scores, using the reflect and square root method, allowed these fatigue scores to be interpreted the same way as the PROMIS scores, where a higher number means higher fatigue. In this case, correlations that are actually positive before transformation appear to be negative. This change is important to note in interpreting the findings of this study.

Physical activity count variables in all time points had skewness and kurtosis/standard error well over the acceptable range (See Table 8) of 1.96 (Ghasemi & Zahediasl, 2012) or 2.58 (Laerd Statistics, 2015). Data was positively skewed, so square root transformation was attempted but did not bring skewness and kurtosis values within acceptable levels. Log 10 transformation was carried out, yielding skewness and kurtosis values <2 for all but one value (2.129), which was still in the acceptable range.

Table 8. Original and Transformed Variables

Variable	Skewness	Std error	Skewness/ Std error	Kurtosis	Std error	Kurtosis/ Std error
FACT-F (baseline)	-1.628	.316	-5.15	3.620	.623	5.80
FACT-F (midpoint)	-.624	.316	-1.97	-.647	.623	-1.04
FACT-F (completion)	-.670	.319	-2.10	.167	.628	0.27
Total activity counts (baseline)	1.265	.316	4.00	1.878	.623	3.01
Evening activity counts (baseline)	2.868	.319	8.99	11.171	.628	17.79
Total activity counts (midpoint)	1.806	.325	5.56	5.370	.639	8.40
Evening activity counts (midpoint)	1.622	.325	4.99	3.240	.639	5.07
Total activity counts (completion)	2.044	.316	6.47	4.593	.623	7.37
Evening activity counts (completion)	1.777	.316	5.62	2.979	.623	4.78
Transformed Variables						
FACT- reflect and square root						
FACT-F (baseline)	.533	.316	1.687	-.190	.623	-0.305
FACT-F (midpoint)	.045	.316	0.142	-1.150	.623	-1.846
FACT (completion)	-.111	.319	-0.348	-.862	.628	-1.373
Activity counts- Log transformed						
Total activity counts (baseline)	-.285	.316	-0.902	.010	.623	.016
Evening activity counts (baseline)	.057	.319	0.179	.251	.628	0.340
Total activity counts (midpoint)	-.395	.325	-1.22	.580	.639	0.908
Evening activity counts (midpoint)	-.692	.325	2.129	1.282	.639	2.006
Total activity counts (completion)	.022	.316	0.070	.424	.623	0.681
Evening activity counts (completion)	-.107	.316	-0.339	-.429	.623	-0.689

BMI= Body Mass Index; FACT-F= Functional Assessment Cancer Treatment-Fatigue, Hgb= Hemoglobin, PROMIS-SD= Patient Reported Outcomes Measurement Information System-Sleep Disturbance; Total activity counts= Actical accelerometer daily counts per minute; Evening activity counts = 1400-1800 Actical accelerometer counts per minute

Results

Fatigue

Fatigue increased at midpoint of therapy and persisted at completion. FACT-F means at baseline (M= 43.09, SD= 9.26), midpoint of therapy (M= 40.14, SD= 10.08), and completion (M= 39.64, SD= 9.73) showed a clinically significant difference in mean fatigue scores, as measured by a decrease in FACT-F >3. This approach of determining clinical significance of fatigue based on a change in FACT-F > 3 is based on a previous report (Feng et al., 2016).

Relationships between fatigue and study variables other than physical activity are illustrated in Table 9. At baseline, prior to EBRT, age had a negative correlation with FACT-F scores (r= -.29, p=.03), indicating that older participants reported less fatigue than younger participants. No relationship was found between age and fatigue at subsequent time points. BMI was not significant at baseline but was positively correlated with fatigue scores at midpoint (r=.32, p=.01) and completion of therapy (r=.30, p=.03). This correlation indicates higher fatigue in participants with higher BMI. Hemoglobin at midpoint was negatively correlated with fatigue at midpoint (r=-.48, p=<.005) and completion of therapy (r=-.40, p=.002), indicating worsening fatigue with lower hemoglobin levels. Hemoglobin at completion was also negatively associated with fatigue at midpoint (r= -.53, p<.005) and completion of therapy (r=-.41, p=.001). PROMIS-SD was correlated with fatigue at all time points, indicating worsening fatigue occurring with worsening sleep disturbance.

Table 9. Pearson Correlations Between Fatigue Scores and Non-Activity Study Variables

Variable		Age	BMI	Hgb (baseline)	Hgb E (midpoint)	Hgb F (completion)	PROMIS-SD (baseline)	PROMIS-SD (midpoint)	PROMIS- SD (completion)
FACT-F (baseline)	Pearson Correlation	-.29*	0.23	0.11	-0.12	-0.18	.49**	.38**	.48**
	Sig. (2-tailed)	0.03	0.09	0.43	0.38	0.18	<.005	0.004	<.005
FACT-F (midpoint)	Pearson Correlation	-0.12	.32*	-.30*	-.48**	-.53**	.34*	.33*	.47**
	Sig. (2-tailed)	0.37	0.01	0.02	<.005	<.005	0.01	0.01	<.005
FACT-F (completion)	Pearson Correlation	-0.11	.30*	-0.21	-.40**	-.41**	.31*	.34*	.47**
	Sig. (2-tailed)	0.43	0.03	0.12	0.002	0.001	0.02	0.01	<.005
	N	56	56	56	54	56	56	56	56

** Significance= p <.05 based on a 2-tailed alpha of 0.05

BMI= Body Mass Index; FACT-F= Functional Assessment Cancer Treatment-Fatigue, Hgb= Hemoglobin, PROMIS-SD= Patient Reported Outcomes Measurement Information System-Sleep Disturbance; Total activity counts= Actical accelerometer daily counts per minute; Evening activity counts = 1400-1800 Actical accelerometer counts per minute

Data transformation: FACT-F square root; Activity counts Log 10

Table 10: Pearson Correlations Between Activity and Non-Fatigue Study Variables

Variable	Age	BMI	Hgb (base-line)	Hgb (mid-point)	Hgb (completion)	PROMIS-SD (base-line)	PROMIS SD (mid-point)	PROMIS SD- (completion)
Total activity counts (baseline)	-0.26	-0.14	0.05	0.25	0.12	-0.01	0.15	0.06
	0.05	0.29	0.72	0.07	0.38	0.92	0.26	0.68
Evening activity counts (baseline)	-0.22	-0.21	0.00	0.12	-0.05	0.05	0.10	0.10
	0.10	0.13	0.98	0.38	0.71	0.74	0.45	0.46
Total activity counts (midpoint)	-0.22	-0.10	-0.03	0.09	-0.04	-0.15	0.00	-0.04
	0.11	0.50	0.86	0.52	0.77	0.30	0.99	0.80
Evening activity counts (midpoint)	-0.15	-0.07	-0.04	0.17	-0.03	-0.07	-0.09	0.01
	0.27	0.63	0.77	0.23	0.84	0.63	0.53	0.96
Total activity counts (completion)	-0.26	-0.22	0.14	0.18	0.10	0.05	0.11	0.05
	0.05	0.11	0.30	0.18	0.45	0.72	0.40	0.74
Evening activity counts (completion)	-0.19	-0.18	0.07	0.17	0.08	0.09	0.05	0.11
	0.17	0.18	0.62	0.23	0.57	0.51	0.69	0.44

** Significance= p <.05 based on a 2-tailed alpha of 0.05

BMI= Body Mass Index; FACT-F= Functional Assessment Cancer Treatment-Fatigue, Hgb= Hemoglobin, PROMIS-SD= Patient Reported Outcomes Measurement Information System-Sleep Disturbance; Total activity counts= Actical accelerometer daily counts per minute; Evening activity counts = 1400-1800 Actical accelerometer counts per minute

Data transformation: FACT-F square root; Activity counts Log 10

Table 11. Pearson Correlation Between Fatigue and Activity

Variable	Total activity counts (baseline)	Evening activity counts (baseline)	Total activity counts (midpoint)	Evening activity counts (midpoint)	Total activity counts (completion)	Evening activity counts (completion)
FACT-F (baseline)	-0.04	-0.02	-0.04	-0.06	-0.02	-0.11
	0.78	0.86	0.79	0.65	0.87	0.40
FACT-F (midpoint)	-0.14	-0.10	-0.10	-0.07	-0.18	-0.12
	0.29	0.46	0.49	0.62	0.17	0.39
FACT-F (completion)	-0.15	-0.17	-0.17	-0.18	-0.25	-0.17
	0.26	0.21	0.23	0.21	0.07	0.21

** Significance= p <.05 based on a 2-tailed alpha of 0.05

BMI= Body Mass Index; FACT-F= Functional Assessment Cancer Treatment-Fatigue, Hgb= Hemoglobin, PROMIS-SD= Patient Reported Outcomes Measurement Information System-Sleep Disturbance; Total activity counts= Actical accelerometer daily counts per minute; Evening activity counts = 1400-1800 Actical accelerometer counts per minute

Data transformation: FACT-F square root; Activity counts Log 10

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Physical Activity

Total activity counts and evening activity counts did not correlate with any of the study variables (See Table 5). The relationship between age and physical activity approached significance (p=0.05) at baseline (*r*=-.26) and completion (*r*=-.26) indicating lower activity levels in older participants. (See Table 10).

Relationship of Fatigue and Physical Activity

Physical activity, both total and evening, did not show correlation with fatigue scores at baseline, midpoint or completion of therapy. (See Table 11).

Regression Analysis

Multiple linear regression analysis was carried out to identify the independent predictors of fatigue (e.g., BMI, hemoglobin, PROMIS-SD and physical activity counts) at midpoint of therapy and at conclusion of therapy while adjusting for baseline fatigue score. Age was not correlated with fatigue at midpoint or conclusion of therapy, thus was not included in the model. Four separate models were carried out. All models used BMI, hemoglobin and PROMIS-SD at their respective time points, as well as baseline FACT-F scores. Transformed variables were used for FACT-F and physical activity counts, as previously described. Regression models were created as below:

1. Midpoint of therapy: total physical activity counts
2. Midpoint of therapy: 1400-1800 physical activity counts
3. Conclusion of therapy: total physical activity counts
4. Conclusion of therapy: 1400-1800 physical activity counts

Assumptions for all models were assessed as follows. Multicollinearity was not present, as no correlations greater than 0.7 were found. Durbin-Watson statistics were all relatively close

to 2.0 indicating independence of errors. Linearity and homoscedasticity were assessed using visual inspection of scatterplots for each variable and were not found to be problematic. All tolerance values were greater than 0.1, indicating that collinearity was not present. Outliers were assessed, and no standardized residuals were greater than ± 3. Three leverage values were greater than 0.2; however, no Cook's distance values were greater than 1. No outliers were removed from analysis. Normality was assessed by visual inspection of a histogram and P-P plot of regression standardized residual.

The regression models were predictive of fatigue score at both midpoint and completion of therapy, using separate models for total physical activity count and evening physical activity count.

Midpoint of therapy: Model 1: $p<.005$, adj. $R^2 = .627$. Model 2: $p<.005$, adj. $R^2 = .628$

Completion of therapy: Model 3: $p<.005$, adj. $R^2 = .513$. Model 4: $p<.005$, adj. $R^2 = .481$.

Table 12. Summary of Multiple Regression Analysis-Midpoint, Total Physical Activity Counts

Variable	*B*	SE_B	*B*	*P*
(Constant)	6.468	2.033		.002
FACT-F (baseline)	.662	.097	.622	<.005
BMI	.049	.028	.149	.083
Hgb (midpoint)	-.503	.113	-.371	<.005
PROMIS-SD (midpoint)	.006	.014	.036	.688
Total activity counts (midpoint)	-.156	.503	-.026	.758

Note. Dependent Variable: FACT-F (midpoint)
B= unstandardized regression coefficient; SE_B = Standard error; β = standardized coefficient
BMI= Body Mass Index; Hgb= Hemoglobin, PROMIS-SD= Patient Reported Outcomes Measurement Information System-Sleep Disturbance; Total activity counts= Actical accelerometer daily counts per minute

For all four models, hemoglobin and baseline fatigue were significant predictors of fatigue at midpoint and completion of therapy. BMI, PROMIS-SD and evening physical activity counts did not add significantly to any of the models. Total physical activity counts were a

significant predictor of fatigue at completion of therapy only. See Tables 1-4 for regression coefficients and standard errors.

Table 13. Summary of Multiple Regression Analysis – Midpoint, 1400-1800 Physical Activity Counts

Variable	*B*	SE_B	*B*	*P*
(Constant)	5.993	1.972		.004
FACT-F (baseline)	.664	.096	.623	<.005
BMI	.051	.028	.154	.074
Hgb (midpoint)	-.518	.114	-.382	<.005
PROMIS SD (midpoint)	.005	.014	.035	.697
Evening activity counts (midpoint)	.177	.353	.042	.618

Note. Dependent Variable: FACT-F (midpoint)
B= unstandardized regression coefficient; SE_B = Standard error; β = standardized coefficient
BMI= Body Mass Index; Hgb= Hemoglobin, PROMIS-SD= Patient Reported Outcomes Measurement Information System-Sleep Disturbance; Evening activity counts= Actical accelerometer 1400-1800 counts per minute

Table 14. Summary of Multiple Regression Analysis-Completion, total Physical Activity Counts

Variable	*B*	SE_B	*B*	*P*
(Constant)	5.547	2.501		.031
FACT-F (baseline)	.521	.113	.503	<.005
BMI	.027	.032	.085	.397
Hgb (completion)	-.298	.139	-.217	.038
PROMIS SD (completion)	.020	.016	.146	.202
Total activity counts (completion)	-.949	.470	-.196	.049

Note. Dependent Variable: FACT-F (completion)
B= unstandardized regression coefficient; SE_B = Standard error; β = standardized coefficient
BMI= Body Mass Index; Hgb= Hemoglobin, PROMIS-SD= Patient Reported Outcomes Measurement Information System-Sleep Disturbance; Total activity counts= Actical accelerometer daily counts per minute

Table 15. Summary of Multiple Regression Analysis – Completion, 1400-1800 Physical Activity Counts

Variable	*B*	SE_B	*B*	*P*
(Constant)	4.458	2.519		.083
FACT-F (baseline)	.508	.118	.491	<.005
BMI	.036	.032	.113	.273
Hgb (completion)	-.310	.144	-.227	.036
PROMIS SD (completion)	.020	.017	.145	.227
Total activity counts	-.332	.381	-.089	.387

Note. Dependent Variable: FACT-F (completion)
B= unstandardized regression coefficient; SE_B = Standard error; β = standardized coefficient
BMI= Body Mass Index; Hgb= Hemoglobin, PROMIS-SD= Patient Reported Outcomes Measurement Information System-Sleep Disturbance; Evening activity counts= Actical accelerometer 1400-1800 counts per minute

Summary of Findings

Fatigue scores had significant Pearson's correlations with BMI and hemoglobin at midpoint and completion of therapy. Higher BMI and lower hemoglobin were associated with higher fatigue scores. PROMIS-SD scores correlated with fatigue scores in all time points, indicating that worsening fatigue and sleep disturbance may co-occur. Total physical activity and evening physical activity were not correlated with any of the study variables.

Regression models were predictive of fatigue at midpoint and completion of therapy, with baseline fatigue and hemoglobin showing significance in all models. Total physical activity counts at completion were predictive of fatigue at that time point.

CHAPTER V

DISCUSSION

This chapter presents a summary of the study, conclusions drawn from the study, implications and recommendations for future research.

Summary

Fatigue is reported to be the most distressing side effect of radiation therapy (RT), negatively effecting physical function and quality of life (Minton et al., 2013). This study explores the relationship of fatigue with free-living activity measured through accelerometry, which has been largely unexplored in men receiving RT (EBRT) for prostate cancer. Finding measures to predict, treat, and help prevent fatigue can improve long-term outcomes in cancer treatment.

The purpose of this study was to explore the adjusted relationship between physical activity count and perceived fatigue scores in men with non-metastatic prostate cancer, receiving external beam RT at beginning, midpoint, and end of therapy.

Research Questions:

1. Is there a relationship between physical activity and fatigue at baseline, midpoint of therapy, and conclusion of therapy?
2. Does physical activity predict fatigue at midpoint, and completion of EBRT?

The National Institutes of Health Symptom Science Model (NIH-SSM) was the theoretical framework guiding this study. The basic premise of the NIH-SSM is that complex symptoms can be classified into various phenotypes, which then have associated biomarkers

which can lead to clinical applications. This study will contribute to the connection between symptoms and phenotype of cancer-related fatigue.

An observational, correlational study was utilized to examine the relationship between physical activity level (activity counts) and perceived fatigue at three time points, baseline (prior to EBRT), midpoint (Day 19-21), and post-therapy (Day 38-42). This study assessed free-living physical activity, measured with an accelerometer and through daily logs and perceived fatigue, measured with the Functional Assessment of Cancer Therapy-Fatigue FACT-F at the beginning, midpoint, and conclusion of EBRT in men with prostate cancer.

The study was conducted at the National Institute for Nursing Research (NINR). Data was collected by the NINR team at the Hatfield Clinical Research Center of the National Institutes of Health (NIH). Data was gathered from study databases, participant records, and the NIH Clinical Center medical record. Accelerometry data was retrieved from the secure NINR server. Accelerometry data was inspected and cleaned by the investigator. This process includes determining amount of time the device was worn, locating and removing periods of non-wear, assessing for erroneous values, and determining physical activity counts (Deere et al., 2016). Physical activity counts were calculated for the entire wear period and for the hours of 2:00pm-6:00pm, a time period shown to have significant radiation-induced fatigue in an animal model (Renner et al., 2016).

Statistical analysis was conducted to determine correlations between physical activity count and fatigue scores. Pearson's correlation was conducted with each variable (fatigue score, physical activity count, age, BMI, hemoglobin level, sleep disturbance score, and age) at the three study time points. Linear regression analysis investigated if there was a relationship between perceived fatigue scores and physical activity counts at the three study time points,

while adjusting for baseline fatigue score. Other variables used in regression analysis include age, BMI, hemoglobin, and sleep score, all continuous variables. Linear regression analysis was utilized with fatigue and physical activity count as the dependent and independent variables, respectively, controlling for baseline fatigue and physical activity, age, BMI, hemoglobin, and sleep as potential confounding variables.

Major Findings

Few studies have examined objectively measured physical activity, using an accelerometer along with fatigue measured with the FACT-F in men receiving EBRT for prostate cancer. Fatigue was correlated with sleep disturbance in all study time points and with hemoglobin at midpoint and completion of therapy. Physical activity reached a p=.05 when correlated with age at baseline and completion of therapy but was not correlated with other study variables. Pearson's correlation showed no relationship between physical activity and fatigue. Hemoglobin and baseline fatigue were predictive of fatigue in all time points, using regression analysis. Total physical activity counts were predictive of fatigue at completion of therapy. This study reinforces the relationship of fatigue with hemoglobin and sleep disturbance as well as sleep disturbance and baseline fatigue as predictors of fatigue during treatment and at completion of EBRT. Total physical activity had not been identified as a predictor of fatigue at completion of therapy in this population prior to this study. Table 16 highlights findings at each study time point.

Table 16. Summary of findings by time point

	Baseline	Midpoint	Completion
Correlations with increased Fatigue	Sleep disturbance	Sleep disturbance	Sleep disturbance
	Younger age	Lower hemoglobin Higher BMI	Lower hemoglobin Higher BMI
Correlations with decreased Physical Activity	Older age (p=.05)		Older age (p=.05)
Predictors of fatigue	--	Lower hemoglobin Baseline fatigue	Lower hemoglobin Baseline fatigue Total physical activity counts

Findings Related to the Literature

Trajectory of Fatigue

The trajectory of fatigue in this study followed the general trend of fatigue symptoms during EBRT, as previously published, which is worsening at midpoint (Feng et al., 2017; Feng, Wolff et al., 2016; Filler et al., 2016; Hsiao, Reddy, Chen & Saligan, 2015). However, this study did not find any improvement in fatigue symptoms at completion of EBRT. While means at baseline (M= 43.09, SD= 9.26), midpoint of therapy (M= 40.14, SD= 10.08, and completion (M= 39.64, SD= 9.73) did not differ greatly, a clinically significant difference in mean fatigue scores, as measured by a decrease in FACT-F >3, was found between baseline and completion of therapy. This approach of determining clinical significance of fatigue is based on a previous report (Feng et al., 2016).

The trajectory of fatigue observed in this study is consistent with other cancer populations receiving RT, or even those receiving chemotherapy or a combination of chemo and radiation therapies. Fatigue, worsening during therapy and continuing to completion, has been noted in breast cancer (Dhruva et al., 2010; Porrier, 2006) and in stem cell transplantation

(Hacker, Kim, Park & Peters, 2017). These findings confirm the behavioral consequences of cancer therapies, which may be explained by several physiological processes.

Correlates of Fatigue

Fatigue was correlated with several factors in this study. At baseline, fatigue was negatively correlated with age, indicating that younger participants reported greater fatigue. This finding is congruent with findings in patients undergoing RT (Poirier, 2006) and specifically patients receiving EBRT for prostate cancer (Chao, Doucett, Raizen, & Vapiwala, 2018; Miaskowski et al., 2008). Since the mean age of participants is around retirement age, it is possible that younger participants were still in the workforce and faced with daily activities and stressors that may be fatiguing, with less time for rest or other self-care activities than their older, retired counterparts. In individuals with breast cancer, having children at home, being employed and younger age were all correlated with worse fatigue (Dhruva et al., 2013). In our study the correlation did not persist during or after therapy; however, and may indicate greater importance of other factors, such as BMI and hemoglobin which were correlated with fatigue at midpoint and completion of therapy, despite no relationship being evident at baseline.

BMI was correlated with fatigue at midpoint and completion of therapy. This correlation was found in colorectal cancer survivors (Vissers et al., 2017) and breast cancer (Gerber et al., 2011), but was not found in another breast cancer study (Kenzik et al., 2018). BMI did not differ between fatigued and non-fatigued groups in men receiving EBRT for prostate cancer (Feng, Espina & Saligan, 2018). Given the wide-ranging effects of elevated BMI, including increased risk for hypertension, diabetes mellitus, coronary heart disease and stroke, among others, (NHLBI, 2013), it is not surprising that men with a higher BMI may be less prepared physiologically to deal with the stresses of RT, thus reporting greater fatigue. Adipose tissue is

known to increase inflammation and insulin resistance and lead to dyslipidemia which can contribute to chronic disease (Gerber et al., 2011; Guttieriz, Puglisi & Hasty, 2009; Vissers et al., 2017). Inflammation is a proposed mechanism of fatigue (Saligan et al., 2015) and reduction in inflammatory markers associated with exercise have been correlated with decreased fatigue (Hojan et al., 2017).

Anemia is a well-documented factor in radiation-induced fatigue (Cella et al., 2002; Feng et al., 2015; Hsiao, Daly & Saligan, 2016), and a decrease in hemoglobin was significantly associated with fatigue in this study. Similar to BMI, baseline hemoglobin level was not correlated with fatigue, but was significantly associated with fatigue at both midpoint and completion of therapy. Destruction of blood cells during radiation eventually results in less oxygen delivery to tissues resulting in fatigue (Feng et al., 2015; Khoshbin et al., 2014; Pinkawa et al., 2014).

Sleep disturbance was associated with fatigue in all time points of this study. Cancer related fatigue and sleep disturbance often occur as part of a symptom cluster and are thought to have similar etiologies stemming from inflammation, eventually leading to skeletal muscle dysfunction, manifesting as fatigue and sleep problems, among others (Charalambous et al., 2019; Saligan et al., 2015). This has been observed in breast cancer (Berger, Kupzyk, Djalilova & Cowan, 2019; Overcash, Tan, Patel & Noonan, 2018), and sleep disturbance has been shown to co-occur in men receiving EBRT for prostate cancer, which may be worsened by urinary symptoms, specific to this population (Feng, Fuss, Dickinson, Ross & Saligan, 2019).

Physical Activity

Physical activity did not vary greatly between time points but did show a downward trend over time. Means for total physical activity and evening physical activity trended down at

midpoint and reduced further at completion of therapy, despite remaining well within the standard deviation.

Total physical activity was not significantly correlated with any of the study variables, although a p= .05 was found between total physical activity and age at baseline and completion of therapy. Older participants tended to be less active than younger participants, in this study. These mixed results are not surprising, given the mixed effects of age on physical activity in the literature. Older men with prostate cancer were less likely to exercise (Bohn, Fossa, Wisloff & Thorsen, 2019), and older patients with cancer related fatigue were more likely to be sedentary (Wolvers et al., 2017). However, age was also reported to not be associated with physical activity level in cancer survivors (Dennett, Peiris, Shields & Prendergast, 2018). It is possible that physical activity levels are dictated more by social roles, where younger participants who are in the workforce or involved in more social activities simply need to be more active. Not working or being retired was associated with a decrease in physical activity, with physical activity levels peaking at age 60 and decreasing with age (van Adrichem et al., 2018). This rationale may explain the association of age and fatigue observed at baseline, in this study. Younger participants may not be more physically active by choice but because they feel the need to meet their daily obligations, possibly even despite worsening fatigue.

Fatigue has been shown to increase in the afternoon and evening in patients treated with RT for non-metastatic cancer (Dhruva et al., 2013; Miaskowski & Aouizerat, 2012) and was observed in an animal model as well (Renner et al., 2016). Evening physical activity was not associated with other variables in this study. These values had very large standard deviations due to the shorter period of time observed. While data was not classified into physical activity categories, anecdotally, the researcher noted long bouts of sedentary behavior during these hours

in some participants. Sedentary behavior during evening hours, in this population, warrants further investigation.

Physical activity was not correlated with BMI, in any study time points. BMI was related to physical activity in breast cancer patients in a structured exercise program (Kenzik et al., 2018) and in colon cancer but has not been significant in the prostate cancer population (Feng et al., 2018; Feng, Espina & Saligan, 2018).

Physical Activity and Fatigue

A major goal of this study was to investigate the relationship of physical activity and fatigue in men receiving EBRT for prostate cancer. A mechanism proposed in a breast cancer study states individuals who exercise regularly get the benefit of decreased serum pro-inflammatory cytokines, increased insulin sensitivity and improved glucose uptake seen with exercise and failure to mitigate these factors may lead to fatigue (Gerber et al., 2011).
This study investigated overall daily physical activity related to fatigue. Previously, a relationship was observed by Minton and Stone (2012) and Jim et al. (2011) using this methodology. In this study no correlations were found with fatigue and total or evening physical activity counts, however physical activity was predictive of fatigue at completion. The literature in this area is mixed. Fatigue was correlated with physical activity in patients with lymphoma (Vermeate, Wolter, Verhoef & Gosselink, 2014), but not in advanced cancer (Yennurajalingam et al., 2016). In prostate cancer, while deemed clinically significant by the authors, increasing physical activity was not found to be statistically significant in relation to fatigue as measured as a subscale of quality of life (Gaskin et al., 2016). A strong inverse relationship was found between physical activity and fatigue, with fatigue being a limiting factor in activity for cancer survivors treated with hematopoetic stem cell transplant (Hacker et al., 2017). That study utilized

an accelerometer capable of recording fatigue in real time, rather than questionnaires that require recall. This may be a useful method to consider in future research.

This study examined physical activity counts as a continuous variable and did not categorize physical activity as sedentary, light or moderate. In the literature, fatigue was associated with increased sedentary time (Phillips et al., 2016), and the amount of decline in physical activity seen as the day progresses (Timmerman et al., 2015). The method used in this study is unable to detect an increase in sedentary time for a particular participant or track it over time.

Predictive Model

It may be possible to predict fatigue based on other known factors. Identifying individuals at risk for fatigue may allow for timely education and interventions. Hemoglobin and baseline fatigue were significant predictors of fatigue at midpoint and completion of therapy. This confirms previous work in patients with prostate cancer undergoing EBRT where hemoglobin was predictive of fatigue (Feng et al., 2015), also demonstrating baseline fatigue as predictive of fatigue during treatment. Baseline fatigue has been shown to predict fatigue during therapy in mixed cancers (Susanne et al., 2015) and in breast cancer (Schmidt et al., 2015).

Total physical activity was predictive of fatigue at completion of therapy, in this study. The negative correlation observed indicates an inverse relationship between physical activity and fatigue; meaning, more active individuals are likely to be less fatigued, or less fatigued individuals are more active. This finding has been noted in breast cancer (Berger et al., 2019; Gerber et al., 2011) but to our knowledge, this predictive relationship has not been noted in men with prostate cancer in a study using objective measurement of physical activity.

Conclusions

This study has further demonstrated the correlation of hemoglobin and sleep disturbance with fatigue in men with prostate cancer, as found in previous studies. It has solidified the concept that hemoglobin at baseline is a valid predictor of fatigue and demonstrated that decreased physical activity is predictive of fatigue at completion of therapy.

Physical activity showed no correlation with study variables at baseline or midpoint but was predictive of fatigue at completion of therapy. Age and physical activity approached significance at p=.05 both at baseline and completion of therapy. Possibly, a larger sample size would have yielded significant results, indicating lower levels of physical activity with increasing age. At baseline, younger participants manifested greater fatigue. This suggests that physical activity and fatigue are largely separate constructs in this population.

Physical activity was predictive of fatigue at completion of therapy. Perhaps by this point, the mental and physical toll taken by a busy schedule of daily radiation and the ensuing fatigue manifests as a decrease in physical activity, but this is not evident prior to that time. A noticeable decrease in physical activity should warrant assessment for fatigue.

Most physical activity research is not limited only to men; therefore, factors unique to them may be overlooked. There may be a sense of pressure to work for financial reasons or to provide for the needs of family members. Men may feel that showing signs of fatigue by slowing down physical activity may be seen as a sign of weakness.

The mean age of this study is approximately 65 years and individuals in this age range can have responsibilities that must be attended to, regardless of fatigue. They may still be in the workforce, unable to alter their daily routine significantly. They may have dependent spouses, children or grandchildren who depend on them for daily support. The treatment itself and the

need for travel to and from appointments may increase their physical activity level and mask any effect fatigue has on their mean daily physical activity. No longer having the need for daily appointments could lead to a decrease in physical activity or allow activity to be more in line with what feels appropriate to the individual. The effect of radiation is cumulative and, in many cases, persists beyond treatment. As time goes on, the men's ability to cope with fatigue may decrease and physical activity may subsequently decrease as well.

This study did not quantify time spent in sedentary activity; however, based on observation of raw physical activity data, many participants had sedentary lifestyles, even at baseline. With less total physical activity to begin with, the effect of fatigue on decreasing physical activity may not be noticeable.

Nursing Implications

This study reinforces that hemoglobin, sleep disturbance and baseline fatigue are strong predictors of fatigue in men receiving EBRT for prostate cancer. Mean hemoglobin levels decreased by > 1 mg/dl from baseline to completion, decreasing from 13.98 mg/dl to 12.77 mg/dl. This decrease crosses the threshold of anemia, 13.2 mg/dl for white men over 60 (Beutler & Waalen (2006) and can be considered clinically significant. Healthcare professionals should monitor for these factors and provide appropriate patient teaching regarding the likelihood of fatigue. A decrease in physical activity is predictive of fatigue at completion of therapy. Patients, families and health care professionals should monitor for changes in physical activity and be alert for subsequent fatigue. Knowing when to expect symptoms may reduce distress felt by the patient and family and allow daily activities to be planned accordingly.

Except for at completion of therapy, there was no relationship between physical activity and fatigue, further emphasizing the subjective experience of fatigue. An individual may be

experiencing fatigue, but it may not be readily apparent since physical activity level is not affected. Factors such as employment, home obligations and attitudes about fatigue should be explored. If physical activity is noted to decrease, this may represent an increase in fatigue or decreased ability to deal with its effects.

In this study, fatigue was worse in younger individuals at baseline and was not related to physical activity until completion of therapy. This indicates that external factors such as work, family or other commitments may play a role. Younger patients should be assessed for fatigue so that education and possible interventions can be provided.

Structured exercise consisting of both endurance activities such as walking and resistance exercise such as the use of light weights is recommended both during and following cancer treatment to help reduce fatigue (NCCN, 2017). In younger, more active patients, individualized timing of activities may be important to allow for rest periods, understanding that the need for home and work activities may be greater and may be perceived as more fatiguing. A possible nursing care plan may include planning ADLs and IADLs to allow for periods of rest while incorporating endurance and resistance exercise to potentially help mitigate fatigue. This may lead to an overall increase in physical activity but may be more congruent with the patient's energy level.

Future Research

Physical activity data should be incorporated with fatigue scales and other measures to further refine the phenotype of cancer related fatigue. Similar to phenotype development using fatigue scales (Feng et al., 2016), categories based on physical activity level could be used to explore biomarkers for individuals likely to experience a decrease in physical activity. This will require use of newer devices capable of clearly differentiating sedentary from light activity.

Future research in this area should examine changes in physical activity from morning to evening, since fatigue is thought to worsen as the day goes on (Dhruva et al., 2013; Miaskowski & Aouizerat, 2012). Patterns of fatigue could be identified, and daily activities can be planned accordingly.

Physical activity should be categorized to determine sedentary time to compare sedentary and more active individuals in relation to fatigue. Currently available devices are more sensitive to sedentary activity than those used in this study and may offer the possibility of real-time fatigue monitoring. Newer devices also have a greater ability to monitor movement during sleep. Determination of accelerometer non-wear should be further explored in this population. It is possible that 120 minutes of zero counts is not sufficient and may result in removal of sedentary activity.

Variables such as employment status and participation in regular exercise programs should be examined in the context of fatigue and physical activity. Social factors such as employment, marital status and social activity should be incorporated into research studies to explore potential non-biologic causes for increased fatigue, especially in younger individuals.

Fatigue is known to persist beyond treatment in men receiving EBRT for prostate cancer (Feng et al., 2019). Measurement of physical activity at 6 months, 1 year or more after therapy will provide insight into long term consequences of fatigue.

Sleep disturbance correlated with fatigue at all time points. Sleep has been found to co-occur with fatigue in breast cancer (Berger et al., 2019) and in men with prostate cancer treated with EBRT (Feng et al., 2019). In this population of men urinary symptoms are also found to be a contributing factor (Feng et al., 2019). Future research on the confluence of these symptoms and possible interventions is warranted.

Causation in the relationship between fatigue and physical activity is not clear. It cannot be completely determined if fatigue is a limiting factor in activity or if increasing activity mitigates fatigue. While activity interventions have been shown to improve fatigue, many of these studies were done in breast cancer, with populations who may be younger and with fewer comorbid conditions. In a meta-analysis, physical activity had no significant effect on fatigue in colon cancer (Brandenbarg, Korsten, Berger & Berendsen, 2018). Hacker (2017) suggests that fatigue may be a limiting factor in physical activity and there might not be a two-way relationship in stem cell transplant recipients. The relationship between physical activity and fatigue should be further explored in different cancer populations. Timing and intensity of exercise interventions should be tailored to individuals based on cancer type and other factors. Since activity at completion is predictive of fatigue, adjustments in daily routine to allow for rest along with increased physical activity may be of benefit. Qualitative or mixed methods research in this area may be useful to determine the relationship between fatigue and activity. Through interviews or questionnaires, the idea of fatigue as a limiting factor of physical activity or of a sense of improvement in fatigue gained from exercise and/or increased daily physical activity could be explored.

This study found baseline fatigue, hemoglobin and sleep disturbance were predictive of fatigue at midpoint and completion of therapy in men receiving EBRT for prostate cancer. Physical activity at completion of therapy was predictive of fatigue. Interventions for fatigue may be targeted for this time. Given the lack of relationship between fatigue and physical activity during therapy, a variety of other factors, including social, emotional and daily patterns of activities should be explored. Patients, families and health professionals should be aware that fatigue is likely even in the absence of a noticeable change in physical activity.

APPENDICES

Appendix A: NIH Activity Record

Instructions for Activity Record

The purpose of this questionnaire is to help understand what you are doing while you are using the Actical. Please fill out this questionnaire on _____ until _____. In the activity space, write the activity **that you feel best describes** what you were doing during that hour of the day. If what you were doing takes longer than one hour, write it again for as long as you continue to do the activity. Do this for each hour of the day and night.

Example

Day 1	Afternoon
Hour Beginning At	Activity
12:00 noon	Prepare Lunch, Eat Lunch
1:00 p.m.	Clean Kitchen

Activity Record

Initials_____ Age_____ Day/Date_____

Day 1	**Morning**
Hour Beginning At	Activity
4:00 AM	
5:00 AM	
6:00 AM	
7:00 AM	
8:00 AM	
9:00 AM	
10:00 AM	
11:00 AM	
12:00 PM	
	Afternoon
1:00 PM	
2:00 PM	
3:00 PM	
4:00 PM	
5:00 PM	
6:00 PM	
7:00 PM	
8:00 PM	
9:00 PM	
10:00 PM	
11:00 PM	
12:00 AM	
	Morning
1:00 AM	
2:00 AM	
3:00 AM	

Activity Record

Initials_____ Age_____ Day/Date_____

Day 2	**Morning**
Hour Beginning At	Activity
4:00 AM	
5:00 AM	
6:00 AM	
7:00 AM	
8:00 AM	
9:00 AM	
10:00 AM	
11:00 AM	
12:00 PM	
	Afternoon
1:00 PM	
2:00 PM	
3:00 PM	
4:00 PM	
5:00 PM	
6:00 PM	
7:00 PM	
8:00 PM	
9:00 PM	
10:00 PM	
11:00 PM	
12:00 AM	
	Morning
1:00 AM	
2:00 AM	
3:00 AM	

Actical Instructions

The Actical measures your activity level. In this study, the monitor should be worn for 3 consecutive week days and 1 weekend day, starting from the date and time we discussed with you. To put on the monitor, place the monitor around your waist using the adjustable belt provided.

Your start date and time is, _____

Your end date and time is, _____

We would greatly appreciate if you can indicate date and approximate time if possible of your activities using the activity log and also note and explain any malfunctions or problems with the Actical. Your feedback helps us to better interpret the data as well as improve the ease and comfort of the device for our patients and volunteers.

_____

_____

_____

_____

_____

Remember. . .

The Actical is NOT waterproof. Please take it off during showering and other water activities.

Thanks!

Appendix B: Demographic Form

Study ID: _____

Sociodemographic Data Sheet

Date: _____

Race:
___ White
___ Black/African American
___ Native Hawaiian/Other Pacific Islander
___ Asian
___ Native American/Alaskan Native
___ Other (specify: _____)
___ Unknown

Ethnicity:
___ Hispanic/Latino
___ Not Hispanic/Latino
___ Unknown

Education:
___ 8th or less
___ 9-12th grade, did not graduate
___ High school grad/GED
___ Vocational/technical school
___ Assoc degree/some college
___ Bachelor's degree
___ Advanced degree
___ Other (specify: _____)
___ Unknown

Marital Status:
___ Married
___ Widowed
___ Single
___ Divorced/Separated
___ Living as married
___ Unknown

Persons in Household:
___ Live alone
___ Live with 1 other person
___ Live with 2-4 others
___ Live with 5 or more others
___ Unknown

Employment Status:
___ Employed outside home/full time
___ Employed outside home/part time
___ Homemaker, employed at home
___ Retired
___ Disabled
___ In school
___ Not working
___ Unknown

Appendix C: Data Abstraction Form

Study ID: _____

Biological Markers Data Sheet

Date. _____

Initial Diagnosis Date of Primary Tumor: _____

Combined Gleason Score (Tumor Grade): _____

Positive Score/Number of Cores _____

Vascular Involvement _____

Volume of Gland: _____ cubic cm **Size measured by:** TRUS vs CT (circle one)

Baseline PSA Value/Date: _____ **End Study PSA Value/Date:** _____

Clinical T-Stage (per AJCC 6th edition): ___ T1c ___ T2, NOS ___ T2a ___ T2b

Bone Scan results: _____

Performance Status (Zubrod): _____

0 – Full active, able to carry on all predisease activities without restriction (**Karnofsky 90-100**).
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (**Karnofsky 70-80**).
2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (**Karnofsky 50-60**).
3 – Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (**Karnofsky 30-40**).
4 – Completely disabled. Cannot on any self-care. Totally confined to bed or chair (**Karnofsky 10-20**).

Karnofsky Performance Scale

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self, unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Appendix D: FACT-F

FACIT-F (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix E: HAM-D

HAMILTON DEPRESSION RATING SCALE (HDRS)

NAME	Hospital ID #	Date of Visit

	Rate each category using the scale to the right. (Circle the response)	None	Mild	Moderate	Severe	Very Severe
1	Depressed Mood (Sadness, hopelessness, helplessness, worthlessness)	0	1	2	3	4
2	Feelings of Guilt	0	1	2	3	4
3	Suicide	0	1	2	3	4
4	Insomnia Early	0	1	2		
5	Insomnia Middle	0	1	2		
6	Insomnia Late	0	1	2		
7	Work and Activities	0	1	2	3	4
8	Retardation	0	1	2	3	4
9	Agitation	0	1	2		
10	Anxiety Psychic	0	1	2	3	4
11	Anxiety Somatic (physiological concomitant of anxiety, such as: GI, C-V, RESP, frequent urination, sweating)	0	1	2	3	4
12	Somatic Symptoms Gastrointestinal	0	1		2	
13	Somatic Symptoms General	0	1		2	
14	Genital Symptoms (such as loss of libido, menstrual disturbances)	0	1		2	
15	Hypochondriasis	0	1	2	3	4
16	Loss of Weight	0	1		2	
17	Insight	0	1		2	
18	Diurnal Variation	0	1		2	
19	Depression and Derealization (such as feelings of unreality and nihilistic ideas)	0	1	2	3	4
20	Paranoid Symptoms	0	1	2	3	4
21	Obsessional and Compulsive Symptoms	0	1		2	

FORM COMPLETED BY_____ Total HDRS SCORE ☐☐

Appendix F: PROMIS-SD

PROMIS Item Bank v. 1.0 – Sleep Disturbance

Sleep Disturbance – Short Form 1

Please respond to each item by marking one box per row.

In the past 7 days...

	Not at all	A little bit	Somewhat	Quite a bit	Very much
My sleep was restless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I was satisfied with my sleep	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
My sleep was refreshing	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days...

	Never	Rarely	Sometimes	Often	Always
I had trouble staying asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I had trouble sleeping	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I got enough sleep	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days...

	Very poor	Poor	Fair	Good	Very good
My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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