CLINICAL STUDY PROTOCOL

Fatigue in Young Adults with Cancer

Step-Up Intervention for Self-Management of Fatigue in Young Adults Receiving Chemotherapy

Jeanne M. Erickson, PhD, RN, AOCN

Version Number 6 August 16, 2017

PROTOCOL SIGNATURE PAGE

Protocol No.: PRO00027448 **Version Date:** 3/30/17

1. I agree to follow this protocol version as approved by the MCW Scientific Review Committee (SRC), Institutional Review Board (IRB) and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigator's Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572) and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

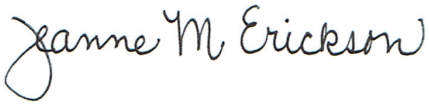
MCW Principal Investigator / Study Chair

Jeanne M. Erickson

Printed Name

3/30/17

Signature Date



Title: Step-Up Intervention for Self-Management of Fatigue in Young Adults Receiving Chemotherapy

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FDA IND No.: NA

MCW Protocol No.: IRB will assign.

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REVISION HISTORY

Revision history is presented in reverse order so that the information pertaining to the most current version of the protocol is presented first in this section.

Version 6, Version Date 8/16/17

Version 6 includes a revision to the procedures that include calls or emails to study participants to remind them to return the accelerometer promptly after the baseline and post-study periods.

Version 5, Version Date 3/30/17

Version 5 includes revisions requested by the Scientific Review Committee on March 14, 2017.

Version 4, Version Date 10/16/16

Version 4 reflects wording changes requested during IRB pre-review on October 10, 2016.

Version 3, Version Date 08/30/16

Version 3 reflects the inclusion of Children's Hospital of Wisconsin as a second site for the study. Kristin Bingen, PhD and Nancy Peret, RN were added to the study team.

Version 2, Version Date 07/26/2016

Version 2 reflects refinement of study procedures after meeting with study team on July 22, 2016. This version will be sent to Dr. James Thomas to request documentation of approvals by Faculty Review Committee and Scientific Review Committee as discussed in a meeting on July 11, 2016.

Version 1, Version Date 06/23/2016

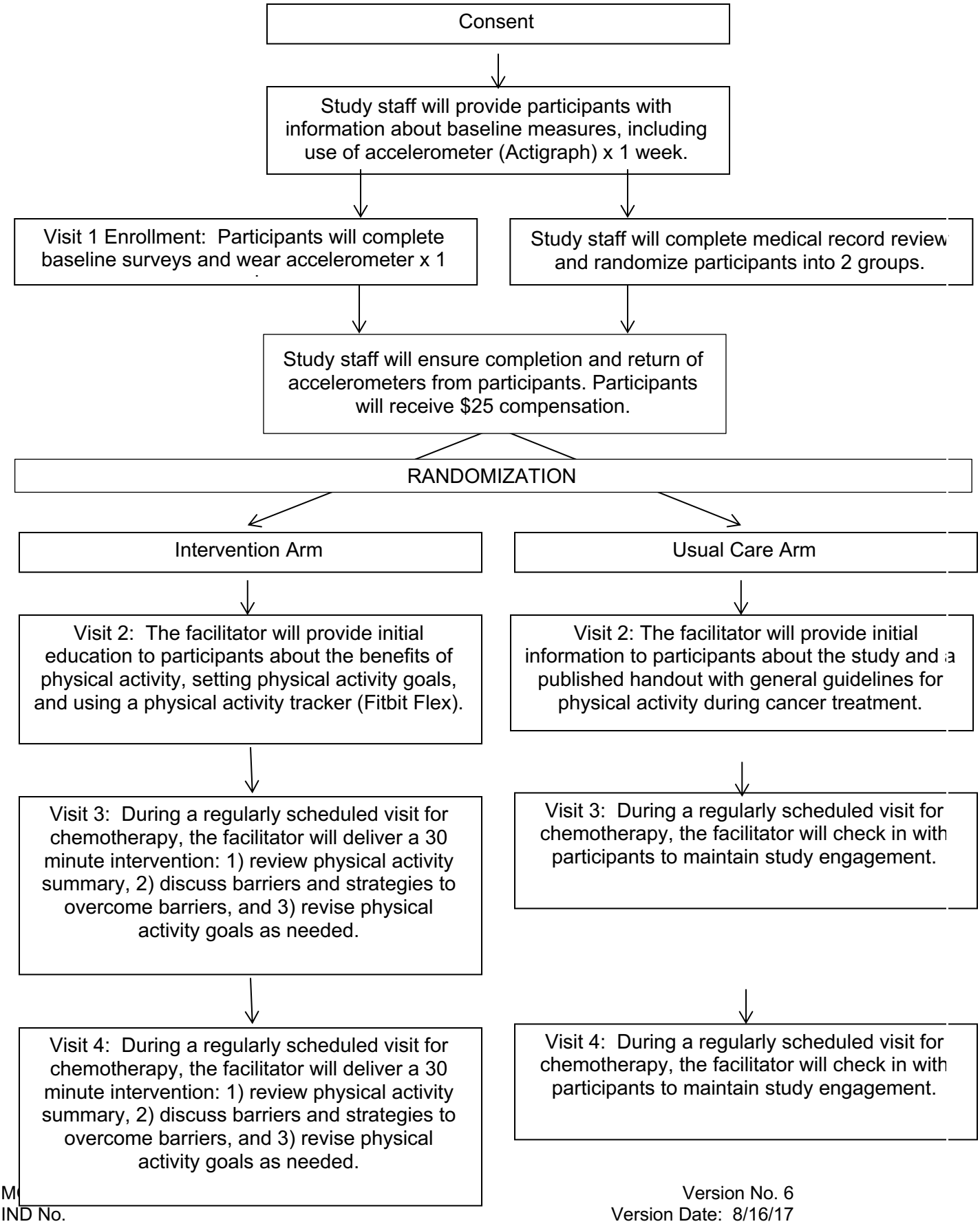
This draft was sent to OCCRIC on 6/24/16 as initial notification of the proposed study.

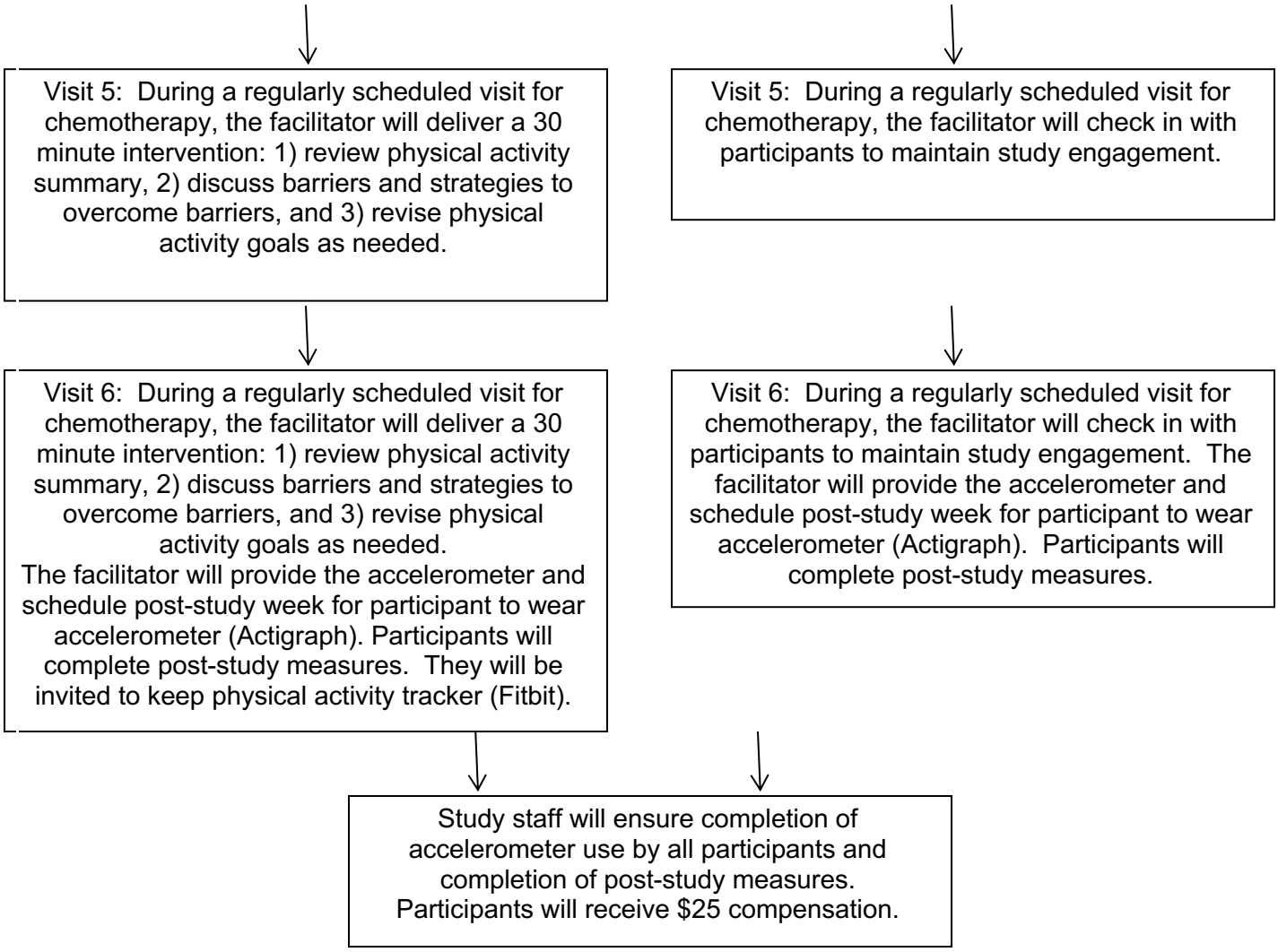
PROTOCOL SUMMARY

Title	Step-Up Intervention for Self-Management of Fatigue in Young Adults Receiving Chemotherapy
Protocol Number	
IND Sponsor	N/A
Principal Investigator /Study Chair/ Coordinating Center/Sponsor-Investigator	Jeanne M. Erickson, PhD, RN, AOCN
Study Sites	Froedtert Hospital/MCW Cancer Center and Children's Hospital of Wisconsin
Clinical Trial Phase	N/A
Study Disease	N/A
Main Eligibility Criteria	1) Young adults between the ages of 18 and 39 years; 2) have a diagnosis of cancer; 3) are within the first 2 months of a chemotherapy regimen that will last at least another 3 months; 4) are ambulatory without assistance; 5) have written consent from their physician to participate; 6) have the ability to understand English; 7) have access to a computer and the Internet,
Study Rationale	Despite decades of research, fatigue remains one of the most distressing symptoms and a disabling problem for young adults with cancer. Interventions to increase physical activity have been shown to relieve fatigue in patients receiving chemotherapy, but no studies have tested a physical activity intervention to improve fatigue in young adults receiving chemotherapy. Young adults with cancer acknowledge unmet needs for information and interventions related to physical activity, and they have concerns about how and when to return to physical activity during treatment.
Primary Objectives	To determine the impact of a physical activity intervention on the self-management process variables of self-efficacy and self-regulation and their relationships to physical activity and fatigue severity.
Secondary Objectives	To determine the preliminary efficacy of a physical activity

	intervention on outcomes of physical activity and fatigue severity.
Endpoints	Self-efficacy for physical activity Self-regulation for physical activity Physical activity (steps/day) Symptom severity Fatigue severity
Study Design	A randomized experimental design with an intervention group and a usual care group
Study Agent/ Intervention Description	The physical activity intervention is based on the Individual and Family Self-Management Theory (IFSMT) and includes 3 components: 1) education about the benefits of physical activity during chemotherapy; 2) guidance and resources to help the young adult set physical activity goals during chemotherapy and to self-monitor progress toward goals with a tracking device; and 3) ongoing collaboration with a physical activity coach.
Number of Subjects	75 young adults will be recruited.
Subject Participation Duration	Patients will continue in the study for approximately12 weeks.
Duration of Follow up	No follow-up after completion of study measures at 12 weeks
Estimated Time to Complete Enrollment:	20 months
Statistical Methodology:	Descriptive statistics will be used to describe and summarize the context variables related to the sample. Variables with significant patterns of variation will be explored as potential covariates. Field notes from sessions with the coach will be recorded and organized
Safety Assessments	The Safety Monitoring Committee of the P20 Center, the Self-Management Science Center at UWM, will be responsible for monitoring the data safety of this pilot project.
Efficacy Assessments	NA
Unique Aspects of this Study	NA

SCHEMA


Consent
Study staff will provide participants with information about baseline measures, including use of accelerometer (Actigraph) x 1 week.
Visit 1 Enrollment: Participants will complete baseline surveys and wear accelerometer x 1
Study staff will complete medical record review and randomize participants into 2 groups.
Study staff will ensure completion and return of accelerometers from participants. Participants will receive $25 compensation.
RANDOMIZATION
Intervention Arm
Usual Care Arm
Visit 2: The facilitator will provide initial education to participants about the benefits of physical activity, setting physical activity goals, and using a physical activity tracker (Fitbit Flex).
Visit 2: The facilitator will provide initial information to participants about the study and a published handout with general guidelines for physical activity during cancer treatment.
Visit 3: During a regularly scheduled visit for chemotherapy, the facilitator will deliver a 30 minute intervention: 1) review physical activity summary, 2) discuss barriers and strategies to overcome barriers, and 3) revise physical activity goals as needed.
Visit 3: During a regularly scheduled visit for chemotherapy, the facilitator will check in with participants to maintain study engagement.
Visit 4: During a regularly scheduled visit for chemotherapy, the facilitator will deliver a 30 minute intervention: 1) review physical activity summary, 2) discuss barriers and strategies to overcome barriers, and 3) revise physical activity goals as needed.
Visit 4: During a regularly scheduled visit for chemotherapy, the facilitator will check in with participants to maintain study engagement.


Visit 5: During a regularly scheduled visit for chemotherapy, the facilitator will deliver a 30 minute intervention: 1) review physical activity summary, 2) discuss barriers and strategies to overcome barriers, and 3) revise physical activity goals as needed.
Visit 5: During a regularly scheduled visit for chemotherapy, the facilitator will check in with participants to maintain study engagement.
Visit 6: During a regularly scheduled visit for chemotherapy, the facilitator will deliver a 30 minute intervention: 1) review physical activity summary, 2) discuss barriers and strategies to overcome barriers, and 3) revise physical activity goals as needed.
The facilitator will provide the accelerometer and schedule post-study week for participant to wear accelerometer (Actigraph). Participants will complete post-study measures. They will be invited to keep physical activity tracker (Fitbit).
Visit 6: During a regularly scheduled visit for chemotherapy, the facilitator will check in with participants to maintain study engagement. The facilitator will provide the accelerometer and schedule post-study week for participant to wear accelerometer (Actigraph). Participants will complete post-study measures.
Study staff will ensure completion of accelerometer use by all participants and completion of post-study measures.
Participants will receive $25 compensation.

Study Calendar

STUDY CALENDAR						
	Visit 1 (EN)	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
All Participants						
Medical Record Review Form	X					
Individual and Family Information Form	X					
Godin Leisure Time Index	X					
Physical Activity Assessment Inventory	X					X
Self-regulation Index for Physical Activity	X					X
PROMIS-29 (Multiple symptom severity)	X					X
PROMIS-Fatigue Short Form	X					X
Wear accelerometer (Actigraph) x 1 week	X					X
Intervention Group Participants						
The facilitator will provide initial education to participants about the benefits of physical activity, setting physical activity goals, and using a physical activity tracker (Fitbit Flex).	X					
During regularly scheduled visits for chemotherapy, the facilitator will meet with participants to deliver a 30 minute intervention: 1) review physical activity summary, 2) discuss barriers and strategies to overcome barriers, and 3) revise physical activity goals as needed.		X	X	X	X	X
Physical activity visit summary report		X	X	X	X	X
Evaluation of intervention components						X
Usual Care Group Participants						

STUDY CALENDAR						
The facilitator will provide initial education about the study and a published handout with general guidelines for physical activity during cancer treatment.	X					
During regularly scheduled visits for chemotherapy, the facilitator will meet with participants to maintain engagement in the study and identify any issues related to physical activity or participation in the study.		X	X	X	X	
Usual care visit summary report		X	X	X	X	

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1 SPECIFIC AIMS

Over 70,000 adolescents and young adults (AYAs) between the ages of 15 and 39 years are diagnosed with cancer each year in the United States.[1] These young patients have a unique cancer profile and frequently face months of therapy, often associated with distressing adverse side effects and decreased quality of life. Despite decades of research, fatigue remains one of the most distressing symptoms and a "major and disabling problem" for AYAs with cancer.[2] Persistent fatigue is implicated as one cause for the poor physical and emotional health-related quality of life outcomes in this young group of patients.[3]

Like many patients, AYAs receiving chemotherapy get caught in a cycle of cancer-related fatigue, which leads to decreased physical activity (PA), which contributes to deconditioning and more fatigue.[4] An array of interventions designed to increase PA have been shown to relieve fatigue in patients with cancer receiving chemotherapy, but most of this evidence emerges from studies with middle-aged adults receiving treatment for the most common cancers. To date, no studies have tested a PA intervention to improve fatigue in AYAs receiving chemotherapy.[5] AYAs with cancer acknowledge unmet needs for information and interventions related to PA, and AYAs report concerns about how and when to return to PA during and after treatment.[6-9]

An effective PA intervention, implemented early in the chemotherapy treatment process, is needed to prevent the cycle of fatigue and inactivity in AYAs that is associated with negative outcomes.[4] A multi-strategy intervention that includes components of education, negotiated goal-setting, and individualized feedback, can meet this need to enable AYAs to incorporate realistic goals to stay physically active on their own. During treatment, AYAs need to adjust PA goals based on their chemotherapy administration schedules and the predictable patterns of chemotherapy-related fatigue in order to prevent weeks of decreasing activity. Most studies report that PA is safe and well-tolerated by patients receiving chemotherapy, including patients with leukemia and lymphoma, which are common cancers in AYAs.[10-12] Patients receiving chemotherapy can safely begin a program of low-to moderate-intensity PA on their own.[13-15] Furthermore, home-based approaches may result in better maintenance of PA for AYAs with cancer who are in active treatment and who may be unwilling or unable to travel to supervised programs at alternate locations.[6, 16,17]

Self-management is the dynamic process by which individuals integrate strategies to manage their disease, including management of treatment-related symptoms, such as fatigue. For individuals with a chronic disease, such as cancer, this self-management process will last a lifetime, requiring the adoption of healthy lifestyle habits. The Individual and Family Self-Management Theory (IFSMT) outlines factors related to the individual's knowledge and beliefs, self-efficacy and self-regulation, which impact the self-management process to improve outcomes.[18] Self-efficacy is a predictive factor for participating in PA, and promoting AYAs' self-efficacy for PA needs to be explored as a strategy to improve self-management of fatigue.[19]

The purpose of this research is to study a 12-week PA intervention to improve self-management of fatigue in AYAs receiving chemotherapy. The intervention will include components of education, negotiated collaboration to set individual PA goals during chemotherapy cycles, and tools for self-monitoring PA. The aims of this study are:

1. To determine the impact of the PA intervention on the self-management process variables of self-efficacy and self-regulation and their relationships to PA and fatigue severity.
2. To determine the preliminary efficacy of the PA intervention on outcomes of PA and fatigue severity.

2 BACKGROUND

Fatigue in Adolescents and Young Adults (AYAs) with Cancer

Fatigue is one of the most prevalent and severe symptoms in adolescents and young adults (AYAs) with cancer.[2] 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"[20] (p1), cancer-related fatigue causes significant distress for AYAs and interferes with physical activities, social function, and mood.[2, 21] AYAs commonly report that fatigue occurs with other troubling symptoms, such as poor sleep, nausea, and pain, and within these symptom clusters, fatigue is frequently named as the priority symptom.[22] AYAs with cancer have shown greater symptom severity, including fatigue, than children and older patients. [23, 24] The higher level of fatigue in AYAs may be due to their accelerated physical and cognitive growth, hormone-related changes, as well as their involvement in multiple activities of this developmental period (school, work, relationships, and parenting).[3]

Cancer-related fatigue is worst during the treatment period.[2, 25] During cycles of chemotherapy, fatigue levels may follow a predictable and fluctuating pattern of increasing in the days after each cycle but improving before the next cycle.[2, 26] Studies also show that fatigue may be a persistent long-term problem, even for AYAs who have completed treatment.[2,27,28]

Physical Activity as an Evidence-based Intervention to Manage Fatigue in AYAs

Major oncology professional organizations recommend physical activity as an evidence-based intervention to manage fatigue, although most of this evidence comes from studies with adults who have the most common cancers, such as breast and prostate cancer. [29] Diverse PA programs for people with cancer have included aerobic and muscle-strengthening activities, such as walking, cycling, and yoga, and most programs last between 5 and 12 weeks.[30-33]

No trials have examined a PA intervention with YAs currently receiving treatment, and minimal PA studies have been conducted with patients who have the common diagnoses of this age group, such as lymphoma, leukemia, sarcoma, and germ cell tumors. A few PA interventions have targeted young adults with cancer who have completed cancer treatment, confirming that these patients are interested and able to participate in PA programs, especially when recommended by PA experts.[34-36]

Many young adults receiving cancer treatment unfortunately get caught in a cycle of cancer-related fatigue, which leads to decreased PA and physical fitness, which contributes to increased severity of fatigue and other symptoms.[4] Studies confirm that PA declines in YAs during chemotherapy and persists into the years following cancer therapy.[7,17,37,38] In addition, YA cancer survivors acknowledge unmet needs for information and interventions related to PA.[6-9] A recent analysis of topics and needs communicated by AYAs with cancer in an online forum suggests that YAs are interested in exercise for enjoyment, overall well-being, and weight management, but they do have concerns about safety and physical limitations and how/when to return to exercise post-treatment.[9] AYAs with cancer cite barriers to PA similar to a healthy comparison group, such as lack of energy, lack of self-discipline, lack of skills, and no companions, but AYA cancer survivors may be less likely to cite 'lack of time' as a significant barrier.[9,17] An effective PA intervention, implemented early in the

chemotherapy treatment process, is needed to prevent the cycle of fatigue and inactivity in AYAs that is associated with negative outcomes.

Theoretical Framework

The Individual and Family Self-Management Theory (IFSMT) will be used as a framework for this study.[18] This theory proposes three inter-related dimensions of context, process, and outcomes related to individuals' self-management behaviors. Contextual factors refer to the individual and family, the individual's health status, and the physical and social environment which influence self-management. The process dimension includes knowledge and beliefs, behavior-specific self-efficacy and self-regulation, and social facilitation. Outcome variables may be proximal, such as condition-specific self-management behaviors, and/or distal, such as quality of life or health care costs.

The IFSMT acknowledges the specific developmental and cancer-related needs of AYAs that influence their self-management behaviors. The intervention in this study (The "Step-Up" Study) contains three components which target the self-management process: 1) education about the benefits of PA and symptom management to improve AYAs' knowledge and beliefs and self-efficacy for PA, 2) resources to increase AYAs' use of self-regulation behaviors related to PA, and 3) ongoing negotiated collaboration with a facilitator to promote PA. The impact of the intervention on the proximal outcome of engagement in PA and on the distal outcome of fatigue severity will be measured. (Figure 1).

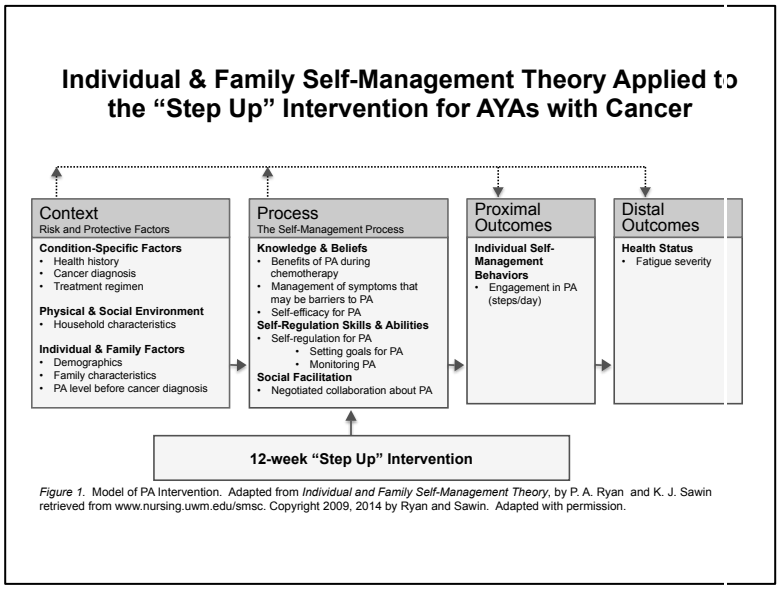

Figure 1. Model of PA Intervention. Adapted from *Individual and Family Self-Management Theory*, by P. A. Ryan and K. J. Sawin retrieved from www.nursing.uwm.edu/smsc. Copyright 2009, 2014 by Ryan and Sawin. Adapted with permission.

Innovation

This study is focused on PA research with the understudied group of AYAs with cancer. It is the first study to apply the IFSMT as a framework to identify effective interventions to help AYAs increase their PA as a strategy to manage fatigue, examining whether improved self-efficacy and self-regulation for PA as well as social facilitation will result in desired behavior changes. The intervention will be offered to AYAs who are currently receiving treatment and will be integrated into their regularly scheduled visits for chemotherapy administration, an important step to translate this evidence-based intervention into practice settings. Finally, since the intervention focuses on PA as a self-management behavior, the study will provide evidence about the impact of a less intensive and less expensive approach to improving PA, which may be a more relevant, meaningful, and feasible PA intervention for all AYAs with cancer.

Preliminary work

The multidisciplinary team comprises a unique combination of expertise in AYA oncology and PA research. Dr. Erickson is an oncology nurse researcher with over 30 years of clinical oncology experience. She has conducted previous studies that described patterns of fatigue during chemotherapy cycles and the negative effects of symptoms such as fatigue and sleep-wake disturbances on the daily activities and quality of life of AYAs receiving chemotherapy.[22, 26, 39] She has also demonstrated the feasibility and acceptability of

measuring PA and symptoms in AYAs receiving chemotherapy.[40] Dr. Stolley is a clinical psychologist with expertise in intervention trials related to improving PA and nutrition in cancer survivors, including adolescents. Dr. Swartz has over 15 years of experience as a scientific investigator in the areas of physical activity and sedentary behavior assessment. Dr. Charlson is a medical oncologist with a clinical focus on the treatment of young adult patients with sarcoma and breast cancer.

3 STUDY DESIGN

General description
The "Step-Up" Study will use a randomized experimental design to examine the preliminary efficacy of the physical activity intervention in AYAs who are receiving chemotherapy that will last approximately 12 weeks.

Number of Subjects
Seventy-five AYAs will be recruited from the Froedtert Hospital/Medical College of Wisconsin (FH/MCW) Cancer Center and Children's Hospital of Wisconsin.

Primary Endpoints
The primary endpoints for the study include self-efficacy for physical activity, self-regulation of physical activity fatigue severity, physical activity, and fatigue severity.

The following table summarizes the proposed instruments for the study:

IFSMT factor	Variable	Measure	Pre	Post
Condition-specific: Individual	Demographics, health history, diagnosis, treatment regimen	Medical Record Review Form	x	
Condition-specific: Individual and family	Individual, household and family characteristics	Individual and Family Information Form	x	
Condition-specific: Individual	Usual amount of PA before diagnosis (self-reported)	Godin Leisure Time Index[41]	x	
Process: Self efficacy	Self-efficacy for PA	Physical Activity Assessment Inventory[42]	x	x
Process: Goal-setting and self-monitoring	Self-regulation skills and abilities	Self-Regulation Index for PA[43]	x	x
Process: Negotiated collaboration	Perceptions of the intervention, preferred features of the PA tracker and facilitator	Evaluation of Intervention (intervention group only)		x
Proximal outcome: PA behaviors	# days worn, daily and weekly goals, daily step counts	PA and use of PA tracker (Fitbit) (intervention group only)	throughout	
Proximal outcome: PA behaviors	PA (steps/day)	Blinded accelerometer (ActiGraph GTX3+) x 7 days	x	x
Distal outcome: Symptom severity	Intensity of emotional distress, fatigue, pain, physical function, sleep disturbance, satisfaction with participation in social roles	PROMIS-29[44]	x	x
Distal outcome: Fatigue severity	Fatigue frequency, duration, intensity and impact of fatigue on activities	PROMIS – Fatigue Short Form[44]	x	x

Randomization
Patients will be randomized into two groups (intervention and usual care) using the Excel 'RAND' function to create a randomization chart forcing 38 into the intervention arm and 37 into the usual care arm.

Study Timeline
Primary Completion

The study will reach primary completion 19 months from the time the study opens to accrual.

Study Completion

The study will reach study completion 22 months from the time the study opens to accrual.

4. PATIENT SELECTION

Inclusion Criteria

Patients eligible for the study will be:

1) between the ages of 18 and 39 years of age;[1]
2) have a diagnosis of cancer;
3) are within the first two months of a chemotherapy regimen that will last at least another 3 months;
4) are ambulatory without assistance;
5) have written consent from their physician to participate;
6) have the ability to understand English;
7) have access to a computer and the Internet.

The goal of this study is to deliver the intervention as early in the treatment period as possible, but we recognize that recruiting and completing baseline measures before chemotherapy begins may be a burden to patients and a barrier to recruitment. The lower age limit for AYAs will be set at 18 years rather than 15 years in order to use one set of instruments which have been validated only for adults over age 18 years. AYAs with any diagnosis of cancer will be included in this exploratory pilot study.

Exclusion Criteria

Patients will be excluded from enrolling in the study if they have symptoms of uncontrolled cardiopulmonary disease, uncontrolled neurological disease, delayed wound healing from surgery, a high risk of bone fracture, or pre-existing peripheral neuropathy. Physicians will be asked to give written approval to indicate that patients do not have any of these contraindications to physical activity.

5. STUDY PROCEDURES

Recruitment Process

A member of the study team will screen clinic schedules at FH/MCW Cancer Center and clinic schedules in the Pediatric Hematology/Oncology Clinic to identify every AYA who meets the inclusion criteria. Clinic staff will ask eligible patients if they are willing to speak

with a member of the study team about the study. Eligible participants will be given time - over days, if necessary and possible - to consider study participation after hearing the details of the study. A member of the study team will complete the informed consent process with AYAs using an open exchange, reading through the informed consent document together, and allowing for assessment of comprehension and discussion of questions and concerns. A member of the study team will obtain written consent from the patient's primary provider to indicate the patients do not have any contraindications to physical activity.

A signed informed consent form copy will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the MCW Cancer Center Clinical Trial Management System. The system is password protected and meets HIPAA requirements.

Study Procedures

1. Visit 1 Enrollment

Following informed consent, a study team member will administer baseline surveys to all participants. Participants will receive instructions about wearing an accelerometer (Actigraph) for 1 week and how to return the accelerometer (Actigraph).

Participants will be asked for their preferred method of contact (email or phone call) to be reminded to return the accelerometer after one week of wear. A study team member will contact participants after the one-week period and remind them to return the accelerometer promptly in the mailing envelope that was provided.

Participants will be randomized to the intervention group or the usual care group.

2. Visit 2 (next regularly scheduled visit for chemotherapy)

Intervention group participants will meet with the facilitator, who will provide initial education about the benefits of physical activity and strategies to overcome barriers to physical activity, help the participants to set physical activity goals based on ability and preferences, and educate the participant on using a physical activity tracker (Fitbit Flex).

Usual care group participants will meet with the facilitator who will provide initial information to participants about the study and a published flyer about general guidelines for physical activity during treatment.

3. Visits 3, 4, 5, 6 (next regularly scheduled visits for chemotherapy – at intervals of approximately 3 weeks but may range from every 2-4 weeks based on chemotherapy schedule)

Intervention group participants will meet with the facilitator who will deliver a 30 minute intervention: 1) review physical activity summary over the past weeks, 2) identify barriers and discuss strategies to overcome barriers to physical activity, and 3) revise physical activity goals as needed. The facilitator will record physical activity data from the tracking device (Fitbit Flex), discussion notes about the barriers and strategies, and physical activity

goals. Any experiences or complications that might affect physical activity will be recorded, such as hospitalizations.

Usual care group participants will meet with the facilitator to maintain engagement in the study. The facilitator will record any experiences or complications that might be pertinent to the study, such as hospitalizations and enrollment in any activities related to physical activity.

At study visit 6, all participants will complete post-study surveys and will receive instructions about wearing an accelerometer (Actigraph) for 1 week and how to return the accelerometer (Actigraph).

A study team member will contact participants after the one-week period and remind them to return the accelerometer promptly in the mailing envelope that was provided.

Following completion of the study, a member of the study team will ensure completion and return of accelerometer (Actigraph) use by all participants. All participants will receive $25 compensation. Intervention participants will complete an additional post-study survey to evaluate components of the intervention and be invited to keep the physical activity tracker (Fitbit Flex).

6. STATISTICAL ANALYSIS

Sample Size

In an a priori power analysis using a mediation model that includes 4 predictors (intervention variable, self-efficacy, self-regulation, and PA), a total sample of 68 participants (34 in each group) would be needed to detect a medium-sized effect at a 0.10 significance level with 80% power. The power analysis was completed by using an online sample size calculator (http://www.danielsoper.com/statcalc/calculator.aspx?id=1) based on the above information. Physicians at FH/MCW and CHW saw approximately 300 AYAs with a new cancer diagnosis in 2012, and about half of those AYAs received chemotherapy. Assuming a 50% enrollment rate and 10% attrition, 75 AYAs will be recruited from these sites for a final sample of 68.

Data Management and Analysis

Questionnaire data will be collected electronically using REDcap surveys, and accelerometer (Actigraph) data will be analyzed using respective software. For the intervention group, weekly PA data will be transcribed from the PA tracker (Fitbit Flex) dashboard to REDcap files at each visit. All REDcap data will be exported to SPSS for analysis. Descriptive statistics will be used to describe and summarize the context variables related to the sample. Variables with significant patterns of variation will be explored as potential covariates. Missing values will be identified and reviewed for patterns of missingness, and the percentage of missing data will be calculated. If missing data are less than 5%, pairwise deletion will be used in data analysis, meaning all available cases will be used. If missing data are greater than or equal to 5%, Little's Chi-square test will be used to check if data are missing at random. If missing at random is assumed, multiple imputation method will be used. Field notes from sessions with the facilitator related to barriers and self-management strategies as well as notes from post-study debriefing interviews will be recorded and organized by participant visit.

After all study queries and analyses are completed, the data/PHI will not be destroyed but will be archived in a secure long-term storage site in order to keep an accurate record of screened and enrolled subjects for the sponsor and potential audit purposes only specific for this study. Data/PHI would not be destroyed until permission is granted by the sponsor to destroy the records.

Statistical Analyses

Specific Aim 1: To determine the impact of the PA intervention on the self-management process variables of self-efficacy and self-regulation, data analysis will examine differences in baseline and post-study measures of self-efficacy and self-regulation for each group. Group differences will be compared using t-tests to determine the effect of the intervention on these process variables. A mediation model will be used to describe the relationships of self-management process variables (self-efficacy and self-regulation) to PA (steps/day by accelerometer) and fatigue severity where self-efficacy and self-regulation are the main mediators of the intervention, PA is the second mediator, and fatigue severity is the dependent variable. The direct and indirect effect of treatment on PA and fatigue severity will be determined by the following steps:[45, 46]

Step 1. The regression of the fatigue severity on the intervention variable, ignoring the mediators, is significant.
Step 2: The regression of the main mediators on the intervention variable is significant.
Step 3: The regression of the second mediator (PA) on the main mediators (self-efficacy and self-regulation), controlling for the intervention, is significant.
Step 4: The regression of the fatigue severity on the second mediator (PA), controlling for the main mediators (self-efficacy and self-regulation) and the intervention, is significant.
Step 5: The regression of the fatigue severity on the intervention, controlling for the mediators, is non-significant and nearly-zero. In this case, the effect of intervention on fatigue severity is indirect through the mediators. If regression of the fatigue severity on the intervention, controlling for the mediators, is still significant, then the effect of treatment on fatigue severity is direct.

From the regression models, unstandardized regression coefficients and their standard errors will be calculated for the associations between the intervention variable and the mediators as well as between the fatigue severity and the mediators. The Sobel test will be used to test if the mediation effect is statistically significant.[45-49] Data from field notes from the intervention group participants will be analyzed using qualitative, inductive content analysis procedures to identify themes related to self-efficacy and self-regulation skills.

Specific Aim 2: To determine the preliminary efficacy of the PA intervention on outcome variables of PA (steps/day by accelerometer) and fatigue severity, data analysis will examine differences in baseline and post-study measures of PA (steps/day by accelerometer) and fatigue severity (PROMIS-29 and PROMIS Fatigue scores) for each group. Group differences will then be compared using t-tests to detect the effect of the PA intervention on these outcomes. Direct and indirect effect of the intervention on fatigue severity will be studied using the mediation model discussed in Aim 1. Quantitative data about the fidelity of the intervention will be used to estimate the dose of the delivered intervention for each participant and to explore whether there was a dosage effect on the outcomes.

7. ADVERSE EVENTS

Data and Safety Monitoring Plan

a. Monitoring Entity. The Safety Monitoring Committee of the P20 Center, the Self-Management Science Center at UWM, will be responsible for monitoring the data safety of this pilot project. The Safety Monitoring Committee includes the Pilot Core Director (M. Fendrich), Pilot Core Methods/Content Expert (C. Kovach), and two members independent of the P20 Center (C. Huang, Biostatistician, and A. Harley, Community and Behavioral Health Promotion). The P20 Center Director (R. Schiffman) is responsible for submitting necessary reports to NINR**.**

b. Procedures

1. Monitoring study safety. The Pilot Project Director (J. Erickson) will meet bi-weekly with the study team to review study enrollment, compliance with IRB requirements, including informed consent, verification of source documents, and compliance with study procedures. The Pilot Project Director will report at the P20 Center Pilot Projects bi-weekly meetings with the Pilot Core Director any concerns related to study safety identified by the project team. At the point when 10% of the participants are enrolled and at random intervals throughout the duration of the study, the Pilot Core Director or Methods Expert will review the informed consents for compliance to IRB requirements. The Pilot Project Director will provide the necessary study documents for review as requested.

2. Minimizing research-associated risk. This pilot project is anticipated to be minimal risk, but potential risks are that participants may experience psychological discomfort or distress when reflecting upon their personal experiences about cancer and cancer-related symptoms and/or physical discomfort, distress, or injury related to following a low-intensity physical activity (PA) plan. The Pilot Project Director (J. Erickson) will investigate any research-associated risks that are identified by the study team members and will report these concerns to the P20 Center Principal Investigator (R. Schiffman) or the Pilot Core Director (M. Fendrich) so that these concerns can be addressed.

The following actions will be outlined in the study procedures to protect against risks:

Psychological discomfort or distress. The facilitator and other members of the study team will be educated about how to recognize emotional distress and to make every effort to provide psychosocial support when emotional distress is evident. In the event that any participant demonstrates or self-reports a high level of distress, a member of the study team will conduct a further assessment. With the participant's consent, the study team may inform the participant's health care provider of the emotional distress in order to make adjustments to the care plan or suggest referrals for specialized care. No information will be disclosed to another party without the participant's consent unless there is imminent danger to the participant or others.

Physical discomfort, distress, or injury related to following a low-intensity physical activity (PA) plan. According to the American College of Sports Medicine, PA is safe and beneficial for patients during cancer treatment, and baseline exercise-testing is not required for patients to participate in low- to moderate-intensity PA, such as walking or resistance training. We will exclude patients who have contraindications to PA, which may include symptoms of uncontrolled cardiopulmonary disease, uncontrolled neurological disease, delayed wound healing from surgery, a high risk of bone fracture, or preexisting peripheral neuropathy, and we will obtain written approval from the

patient's physician to indicate none of these conditions apply. Patients will receive information from the facilitator about PA safety at the start of the study and will be advised to set PA goals based on their baseline PA level and to respect their own physical limitations. Participants will be reminded to complete 'pre-exercise' screening every day, and they will be advised not to engage in PA if they have any of the following conditions: 1) heart palpitations or chest pain; 2) fever greater than 38o C; 3) shortness of breath at rest; 4) new bruises or ongoing bleeding; 5) uncontrolled pain or nausea; 6) dizziness. They will be advised not to resume PA until these conditions resolve, and they should contact their health care provider about the condition if the problem is new and/or severe. PA studies have been safely carried out with patients undergoing intensive chemotherapy who have platelet values as low as 20,000/mm^3 and leucocytes < 1.0X109/L, and no studies have shown PA complications related to bleeding or infection. At each visit, the facilitator will discuss PA safety with each participant, explore any concerns about physical discomfort or distress that may be related to PA, and any new symptoms that may be a contraindication to PA. The facilitator will consult with the patient's care providers if there are any concerns about continuing the PA study.

3. Protecting confidentiality of participant data. Only study team members will have access to participant data. Participant data will be listed using a study ID number, and identifiable personal health information (PHI) will be stored separately from other study data. Data from surveys, accelerometers (Actigraphs), and PA trackers (Fitbits) and from facilitation and interview sessions will be stored on password-protected computers with access limited to study personnel. The Pilot Project Director will monitor all project-related computers and devices used in the study for compliance with data security protocols. Data analyses will be conducted without identifiers. The Pilot Project Director will report any data security issues to the P20 Principal Investigator.

c. Adverse Events and Unanticipated Problems. This pilot project is identified as minimal risk, and adverse events are not expected. The study team will review study activities and participant involvement at each bi-weekly team meeting with attention to identification of any unexpected events or problems. Should an adverse event or unanticipated problem occur, the project team will immediately contact the Pilot Project Director (J. Erickson), who will contact the P20 Center Principal Investigator (R. Schiffman). The PI will assess the event or problem and notify the IRB and NINR, including the plan to address the problem.

d. Multi-site Studies. This is not a multi-site study.

e. External Factors. Before each quarterly meeting with the P20 DSM Team, the Pilot Project Director (J. Erickson) and Project Co-Investigators (J. Charlson and M. Stolley) will review any changes in practice or policy at Froedtert Hospital/MCW Cancer Center that would affect this study. They will also review any relevant new literature or research that would impact the safety of the participants or ethics of the study. The Pilot Project Director will present a summary of these relevant external factors at the quarterly P20 Center meetings.

f. Advanced Plan for Analysis. An advanced plan for interim and/or futility analysis is not planned for this pilot project.

g. Subject Complaints. If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

The investigator will assess all adverse events and determine reporting requirements to the MCWCC Data and Safety Monitoring Committee (DSMC) and MCW's Institutional Review Board.

8 REGULATORY COMPLIANCE, ETHICS AND STUDY MANAGEMENT

Ethical Standard and Investigator Compliance

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

The principal investigator/study chair) will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor or other authorized representatives of the principal investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

Study Team

The study team consists of the principal investigator, the clinical research coordinator (CRC), the study facilitator, and the research assistant (RA). The study team will meet with the biostatistician, co-investigator, and study consultants as needed while the study is open to accrual.

9 DATA HANDLING AND RECORD KEEPING

Data Management Responsibilities

The principal investigator oversees the collection and management of study data.

The clinical research coordinator (CRC) is responsible for documentation related to the recruitment and enrollment of study participants and collection of baseline and post-study measures. The CRC is responsible for registration of study participants in OnCore and for completion of study surveys using RedCap.

The study facilitator is responsible for documentation of data collected with all participants during regular study visits, including documentation of the delivery of the intervention components.

The research assistant (RA) is responsible for analysis of accelerometer (Actigraph) data and data entry into RedCap files.

Only study team members will have access to participant data. Participant data will be listed using a study ID number, and identifiable personal health information (PHI) will be stored separately from other study data. Data from surveys, accelerometers (Actigraph), and PA trackers (Fitbit) and from facilitation and interview sessions will be stored on password-protected computers with access limited to study personnel. The Pilot Project Director will monitor all project-related computers and devices used in the study for compliance with data security protocols. Data analyses will be conducted without identifiers. The Pilot Project Director will report any data security issues to the P20 Principal Investigator.

The Pilot Project Director (J. Erickson) will meet bi-weekly with the study team to review study enrollment, compliance with IRB requirements, including informed consent, verification of source documents, and compliance with study procedures. The Pilot Project Director will report at the P20 Center Pilot Projects bi-weekly meetings with the Pilot Core Director any concerns related to study safety identified by the project team. At the point when 10% of the participants are enrolled and at random intervals throughout the duration of the study, the Pilot Core Director or Methods Expert will review the informed consents for compliance to IRB requirements. The Pilot Project Director will provide the necessary study documents for review as requested.

The principal investigator will maintain study data for five years.

The principal investigator will assume ownership of the data, along with the UWM Self-Management Science Center, and has responsibility for publishing the data.

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