MELVIN AND BREN SIMON CANCER CENTER

INDIANA UNIVERSITY

Evaluation of an Exercise intervention for Vincristine induced peripheral neuropathy in pediatric cancer patients

INDIANA UNIVERSITY PROTOCOL IUSCC-0607

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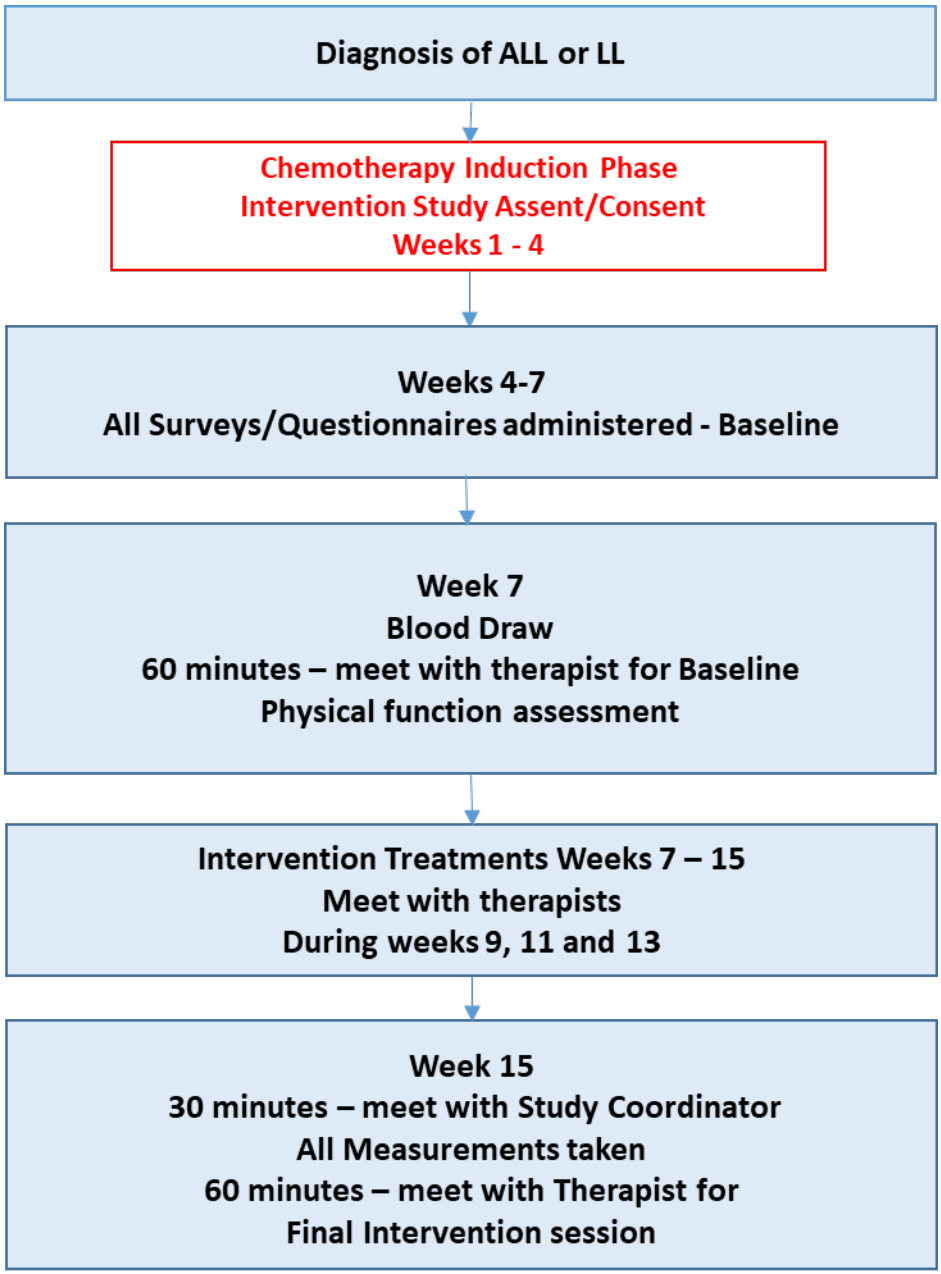


B. SPECIFIC AIMS

Although there are only a few studies examining the long-term sequelae of cancer treatment in the pediatric population, the overarching conclusion is, during adulthood, these **survivors will have a significant increase in chronic health issues, such as obesity, type 2 diabetes, metabolic syndrome and cardiovascular disease**[1-4]. **These health issues have a high cost for individuals and society**. Researchers hypothesize that the development of these conditions is due to survivors having a *higher risk of motor impairment because*

of exposure to vincristine. Vincristine is a chemotherapeutic agent used in a multi-drug regimen to treat pediatric, adolescent and young adult (AYA) cancers, particularly acute lymphoblastic leukemia (ALL) and Lymphoblastic lymphoma (LL).

Exposure to vincristine during the first four weeks of treatment induces *clinically significant neuropathy in 78% of children[5]. The trajectory for children with intermediate to severe neuropathy peaks around week 14 [5].* All forms of neuropathy, sensory, motor, and autonomic can arise in children and adolescents; however, *motor deficits are the most frequent* and can persist into adulthood[6]. With the increase in use of multi-drug chemotherapy, *survival of children with ALL and LL has reached between 80% - 90%[7,8].* Thus, the health impact of VIPN in adult survivors of pediatric cancer is now becoming apparent.

Despite the 80% - 90% survival rate, there are no effective treatments or interventions for vincristine-induced peripheral neuropathy (VIPN) and one is urgently needed. *Our long-term goal is to develop and implement interventions to minimize the persistent effects of VIPN.* The proposed study will assess the feasibility of exercise (EX) as a therapeutic intervention for pediatric patients with ALL and LL who have clinically significant VIPN. The EX component will be a mix of aerobic, dynamic resistance and isometric exercises. Emerging data support the notion that **exercise protects against** chemotherapy-induced peripheral neuropathy (CIPN)[9] **and may help repair damaged nerves** after CIPN develops[10]. Specifically, exercise increases many molecular signals, such as nerve growth factor (NGF), growth associated protein 43 (GAP 43) and synapsin (SNAP1), which induce axonal repair in peripheral nerves[11]. Exercise also decreases levels of serum chemerin[12], a pro-inflammatory protein and genetic marker associated with VIPN in children. The *primary objective* of this study is to assess the feasibility as well as determine preliminary effect size estimates of EX in preparation for a fully powered efficacy trial. Forty children and AYA (ages 5-25 years) who are on treatment for ALL or LL and exhibit a total neuropathy score of 3 or greater, will be recruited. The impact of EX on the subject's total neuropathy and quality of life, will be measured at baseline (T1) and following the 8-week study (T2). Our study will address the following specific aims:

Aim 1: Evaluate the feasibility and acceptability of EX as an intervention for VIPN in pediatric patients with ALL and LL
Hypothesis 1: Subjects will complete ≥ 50% of the EX sessions during the 8-week intervention.
Hypothesis 2: Children, AYA and parents will report satisfaction with the intervention and its components.

Aim 2: Estimate preliminary effect sizes of the EX intervention.
Hypothesis 1: The EX intervention will lead to improved VIPN (lower TNS-PV scores) at the end of the intervention T2 (14 weeks: primary endpoint) compared to baseline T1 (6 weeks)
Hypothesis 2: The EX intervention will lead to improved secondary outcomes of VIPN (lower P-CIN scores), Neuropathic pain (lower NPS and CTCAE scores), Quality of Life (higher Peds QL V4 scores), and Physical activity (higher total activity time, more time with higher heart rate throughout the day, more exercises completed, and higher oxygen consumption) for patients at the end of the intervention (T2) compared to baseline (T1).
Hypothesis 3: The EX intervention will lead to increases in Biomarkers of NGF, SNAP1, GAP 43, and PDGF-BB and Chemerin at the end of the intervention (T2) compared to baseline (T1).
Hypothesis 4: Changes in key predictor variables (e.g. self-efficacy, outcome expectations, support) will be associated with changes in outcomes (e.g. neuropathy, pain, and quality of life).

C. BACKGROUND & RATIONALE

Vincristine-induced peripheral neuropathy (VIPN)

The most diagnosed pediatric cancer (ages 0-19) is leukemia (26%) with acute lymphoblastic leukemia (ALL) being the most common (75%) [7], while lymphoblastic lymphoma (LL) is a fast-growing type of Non-Hodgkins Lymphoma (NHL) accounting for 2% of all NHLs[13]. Patients with both ALL and LL receive Vincristine as part of their standard treatment plan utilizing the same treatment and dosing schedule[13].

Due to improved multidrug treatment regimens over the past 40 years, the 5-year survival rate for these children has increased from 57% to 80% - 90% [7,14]. However, **due to vincristine exposure, we know that approximately 78% of the children with ALL will develop severe peripheral neuropathy (Vincristine-induced peripheral neuropathy: VIPN)**[5]. To date there is no study on children with LL. VIPN is observed very early in treatment, usually within the first four weeks [15]. The development of VIPN is characterized by progressive motor, sensory and autonomic loss of function and usually results in dose reductions of vincristine during treatment and thus an overall loss of therapeutic efficacy [16-18]. While we know that methotrexate, another chemotherapeutic agent used in the treatment of ALL, can also have toxic effects, severe neuropathy induced by this drug is very rare (<1%) and manifests as a reversible optic neuropathy not a peripheral neuropathy[19,20]

Long-term health outcomes in survivors of childhood cancers

The development of VIPN not only jeopardizes therapy, but also negatively affects the function and quality of life for children long after the completion of treatment [21-24]. Due to the increase in survival rate of children with cancer, researchers are able to more accurately assess the increased risk of severe diseases in adulthood as a result of chemotherapy exposure. A study of 531 adult survivors of pediatric cancer, who were on average 32 years post diagnosis, produced evidence that exposure to cumulative doses of vinca-alkaloids significantly increases the risk of motor impairment, but not sensory impairment, in adulthood[22]. Additional studies have also shown significant increases in obesity, type 2 diabetes, metabolic syndrome and cardiovascular disease[1-4]. Unfortunately, evidence indicates that these survivors will not only experience at least one chronic condition (70%), but also at least one severe or life-threatening condition (>40%) in adulthood[25,26]. To have increased risk to anyone of these conditions in adulthood is a major medical burden to the individual as well as society.

Metabolism of vincristine and association with neuropathy

Dr. Renbarger's laboratory has been conducting research focused on VIPN in the pediatric population for more than a decade, and she is considered one of the leading experts in this field. Her research team has significantly moved this field forward by determining that vincristine is metabolized more efficiently by CYP3A5 enzyme as compared to CYP3A4 [27,28] and that the CYP3A5*1 allele, which is responsible for the fully functioning enzyme, is more prevalent in the African American population as compared to Caucasians [29,30]. Furthermore, they revealed severity of VIPN is significantly worse in the Caucasian children without CYP3A5*1 allele [30]. These findings strongly impact the dosing strategy of children and AYA receiving vincristine as part of their chemotherapy regimen.

Measurement of neuropathy in children, adolescent and young adults

In addition to understanding the clinical pharmacology of vincristine, Dr. Renbarger and her collaborators have validated a modified version of the Total Neuropathy Score specifically for pediatric patients receiving vincristine TNS-PV[5]. The benefit of this version is its sensitivity to change over time (15 weeks) and feasible for use in children $\geq$ 6 years of age.

Potential biomarkers associated with VIPN

A recent genome wide association study conducted in our laboratory revealed two significant single nucleotide polymorphisms (SNP) in a large cohort of pediatric patients with ALL. One SNP, rs10454966 is part of the COCH gene and is associated with progressive hearing loss and vestibular imbalance [31,32]. Two studies of pediatric cancer survivors found hearing loss to be more prevalent in survivors as compared to controls [26,33],

suggesting the COCH gene SNP as a potential indicator of future hearing loss. The second SNP, rs7963521 is associated with plasma/serum levels of Chemerin [34]. Chemerin, a protein, is processed from its preprochemerin form and can be involved in angiogenesis [35], adipogenesis [36], osteoblastogenesis [37] or inflammatory processes [38-40] pathways affected by chemotherapy. Recently, one study identified chemerin levels as an independent predictor for 5-year mortality in patients with gastric cancer [41]. Given our preliminary findings it is important to investigate further into *Chemerin as a novel target for understanding neuropathy, a potential biomarker for dosing vincristine during treatment and as an indicator of long-term consequences of treatment.*

Our research team has discovered two other potential biomarkers, Platelet Derived Growth Factor BB (PDGF-BB) and Interleukin 13 (IL-13)[42]. Utilizing blood samples from pediatric ALL patients, Dr. Renbarger discovered PDGF-BB levels were negatively associated with worse peripheral neuropathy, while IL-13 was positively associated with it. The study proposed in this application is going to verify the preliminary data found for these biomarkers.

Following peripheral nerve injury many neurotrophins and proteins are expressed to aid in the nerve repair process. In addition to the biomarkers found in our research study, PDGF-BB and IL-13, we will also measure three markers of neuronal repair: nerve growth factor (NGF), synapsin 1 (SNAP1), and growth associated protein 43 (GAP43). Molteni and colleagues (2004) demonstrated in a rodent model of nerve crush injury that rodents which exercised also displayed enhanced regrowth of axons that were associated with increased levels of NGF, GAP43, and SNAP1[11]. There is also extensive evidence on the positive effects of exercise on sensory nerves and neuropathic pain. Cooper et al (2016) recently published a review on this topic discussing the mechanisms underlying exercise and explaining the role of the NGF, SNAP1, and GAP43 in the repair process[10].

Exercise for pediatric neuropathy

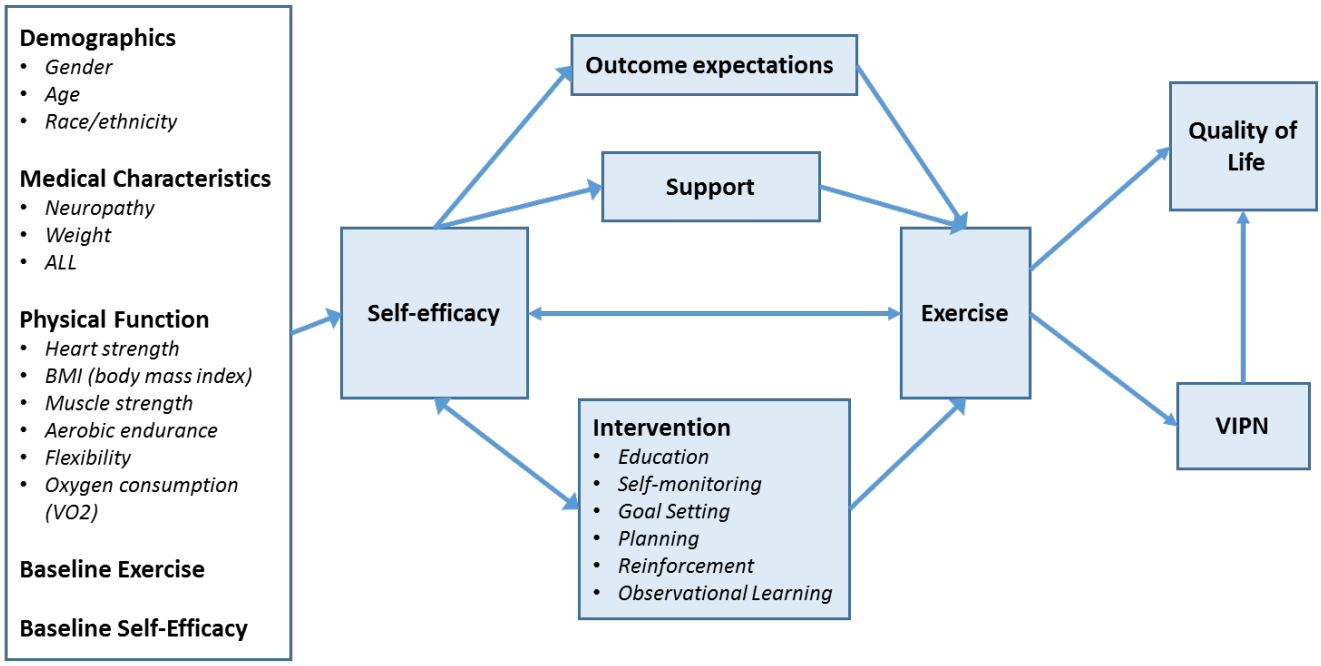
Currently, there are only a few prevention and treatment studies in children and AYA with chemotherapy induced peripheral neuropathy (CIPN) and they all utilize pharmacotherapies as their interventions. These clinical trials have used carbamazepine – showing a small effect [43], oral glutamic acid – mixed results [44,45], and pyridoxine and pyridostigmine – beneficial in isolated cases [46]. Even when searching extensive journal databases with broad terms such as, physical therapy interventions in pediatric patients with CIPN, no results are found [47]. Although there is no evidence in the pediatric population, there is some data in the adult population to support exercise as an intervention for CIPN. In a randomized trial with 314 adults experiencing CIPN, – 6 weeks of walking and resistance training – induced a significant decrease in neuropathy as compared to usual care [48]. A second smaller study examined 31 adults with lymphoma during chemotherapy treatment and found that 36 weeks of twice a week exercise significantly improved peripheral neuropathy symptoms[9]. Two key pre-clinical studies modeling nerve transection, demonstrated the impact of exercise in their model by showing animals assigned to running on a treadmill following injury had significantly greater axonal growth and when combined with Schwann cell grafts exercise could significantly increase myelin in the regenerated fibers of the animals[49,50]. Currently, the benefits of exercise on neuropathy have not been studied at all in the pediatric population, even though the National Comprehensive Cancer Network set forth clinical practice guidelines in oncology for survivors regarding healthy lifestyle habits in 2014[51], with **a *major emphasis on exercise***.

D. INNOVATION

Our trial has several innovative features including: (1) The only pediatric trial to develop a non-pharmacological VIPN intervention; (2) Estimating effect sizes for a subsequent fully-powered efficacy trial of a non-pharmacological approach for VIPN; and (3) Including biomarkers as a secondary outcome measure to predict severity of VIPN.

E. CONCEPTUAL MODEL

Social Learning Theory Model of Health Behavior (Bandura, 2004)



Social Learning Theory (SLT) developed by Bandura [52] is the framework for the interventions and approach in this proposed study. SLT proposes that learning is an interaction between cognitive processes, observation, and reinforcement in a social context, emphasizing both internal and external factors in the learning process[53]. Previous EX studies in children have demonstrated the importance of SLT constructs. Although there are several individual constructs within SLT that are important to increasing EX in children, it is important to note that these constructs also have a strong influence on each other and that *it is the interaction of these constructs that underlie the model*.

The key constructs of SLT relevant to this study are described below:

Self-efficacy: Self-efficacy is the belief an individual possesses regarding their ability to influence the events of their lives[54]. A person with high self-efficacy is more likely to complete a challenge or try again should they not succeed. Studies have consistently shown an increase in EX participation as self-efficacy increases[55,56], as well as increases in self-efficacy as EX participation increases[57]. Two of the main sources of self-efficacy are mastery (performance) experiences and vicarious experiences. When a person successfully carries out a task, he or she will believe that they have the capabilities necessary to repeat the behavior (i.e., mastery experiences).

Support: Social support is the perception one is cared for and has the necessary assistance from others in his/her social network. Support can arise from any person in the individual's social network, such as parent, sibling, physician, or peers. There is evidence showing the total physical activity metabolic equivalents (PA Mets) of pediatric cancer survivors are positively correlated with mother, father, and sibling total PA Mets[58].

Gilliam and colleagues also found a positive effect on PA as a result of family and peer interactions; however, they also demonstrated an indirect effect of support: an increase in self-efficacy[59]. We are also including physicians and therapists in our analysis as evidence indicates they have an influence on adult patient PA. Calfas and colleagues found that physicians who add just 3–5 min of EX counseling during their patient meetings and enlist a health educator to call for a few minute "booster" 2 weeks later were able to increase sedentary patient's PA by 37 min per week in patients compared to a control group with no intervention[60].

Outcome expectations: Outcome expectations are the underlying beliefs an individual has about the likelihood and value of the consequences of their behavior[61]. These expectations motivate individuals to engage in behaviors in order to achieve the desired outcome. Individuals who expect exercise to improve their health are more likely to engage in exercise and to endorse positive health outcomes as a result.

Theory of the Exercise Intervention

Education: Education involves increasing health-related knowledge and teaching participants about the benefits of exercise. Education is expected to motivate patients to engage in exercise and increase expectations that their VIPN, health, and quality of life will improve as a result of their engagement in exercise. Cancer survivors report that they are more willing to participate in physical activity if their Healthcare Providers recommend it[62]. Education may help to diminish the overly cautious approach of caregivers, which has been acknowledged as one of the limiting factors of physical activity participation[63].

Self-Monitoring: Self-monitoring is being aware of and tracking one's own behavior. Self-monitoring improves engagement in physical activity and enhances self-efficacy for physical activity. Wearing an activity tracker and keeping logs of exercise are forms of self-monitoring that have frequently been used in previous exercise research. There is an exercise study which shows that children wearing Fitbits use them to self-regulate and as a result increase their activity levels as shown by an increase in their overall steps[64]. It also allows patients to determine if they are reaching their health-related goals.

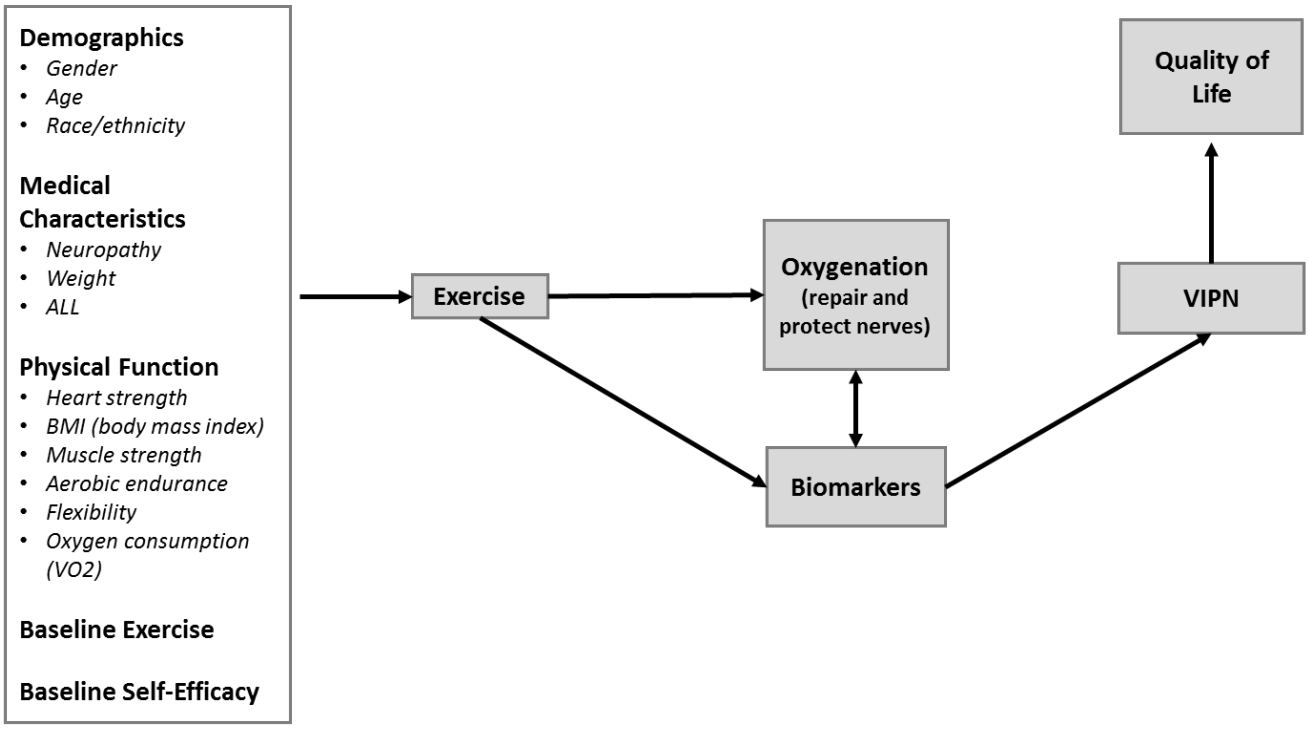
Goal Setting: Goal setting motivates individuals to improve their health and quality of life. Better performance is observed when individuals set goals that are specific and challenging and when individuals were provided feedback support regarding their progress to their goal[65]. In our study, the exercise therapist will assist patients in setting exercise goals and will provide support and providing feedback. We expect that setting goals will help patients to remain motivated and increase self-efficacy for exercise.

Planning: Planning requires the individual to develop an action plan to reach their goals. This involves identifying times and locations for exercise, identifying potential barriers to exercise participation, and problem-solving with the exercise therapist about how to overcome barriers to exercise. Planning improves the likelihood that patients will reach the exercise goals that they set and, in turn, will enhance self-efficacy[66].

Reinforcement: Reinforcement is a process that encourages a specific behavior to reoccur over time. We will use one-on-one meetings with therapists, Fitbit trackers, and parents/family to reinforce participants to engage in exercise. This will provide multiple opportunities for encouragement and positive feedback. Reinforcement is expected to enhance self-efficacy, which, in turn, will motivate participants to engage in exercise. There is evidence to suggest that in addition to parental support, peer support can be reinforcing [67], thus we will use the exercise videos with the age appropriate peers as a form of reinforcement.

Observational learning: Observational learning is a change in one's behavior as a result of that individual being exposed, either through interpersonal interaction or media, to a specific behavior, particularly by peer modeling[61]. Observing someone similar to you achieve success on a similar task can increase self-efficacy. Thus, we will use similar-aged children and AYA to demonstrate the EXs on each video in order to support observational learning and enhance self-efficacy for exercise.

Biological Theory Model of Vincristine-induced Peripheral Neuropathy



Biological Theory of VIPN

Exercise: EX increases oxygen to all organ systems, including the nervous system [10]. Emerging data support the notion that EX protects against chemotherapy-induced peripheral neuropathy (CIPN) and may help repair damaged nerves after CIPN develops. Exact EX prescriptions have not yet been developed, but the more hours spent in moderate-to-vigorous activity, the less peripheral neuropathy experienced[68].

Oxygenation: The increase in oxygen which occurs during exercise (both aerobic and resistance) has been shown to increase NGF[69], SNAP1[70], and GAP 43[11] in rodent models of exercise. In addition, oxygenation enhances the pathway that increases Myelin Basic Protein (MBP), thus helping maintain myelin homeostasis[71]. Myelin is important for nerve conduction and is targeted during chemotherapy[72], thus maintaining healthy myelin sheaths around the axons is necessary to minimize neuropathy.

Biomarkers: We have selected three key factors, NGF, SNAP1 and GAP 43 known to have a role in neuronal repair[10] and one involved in myelination disease, PDGF-BB[73] to investigate in the current study. These factors should increase to compensate for any neuronal damage inflicted by the chemotherapy. In addition, we have data suggesting that the cytokine, IL-13 is also associated with VIPN[42]. In this instance, the higher the IL-13 plasma levels the worse the neuropathy, therefore we expect exercise to decrease this cytokine.

Quality of Life: Childhood and AYA cancer has a considerable negative effect on a child's physical wellbeing due to chemotherapy, radiation and the resultant side effects of each. Improving the symptoms that result from cancer treatment (e.g., VIPN) and decreasing symptom burden is related to improved quality of life in this population. Further, exercise has been shown to improve both muscle weakness and low cardiorespiratory fitness[74] for childhood and AYA cancer survivors, which may also improve their quality of life.

F. ELIGIBILITY CRITERIA

F.1 Inclusion criteria

Participants will be eligible for this study if they are:

(1) age ≥ 5 and ≤ 25 years, (Riley Hematology/Oncology division accepts patients through age 25)

(2) have been initially diagnosed with acute lymphoblastic leukemia (ALL), or lymphoblastic lymphoma (LL) and may also be a relapsed diagnosis,

(3) will undergo the standard of care treatment for ALL or LL with vincristine.

(4) will have a TNS-PV score of 3 or greater at week 6

F.2 Exclusion Criteria

Participants will be ineligible for this study if they have:

(1) baseline peripheral neuropathy greater than grade 1 (prior to receiving any doses of vincristine),

(2) evidence of significant liver dysfunction,

(3) Down's Syndrome,

(4) pregnancy,

(5) severe illness or infection,

(6) current active treatment with erythropoietin,

(7) administration of vitamin supplements above 100% of the recommended daily allowance

G. PATIENT RECRUITMENT

Potential subjects will be recruited from the Riley Hospital for Children (Riley) and IU North Hospital. Riley medicine doctors are dedicated to the care of pediatric, adolescent and young adults ages 1-25. Study personnel will work with the clinicians in the Riley Department of Hematology Oncology to obtain the names of patients who have diagnoses of acute lymphoblastic leukemia (ALL) or Non- Hodgkin's Lymphoma-lymphoblastic lymphoma (LL) and are planning to undergo vincristine treatment. Patients will be recruited during their first 4 weeks of vincristine treatment.

Potential minor subjects and their parents/legal guardians may be approached by their physician and/or study personnel with information about this study. Patients and their parents/legal guardians who are interested in participating in the study will undergo the informed consent process. Informed consent will be only obtained by trained and authorized study personnel or investigators. Patients and their parents/legal guardians may be given a study flyer with contact information at the time of consent.

After consent, eligibility will be verified by a member of the study team and the patient will be registered (i.e., enrolled) to this study. The original, signed, IRB-approved Informed Consent Document and all regulatory files will be maintained by the Pediatric Clinical Trials Office (PCTO). Applicable regulatory documents must be completed and on file prior to registration of any subjects.

H. RESEARCH DESIGN

This is a multi-center study to test the feasibility of pediatric and AYA patient adherence to a single intervention (exercise: EX) during the consolidation phase of vincristine treatment for Acute Lymphoblastic Leukemia or

Lymphoblastic Leukemia. Fitbit activity tracker data and questionnaires will be used for assessing adherence and feasibility. We will use a pre and post intent-to-treat design. Forty subjects will be recruited and enrollment is expected to last 24 months.

H.1 Sample size justification

We plan to enroll 40 children and AYA who develop VIPN so that we will have at least 34 children and AYA who will complete the 14 week time point (assuming a 15% attrition rate based on this population). This study is sufficiently powered to detect a .5 SD difference in TNS-PV at the 14 week time point with 80% power based on a paired t-test with type I error set at .05. In a previous study of TPN-VS (Smith et al.) assessments from children with high severity VIPN resulted in TNS-PV of (n = 165 assessments from 14 children, mean = 8.02, SD = 5.22), for middle severity (n = 559 assessments from 70 children, mean = 4.22, SD = 3.01), and for low severity TNS-PV (n = 342 assessments from 25 children, mean = 1.94, SD = 1.86). Based on a pooled SD = 3.17 from these three groups, there is approximately a 1.9 SD difference in mean TNS-PV between the high and low severity groups, a 1.2 SD difference between the high and middle severity groups and a .7 SD difference between the middle and low severity groups. Thus if our children and AYA mimic the middle severity group prior to treatment we should be adequately powered to detect if our intervention is able to move them to low severity. Additionally, in pilot data (unpublished) TNS-PV at baseline (1 month) was 3.36 with SD = 3.66. With 34 children and AYA, we will have 80% power to detect a 2 point change in TNS-PV (which is considered clinically meaningful) assuming a SD = 3.66 at both time points and .4 correlation between time points with a paired t-test with type I error set at .05. For FACES (range 0 to 5), based on Smith et al, we estimate the pooled SD =.7 for high, middle, and low severity groups. With a sample size of 34, we are powered to detect a .35 mean difference in FACES, based on a paired t-test with type I error set at .05.

For other outcomes, which we do not have pilot data, we will still be able to detect a .5 SD difference in the mean based on a two-sided paired t-test with type I error set at .05. Even if we do not detect statistically significant differences in these outcomes in the proposed study, estimated means and SDs can be used for planning larger studies in the future.

H.2 Fitbit tracker justification

The Fitbit activity tracker was chosen for this feasibility study due to its versatility and effectiveness within younger populations of children. The FitBit's ease of use, comfort, design and feedback features were important factors for all age groups (children and AYA). Researchers in some studies utilized the Fitbit activity tracker to assess adherence to home-based activity programs[75].

I. PROCEDURES

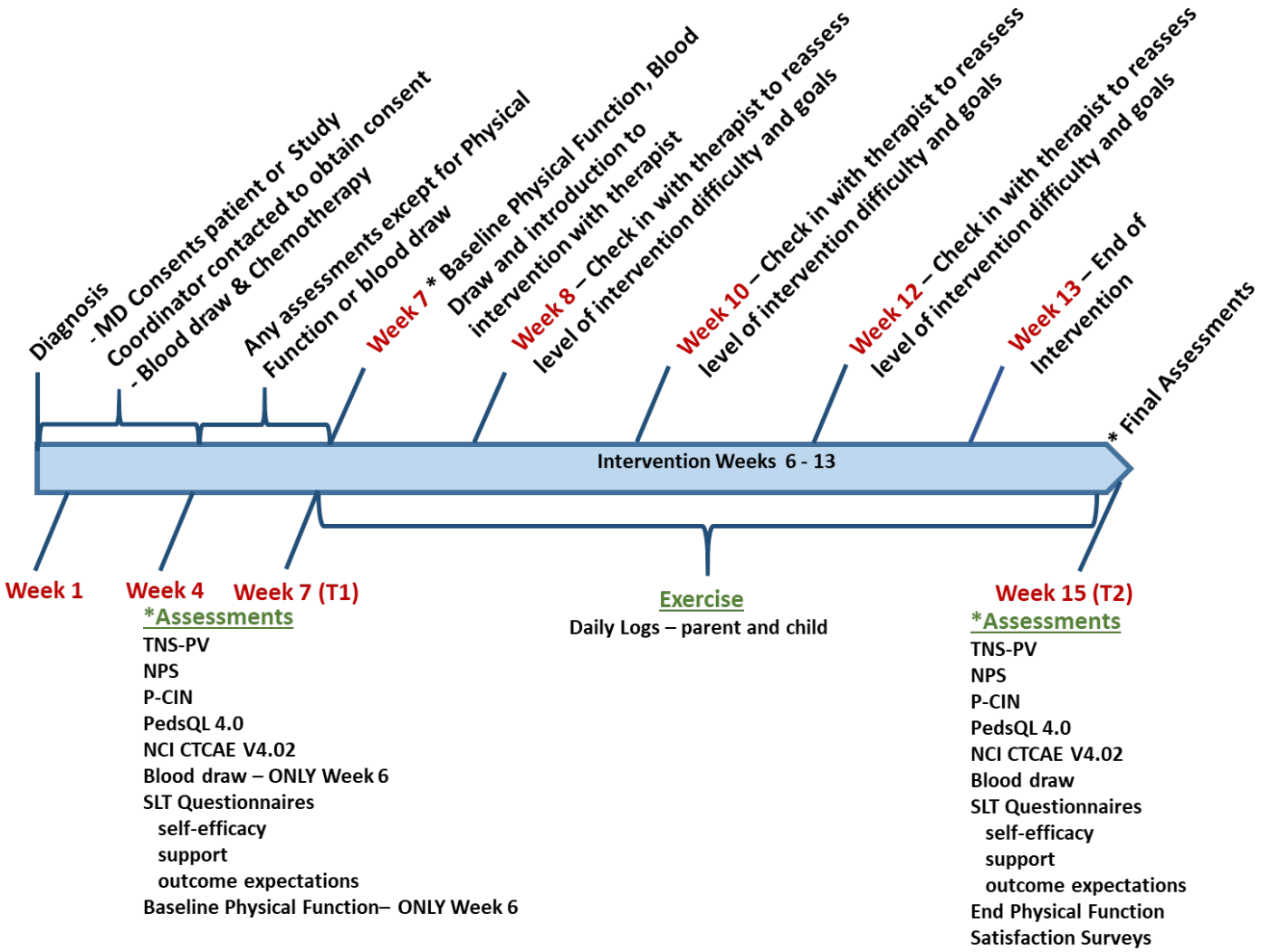
I.1 Overview

For this feasibility study, 40 pediatric patients with a diagnosis of ALL or LL who have a TNS of $\geq$3 at the end of four weeks of vincristine treatment will be enrolled from Riley Hospital for Children, Indiana University Health North Hospital, . Children and AYA will be recruited during their first four weeks after diagnosis and if they have a TNS $\geq$3 at the time of baseline (week 4-6 T1) they will be enrolled into the study. During T1 patients will complete all questionnaires, neuropathy exams, and provide blood samples and then again at week 14 (T2). Neuropathy exam may be performed during weeks 4 through 6 to accommodate regimented clinical visits. Exercise assessments will be performed on week 7.Subjects will check-in with the exercise therapist during weeks 9, 11, and 13 at a minimum, or once a week during the study if they choose (weeks 7-15). These in-

person sessions will take approximately 15 minutes, and the therapist will provide education, evaluate the subject's exercise plan, review exercises, set goals, and make plans to optimize adherence to the exercise program.

All study visits will take place before or after routine clinic visits so that patients and their families do not have to make additional trips to the four hospital sites. EX sessions will be completed by patients at home using instructional videos that will be given to participants during their study orientation.

I.2 Intervention timeline



I.3 Exercise (EX) Intervention

The EX intervention will include both an in-person exercise schedule and at-home video EX sessions (See Appendix I and II). The EX intervention will be designed and led by an AFAA (Athletics and Fitness Association of America) certified physical fitness trainer with fifteen years' experience and a professional with a PhD in an Exercise Science related field.

In-Person Exercise Sessions:

The first session will be completed at one of the four hospital sites with the EX intervention specialist during the baseline visit. Patients will check-in with their intervention specialist during routine visits to one of the sites or phone on weeks 8, 10, and 12 at a minimum throughout consolidation treatment, or once per week if they choose (weeks 7-15). In-person sessions will last approximately 15 minutes each during which time the therapist will provide *education* on the importance of exercise for VIPN, review the exercises, reassess difficulty level, *set exercise goals* for the following week, and *plan* to reach these goals. Reviewing exercises will demonstrate that the patient has learned exercises through *observational learning* from the therapist and peer models on the exercise videos. In-person sessions will also allow the therapist to provide *reinforcement* for the patient's progress.

If the patient or the study team are unable to meet in person the intervention specialist will contact the patient via their prefer contact method (phone call, email, Skype). These sessions will follow the format of the in-person sessions. Education, assessment of difficulty level, set exercise goals and plan will all be discussed during the remote check-in.

Home Exercise Sessions:

At baseline, participants will have access to the exercise videos via the study website or they will be downloaded to the study tablet, with 3 chapters of EX sessions to be completed at home with video instruction. Patients will be asked to complete home EX sessions 6 times per week for 8 weeks (week 6 through week 13) during the consolidation phase of treatment. A Daily Exercise Log is available to record exercise chapters, fatigue level and time of day exercised (See Appendix III). Patients may choose their rest day each week. Each EX session will last approximately 15 minutes. The at-home videos will have the therapist and three children and AYA who are of similar age to the patients demonstrate the exercises. This design is critical for supporting the *observational learning* component of the intervention. Two videos will be available for the study: one for ages 5 – 10; one for ages 11 – 25.

The EX intervention includes both Resistance Training and Aerobic Training. Each patient will receive an EX video with three chapters of Resistance Training and three chapters of Aerobic Training. Resistance Training is the use of resistance to muscular contraction to build strength, endurance, and size to the muscles involved. It also strengthens joints involved within the skeletal system. A beginner chapter, an intermediate chapter, and an advanced chapter will be designed for patients to have the option to advance as their bodies become more or less conditioned. Beginner level EXs will be a whole-body seated muscle fatigue chapter, the intermediate EXs will be a whole-body Thera-band bridge chapter, and the advanced chapter will be a whole-body calisthenics chapter.

The three Aerobic Training chapters will be similar in design to the Resistance Training chapters. Aerobic Training is various sustained exercises that stimulate and strengthen the heart and lungs, thereby improving the body's utilization of oxygen. A beginning chapter, an intermediate chapter and an advanced chapter will be designed. The beginning Aerobics Training chapter will be a seated program for the least conditioned patients. The intermediate chapter will be a bridge chapter for those patients where more strenuous aerobic training can be incorporated, and the advanced chapter will be a whole-body aerobics training chapter (consisting of a variety of gross motor movements; often rhythmical without equipment or apparatus) for patients with the most conditioned overall major muscle groups who can safely participate in whole-body aerobic training against gravity.

Each EX chapter will be designed with three core, three lower body, and three upper body EXs. Each EX within a chapter will last fifty seconds for a total of ten minutes for the EX portion of each chapter. An additional two and a half minutes of warm-up and cool-down at the beginning and end of each session will total one fifteen minute session (See Appendix I for EX schedule). The EX intervention is designed for patients to

gradually progress through the different EX chapters. Thus, patients can start at a level (e.g., chair EXs) that will likely be within their capabilities and provide a sense of accomplishment.

Each EX chapter will EX muscle groups in the following order: 1) lower body EXs, 2) upper body EXs and, 3) core strengthening EXs. Each muscle group will follow the order of largest muscle group to smallest muscle group. The EX chapters will follow a Recovery Program format in which larger muscle groups are exercised before smaller muscle groups to prevent fatigue and optimize adherence. The Whole-Body Recovery Program will ensure that the weakest or the most deconditioned muscle groups will have the chance to become reconditioned as all muscle groups (agonist and antagonist) are utilized. Engaging all major muscle groups simultaneously will strengthen all joints involved.

I.4 Demographic and Clinical Data Collection/Measures

Demographic and Medical Information

Demographic data obtained at time of consent will include race, age, gender, ethnicity, and pre-diagnosis exercise level prior to diagnosis. We will use age and baseline exercise level as covariates. Exercise levels will be determined by the exercise therapist based on the recommendations from the World Health Organization for children 5-17 which is seven hours per week of aerobic activity[76]. The therapist will ask the child about their pre-diagnosis activity level and record it on the physical assessment form. The categories will be as follows: below recommended level of activity, at recommended level of activity, and above recommended level of activity. All medical information (dates and doses of vincristine) will be collected by the study coordinator from the subject's medical records.

Vincristine-induced Peripheral Neuropathy

Total Neuropathy Score - Pediatric Vincristine (TNS-PV): The TNS-PV is a multidimensional instrument that will be used to measure peripheral neuropathy symptoms and signs in children from 5-25 years old receiving vincristine. Modified from the original Pediatric Total Neuropathy Score (Ped-TNS)[5], the instrument assesses proximal extension of numbness, tingling, and neuropathic pain, vibration and temperature sensation, strength, tendon reflexes, constipation (autonomic neuropathy), and hoarseness/voice (cranial nerve neuropathy) [77]. A multiplexed measuring system was developed that simultaneously ranks the 8-10 subjective and objective parameters. These parameters provide qualitative information on symptoms, nerve conduction and sensory tests on a scale of 0 for 'none' to 4 for 'severe'. The individual scores are added together to provide a single measure of neuropathy called a Total Neuropathy Score (See Appendix IV).

Total Neuropathy Score – Clinical Evaluation (TNSc): The best acknowledged method to assess the severity and changes in chemotherapy-induced peripheral neurotoxicity is through determination of the Total Neuropathy Score. The TNSc is an instrument that will be used to measure peripheral neuropathy symptoms and signs in young adults from 19-25 years old receiving vincristine. The TNSc (See Appendix V) consists of seven items with scores correlating significantly with the National Cancer Institute-Common Toxicity Criteria v. 2.0 ($p < 0.001$, $r^2 = 0.77$, $r = 0.88$, 95% confidence limits 0.849–0.914). With a test-retest coefficient of 0.86-0.87 (Academy of Oncologic Physical Therapy). The TNSc is more sensitive than the NCI-CTC 2.0 in detecting mild sensory damage because it detected changes in the range of 1–3 points even in 50% of those patients who were scored as unchanged using the NCI-CTC 2.0 score[78].

Pediatric Chemotherapy-Induced Neuropathy (P-CIN) Survey: the Pediatric Chemotherapy-Induced Neuropathy Survey (P-CIN) is a self-report measure of pain for ages 5-17. The P-CIN is designed to rate symptoms of CIPN (numbness, tingling and pain over the past 2-3 days). The P-CIN consists of 13 items for ages 5-17. Each of the 12 items is rated using the 6-point Faces Pain Scale (See Appendix VIII).

Neuropathic Pain

Pediatric Neuropathic Pain Scale (NPS) - Five: The Neuropathic Pain Scale (NPS) was designed to assess the distinct pain qualities associated with neuropathic pain. The NPS consists of 5 items which are rated on a scale of 0 to 10 (0="no pain" to 10="severe pain"). Each question examines an individual aspect of pain and is measured independently[15]. The rating scale is based on the Faces Pain Rating Scale – Revised (FPS-R) which is a self-report measure of pain intensity that was developed for children[79] (See Appendix VII and VIII).

The NCI Common Terminology Criteria for Adverse Events (CTCAE) V4.02: This scale grades adverse events occurring after chemotherapy in cancer patients and explores the quality of life (QOL) findings among post therapy cancer patients. The NCI CTCAE is a descriptive terminology that can be utilized for pain (Appendix IX) reporting and is required to be completed for all cancer studies[80].

Quality of Life

Pediatric Quality of Life Inventory (PedsQL 4.0): The PedsQL is a modular approach to measuring health-related quality of life in healthy children and those with acute and chronic health conditions. The PedsQL integrates generic core scales and disease-specific modules into one measurement system (Appendix X). The 23-item PedsQL generic core scales and disease-specific scales were designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning. For the purpose of this study, we will only be utilizing the generic core scales section of the inventory. This measure is tailored to 5 different age groups: toddlers (2-4); children (5–7); children (8-12); teens (13-18); and young adults (18-2). The Child and Parent Reports (ages 5-7), Children (ages 8-12) and Teens (ages 13-18) are made up of 23 items comprising 4 dimensions: Physical functioning; Emotional functioning; Social functioning, and School functioning. Patient participants will complete the child-report questionnaire, and their parents will complete the parent-report version (See Appendix X).

Ferrans & Powers Quality of Life Index: Total quality of life will be measured using the Ferrans and Powers Quality of Life Index Version III and is a 66-question index designed to evaluate social, psychological, family, and health satisfaction (See Appendix XI). This assessment is valid for ages 19 and above. Higher scores indicate greater satisfaction in quality of life with an internal Cronbach's alpha of 0.93[81].

Social Learning Theory Questionnaire

Self-Efficacy: There is currently no exercise self-efficacy scale for children and AYA's with cancer. We have adapted the Bartholomew physical activity self-efficacy scale for children and AYA's for use in our study[82] We have adapted the original self-efficacy scale by adding two questions that are specifically neuropathy related and replaced the term exercise where physical activity had been used. Responses to the questions are limited to Yes/No and not applicable. (See Section 1 Appendix XII).

Support: The support module was taken from a larger validated scale developed by Liang et al (2014) which measures physical activity self-efficacy, enjoyment, and exercise social support for children[83]. The support section of the questionnaire consists of 10 questions rated on a 5 point scale from None to Very often. The items assess support children and AYA's receive from parents and peers to facilitate exercise. We have adapted the term physical activity to the term exercise for this study (See Section 2 Appendix XII).

Outcome Expectations: We adapted an existing exercise outcomes expectations questionnaire from the adult literature for the purposes of our study. The survey consists of 10 items targeting exercise outcome expectations. Patients are asked to rate each item on a 5 point scale. Items were edited for developmental level/appropriateness[84]. (See Section 3 Appendix XII)

Physiological Parameters

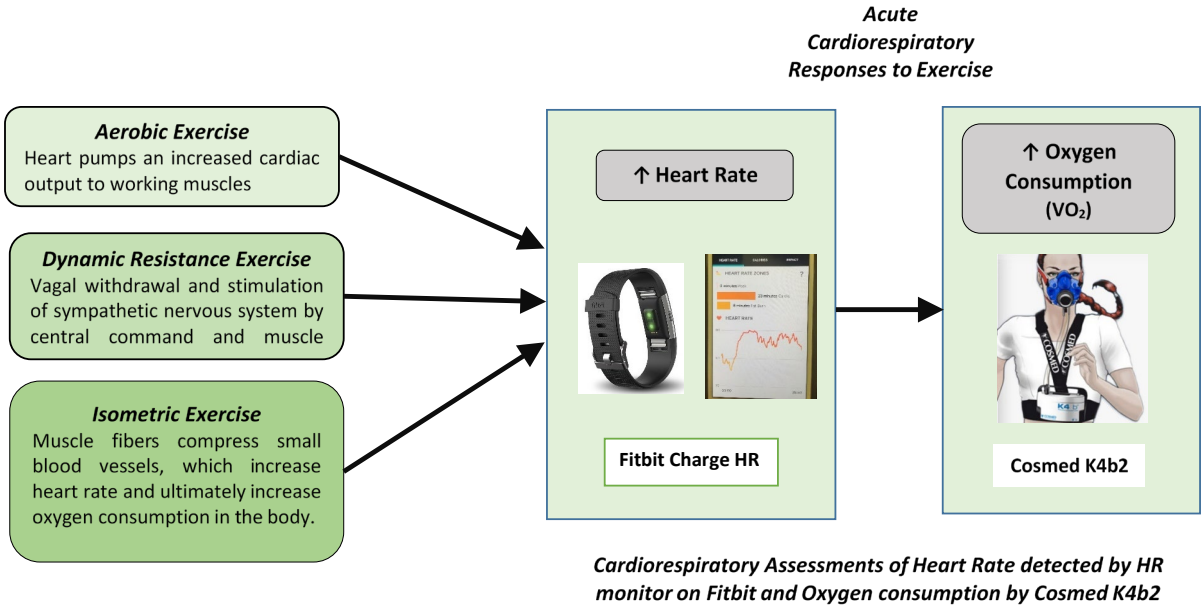
Fitbit activity tracker: All patients will be instructed to wear their Fitbit activity trackers every day during waking hours throughout the intervention period. The Fitbit activity tracker (specifically the Charge 2) has a five-day battery life and an "always-on" heart rate tracking system. It is an accelerometer that is worn like a small wristband and records data on movement (steps, HR, distance and activity), total activity minutes, heart rate and total minutes of inactivity including sleep. The data is stored on the device and then can be downloaded wirelessly to a computer [75].

An integral component of wearable activity trackers, such as Fitbit, is the automation of real-time physical exercise tracking and heart rate [85]. The Fitbit activity tracker builds upon pedometer-based activity interventions with a more sophisticated interface using the Internet or a mobile application. This allows for the implementation of behavioral change techniques, tailoring of goals, tracking of progress and documenting adherence to home-based EX protocol with minimal use of resources [85,86]. There is an exercise study which shows that children wearing Fitbits use them to self-regulate and as a result increase their activity levels as shown by an increase in their overall steps[64].

Even though the EX sessions are not purely aerobic EX, the Fitbit can detect increases in heart rate during these sessions. Specifically, the EX sessions include aerobic EX, dynamic resistance training, and isometric EXs and thus, will rely on both aerobic and anaerobic energy sources. During aerobic components of the program, the heart must do more work to pump an increased cardiac output to working muscles, and heart rate generally increases in a linear fashion to increases in EX intensity. Heart rate increases during dynamic resistance EX will be due initially to vagal withdrawal and then stimulation of sympathetic nervous system by central command and from muscle chemo and mechanoreceptors. During isometric EX, muscle fibers compress small blood vessels, preventing new oxygen-laden blood from reaching affected muscle tissue. Thus, as long as the muscle contraction is maintained, heart rate will steadily rise. Therefore, detectable elevations in heart rate are expected during EX sessions, albeit through several different mechanisms. Although the immediate effect of isometric exercises is to inhibit blood flow and therefore oxygen to the muscles, the long-term effects are vasodilation, thus an increase in oxygen. In addition, isometric exercises help maintain strength of the muscles and enhance stabilization. These types of exercises are often included in rehabilitation situations and therefore can contribute to improving neuropathy[87].

Six Minute Walk Test: The Six- minute walk test (6MWT) is used to assess subjects' functional exercise capacity. This assessment will be conducted by an exercise professional during week 7 (T1) and week 15 (T2) physiological assessments. The 6MWT will be conducted following the American Thoracic Society Guidelines [88] and our standard operating procedures. Subjects will be asked to walk as far as possible for 6 minutes. They will be assessed on how far of a distance is walked over the course of these six minutes. Subjects will be allowed to slow down, stop and rest as needed. They will be asked to resume walking with they are able. This assessment will be performed at all sites.

Romberg Balance Test: The Romberg Balance is an assessment of the subjects balance and proprioception[89]. The patient will be asked to remove their shoes, stand with their feet together, arms held to their side or crossed in front of their chest. They will be asked to stand quietly with their eyes open and subsequently with their eyes closed. The assessor will maintain close proximity to the subject in case there is a loss of balance. Subjects will then be asked to stand heel to toe with one front directly in front of the other. Similar to the first portion of the test patients will be asked to perform this assessment with eyes open and eyes closed. Subjects will be assessed by counting the second they are able to maintain balance.



Cardiorespiratory Assessments of Heart Rate detected by HR monitor on Fitbit and Oxygen consumption by Cosmed K4b2

The baseline Standardized Fitness Assessment: The fitness assessment will evaluate the general health and physical characteristics of each patient (See Appendix XIII). Specifically, data will be collected regarding height, weight, resting heart rate, blood pressure, body composition (ratio of lean body mass to fat mass), lower back and hamstring flexibility, aerobic fitness and physical strength. All tests will be age appropriate. This information will be used to determine the initial exercise level most appropriate for the subject to begin the intervention study.

Adherence

Adherence will be measured by self-report of session completion (See Appendix III) and activity tracking via FitBit. All participants will be asked to fill out a short 5 question survey following their EX session regarding their workout, energy level, food intake, and sleep quality. Parents will be asked to initial and review the questions and add any additional comments they feel would be helpful for us to know. The Daily Log is designed not just to aid the child in planning and goal setting, but also to give parents an opportunity to provide positive reinforcement for the child's daily exercise. The patients will also be asked to hit a start EX button on the FitBit at the beginning of the intervention which shows that they have started the video and then hit it again upon completion. The instructor in the video will prompt the child to start and stop their FitBit as a reminder.

Acceptability

Patient Satisfaction Survey: This satisfaction survey was adapted from an existing exercise intervention satisfaction survey [90]. The satisfaction survey consists of 13 items, and they will be asked to respond to each item using a 5 point scale. Patients will provide feedback on the exercise program, exercise videos and therapist support. There is also an open response question for additional feedback (See Appendix XIV).

Parent Satisfaction Survey: Parents will also be asked to complete a satisfaction survey regarding the exercise program, exercise videos, and therapist support. To assess the satisfaction of the parents/caregivers of pediatric cancer patients (peripheral neuropathy symptoms) while participating in an exercise intervention during the Consolidation Phase of chemotherapy[90]. The satisfaction survey consists of 13 items, and they will be asked to respond to each item using a 5 point scale. (See Appendix XV)

Domain, Measurements and Schedule for Study Outcomes

Domain	Measure	# Items	Schedule	
			T1	T2
Predictors				
Demographics	Gender, age, race/ethnicity, pre-diagnosis exercise level		**X**	
Medical Characteristics	Neuropathy, Weight, ALL/LL diagnosis		**X**	
Physical Functioning	Baseline Standardized Fitness Assessment	**13**	**X**	
Self-efficacy	SLT Exercise Questionnaire	**10**	**X**	
Outcome Expectations	SLT Exercise Questionnaire	**10**	**X**	**X**
Support	SLT Exercise Questionnaire	**10**	**X**	**X**
Primary Outcome				
Feasibility	Percentage of subjects that can complete the 8-week intervention FitBit data Daily Log	**6**	**Weeks 6-13**	
Acceptability	Patient Satisfaction Survey Parent Satisfaction Survey	**13** **13**		**X**
Secondary Outcomes				
Physical Activity				
Total Activity Time during study	FitBit Tracker Daily Log	**8**	**Weeks 6-13**	
Heart Rate	FitBit Tracker	**NA**		
Exercise	Fitbit Tracker Daily Log	**8**		
Biomarkers				
Germline DNA Chemerin levels PDGF-BB levels IL-13 levels GAP 43 Synapsin NGF	Blood Draw	**NA**	**X**	**X**

Neuropathy				
	NCI CTCAE Version 4.02	**2**		**X**
	Total Neuropathy Score - Pediatric Vincristine (TNS-PV)	**25**	**X**	**X**
	Total Neuropathy Score - Clinical (TNSc)	**7**	**X**	**X**
Pain				
	P-CIN Pediatric Chemotherapy-Induced Neuropathy Patient Reported Outcome	**13**	**X**	**X**
	Pediatric Neuropathic Pain Scale - Five	**6**	**X**	**X**
Quality of Life				
	Peds QL V4 Scale	**23**	**X**	**X**
	Ferrans and Powers	**66**	**X**	**X**

I.5 Blood Sample Collection

This study will include collection of a minimum of 15 mL of whole blood at 2 time points: baseline or pre-intervention (week 6) and post-intervention (week 14). Blood samples will be stored at -80°C until analysis for germline DNA, chemerin levels, NGF, SNAP1, GAP43 and cytokines PDGF-BB and IL-13. Whenever possible, blood will be drawn at the same time as blood is drawn for routine clinical purposes. Blood will always be drawn by trained technicians. Please refer to the Laboratory Manual for this study for blood collection, processing, transfer and storage instructions.

I.6 Data Processing and Storage

Survey Data: All survey study data collected will be stored in the Research Electronic Data Capture (REDCap) database. REDCap is managed through the Department of Biostatistics in the Indiana University School of Medicine. Access to the password-protected database will be limited to study personnel, and any data shared outside of the study team will be de-identified prior to distribution.

Fitbit Data: The Fitbit data will be automatically imported to a Fitbit application on the company's secure server and then uploaded automatically to an excel file. The data will be downloaded weekly to a password protected master excel file folder stored on a university secured server and managed by the Bioinformatics core (See human subjects section for further details). All physiological measures: Heart Rate, Steps, Distance and Activity, will be captured using the Fitbit Charge HR.

OnCore®: Individual patient registration will be done in the OnCore® database. All protocol deviations, study status updates (IRB approval, open to accrual, etc.), IRB approvals, current protocol and consent, and any serious adverse events should they occur. The OnCore® database is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. OnCore® was developed by Forte Research Systems, Inc. and is used by the IUSCC Clinical Trials Office (CTO) and supported by the Indiana Clinical and Translational Sciences Institute (CTSI). OnCore® properly used is compliant with Title 21 CFR Part 11.

OnCore® provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IUSCC Data Safety Monitoring Committee (DSMC).

I.7 Treatment fidelity

Treatment fidelity will be ensured by instruction from the Ex therapists at the initial study visit, every other week check-in sessions, and home practice with the exercise videos. At check-in sessions, therapists will review Exs with participants and instruct them in new Exs. Further, videos are tailored to participant age and level of physical functioning. All EXs will be prescribed by the Ex therapist using the Karvonen Formula. The Karvonen Formula is a mathematical formula that helps you determine your target heart rate (HR) training zone. This formula uses maximum and resting heart rate with the desired training intensity to determine a target heart rate zone.

Treatment Fidelity Focus	**Description of Treatment Fidelity Indicators**
Design	The intervention was developed based on Social Learning Theory with main construct focus on self-efficacy.
Training	The therapists are trained exercise professionals. They are designing and leading the EX program and will perform all individual exercises together to ensure agreement of the performance expectation. One or both therapist will train the children and AYA's who will demonstrate the exercise on the video.
Delivery	Each participant will receive a video of the exercises that are age appropriate and are suitable to their physical abilities. The videos will allow for a standardized intervention delivery for each subject.
Receipt	Each participant will wear a Fitbit and upon starting the EX session will click the button on the side of the device to record the activity. All subjects will be reminded to start and stop their Fitbits by the children and AYA's demonstrating the exercises on the video. All data from the Fitbit is collected via Fitabase (secure data site). There is also a pre and post survey each participant completes prior to and after their session (8 questions in total). The parent may add comments to the survey if they desire, but their initials are required.

I.8 Compensation for Participation

Upon completion of the study, each subject will get to keep the Fitbit device that has been utilized for physical and aerobic training tracking. Upon completion of this study a small end-of-study token in appreciation of the study participant's participation may be given.

J. DATA ANALYSIS

J.1 Baseline Analysis

Baseline analysis. Baseline demographic characteristics as well as baseline general health and physical characteristics will be summarized for all patients. Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) will be provided for all continuous variables and frequency and percent will be provided for all categorical variables. All continuous scale outcomes will assessed for normality. If normality does not seem plausible for a given outcome, than Wilcoxon-signed rank tests will be used. Additionally, to examine reasons for attrition, baseline measures will be compared between patients that complete the intervention and those that do not. Continuous measures will be compared with a t-test or Wilcoxon-rank sum test and categorical variables will be compared using a Chi-square test or Fisher's exact test.

J.2 Aim 1 & 2 Analysis

To address Aim 1, adherence in the intervention group will be measured through a 5 question survey at each treatment and also through start/stop on the Fitbit. Adherence scores will be summarized across time with descriptive statistics (N, mean, SD, median, minimum, and maximum). From start/stop information, the proportion of exercise sessions completed and the proportion of patients which complete at least 50% of the exercise sessions along with associated 95% confidence intervals will be estimated. Additionally, descriptive statistics will be provided for the patient satisfaction survey provided at the end of the study.

To address Aim 2, we will use paired t-tests to examine change from baseline (T1) to 14 weeks (T2). For outcomes which are known to be non-normal such as biomarkers, we will use Wilcoxon-signed rank tests. We plan an intent-to-treat analysis. Even if we do not see significant differences, descriptive statistics including means, SD, and effect sizes (differences in means between the two time points divided by pooled SD) will be reported for outcomes along with 95% confidence intervals. All analysis will include checking of assumptions. Additionally, we will also use repeated measures ANOVA to estimate the contrast of interest (change from baseline at 14 weeks) for primary and secondary outcomes, after adjusting for age and baseline activity level.

For activity outcomes obtained from the FitBit, such as patients' daily number of steps, distance, active minutes, and heart rate, we will start with simple techniques such as paired t-tests or Wilcoxon signed-rank tests to compare the mean change in activity level from baseline (T1: summarized over week 6) to treatment end (T2: summarized over week 13). As an exploratory analysis, we will also use a generalized linear mixed model with appropriate distribution (e.g. Poisson) and link function fit to all weekly outcomes to examine changes over time using time as a continuous variable. We expect to have an abundance of information provided from the Fitbit, thus we will estimate descriptive statistics (N, mean, SD, median, minimum, and maximum) for all outcomes (i.e., number of steps, distance, active minutes, and heart rate) at each week to aid in planning future studies.

Based on our conceptual model, we will also examine associations between change scores for predictors and change scores for primary and secondary outcomes. For example, we will estimate Pearson correlations between changes in self-efficacy, outcome expectations, support, neuropathy, pain, and quality of life.

We will also examine whether or not the circulating protein biomarkers at T1 are associated with VIPN severity at T1 using Spearman correlations and whether initial or dynamic levels of the circulating biomarkers are predictive of intervention efficacy. The associations between VIPN and the genetic and circulating biomarkers will be analyzed through generalized linear mixed models, which includes a random subject effect to account for the correlation of observations from the same subject.

J.3 Missing Data

We expect minimal dropout at 14 weeks (primary endpoint for the proposed trial) and have inflated the sample size to account for the expected 15% attrition, so we anticipate it will not create any substantial bias in the results. To aid in future studies, we will compare baseline characteristics among those who complete the study and those who do not to determine if there are any characteristics associated with study completion.

K. RISKS OF PARTICIPATION AND PROTECTION OF HUMAN SUBJECTS

K.1 Risks

Possible risks to participation in this study are breach of confidentiality, physical distress or emotional distress due to study participation. All contact with the participant will be documented beginning at the consent process through completion of the study. All documentation will be reviewed regularly. Any events that might indicate increased participant physical distress or emotional distress will be promptly brought to the attention of the PI and reported to the IRB and DSMC per reporting guidelines listed below. We will promptly report to the IRB any instances of consent withdrawal due to distress. The IRB will be informed at least annually of our data and safety monitoring, summary of participant status, and any changes in the risk of the study.

Prevention of injuries have been addressed through 1) video design, 2) safety reminders during videos and fitness assessment and 3) muscle soreness. The video design is based on a specific gradual workout design to ensure safety for the most deconditioned patients. The study has incorporated beginner (seated or bed), intermediate (bridge between beginner and advanced) and advanced EX chapters.

Reminders of safety will be discussed during the fitness assessment and also incorporated into all videos. The reminders will address proper footwear, proper clothing, workout areas clear of objects, availability of water bottle, ensure someone else is in the house while exercising, finally, if experiencing dizziness, chest pain or injury to stop immediately and tell a parent. Treatment for muscle soreness is to 1) not skip the warm-up or cool down sections of the video, massage the affected muscle groups or soak in a warm tub.

Any injury will be reported per the study guidelines. Video reminders for injury will include 1) knowing where the First Aid Kit is located, 2) knowing where the closest phone is, 3) always reporting an injury to the parent/care-giver and in case of severe injury to dial 911. Each patient and parents will have the phone number to both of the study therapist's to answer any questions. In general, exercise does not provoke cardiovascular events in healthy individuals with normal cardiovascular systems. The risk of sudden cardiac arrest or myocardial infarction is very low in apparently healthy individuals performing moderate intensity, physical activity (Ref. ACSM's Guidelines for Exercise Testing and Prescription, Ninth Edition, 2014, p. 9, Chapter 1, Section: Risks Associated with Exercise).

K.2 Protection

The following measures will be implemented to protect participants against these risks:

All personnel will be trained in the importance of and measures to protect patient confidentiality. Several measures will be taken to protect patient confidentiality. One measure will be assigning each participant a unique 6-digit identification number and using this number to identify the participant on all data collection forms. All data collected from participants will be kept separate from identifying information by the use of this unique identification number. Any information collected on paper forms or by phone will be entered into the REDCap database by a study team member. The paper forms will be filed in a locked file cabinet in the locked office space of the PI or project manager at Riley Hospital. Only those study team members who need access to this information will be allowed by the PI or project manager.

Analyses will include only summaries of data; personal identifiers will be excluded. All personnel who are involved in the design or conduct of this research will have demonstrated successful completion of human subjects training.

Since this study involves a very large amount of data to be collected from the Fitbit tracker, we have put procedures in place to ensure the integrity of the data transmitted and to allow consistent handling of the clinical data. The Bioinformatics Core team at Indiana University has developed a web-based platform for the collection, integration, analysis and dissemination of both the clinical and biomarker data. The platform provides a framework for the collection of biomarker data (i.e. cytokines and chemerin levels), the collection and the analysis of the data. The web-based platform is easy to use with all the necessary securities to protect the confidentiality and integrity of the data. All data are stored in a deidentified/HIPAA compliant manner. The platform is developed using the Linux-Apachedcmx,m, xz-MySQL-PHP platform and CakePHP. This platform is widely used across the Internet. Security is obtained by encryption (SSL).

K.3 Reporting to the IRB

1. Unanticipated problems involving risks to subjects or others will be reported promptly to the IRB if they:

- unexpected;
- related or possibly related to participation in the research; and
- suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it will be reported at the time of continuing review.

2. Prompt reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

K.4 Reporting to the IUSCC Data Safety Monitoring Committee

Regardless of study sponsorship, the study team must enter all initial and follow-up SAE, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or coordinator. Expedited reports may include IRB Prompt Report Forms and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is in addition to any other regulatory bodies to be notified (i.e. IRB, FDA, pharmaceutical company, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly.

IUSCC Data Safety Monitoring Plan (DSMP)

Investigators will conduct continuous review of data and patient safety. **Quarterly review meetings** for low risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Quarterly** meeting summaries should include review of data, the number of patients, significant toxicities as described in the protocol, and responses observed. Summaries will be submitted quarterly and reviewed by the DSMC for review. Submit to DSMC@iupui.edu.

Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing/monitoring. Reports will be forwarded to the DSMC for review.

Early Study Closure

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the Data Safety Monitoring Committee. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review of the investigator reports.

Reporting Guidelines

The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed direct view of reports within the Clinical Trials Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore® and reviewed by the DSMC chair and/or coordinator monthly.

Study Accrual Oversight

Accrual data will be entered into the IU Simon Cancer Center OnCore® system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.

Protocol Deviations

Protocol deviations are entered into OnCore® and reviewed by the DSMC chair and/or coordinator monthly.

L. STUDY WITHDRAWAL/DISCONTINUATION

Criteria for removal from the study are as follows:

- The participant expresses significant distress related to completion of the study (the PI will refer the participant to clinical services if needed).
- The participant provides verbal or written notification that s/he has decided to discontinue study participation.

Any other reason for which the principal investigator believes the participant should be withdrawn.

M. PATIENT CONSENT AND PEER JUDGEMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

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O. APPENDICES

All appendices listed below can be found in a separate PDF document.

APPENDIX I – Exercise Schedule

APPENDIX II – Exercise Video Outline

APPENDIX III – Daily Exercise Log

APPENDIX IV – Neuropathy: Total Neuropathy Score (TNS-PV)

APPENDIX V – Clinical Total Neuropathy Score (TNSc)

APPENDIX VI - Pediatric Chemotherapy-Induced Neuropathy Patient v4 (P-CIN) Survey

APPENDIX VII – Pediatric Neuropathic Pain Scale Five

APPENDIX VIII – Pain: FACES Pain Rating Scale

APPENDIX IX – Adverse Events: NCI CTCAE V4.02

APPENDIX X – Quality of Life: Pediatric Quality of Life Inventory: Peds QL Scale 4.0

APPENDIX XI – Ferrans and Powers Quality of Life Cancer v3

APPENDIX XII - Self-efficacy, Support and Outcome Expectations Questionnaire

APPENDIX XIII – Standardized Fitness Assessment

APPENDIX XIV – Patient Satisfaction Survey

APPENDIX XV - Parent/Care Giver Satisfaction Survey