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CHILDREN'S ONCOLOGY GROUP

ALTE1631

A Randomized Web-based Physical Activity Intervention among Children and Adolescents with Cancer

A Group-wide Protocol

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The most current version of the **study protocol** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (ie, patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (ie, unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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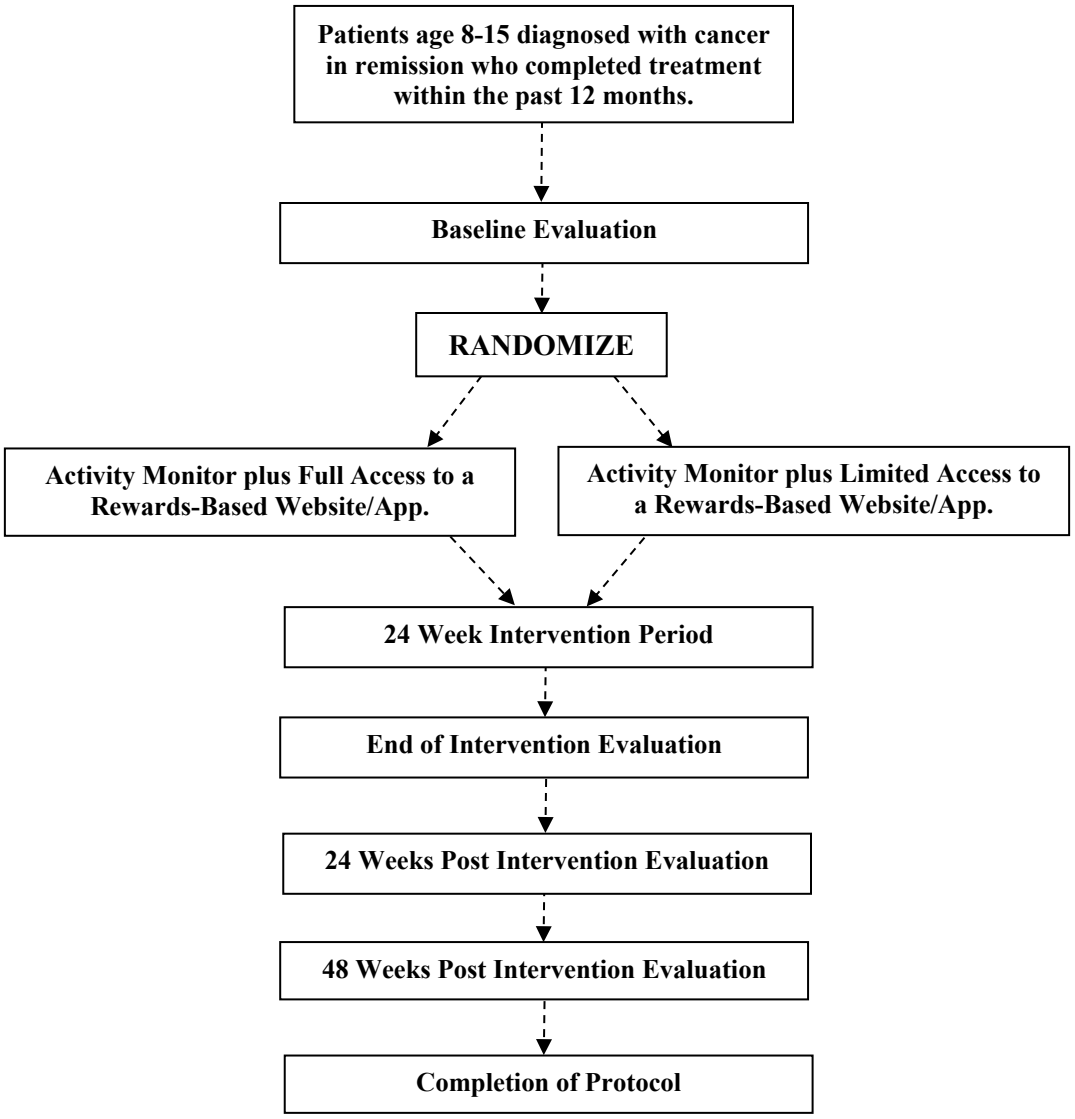
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ABSTRACT

The five year survival rate among children diagnosed with cancer has surpassed 84%. Unfortunately, cure is not without consequences. Childhood cancer survivors are at elevated risk for obesity, low bone mineral density, cardiomyopathy, peripheral neuropathy, and altered psychosocial functioning. Research is critically needed to provide survivors with tools to improve their long term health. Children with cancer are likely to adopt a sedentary lifestyle that persists long into survivorship, and a sedentary lifestyle may perpetuate or exacerbate many of the complications experienced by survivors. Therefore, a portable and generalizable intervention that promotes physical activity and impacts fitness and biomarkers of cardiometabolic health in the first year after treatment may be of particular benefit. The primary goals of this study are to evaluate the effects of a 6 month long rewards-based physical activity intervention on fitness, biomarkers of cardiometabolic health, inflammation, adipokine status, quality of life and school attendance. The study plans to evaluate if the effect of the intervention on markers of cardiometabolic health is mediated by changes in fitness. To achieve this goal the study will utilize a two-arm, prospective, randomized study with an intervention group (N=192) and a control group (N=192). Both groups will receive educational materials encouraging physical activity, including information about activity modifications for common neuro-musculoskeletal deficits (e.g. neuropathy, weakness), and a physical activity tracking device to record physical activity levels and access to a web-based physical activity intervention designed to motivate increased levels of physical activity. Individual physical activity levels are uploaded from the device to the website. Both groups will receive rewards based on physical activity levels. Credits are a type of reward that can be earned to receive small gift cards or monetarily equivalent prizes. Only the intervention group will receive additional details about how to earn this type of reward. Other rewards and encouragement are provided by the website based on the participants' measured physical activity levels. Children who are initially less active still earn rewards as the system is based on individual baseline physical activity. The intervention group will receive full access to a rewards-based interactive website. Full access allows those randomized to the intervention group to interact with other participants. The control group will receive limited access to the same website. The control group will be limited to only see themselves and their own progress. The intervention participants will receive gift cards or prizes during the course of the intervention period. The control group will receive all earned gift cards or prizes at the end of the intervention period. Evaluation time points are planned at baseline, at the end of the 6 month intervention, 6 and 12 months after the end of the intervention.

EXPERIMENTAL DESIGN SCHEMA



1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To compare the effects of a rewards-and web-based physical activity intervention that includes structured social interaction between participants to the same web-based physical activity intervention that does not include structured social interaction on fitness among children and adolescents following treatment for cancer.

1.2 Secondary Aims

1.2.1 To evaluate the effect of a rewards-based, socially interactive, web-based physical activity intervention on markers of cardiometabolic health among children and adolescents following treatment for cancer (compared to the same web-based physical activity intervention without social interaction).

1.2.2 To evaluate the effect of a rewards-based, socially interactive, web-based physical activity intervention on physical activity, quality of life, fatigue, and school attendance among children and adolescents following treatment for cancer (compared to the same web-based physical activity intervention without social interaction).

1.2.3 To determine if the effect of a rewards-based, socially interactive, web-based physical activity intervention on markers of cardiometabolic health is mediated by changes in fitness among children and adolescents following treatment for cancer (compared to the same web-based physical activity intervention without social interaction).

2.0 BACKGROUND AND HYPOTHESIS

2.1 Introduction

2.1.1 Summary

The five year survival rate among children diagnosed with and treated for cancer has surpassed 84%, with a resultant increase in the population of survivors.[1] Unfortunately, cure is not without consequences. ALL survivors are at elevated risk for obesity, low bone mineral density, cardiomyopathy, peripheral neuropathy, and altered psychosocial functioning.[2-6] To date, most studies have focused on documenting these late effects rather than on evaluating interventions with potential to prevent or remediate these problems. Research is critically needed that provides survivors with tools to improve their long-term health.

2.1.2 Physical Activity and Chronic Disease

Suboptimal physical activity is associated with long-term health problems among childhood ALL survivors, and may be either the cause of or the result of cardiopulmonary compromise and musculoskeletal impairment.[7] Loss of lean muscle mass,[8-10] chemotherapy-induced gastrointestinal toxicity,[11] and fatigue[12,13] during treatment may precipitate early reduction of physical activity,[14] creating an

inactivity habit that perpetuates early problems and leads to a sedentary lifestyle. Survivors of childhood cancer are at increased risk of musculoskeletal problems,[15] obesity,[15] metabolic syndrome,[16] and cardiovascular disease,[17,18] all of which are chronic health conditions more common in physically inactive persons. Childhood cancer survivors are also less likely than their siblings to meet recommended physical activity guidelines (46% vs. 52%) and more likely to lead an inactive lifestyle.[19] Among childhood cancer survivors, an inactive lifestyle increases the risk of developing hypertension, dyslipidemia, diabetes, and obesity by almost 70%.[20] Additionally, cancer survivors are 4.2 times more likely to die of a cardiac event than members of the general population.[21]

2.1.3 Fitness

Impaired cardiopulmonary and musculoskeletal fitness have been reported among children during or following treatment for cancer. Much of this work has been done in survivors of Acute Lymphoblastic Leukemia (ALL). For example, San Juan et al[22] compared cardiopulmonary fitness among 15 children with ALL during maintenance chemotherapy to age- and sex-matched controls. Children with ALL had a mean peak oxygen uptake deficits of 6.6 ± 6.7 mL/kg/min. Warner et al[23] reported lower mean peak oxygen uptake among male (7.7 mL/kg/min) and female (10.8 mL/kg/min) survivors of leukemia when compared to siblings. Van Brussel et al[24] verified these findings in a meta-analysis that included 102 ALL survivors and 99 controls. ALL survivors had a mean decrease in exercise capacity of 6.0 ± 12.4 mL/kg/min, 13% lower than expected. Marchese et al[25] reported decreased knee extension and ankle dorsiflexion strength among a group of 5-14 year old children during treatment for ALL, and Wright et al[26] reported decreased overall and hand grip strength in children one plus years after treatment for ALL. Two additional studies have also reported strength deficits among young adult survivors of childhood ALL.[27,28] In our recently published study (R01CA132901) of physical performance outcomes, we also evaluated cardiopulmonary fitness and muscle strength among young adult survivors of childhood ALL, 60% of whom were not exposed to cranial radiation. Survivors had peak oxygen uptake values 3.4±7.2 mL/kg/min ($p < 0.001$) and peak quadriceps torque values 31.8±59.4 Nm/kg ($p < 0.001$) lower than age-, sex-, and race-matched controls (N=365).[29] However, ALL survivors are not the only diagnostic group at risk for poor fitness. A recent meta-analysis of 16 papers, including 1413 pediatric cancer survivors of varying diagnoses and 1215 non-cancer controls reported that both physical activity and fitness were lower in survivors than in controls (g=-0.889; 95% CI-1.648-0.130, p=0.022 and -1.435; 95% CI -2.615-0.255, p=0.017).[30]

2.1.4 Metabolic Syndrome, Inflammatory Biomarkers, Adipokines

Long term survivors of childhood cancer are at increased risk for symptoms of metabolic syndrome including obesity, insulin resistance, glucose intolerance, hypertension, and dyslipidemia.[16] Among 1598 adult survivors of childhood cancer (median age, 32.7 years), 31.8% met criteria for the metabolic syndrome, most commonly hypertension (53.0%), elevated fasting glucose (38.2%) and low high density lipoprotein (HDL) (38.2%) among males, and low HDL (42.6%), increased waist circumference (42.6%) and hypertension (40.6%) among females. Pluimakers et al recently published a review describing the components of, and risk factors for, metabolic syndrome among childhood cancer survivors, indicating that cranial, abdominal or total body radiation exposure, higher body mass index

at diagnosis, development of growth hormone or gonadal deficiency, and inactivity were the most common risk factors.[31]

In addition, evidence indicates that some children treated for cancer have elevated levels of inflammatory biomarkers, adipokines, and early evidence of vascular disease soon after treatment,[32] and into survivorship.[33,34] One group of authors reported higher levels of highly sensitive C-reactive protein and leptin among ALL survivors (N=74, median age 15 years, 49% female) with ≥ 2 metabolic syndrome components when compared to those with < 2 metabolic syndrome components,[35] and another group reported higher fat mass and corresponding increased circulating leptin levels among 49 male ALL survivors (median age 39 years) compared to age matched healthy controls.[36] Heikens et al reported both an altered metabolic profile (elevated systolic blood pressure, altered body composition and unfavorable lipid profiles) and a larger carotid intima-media thickness among survivors of childhood onset central nervous system tumors (N=26, mean age 25.8 years) when compared to healthy controls.[37]

2.1.5 Fatigue and Quality of Life

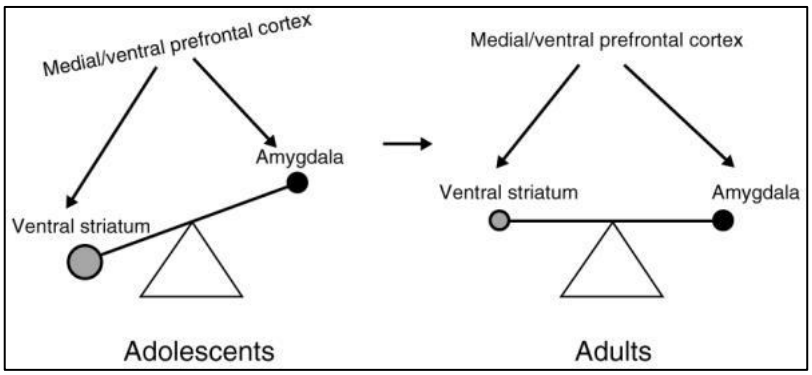
Increased fatigue, diminished ability to participate in everyday tasks, and reports of poor health related quality of life are also reported by children with cancer during and after treatment.[38,39] Sung et al reported reduced physical health related quality of life among 27% of 206 children in first remission and during treatment for ALL,[40] and van Listenburg et al reported sleep associated reductions in quality of life among seventeen children during maintenance therapy for childhood ALL.[39] A systematic review of symptoms reported by children during treatment for cancer indicated that over half (51%) of children report lack of energy.[41] The rates of fatigue and poor quality of life measured with the mental component summary of the SF-36 among long term survivors of childhood cancer are estimated at 16.1%[38] and 20.2%[38], respectively.

2.1.6 Exercise Interventions among Children with and without Cancer Diagnoses

Physical activity interventions may be able to stimulate habitual physical activity, improve cardiopulmonary and musculoskeletal function, normalize metabolic biomarkers, decrease fatigue, and improve quality of life and school attendance if initiated soon after treatment for childhood cancer.[42-46] A recent literature review (15 studies, 302 participants) of exercise interventions among children during treatment or soon after treatment for childhood cancer indicated that exercise can influence cardiopulmonary fitness,[47] muscle strength,[48] and fatigue[49] in children with or who have survived cancer. Unfortunately, none of the studies in this review evaluated the effects of exercise interventions on levels of habitual physical activity or metabolic health. However, in general pediatric and adolescent populations, exercise interventions are associated not only with improved cardiopulmonary fitness,[50] musculoskeletal health,[51] and vitality,[52] but also with increased levels of habitual physical activity,[53] and improved metabolic function[54,55] and an improved inflammatory and adipokine profile.[56,57] Vanhelst et al[53] reported increased levels of habitual physical activity after a 12 month weekly physical activity intervention among 37 young adolescents who were obese, and Carrel et al[54] reported improved body composition and insulin sensitivity among 35 normal weight middle-school-aged children after a nine month exercise intervention. We based the length of our planned intervention on a review of nine

information and communication technology based interventions designed to improve physical activity levels among children and adolescents. The authors reported study durations ranging from 2 weeks to 2 years.[58] The intervention with the largest effect size (0.8 for boys, 1.2 for girls) used an activity monitoring device (pedometer) and was six months in length.[59]

2.1.7 Neurobiological and behavioral support for our proposed intervention



The use of an intervention that provides tangible, but nominal rewards (points, access to internet games and on-line applications) to encourage physical activity is supported by the theoretical work of Ernst[60] who describes a Triadic Neural Systems Model of motivated behavior. Cognition and affective development among older children and adolescents requires the interaction of neural systems that mediate threat, reward and cognitive control. The rewards system includes dopaminergic neurotransmission sites (striatum, medial/orbital prefrontal cortices); the threat system emotional regulation sites (amygdala, hippocampus and insula); and the control system cognitive control sites (prefrontal areas that encode inhibition/monitoring/conflict detection & resolution).[61] Functional neuroimaging indicates that rewards[62-64] and threat systems[65-67] follow a curvilinear developmental trajectory, and are most sensitive during older childhood and adolescence. Control processes mature linearly with age.[68,69] This results in an unbalanced system among older children and adolescents whose physiology initially favors reward seeking behaviors. Thus, when learning or gaining a new behavior older children and adolescents are first guided by extrinsic motivators. Fortunately, theory also indicates that once a child/adolescent begins to experience success with the new behavior (physical activity), it becomes more enjoyable and the need for extrinsic rewards decreases.[61] Initial success promotes a sense of competence; activity choices foster autonomy. With increasing competence and autonomy, the child/adolescent begins to establish their own activity goals, gaining intrinsic satisfaction from personal accomplishment. The transition from extrinsic rewards to enjoyed behavior should foster adoption and persistence of this new behavior over time.[70]

2.1.8 Physical Activity in Late Childhood and Adolescence among Childhood Cancer Survivors

We have completed a pilot study of the proposed intervention in adolescent survivors at two sites (St. Jude Children's Research Hospital (SJCRH) and Yale University). The pilot compared changes in weekly moderate to vigorous physical activity (MVPA) between an intervention (activity monitor plus rewards-based interactive web-site) and control (activity monitor without website access). Of 174 potentially eligible participants during a seven month enrollment period, 105 (60%

of eligible) agreed to enroll; 98 met inclusion criteria and were randomized. Eighty-two (84% of those randomized) completed the study. Eight of 16 children dropped out of the study at their request and eight were lost to follow-up. Drop out was equally distributed between intervention and control groups. Twenty seven activity monitors were replaced among 19 children (six children required more than one replacement device). At the end of the intervention, mean (SE) weekly minutes of physical activity increased by 31 (20) minutes in the intervention group and decreased by 22 (19) minutes in the control group (p=0.07). The decline in physical activity in the control group is consistent with literature indicating a decline in time spent in MVPA among children as they progress through adolescence.[71,72] The 53 minute/week difference in MVPA is important clinically as investigators from both the Avon Longitudinal Study of Parents and Children (N=4,639) and the European Youth Heart Study show inverse associations between small differences in accelerometer based MVPA levels during childhood and cardiometabolic biomarkers in adolescence.[72,73]

2.2 Hypotheses

2.2.1 Children randomized to the six-month long interactive web-based intervention during the first twelve months after completion of curative therapy will demonstrate lower physiologic cost of walking during a six minute walk test than children randomized to the control condition at the end of the intervention, as well as six months and one year after the intervention is completed.

2.2.2 Children randomized to the six-month long interactive web-based intervention during the first twelve months after curative therapy will have lower blood pressure, body mass index, waist to height ratio, fasting insulin, glucose, and lipid levels and more favorable inflammatory biomarker and adipokine profiles than children randomized to the control condition at the end of the intervention, as well as six months and one year after the intervention is completed.

2.2.3 Children randomized to the six-month long interactive web-based intervention during the first twelve months after curative therapy will report more physical activity, better quality of life, less fatigue, and fewer missed school days than children randomized to the control condition at the end of the intervention, as well as six months and one year after the intervention is completed.

2.2.4 The effect of the interactive web-based intervention on biomarkers of cardiometabolic health will be mediated by changes in fitness as assessed by the six minute walk test.

2.3 Rationale

In summary, survivors of childhood cancer are at risk for low physical activity levels, poor fitness, metabolic syndrome, inflammation, fatigue, and diminished quality of life. Although very few exercise/physical activity interventions for children with cancer have been reported, there is positive evidence that exercise is safe and that it improves cardiopulmonary fitness and muscle strength. Past studies have relied on supervised training which is burdensome for families who must travel to the clinic or hospital. Large multi-site, randomized studies are needed to investigate age-appropriate, motivating, realistic, and portable interventions that are easily incorporated into daily life. We propose a large, multi-site, randomized control study to determine if an interactive web-based

physical activity intervention improves fitness, biomarkers of cardiovascular health and inflammation, adipokine profiles, physical activity, quality of life, fatigue, and school attendance in survivors of childhood cancer who have recently completed therapy.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically

communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

3.1.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

After the initial COG registration, enrollment, and randomization all data entry will be manually entered by the site on CRF which will be submitted directly to the coordinating center at St. Jude.

Institutions who have the protocol open will receive regular email and phone contact from the study team (St. Jude study team, study chair, and physicians who are all active members of COG) to encourage enrollment and track potentially eligible participants. Children on front line treatment protocols are tracked in the COG data system and will be flagged for potential enrollment and the institution PI/CRA

contacted by the study coordinator/PI when they are nearing completion of therapy. Enrollment will be tracked and institutions who are having difficulty will be contacted to provide additional training and to discuss problem-solving strategies.

3.1.4 Inclusion of Women and Minorities
Both males and females of all races and ethnic groups are eligible for this study.

3.1.5 Randomization
Randomization will take place at the time a patient is enrolled via OPEN. The treatment will be randomly assigned based on the statistical design of the trial.

3.2 Patient Eligibility: Inclusion Criteria

Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.**

3.2.1 Age
Patient must be ≥ 8 years of age and < 16 years of age at time of enrollment.

3.2.2 Diagnosis
All cancer cases with an ICD-O histologic behavior code of two "2" (carcinoma in situ) or three "3" (malignant), in remission.

3.2.3 Prior Therapy
Patient must have completed curative therapy (surgery and/or radiation and/or chemotherapy) within the past 12 months at a COG institution.

3.2.4 Performance Status
Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Lansky for patients ≤ 16 years of age. Please refer to performance status scale at: https://www.cogmembers.org/_files/protocol/Standard/PerformanceStatusScalesScoring.pdf

3.2.5 Physical Activity
At the time of consent, patient or parent/guardian reports less than 420 minutes of moderate to vigorous physical activity over the last week.

3.2.6 Patient and at least one parent/guardian are able to read and write English Spanish, and/or French. At least 1 parent/guardian must be able to read and write English Spanish, and/or French in order to assist the patient with using their physical activity tracking device account.

3.3 Patient Eligibility: Exclusion Criteria

3.3.1 Patients with previous Hematopoietic Stem Cell Transplant (HSCT).

3.3.2 Patients with significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or compliance with protocol therapy, or interfere with consent, study participation, follow up, or interpretation of study results.

3.3.3 Female patients who are pregnant are not eligible. Women of childbearing potential require a negative pregnancy test.

3.3.4 Female patient who is postmenarcheal and has not agreed to use an effective contraceptive method (including abstinence) for the duration of study participation.

3.3.5 Patients with a cognitive, motor, visual or auditory impairment that prevents computer use (e.g. unresolved posterior fossa syndrome) are not eligible.

3.4 Regulatory Requirements

3.4.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.4.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 STUDY PROCEDURES

4.1 Patient Identification and Screening

A combined mail, phone, and in-clinic approach will be used to identify and recruit patients. Children on front line treatment protocols are tracked in the COG data system and will be flagged for potential enrollment and the institution PI/CRA will be contacted by the St. Jude study team when they are nearing completion of their therapy regimen. Eligible participants/parents/guardians will be mailed an introductory letter explaining the study along with an informational consent prior to their usual clinic visit. The letter will include a phone number that parents/guardians can call to ask questions about the study or request that no further contact be initiated. A response form will be included in the letter along with a self-addressed, stamped, business reply envelope which will allow the parent or guardian to indicate whether or not their child/teen is interested in participating, whether they want someone to contact them to answer questions, or decline to be in the study. Within two weeks after the letter is mailed, the study coordinator at the treating COG institution will contact each eligible participant that did not send back a response form to discuss the study, ask if they have any questions and to see if they are interested in participating. Those that are interested will be scheduled to come into clinic for consent, enrollment, randomization and baseline evaluation. Eligible participants/parents/guardians may also be directly recruited in clinic.

4.2 Consent

It is recommended that the informed consent conference take place in clinic when the participant comes in for their baseline measures. Study personnel will explain the measures involved in the study, and review the potential risks and benefits. Study personnel will also inform the participant/parent/guardian that they will be randomly placed into an intervention or non- intervention group and that there is a chance that they will not receive the intervention. However, if the intervention is effective, control participants will be given full access to the website when the study is over. When the participant/parent/guardian agrees to participate, the study team will ensure that the potential participant and parent/guardian understands what the research study involves and the potential risks and

benefits. Consent and assent (if applicable) will be signed in accordance with all local, federal and institutional guidelines.

4.3 **Randomization**

After informed consent is signed and eligibility is confirmed, research participants will be enrolled via the OPEN system. They will be randomized to the intervention or the control group. Patients will be stratified by age groups (8-11 and 12-15yrs), diagnosis group (leukemia/lymphoma, bone tumor, CNS tumor, other solid tumor) and gender and randomized 1:1 between the two arms. The physical activity tracking device will be set up for each participant during the baseline assessment. Set up includes creating an account with a generic username and password as well as linking the device to the appropriate group assignment. A case report form will be sent to SJCRH (the study coordinating site) that includes the patient's COG ID, device ID, enrollment date, and group assignment. The local site CRA will collect the parent's/participant's email address/phone number with preferred method of contact in order to send weekly reminders to sync the device, or to reach out if device is never synced, and for participant problems/issues.

4.4 **Educational Handouts**

All participants will receive educational handouts about physical activity (available on the COG Protocol Web Page). Participants will receive the educational handouts again via mail at three and five months into the study to reinforce the importance of physical activity and maintain compliance.

4.5 **Physical Activity Tracking Device**

All participants will be given a physical activity tracking device. Physical activity will be tracked using the tri-axial technology of the device. When they are given the device, participants will be asked to set up an account, with their parent/guardian's assistance and will be instructed on how to use the device with the website and/or their mobile device. Participants will be educated on how to download data using the app on their mobile device. The app is compatible with Android devices, as well as iOS. The mobile device must also support Bluetooth Low Energy, or BLE, which is available in Bluetooth 4.0 and above. When a participant initiates a sync through the app, recorded activity data will automatically transfer to the website. Activity data that is not uploaded through syncing will be lost when the system automatically resets every week.

Participants will be instructed to wear the device on their wrist during their normal daily activities. The physical activity tracking device is waterproof and the band is latex free. The participants will be instructed to clean the devices with just hot water and mild soap. The physical activity tracking device will operate continuously throughout the 24-week intervention and have a memory capacity of 1 week of data. Participants and their parents will be instructed to synchronize the device at least once a week to a mobile device and will receive an email text, or phone call reminder (based on preference) from their local site. When control group participants sync their device, they get basic information related to their physical activity, but they do not get access to other participants' progress. Intervention group participants get full access to the website (described below). All participants, regardless of group, will be asked to go about their normal daily activities and to carry their device daily. The participants who find it difficult to wear the device all the time will be encouraged to wear it for at least some part of the day (two to four hours) during periods when they expect to be active. Other than encouraging the weekly data download (sync), no specific instructions will be given in regard to how frequently they use

the website. Educational handouts and the initial session with the study staff encourage participants to increase physical activity levels to at least 420 minutes per week; however, during the course of the study, participants and their parents will be free to choose for themselves how little or how much they engage in physical activity.

Participants enrolled prior to this version of the protocol will continue to wear the physical activity tracking device they received during their baseline visit and upload data as they were previously instructed until they complete the study. In case of technical issues with using the original device (i.e. platform unavailable), an iPad with the app already downloaded will be provided for use or the enrolling site will contact the participant to complete a manual log to capture physical activity data. Newly enrolled participants will be given a different physical activity device and access to a platform with the same functionality since the previous platform is no longer available for new account creation.

4.5.1 Replacement Devices

We conducted a six month impact trial using a different, but very similar activity device and website intervention. We allowed participants in both the intervention and control groups to get as many replacement activity devices as needed, up until two weeks prior to their study end date. Twenty-seven replacement devices were issued to 19/98 (19%) children (six children have required more than one replacement device). In a larger study conducted by HopeLab, the creator of the device previously mentioned, 14.5% of participants needed a replacement device in the first, 13.6% in the second month, and 7% in the final months of the study. Most of the devices were replaced because they were lost or laundered. The physical activity tracking device is waterproof. We will continue to allow participants to receive replacement devices and will plan conservatively, budgeting for 500 devices for 384 participants (anticipating replacing 30% of devices). At the first clinic visit, each participant will be given contact information to report issues, including lost or broken devices, or ask questions related to using the physical activity tracking device. If the participant or local site contacts the coordinating center reporting that a device is lost or broken, a replacement will be sent.

4.5.2 Help Requests

Local site CRAs will send a 2nd week email or text (depending on preference) that asks about problems with the device and website to participants in both the intervention and control groups. In addition, site CRAs can contact the Central Site via email or toll free number for additional tech support. The email account and voicemail are monitored daily.

4.5.3 Initial Non-Adherence with Uploading Data

Local site CRAs are responsible for contacting the parent/participant. Communication is done via email address/phone number and address the parent provides at the time of enrollment. In addition to the two week email above sent to all parents to see if they need help, a weekly email/text/phone call is sent/made (depending on preference) to encourage syncing the device. Study staff at the coordinating site will be monitoring data uploads. If large gaps in data collection are noted, the local site CRA will be notified and asked to contact the participant to address any issues or barriers to promote increased compliance to data collection.

4.5.4 Children and Adolescents without Internet Accessibility

This intervention may not be well-received or feasible for children and adolescents without internet interest or accessibility, although findings from our pilot study indicate that this will be rare. We did not encounter any children who did not have internet access, at least at school. This intervention is compatible with mobile device technology which may enhance accessibility. If a child/adolescent wants to participate and does not have access to the internet at home or to a mobile device, with parent/guardian permission, study staff from the coordinating center will provide written and verbal (Skype, phone) instructions regarding the device and the website interface to school personnel so the child/adolescent can participate.

4.5.5 Intervention

The intervention component of this study is the interactive reward-based website. The website is a closed system. Only the physical activity tracking device team, study team, and study participants have access. Each participant will be given a physical activity tracking device to wear along with access to the interactive reward-based website. The rewards website is designed to motivate participants to increase their physical activity levels. When participants first log in to the rewards website, they will be able to see other participants and how their activity compares to others.

The interaction component of the study allows participants to see how their activating ranks compared to others and to "like" each other's activity.

Participants will use generic information, not names when they sign up. Privacy is protected as participants are not allowed to use any part of their real name to sign up. The website will not have any identifying information. The platforms used for the study intervention have adopted and adhere to stringent security standards designed to protect non-public personal information against accidental or unauthorized access or disclosure.

The participants randomized into the intervention group will receive full access to the interactive website and app described above. The control participants will access a limited version of the same website and app. The control participants will be limited to only seeing themselves and their own progress. They will not be able to interact or see others progress.

Table 1. Intervention v Control Group

Intervention Materials	Intervention	Control
Educational Handouts	X	X
Physical Activity Tracking Device	X	X
Website/App	Full access (see/interact with others)	Limited access (only see own progress/unable to interact with others)
Gift Cards/Prizes	During Intervention	After Intervention

4.5.5.1 Rewards

Participants earn rewards by being physically active and using the website and app.

1) **Points:** Points are earned while the participant is active. The more active, the more points are earned (250 points for 1 minute of MVPA). Points earned can vary greatly depending on the intensity of

movement and where the device is worn during the activity. How many points a participant earns is entirely dependent on the participant and the types of activities in which they choose to engage.

2) **Credits**: A participant can earn credits for wearing the physical activity tracking device and for being active. A $5 gift card or a monetarily equivalent prize will be awarded for every 5 credits earned.

How to earn 1 credit:

- Wear your Physical Activity Tracking Device for at least 5 days per week
- Sync your Physical Activity Tracking Device at least 5 days per week
- For every 125,000 points (up to 30,000 activity points per day count toward credits)

Only the intervention group will receive additional details about how to earn credits, but both groups have an opportunity to receive gift cards or prizes for credits earned. Providing the details to only the intervention group will help determine whether or not this reward motivates the participants to be more active, as they will receive gift cards during the course of the intervention period. The control group will receive all earned gift cards or prizes at the end of the intervention period.

4.6 Required Evaluations

4.6.1 Pre-Study Evaluations

Potentially eligible participants who agree to be screened for participation will be consented after arriving for their regularly scheduled clinic appointment. Eligibility will be reviewed again at the time of consent. Post-pubertal females will be screened for pregnancy by a urine pregnancy test after consent/assent process at the baseline assessment. The study team will provide urine pregnancy testing kits as needed to sites to screen for eligibility.

4.6.2 Evaluations to Determine Outcomes

There will be 4 evaluation time points and patients will be followed for a total of 18 months.

Evaluation	Baseline Day 0	End of Intervention (24 weeks ±6 weeks)	24 Weeks Post Intervention (48 weeks ±3 months)	48 weeks Post Intervention (72 weeks ±3 months)
Urine Pregnancy Test	X	---	---	---
Biological Markers (see Section 4.7)	X	X	X	X
Study Questionnaires				
Health Related Quality of Life	X	X	X	X
Fatigue	X	X	X	X
School Attendance	X	X	X	X
Functional Assessment				
Anthropometrics	X	X	X	X
Fitness	X	X	X	X
Blood Pressure	X	X	X	X
Physical Activity	X	X	X	X

4.6.3 Evaluations and Tests

4.6.3.1 Study Questionnaires

Health Related Quality of Life and Fatigue: The PedsQL™ 4.0 Generic Core Scale and the 18-item PedsQL™ Multidimensional Fatigue Scale[74] will be filled out by the participant at each time point. The PedsQL instrument is reliable and valid in children and adults with cancer[75,76] and includes a physical functioning scale, an emotional functioning scale, a social functioning scale, a school functioning scale, a total summary score, and both physical and psychosocial health summary scores. The instrument is available in young child, child, adolescent, and adult versions (scales) if child/adolescent agrees and is able. All versions of this instrument are scored on a 0-100 scale.[75-79] The 18-item PedsQL™ Multidimensional Fatigue Scale[77] encompasses three subscales: (1) general fatigue (six items), (2) sleep/rest fatigue (six items), and (3) cognitive fatigue (six items). The format, instructions, Likert response scale, and scoring method are identical to the PedsQL™ 4.0 Generic Core Scales, with higher scores indicating better HRQOL (fewer problems or symptoms). School Attendance: Participants/parents will be asked to indicate the number of missed days of school (of the total days of school available so a proportion can be used for analysis).

4.6.3.2 Anthropometric Assessments

Anthropometric measurements, including height by wall-mounted stadiometer (without shoes), weight by electronic scale, and waist circumference, will be obtained. Trained clinic staff will measure waist girth (cm) with a non-stretching anthropometric tape directly over the skin. Waist circumference will be measured midway between the anterior superior iliac spine and the lower rib margin. Measurements will be recorded to the nearest 0.1 cm. Waist to height ratio has known associations with cardiometabolic risk in children[80] and is calculated by dividing waist circumference by height. Reference values are available.[81] Body mass index (BMI) percentile will be calculated by dividing weight in kilograms by height in meters squared. Reference values from the Centers for Disease Control and Prevention will be used to convert values into percentiles.

4.6.3.3 Resting Blood Pressure

Resting blood pressure will be taken after the participant has been sitting upright in a chair with both feet on the floor for five minutes. The right arm will be supported at the level of the heart. A blood pressure cuff will be selected depending on the size of the participant's arm. The participant will be allowed to rest 5 minutes before the first reading. One to two minutes after the first reading, a duplicate reading will be taken on the same arm to ensure accuracy.[82]

4.6.3.4 Fitness (exercise capacity)

Fitness will be evaluated with the physiologic cost index (PCI) from the six minute walk test. Children are asked to walk as fast as possible for six minutes on a level surface. The distance is recorded in feet but will be converted to meters before analysis.[83] Heart rate is monitored continuously. Stopping, starting, and resting during the test are allowed if

needed. This test requires a stop watch, a corridor reasonably free of obstacles, a measurement wheel, a heart rate monitor, and a lap counter. PCI is calculated in beats per meter from the average heart rate during the walking test minus the resting heart rate divided by meters walked per minute.[84] Although peak oxygen uptake measured with cardiopulmonary exercise testing is the gold standard for fitness, it is not feasible (cost, logistics) across this many potential study sites. The PCI evaluates the energy cost of walking, has little variation by age or sex, and is less likely to have a ceiling effect than distance walked in six minutes.[85,86]

4.6.3.5 Physical Activity

During the six month study period, physical activity will be recorded by the physical activity tracking device (tri-axial accelerometer) and will be automatically transferred to the web-based platform when the device is synced with a mobile device. All data will be transmitted at least weekly from the web-based platform to the data manager at SJCRH via secure file transfer or by manual download and stored by COG ID and device number. The device collects information on intensity and duration of common activities such as walking, jogging, and cycling. Participants will receive the physical activity tracking device with written and verbal instructions at the baseline visit with reinforcement (email, text, or phone call) to encourage device syncing. The text, email, or phone call the week prior to each of the three post-baseline study visits will include reinforcement for device wear. The physical activity tracking device will be activated at the baseline visit. Wearing instructions will also be provided verbally, with demonstration. Study staff will be available by phone to assist if the participants or families have questions about wear.

4.7 Specimen Collection and Submission

Biological samples for this study will be collected after an 8 hour fast. If a participant hasn't fasted for 8 hours, the sample can still be collected but should be as late in the appointment as possible. Details of when the participant last ate or drank anything along with the time of the blood draw should be communicated to the coordinating center. Samples will be drawn by trained personnel and shipped to SJCRH clinical laboratory for processing. Several outcomes including blood parameters will be evaluated at all four time points (see Section 4.6.2). Urine pregnancy testing for post-pubertal females will be completed at baseline. A total of 10 mL of blood will be collected by venipuncture. The following tests will be run on each sample.

Test	Technique	Description
Glucose[a]	Spectrophotometric	Marker of body's homeostatic mechanism involving catabolic (glucagon, catecholamines and cortisol) and anabolic hormones (insulin).
Insulin[a]	ECLIA[b]	Higher levels indicates insulin resistance
Lipid Panel[a]	Colorimetric[c]	Decreased levels of HDL and increased LDL indicate sedentary lifestyle and unhealthy diet. Abnormal panel is a well-known marker of cardiac disease.

Test	Technique	Description
High Sensitivity C-Reactive Protein	Quantitative Immunoturbidimetry	Higher levels indicate an inflammatory state.
Interleukin-6	Highly Sensitive ELISA[d]	Higher levels indicate an inflammatory state.
Tumor Necrosis Factor-Alpha	Quantitative Multiplex Bead Assay	Higher levels indicate an inflammatory state.
Leptin	Highly Sensitive ELISA[d]	Higher levels indicate higher body fat and may indicate leptin resistance.

[a] St. Jude Children's Research Hospital Laboratories are accredited by Clinical Laboratory Improvement Amendments (CLIA) (Id# 44D0028946) and the College of American Pathophysiologists' Laboratory Accreditation Program (LAP#:1585701; AU-ID#: 1181620).

[b] ECLIA: electrochemilumiscent immunoassay.

[c] Colorimetric: 1) Cholesterol using 3 enzymes cholesterol esterase/oxidase/peroxidase 2) HDL 3 enzymes of cholesterol modified by polyethylene glycol/dextran sulfate 3) Triglycerides using 4 enzymes lipoprotein lipase/glycerol kinase/glycerol phosphate oxidase/peroxidase.

[d] ELISA: enzyme-linked immunosorbent assay.

4.7.1 Blood Collection

Sample Time Points:	• Baseline (Day 0) • End of Intervention (24 weeks ± 6 weeks) • 24 Weeks Post End of Intervention (48 weeks ±3 months) • 48 Weeks Post End of Intervention (72 weeks ± 3 months)
Blood Collection Procedure:	• **Tube 1** (glucose, insulin, total cholesterol, HDL, LDL, triglycerides) 2 mL drawn into a green top tube with lithium heparin and polymer gel at the bottom. (BD#367960 or equivalent) • **Tube 2** (CRP) 2 mL drawn into a green top tube with lithium heparin and polymer gel at the bottom. (BD#367960 or equivalent) • **Tube 3** (Alpha TNF) 2 mL drawn into a green top tube with lithium heparin and polymer gel at the bottom. (BD#367960 or equivalent) • **Tube 4** (IL-6) 2 mL drawn into a purple top EDTA tube. (BD#367841 or equivalent) • **Tube 5** (Leptin) 2 mL drawn into plain red top silicone coated tube. (BD#366430 or equivalent)
Specimen Labeling:	Each tube must be labeled with the COG ID number, patient initials, and the date and time the sample was obtained.
Specimen Processing:	**Please see Specimen Collection Manual on the protocol web page.**
Specimen Packaging and Shipping:	Samples should remain frozen until ready for shipping. Blood should be shipped overnight to: St. Jude Children's Research Hospital – Lab Support Attn: Crystal Melloh – COG ALL Stars Trial 262 Danny Thomas Place Mail Stop 250, Room C3001A Memphis, TN 38105 Phone: (901) 595-4867 Email: crystal.melloh@stjude.org

4.8 **Data Collection and Management**

St. Jude Children's Research Hospital will be the data coordinating center for this study. All data collected during the clinic assessments will be filled out on CRFs and sent to SJCRH via fax or email to the study team. All data is to be submitted within 4 weeks of the patient visit time point. The data received will be scanned or hand-entered into a secure, St. Jude owned/maintained database.

Fax: (901) 595-6155
Attention: COG ALL Stars
Email: COGALLStars@stjude.org

4.8.1 Data from Clinic Assessments

4.8.1.1 Data collected during the clinic assessments will be captured on a case report form (CRF). A CRF has been created for each study questionnaire, including Health Related Quality of Life (2 versions exist since age-dependent), Fatigue (2 versions since age dependent), school attendance, functional assessment (includes blood pressure, anthropometrics, and fitness). A CRF has also been created for recording the distribution of the physical activity tracking device and will only be filled out at the baseline assessment visit.

4.8.1.2 Data from blood analyses
Results from the blood testing will be uploaded into St. Jude's secure hospital charting system, created for capturing research only study specific data. The St. Jude study coordinator will 1) fill out a CRF to scan into the study specific database or 2) will import the data into the study specific database. Data will be reported in publications using the template provided by Montoye (http://bjsm.bmj.com/content/early/2016/08/18/bjsports-2015-095947.abstract).[87]

4.8.2 Data from Physical Activity Monitoring
SJCRH study coordinator will download data at least weekly from a secure website into a St. Jude owned database.

5.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

5.1 Off Study Criteria

a) Completion of planned study assessments.
b) Refusal of further participation by patient/parent/guardian.
c) Physician determines it is in the patient's best interest.
d) Patient relapses or develops another cancer.
e) Withdrawal of consent for any further data submission.
f) Pregnancy.
g) Lost to follow-up.
h) Death.

6.0 STATISTICAL CONSIDERATIONS

6.1 Statistical Design

The primary time point for analysis will be at the end of the intervention. This study is powered to detect a 13% difference in PCI between the intervention group and the control group. This percentage corresponds to the decrease in peak oxygen uptake reported among children/adolescents after treatment when compared to peers and in lay terms, represents the difference between climbing or not climbing stairs or between running and walking.[24] Among healthy children, PCI is inversely correlated with oxygen uptake and has a mean value of 0.4±0.125 beats per meter (b/m).[88,89] We plan to enroll 192 participants per group to allow for potential death, relapse, or drop out (~20%). With 154 children per group, we

have 85% power at an alpha level of 0.01 to detect a 13% difference between groups (two sample two-sided t-test). This sample size also gives us power to detect differences noted in the table below for measures of cardiometabolic health, inflammation, leptin, physical activity, fatigue, quality of life, and missed school days.

Measure	Instrument	Time point				Detectable difference	Reference
		1	2	3	4		
Fitness	PCI from six minute walk test	X	X	X	X	0.052 b/m	Geiger[83]
Blood pressure	Blood pressure cuff (mmHg)	X	X	X	X	4 mmHg	Going[90]
BMI percentile	Height with a wall mounted stadiometer (m), weight with an electronic scale (kg)	X	X	X	X	5.4%	Going[90]
Waist to height ratio	Waist circumference (cm), height (cm)	X	X	X	X	3.8%	Kuba[80]
Total cholesterol	Fasting* blood draw	X	X	X	X	16.1 mg/dL	Going[90]
High density lipoprotein	Fasting* blood draw	X	X	X	X	6.6 mg/dL	Going[90]
Low density lipoprotein	Fasting* blood draw	X	X	X	X	13.9 mg/dL	Going[90]
Triglycerides	Fasting* blood draw	X	X	X	X	28.1 mg/dL	Going[90]
HOMA IR	Insulin and glucose – fasting* blood draw	X	X	X	X	0.2	Lee[91]
High sensitivity C-reactive protein	Fasting* blood draw	X	X	X	X	0.79 mg/L	Dowd[92]
Interleukin-6	Fasting* blood draw	X	X	X	X	1.02 pg/mL	Mazur[32]
Tumor necrosis factor alpha	Fasting* blood draw	X	X	X	X	0.69 pg/mL	Mazur[32]
Leptin	Fasting* blood draw	X	X	X	X	0.17 µg/L	Garcia-Mayor[93]
Health Related Quality of Life	PedsQL Core Modules	X	X	X	X	8.6	Varni[79]
Fatigue	PedsQL Multidimensional Fatigue Scale	X	X	X	X	7.1	Varni[74]
School Attendance	Parent Report	X	X	X	X	2.7	(SD 5 days/month)

*Fasting = no food within the last 8 hours, water/black coffee OK

6.2 Patient Accrual and Expected Duration of Trial

The study goal is to enroll 384 children in the given age range from the COG member institutions within 3 years because each child will remain enrolled in the study for approximately 18 months (including follow-up time points.) and our funding is for 5 years. To evaluate our primary outcome, 192 evaluable participants are needed in each of the groups below:

Intervention Group – full access to rewards-based physical activity intervention with a physical activity tracking device, delivered via an interactive website/app with small gift cards or prizes.

Control Group – limited access to rewards-based physical activity intervention, including educational materials and a physical activity tracking device

6.3 Statistical Analysis Methods

The analysis for the primary aim will be conducted by comparing differences between groups in PCI at the end of the intervention. Intent to treat analysis of variance (either transforming the data or employing a non-parametric equivalent if the data are not normally distributed) controlling for the stratification factors (sex, age, and treatment related risk group) will be used for comparison. General linear mixed models will be utilized to evaluate the effects of group assignment on changes in PCI over time to account for repeated measures on individual children, and for potential random effects such as original treating institution. A similar approach will be used to evaluate the outcomes for aims two and three where our interests are to evaluated differences between groups and the effects of group assignment on changes over time in measures of cardiometabolic health, inflammation, quality of life, fatigue, and school attendance. SAS software will be used for these analyses.

Because we will have data on daily MVPA over the course of the 24 week trial, we will use longitudinal methods as described by Fitzmaurice et al[94] to both reduce the data for analysis and assess the impact of group assignment on levels of MVPA levels in the two groups over time. SAS software will be used for these analyses.

For the fourth study aim, we will use a causal inference approach to evaluate whether or not group assignment results in an improved outcome in the presence of a lower PCI (evaluated in aim one). This requires decomposing the averaged total effect into indirect (mediation effects of fitness) and direct effects of group assignment of on the cardiometabolic outcomes. We plan to use a principal stratification method as described by Lynch[95] that classifies participants into strata based on their performance on the PCI (mediator variable) for each group of the randomized intervention. For example, we may have four strata, the intervention group that performed well on the PCI at follow-up, the intervention group that performed poorly on the PCI at follow-up, the control group that performed well on the PCI at follow-up, and the control group that performed poorly on the PCI at follow-up. Mediation analyses would then be based on intent-to-treat effects of group assignment on cardiometabolic health outcome within each strata. STATA software will be used for these analyses.

6.3.1 Missing and Incomplete Data

It is anticipated, based on past experience, missing data for participants who attend visits will be <1%. Additionally, our pilot study using a similar platform to another physical activity tracking device indicates 92% of children who complete the study will download their data from the activity device at least every two weeks. Nevertheless, missing data are possible. To determine bias because of missing data and drop-out, we will do sensitivity analyses of the outcome data of all enrollees, constructing and comparing models that do and do not carry baseline data are evaluable with three of seven days of data. We will also consider using probability weighting to assess bias in our results. To do this, we will compare baseline characteristics of those who remain on study and those who drop out. We will include variables where there are differences in a logistic regression model to determine the probability of participation and use this variable to construct an inverse probability weight for each participant with evaluable outcome data. Analyses with and without weighting will be compared to see if drop-out has an appreciable influence on our study results.

6.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1	1	1	1	4
Asian	5	8	1	1	15
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	11	21	3	5	40
White	80	104	37	51	272
More Than One Race	1	2	3	3	9
Total	98	136	45	61	340

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	2	4	0	0	6
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	2	1	0	0	3
White	12	20	0	1	33
More Than One Race	0	1	0	0	1
Total	17	26	0	1	44

This distribution was derived from the Surveillance Epidemiology and End Results database.

No one will be excluded based on race/ethnicity. Because of the racial distribution of childhood cancer in the United States, and because we are enrolling children from COG member sites across the United States, we expect the sample to be 80% Caucasian, 11% Black, and 8.0% Asian/Pacific Islander. Twenty percent of the total sample is estimated to be Hispanic.

7.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection*". A submission schedule is included.

7.1 Demography Monitoring

Required submission of patient demographic data to NCI for this study will be submitted automatically via OPEN.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Protocol-Specific Requirements for Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

APPENDIX II: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY – ALTE1631
(for children from 8 through 12 years of age)

A Study about Physical Activity in Children and Teenagers with Cancer

1. We have been talking with you about the treatment you received for childhood cancer. Children and teenagers who have received treatment for cancer are at risk for gaining weight and having problems with their bones, muscles and overall health.

2. We are asking you to take part in a research study because you finished your treatment for cancer. A research study is when doctors work together to try out new ways to help people who have been sick. In this study we are trying to learn if using a website will help you become more active and affect your overall health.

3. Children in this study will receive educational handouts about exercise and be given a physical activity tracking device. The device will track how much you exercise. You will be asked to wear the activity monitor every day during the study so you and the study team can measure how active you are. You will also be given access to one of two websites that will track your progress.

4. There will be 4 visits for this study. At each visit, the doctors and nurses will collect blood to run special tests. They will measure your weight, height and around your waist. They will check your blood pressure and have you do a walking test. You will also fill out questionnaires about how you are feeling.

5. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We don’t know for sure if there is any benefit of being part of this study. We hope a benefit to you would be to have better overall health. We hope the information you give us will help doctors learn more about how physical activity affects the health of children and teenagers who had treatment for cancer.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks”. The risk to you from this study is possible pain, bruising, bleeding or infection at the site of the needle stick to draw your blood. You may have questions or feelings come up during this study that may worry or bother you.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. Make sure to ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY – ALTE1631
(for children from 13 through 15 years of age)

A Study about Physical Activity in Children and Teenagers with Cancer

1. We have been talking with you about the treatment you received for childhood cancer. Children and teenagers who have received treatment for cancer are at risk for gaining weight and having problems with their bones, muscles and overall health.

2. We are asking you to take part in a research study because you finished your treatment for cancer. A research study is when doctors work together to try out new ways to help people who have been sick. In this study we are trying to learn if using a website will help you become more active and affect your overall health.

3. Children in this study will receive educational handouts about exercise and be given a physical activity tracking device. The device will track how much you exercise. You will be asked to wear the activity monitor every day during the study so you and the study team can measure how active you are. You will also be given access to one of two websites that will track your progress.

4. There will be 4 visits for this study. At each visit, the doctors and nurses will collect blood to run special tests. They will measure your weight, height and around your waist. They will check your blood pressure and have you do a walking test. You will also fill out questionnaires about how you are feeling.

5. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We don’t know for sure if there is any benefit of being part of this study. We hope a benefit to you would be to have better overall health. We hope the information you give us will help doctors learn more about how physical activity affects the health of children and teenagers who had treatment for cancer.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks”. The risk to you from this study is possible pain, bruising, bleeding or infection at the site of the needle stick to draw your blood. You may have questions or feelings come up during this study that may worry or bother you.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. Make sure to ask your doctors any questions that you have.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2016, Based on November 2018 SEER data submission, posted to the SEER web site, April 2019. https://seer.cancer.gov/csr/1975_2016/, National Cancer Institute. Bethesda, MD
2. Bhakta N, Liu Q, Ness KK, et al: The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). Lancet (London, England) 390:2569-2582, 2017
3. Fulbright JM, Raman S, McClellan WS, et al: Late effects of childhood leukemia therapy. Curr Hematol Malig Rep 6:195-205, 2011
4. Brinkman TM, Zhu L Fau - Zeltzer LK, Zeltzer Lk Fau - Recklitis CJ, et al: Longitudinal patterns of psychological distress in adult survivors of childhood cancer.
5. Gibson TM, Mostoufi-Moab S, Stratton KL, et al: Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970-99: a report from the Childhood Cancer Survivor Study cohort.
6. Hudson MM, Oeffinger KC, Jones K, et al: Age-dependent changes in health status in the Childhood Cancer Survivor cohort.
7. Cox CL, Montgomery M, Oeffinger KC, et al: Promoting physical activity in childhood cancer survivors: results from the Childhood Cancer Survivor Study. Cancer 115:642-54, 2009
8. Karlage RE, Wilson CL, Zhang N, et al: Validity of anthropometric measurements for characterizing obesity among adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort Study.
9. Koskelo EK, Saarinen Um Fau - Siimes MA, Siimes MA: Skeletal muscle wasting and protein-energy malnutrition in children with a newly diagnosed acute leukemia.
10. kumar R, Marwaha Rk Fau - Bhalla AK, Bhalla Ak Fau - Gulati M, et al: Protein energey malnutrition and skeletal muscle wasting in childhood acute lymphoblastic lukemia.
11. Dupuis LL, Boodhan S Fau - Sung L, Sung L Fau - Portwine C, et al: Guideline for the classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients.
12. Edwards JL, Gibson F, Richardson A, et al: Fatigue in adolescents with and following a cancer diagnosis: developing an evidence base for practice. Eur J Cancer 39:2671-2680, 2003
13. Piper BF, Cella D: Cancer-related fatigue: Definitions and clinical subtypes. J Natl Compr Canc Netw 8:958-966, 2010
14. Winter C, Müller C, Hoffmann C, et al: Physical activity and childhood cancer. Pediatr Blood Cancer 54:501-510, 2010
15. Gawade Pl Fau - Hudson MM, Hudson Mm Fau - Kaste SC, Kaste Sc Fau - Neglia JP, et al: A systematic review of selected musculoskeletal late effects in survivors of childhood cancer.
16. Smith WA, Li C Fau - Nottage KA, Nottage Ka Fau - Mulrooney DA, et al: Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study.
17. Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic Health Conditions in Adult Survivors of Childhood Cancer. New Engl J Med 355:1572-1582, 2006
18. Mulrooney DA, Yeazel MW, Kawashima T, et al: Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. Brit Med J 339:b4606, 2009
19. Ness KK, Leisenring WM, Huang S, et al: Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 115:1984-94, 2009

20. Meacham LR, Chow EJ, Ness KK, et al: Cardiovascular risk factors in adult survivors of pediatric cancer--a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev 19:170-81, 2010
21. Armstrong GT, Liu Q, Yasui Y, et al: Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol 27:2328-38, 2009
22. San Juan AF, Chamorro-Vina C, Mate-Munoz JL, et al: Functional capacity of children with leukemia. Int J Sports Med 29:163-7, 2008
23. Warner JT, Bell W, Webb DK, et al: Relationship between cardiopulmonary response to exercise and adiposity in survivors of childhood malignancy. Arch Dis Child 76:298-303, 1997
24. van Brussel M, Takken T, Lucia A, et al: Is physical fitness decreased in survivors of childhood leukemia? A systematic review. Leukemia 19:13-7, 2005
25. Gocha Marchese V, Chiarello LA, Lange BJ: Strength and functional mobility in children with acute lymphoblastic leukemia. Med Pediatr Oncol 40:230-2, 2003
26. Wright MJ, Halton JM, Martin RF, et al: Long-term gross motor performance following treatment for acute lymphoblastic leukemia. Med Pediatr Oncol 31:86-90, 1998
27. Ness KK, Baker KS, Dengel DR, et al: Body composition, muscle strength deficits and mobility limitations in adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 49:975-81, 2007
28. Hovi L, Era P, Rautonen J, et al: Impaired muscle strength in female adolescents and young adults surviving leukemia in childhood. Cancer 72:276-81, 1993
29. Ness KK, DeLany JP, Kaste SC, et al: Energy balance and fitness in adult survivors of childhood acute lymphoblastic leukemia. Blood 125:3411-9, 2015
30. Antwi GO, Jayawardene W, Lohrmann DK, et al: Physical activity and fitness among pediatric cancer survivors: a meta-analysis of observational studies. LID - 10.1007/s00520-019-04788-z [doi].
31. Pluimakers VG, van Waas M, Neggers S, et al: Metabolic syndrome as cardiovascular risk factor in childhood cancer survivors.
32. Mazur B, Mertas A, Sonta-Jakimczyk D, et al: Concentration of IL-2, IL-6, IL-8, IL-10 and TNF-alpha in children with acute lymphoblastic leukemia after cessation of chemotherapy. Hematol Oncol 22:27-34, 2004
33. Ariffin H, Azanan MSA-Ohoo, Abd Ghafar SS, et al: Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging.
34. Siviero-Miachon AA, Spinola-Castro Am Fau - Guerra-Junior G, Guerra-Junior G: Detection of metabolic syndrome features among childhood cancer survivors: a target to prevent disease.
35. Chow EJ, Simmons JH, Roth CL, et al: Increased cardiometabolic traits in pediatric survivors of acute lymphoblastic leukemia treated with total body irradiation. Biol Blood Marrow Transplant 16:1674-81, 2010
36. Jahnukainen K, Heikkinen R, Henriksson M, et al: Increased Body Adiposity and Serum Leptin Concentrations in Very Long-Term Adult Male Survivors of Childhood Acute Lymphoblastic Leukemia. Horm Res Paediatr 84:108-15, 2015
37. Heikens J, Ubbink Mc Fau - van der Pal HP, van der Pal Hp Fau - Bakker PJ, et al: Long term survivors of childhood brain cancer have an increased risk for cardiovascular disease.
38. Ness KK, Gurney JG, Zeltzer LK, et al: The impact of limitations in physical, executive, and emotional function on health-related quality of life among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Arch Phys Med Rehabil 89:128-36, 2008
39. van Litsenburg RR, Huisman J, Hoogerbrugge PM, et al: Impaired sleep affects quality of life in children during maintenance treatment for acute lymphoblastic leukemia: an exploratory study. Health Qual Life Outcomes 9:25, 2011
40. Sung L, Yanofsky R, Klaassen RJ, et al: Quality of life during active treatment for pediatric acute lymphoblastic leukemia. Int J Cancer 128:1213-20, 2011

41. Baggott C, Dodd M, Kennedy C, et al: Multiple symptoms in pediatric oncology patients: a systematic review. J Pediatr Oncol Nurs 26:325-39, 2009
42. Liu RD, Chinapaw MJ, Huijgens PC, et al: Physical exercise interventions in haematological cancer patients, feasible to conduct but effectiveness to be established: a systematic literature review. Cancer Treat Rev 35:185-92, 2009
43. Marchese VG, Chiarello LA, Lange BJ: Effects of physical therapy intervention for children with acute lymphoblastic leukemia. Pediatr Blood Cancer 42:127-33, 2004
44. San Juan AF, Chamorro-Vina C, Moral S, et al: Benefits of intrahospital exercise training after pediatric bone marrow transplantation. Int J Sports Med 29:439-46, 2008
45. San Juan AF, Fleck SJ, Chamorro-Vina C, et al: Effects of an intrahospital exercise program intervention for children with leukemia. Med Sci Sport Exer 39:13-21, 2007
46. San Juan AF, Wolin K, Lucia A: Physical activity and pediatric cancer survivorship. Recent Results Cancer Res 186:319-47, 2011
47. Sharkey AM, Carey AB, Heise CT, et al: Cardiac rehabilitation after cancer therapy in children and young adults. Am J Cardiol 71:1488-90, 1993
48. Keats MR, Culos-Reed SN: A community-based physical activity program for adolescents with cancer (project TREK): program feasibility and preliminary findings. J Pediatr Hematol Oncol 30:272-80, 2008
49. Yeh CH, Man Wai JP, Lin US, et al: A pilot study to examine the feasibility and effects of a home-based aerobic program on reducing fatigue in children with acute lymphoblastic leukemia. Cancer Nurs 34:3-12, 2011
50. Farpour-Lambert NJ, Aggoun Y, Marchand LM, et al: Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. J Am Coll Cardiol 54:2396-406, 2009
51. Behringer M, Vom Heede A, Yue Z, et al: Effects of resistance training in children and adolescents: a meta-analysis. Pediatrics 126:e1199-210, 2010
52. D'Hooge R, Hellinckx T, Van Laethem C, et al: Influence of combined aerobic and resistance training on metabolic control, cardiovascular fitness and quality of life in adolescents with type 1 diabetes: a randomized controlled trial. Clin Rehabil 25:349-59, 2011
53. Vanhelst J, Fardy PS, Mikulovic J, et al: Changes in obesity, cardiorespiratory fitness and habitual physical activity following a one-year intervention program in obese youth: a pilot study. J Sports Med Phys Fitness 51:670-5, 2011
54. Carrel AL, McVean JJ, Clark RR, et al: School-based exercise improves fitness, body composition, insulin sensitivity, and markers of inflammation in non-obese children. J Pediatr Endocr Met 22:409-15, 2009
55. Davis CL, Tomporowski PD, McDowell JE, et al: Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. Health Psychol 30:91-8, 2011
56. Balagopal P, George D, Patton N, et al: Lifestyle-only intervention attenuates the inflammatory state associated with obesity: a randomized controlled study in adolescents. J Pediatr 146:342-8, 2005
57. Bluher S, Petroff D, Keller A, et al: Effect of a 1-Year Obesity Intervention (KLAKS Program) on Preexisting Autonomic Nervous Dysfunction in Childhood Obesity. J Child Neurol 30:1174-81, 2015
58. Lau PW, Lau EY, Wong del P, et al: A systematic review of information and communication technology-based interventions for promoting physical activity behavior change in children and adolescents. J Med Internet Res 13:e48, 2011
59. Lubans DR, Morgan PJ, Callister R, et al: Effects of integrating pedometers, parental materials, and E-mail support within an extracurricular school sport intervention. J Adolesc Health 44:176-83, 2009

60. Ernst M, Pine DS, Hardin M: Triadic model of the neurobiology of motivated behavior in adolescence. Psychol Med 36:299-312, 2006
61. Richards JM, Plate RC, Ernst M: Neural systems underlying motivated behavior in adolescence: implications for preventive medicine. Prev Med 55 Suppl:S7-S16, 2012
62. Ernst M, Nelson EE, Jazbec S, et al: Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. Neuroimage 25:1279-91, 2005
63. Eshel N, Nelson EE, Blair RJ, et al: Neural substrates of choice selection in adults and adolescents: development of the ventrolateral prefrontal and anterior cingulate cortices. Neuropsychologia 45:1270-9, 2007
64. Galvan A, Hare TA, Parra CE, et al: Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J Neurosci 26:6885-92, 2006
65. Guyer AE, Monk CS, McClure-Tone EB, et al: A developmental examination of amygdala response to facial expressions. J Cogn Neurosci 20:1565-82, 2008
66. Killgore WD, Yurgelun-Todd DA: Activation of the amygdala and anterior cingulate during nonconscious processing of sad versus happy faces. Neuroimage 21:1215-23, 2004
67. Monk CS, McClure EB, Nelson EE, et al: Adolescent immaturity in attention-related brain engagement to emotional facial expressions. Neuroimage 20:420-8, 2003
68. Geier CF, Terwilliger R, Teslovich T, et al: Immaturities in reward processing and its influence on inhibitory control in adolescence. Cereb Cortex 20:1613-29, 2010
69. Smith AB, Halari R, Giampetro V, et al: Developmental effects of reward on sustained attention networks. Neuroimage 56:1693-704, 2011
70. Deci E, Ryan R, (Eds): Handbook of self-determination research. Rochester, NY, University of Rochester Press, 2002
71. Sallis JF: Epidemiology of physical activity and fitness in children and adolescents. Crit Rev Food Sci Nutr 33:403-8, 1993
72. Jago R, Wedderkopp N, Kristensen PL, et al: Six-year change in youth physical activity and effect on fasting insulin and HOMA-IR. Am J Prev Med 35:554-60, 2008
73. Stamatakis E, Coombs N, Tiling K, et al: Sedentary time in late childhood and cardiometabolic risk in adolescence. Pediatrics 135:e1432-41, 2015
74. Varni JW, Seid M, Knight TS, et al: The PedsQL 4.0 Generic Core Scales: sensitivity, responsiveness, and impact on clinical decision-making. J Behav Med 25:175-93, 2002
75. Ewing JE, King MT, Smith NF: Validation of modified forms of the PedsQL generic core scales and cancer module scales for adolescents and young adults (AYA) with cancer or a blood disorder. Qual Life Res 18:231-44, 2009
76. Robert RS, Paxton RJ, Palla SL, et al: Feasibility, reliability, and validity of the pediatric quality of life inventory generic core scales, cancer module, and multidimensional fatigue scale in long-term adult survivors of pediatric cancer. Pediatr Blood Cancer, 2012
77. Varni JW, Burwinkle TM, Katz ER, et al: The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer 94:2090-106, 2002
78. Varni JW, Limbers CA: The PedsQL 4.0 Generic Core Scales Young Adult Version: feasibility, reliability and validity in a university student population. J Health Psychol 14:611-22, 2009
79. Varni JW, Seid M, Kurtin PS: PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 39:800-12, 2001
80. Kuba VM, Leone C, Damiani D: Is waist-to-height ratio a useful indicator of cardio-metabolic risk in 6-10-year-old children? BMC Pediatr 13:91, 2013
81. Fryar CD, Gu Q, Ogden CL: Anthropometric reference data for children and adults: United States, 2007-2010. Vital Health Stat 11:1-48, 2012

82. Balady G, Berra K, Golding L, et al: ACSM's Guidelines for exercise testing and prescription (ed 6th). Baltimore, Lippincott Williams & Wilkins, 2000
83. Geiger R, Strasak A, Treml B, et al: Six-minute walk test in children and adolescents. J Pediatr 150:395-9, 399 e1-2, 2007
84. Butler P, Engelbrecht M, Major RE, et al: Physiological cost index of walking for normal children and its use as an indicator of physical handicap. Dev Med Child Neurol 26:607-12, 1984
85. Geiger R, Willeit J, Rummel M, et al: Six-minute walk distance in overweight children and adolescents: effects of a weight-reducing program. J Pediatr 158:447-51, 2011
86. Nene AV, Evans GA, Patrick JH: Simultaneous multiple operations for spastic diplegia. Outcome and functional assessment of walking in 18 patients. J Bone Joint Surg Br 75:488-94, 1993
87. Montoye AHK, Moore RW, Bowles HR, et al: Reporting accelerometer methods in physical activity intervention studies: a systematic review and recommendations for authors. British Journal of Sports Medicine, 2016
88. Engsberg JR, Herbert LM, Grimston SK, et al: Relation among indices of effort and oxygen uptake in below-knee amputee and able-bodied children. Arch Phys Med Rehabil 75:1335-41, 1994
89. Herbert LM, Engsberg JR, Tedford KG, et al: A comparison of oxygen consumption during walking between children with and without below-knee amputations. Phys Ther 74:943-50, 1994
90. Going SB, Lohman TG, Cussler EC, et al: Percent body fat and chronic disease risk factors in U.S. children and youth. Am J Prev Med 41:S77-86, 2011
91. Lee JM, Okumura MJ, Davis MM, et al: Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. Diabetes Care 29:2427-32, 2006
92. Dowd JB, Zajacova A, Aiello AE: Predictors of inflammation in U.S. children aged 3-16 years. Am J Prev Med 39:314-20, 2010
93. Garcia-Mayor RV, Andrade MA, Rios M, et al: Serum leptin levels in normal children: relationship to age, gender, body mass index, pituitary-gonadal hormones, and pubertal stage. J Clin Endocrinol Metab 82:2849-55, 1997
94. Fitzmaurice GM LN, Ware JH: Applied Longitudinal Analysis Hoboken, N.J., Wiley-Interscience, 2004
95. Lynch KG, Cary M, Gallop R, et al: Causal Mediation Analyses for Randomized Trials. Health Serv Outcomes Res Methodol 8:57-76, 2008