

MSK PROTOCOL COVER SHEET

Exercise and QQuality diet After Leukemia: The EQUAL Study

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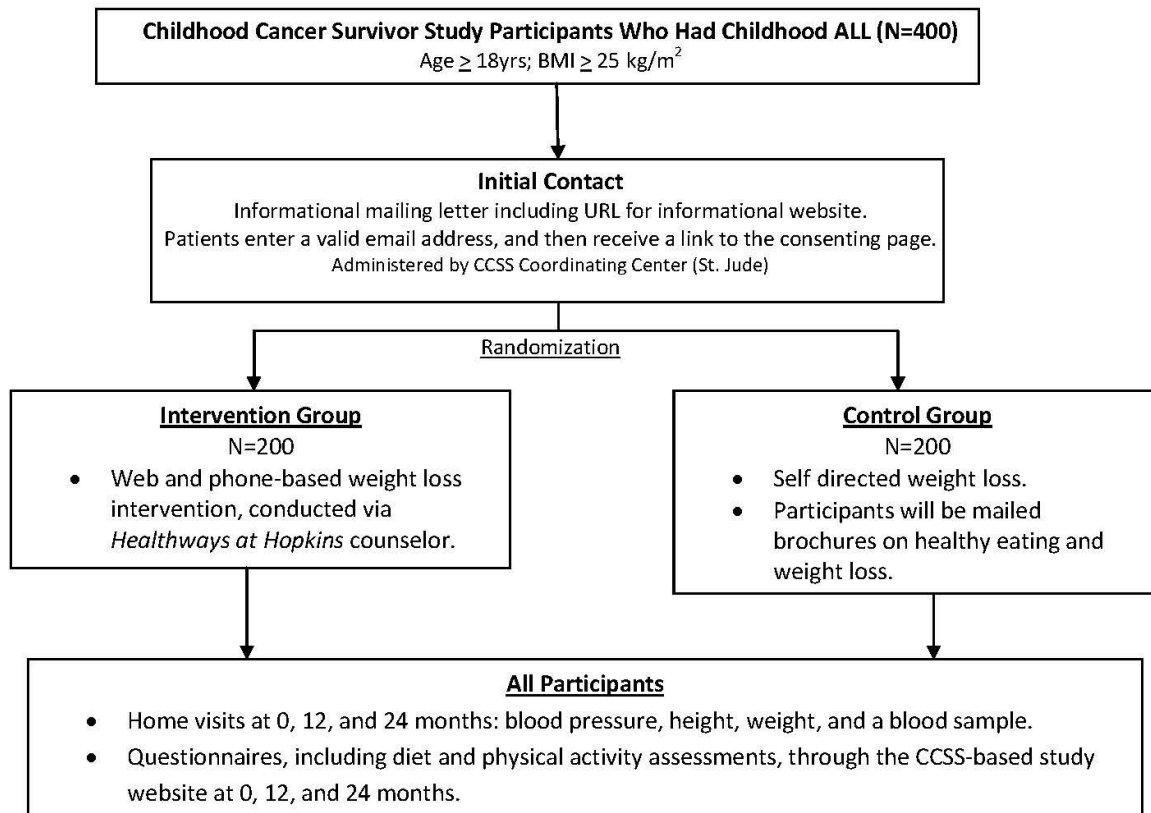
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Childhood acute lymphoblastic leukemia (ALL) is the most common childhood cancer, accounting for almost one-quarter of childhood cancer survivors. As detailed below, adult survivors of childhood ALL are at very high risk for obesity and a host of cardiometabolic diseases. While treatment exposures are not modifiable, evidence suggests that ALL survivors may be able to ameliorate their cardiovascular risk through improvements in diet and physical activity. A landmark study by Appel, Clark, and colleagues, published in the New England Journal of Medicine in 2011, demonstrated that significant weight loss could be achieved entirely through phone- and web-based support, compared to self-directed weight loss among obese community-dwelling adults.

In this NCI-supported study (R01CA187397), Exercise and QUality diet After Leukemia (EQUAL), we will test the effectiveness of a remotely-delivered diet and physical activity intervention, compared to self-directed weight loss, on the deleterious cardiometabolic phenotype observed among adult ALL survivors. Participants will be a nationwide sample of obese and overweight ALL survivors who are enrolled in the Childhood Cancer Survivor Study (CCSS). Participants will be randomized to general information about healthy living and weight loss (control) or to a diet and physical activity intervention led by *Healthways at Hopkins* (Johns Hopkins University PI: Jeanne Clark, MD MPH). All participants will have visits for anthropometric and laboratory data collection at time 0, 12, and 24 month after randomization, conducted via Examination Management Services, Inc (EMSI) phlebotomy service.

As noted, the EQUAL Study will be conducted through the CCSS, a 30-institution cohort study of over 24,000 long-term survivors of childhood cancer (CCSS PI, Gregory Armstrong, MD; MSKCC IRB Protocol #94-069; Site PI, Charles Sklar, MD) that includes an estimated 2,349 overweight and obese ALL survivors who are eligible for the EQUAL Study. The CCSS participants include an original cohort, diagnosed with childhood cancer between 1970 and 1986, and an expanded cohort that was diagnosed between 1987 and 1999. The CCSS Coordinating Center is located at St. Jude Children's Research Hospital in Memphis, TN. CCSS participants were previously consented to be followed in the cohort. Communication with participants is coordinated through the CCSS Coordinating Center staff (as described below) including new studies such as the EQUAL Study that are using the CCSS as a resource. As such, the EQUAL Study will use the existing CCSS infrastructure, which means that eligible participants for the EQUAL Study will be consented and surveys administered by the CCSS Coordinating Center, as described in detail in the following sections.

The schema for the study is below:



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Specific Aim 1: Determine the effectiveness of a 24-month remotely-delivered diet and physical activity intervention, compared to self-directed weight loss, among a nationwide sample of overweight and obese adult survivors of childhood acute lymphoblastic leukemia (ALL).

Hypothesis 1: ***Overweight and obese ALL survivors randomized to the call-center directed intervention will lose on average 2.75kg more than those engaged in self-directed weight loss.***

Specific Aim 2: Calculate the effect of the diet and physical activity intervention, compared to self-directed weight loss, on three key metabolic biomarkers:

- Fasting insulin*
- Leptin:adiponectin ratio*
- Small, dense LDL*

Hypothesis 2: ***Improvements in biomarkers will be greater among participants in the intervention group.***

Specific Aim 3: Calculate the relative contribution of diet and physical activity to weight loss and the three key metabolic parameters.

Hypothesis 3: ***A diet rich in fruits and vegetables and with little meat consumption will result in the greatest benefit.***

Specific Aim 4: Assess the roles of self-efficacy and risk perception on meeting activity and diet goals.

Hypothesis 4: ***Subjects with high self-efficacy and enhanced risk perception will be more likely to make behavioral and nutritional changes.***

3.0 BACKGROUND AND RATIONALE

Acute lymphoblastic leukemia is the most common childhood cancer. Each year, approximately 3,000 new cases of childhood acute lymphoblastic leukemia (ALL) are diagnosed in the United States(1, 2), making childhood ALL the most common childhood cancer. ALL is also a cancer of the very young; children diagnosed with ALL have a mean age of 4 to 7 years old(3, 4). With 5-year survival estimates exceeding 85%(5), the population of ALL survivors has grown dramatically over the past thirty years. Today, an estimated 50,000 adult survivors of childhood ALL are living in the United States(5, 6).

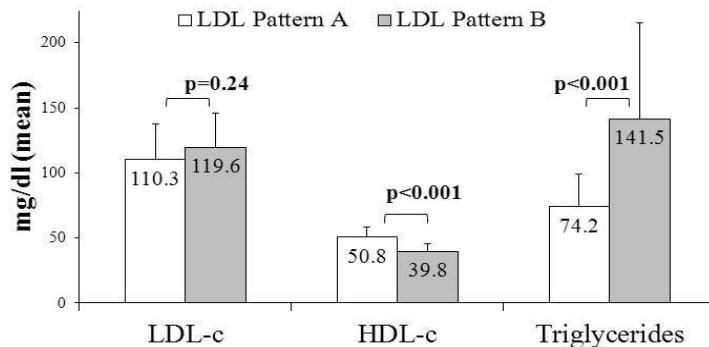
ALL survivors suffer from chronic disease and loss of life. In spite of excellent survival rates, ALL survivors are at very high risk for late occurring morbidity and mortality. In the ALL survivor population, these late effects are primarily cardiometabolic: cardiovascular and metabolic diseases that interact, modify one another, and contribute to cardiovascular death. Indeed, the standardized mortality ratio for death from cardiac causes among 5-year survivors of ALL diagnosed and treated in the 1970s and 1980s is 4.2(7). In our sex-specific cross-sectional comparisons of 118 adult survivors of childhood ALL and regional controls, ALL survivors were more obese, had higher levels of fasting insulin and glucose, were more insulin resistant as measured by the homeostasis model for assessment of insulin resistance (HOMA-IR), and were more likely to have two or more cardiovascular risk factors than the regional controls(8). Analysis via Dual-energy X-ray absorptiometry (DXA) revealed that ALL survivors had lower lean body mass and increased fat mass, i.e. sarcopenic obesity, compared to community controls(9).

Cranial radiotherapy (CRT) is an important risk factor for cardiometabolic disease among ALL survivors. In the Childhood Cancer Survivor Study (CCSS), an NCI-supported (U24 CA55727), collaborative, multi-institutional study of over 20,000 5-year survivors of childhood cancer, female ALL survivors diagnosed before the age of 5 and treated with ≥ 20 Gy CRT had increased odds of being obese (OR 3.81; 95% CI: 2.34, 5.99; P 0.001), compared to sibling controls. Among adult female survivors without a history of CRT, the odds ratio was 1.09 (95% CI: 0.63, 1.71), compared to sibling controls(10). The odds ratio for a diagnosis of diabetes mellitus among male and female ALL survivors in the CCSS with a history of CRT compared to sibling controls was 1.8 (95% CI: 1.2, 2.8; P < 0.01); after adjusting for body mass index (BMI), the odds ratio was 1.6 in this group (95% CI: 1.0, 2.5; P 0.06) compared to sibling controls(11).

The risk of stroke is also increased among ALL survivors: relative risk of history of stroke was 6.6 (95% CI: 3.0, 13.8) compared to siblings without cancer(12). Importantly, strokes were observed even among survivors without a history

Figure 1: Mean LDL-c, HDL-c and triglyceride levels among survivors of childhood ALL with LDL pattern A and pattern B.

A. Males



B. Females

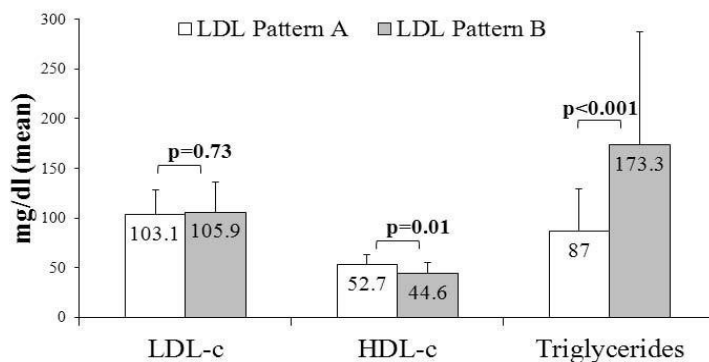
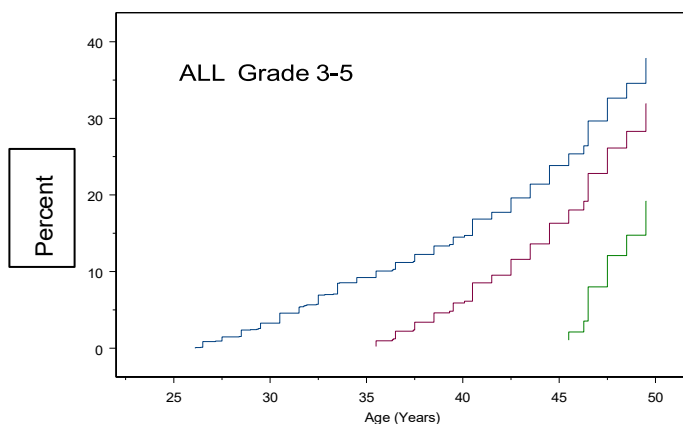


Figure 2: Cumulative incidence of severe, disabling, or life threatening (Grade 3-5) condition among ALL survivors in the CCSS with no previous condition at age 25, 35, or 45 years old.



of CRT(12). Hypertension(13, 14) and elevations of C-reactive protein (CRP) levels(8) following ALL treatment have also been reported; possible mechanisms for this deleterious cardiometabolic phenotype are discussed further below.

We have recently published lipid subfractionation results from 110 long-term survivors of childhood ALL.(Figure 1) Although mean LDL-c levels were normal (108.7 mg/dl), 36% of survivors had more than 50% of LDL cholesterol in small, dense, more atherogenic LDL subfractions ("Pattern B")(15). Furthermore, survivors with the atherogenic LDL Pattern B had lower HDL, higher triglycerides, higher body mass index, more visceral adiposity, more insulin resistance, and were more likely to have the metabolic syndrome than survivors with LDL Pattern A. Clinically, the combination of cardiovascular and metabolic risk factors observed in this cross-sectional analysis present as a childhood ALL survivor with a deleterious cardiometabolic phenotype typified by obesity associated with sarcopenia(8, 16), diabetes mellitus and insulin resistance(8, 11, 17, 18), chronically elevated c-reactive protein levels(8), dyslipidemia(15), hypertension(13, 14), stroke(12), and ultimately cardiovascular death(7).

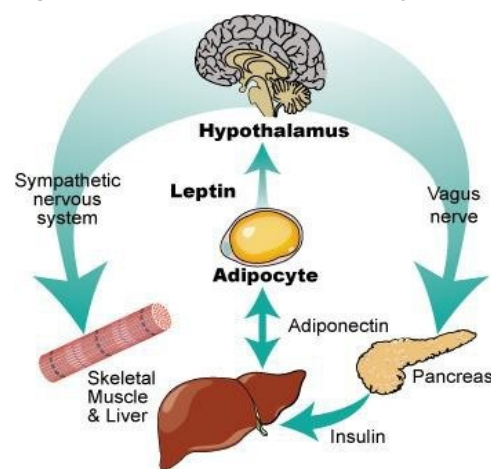
While CRT is an important risk factor for cardiometabolic disease, and thus requires consideration among long-term survivors, the contemporary use of CRT is limited. Concurrent with the decline in use of CRT over the past 35 years, the prevalence of childhood obesity has increased dramatically. Today, many children are obese at the time of diagnosis, and so remain at risk for becoming obese long-term survivors despite non-irradiating therapies. Hence, a diet and physical

activity intervention for weight loss is critically important for obese ALL survivors, regardless of whether or not they were treated with CRT.

Preliminary findings from the CCSS demonstrate that even ALL survivors who are without a severe, disabling, or life threatening condition at age 25, 35, or 45 years old remain at very high risk for subsequent morbidity (**Figure 2**). Furthermore, as the ALL survivor population ages, the interaction between late effects of cancer treatment and chronic disease will become increasingly important(19). Thus, the deleterious cardiometabolic phenotype and the young age at diagnosis of ALL result in an overall reduction in life expectancy of 10.1 years compared to the U.S. general population(4). Presently, the life expectancy for a five-year survivor of childhood ALL is only 54.7 years(4).

Alterations in leptin and adiponectin may be mechanistic. Leptin and adiponectin are peptide hormones secreted by adipocytes (fat cells)(**Figure 3**)(16). Leptin is proportional to total body fat mass and communicates primarily with the hypothalamus regarding satiety and energy usage. Adiponectin is inversely proportional to fat mass and appears to communicate primarily with skeletal muscle and the liver with respect to energy storage. In our cross-sectional analysis of 116 ALL survivors, higher leptin and lower adiponectin were associated with insulin resistance and other measures of body fat, suggesting central leptin resistance(16). A biologic interaction between leptin receptor activity, CRT, and obesity may exist; a polymorphism of leptin receptor activity (Gln223Arg) interacts with CRT in its association with insulin resistance and is independently associated with obesity among female ALL survivors(20).

Figure 3: Leptin and adiponectin system



Diet and physical activity may mitigate these risks.

While treatment history is not modifiable, evidence suggests that ALL survivors may be able to ameliorate their cardiometabolic risk through improvements in diet and physical activity. ALL survivors are typically sedentary, and women treated with CRT are especially inactive(18, 21-23). We recently investigated physical activity and fitness in survivors of childhood ALL. We measured cardiorespiratory fitness by maximal oxygen uptake (VO_2 max) during a graded exercise test on a treadmill and measured physical activity with a multi-sensor activity monitor worn for one week. More than 77% of the women and 59% of the men had low cardiorespiratory fitness; women with a history of CRT and men with a history of

anthracycline therapy were at highest risk for reduced fitness. Average time spent in vigorous physical activity was very low for both genders (6 seconds/day for women and 1.4 minutes/day for men) and was independent of treatment history(24).

Diet is also relevant to cardiometabolic disease among ALL survivors. A study by Robien et al. evaluated ALL survivors from the CCSS and found poor adherence to dietary guidelines(25). In a separate population of ALL survivors, we reported an association between unhealthy diet and increased visceral adiposity, higher systolic and diastolic blood pressure, greater waist circumference, and increased body mass index(26). In that analysis, small improvements in diet appeared to be metabolically beneficial. Differences as small as an additional 0.5 serving of vegetables per day, or 1 more serving of fish per week, were associated with significantly improved body mass index, visceral adiposity, and blood pressure, and lower risk of the metabolic syndrome. Therefore, methods to promote weight loss and increase levels of physical activity are likely to have positive cardiometabolic effects in this setting.

Prior work in non-ALL survivor populations suggests that leptin and adiponectin levels may be modifiable via physical activity, but more research is needed. The HEAL Study, an observational

cohort study of breast cancer survivors with biomarkers measured at 6-8 months and 2-3 years after diagnosis, reported statistically significant inverse associations between physical activity and circulating levels of leptin and CRP(27), although a physical activity intervention was not tested. In contrast, Ligibel and colleagues reported no change in leptin or adiponectin among 101 sedentary, overweight breast cancer survivors randomized to a 16 week exercise intervention or usual care(28). Importantly, the trial was only 16 weeks in duration and the intervention group included only 51 subjects(28). Therefore, while adipokines may be relevant to the deleterious cardiometabolic phenotype observed after ALL therapy, no prior weight loss intervention study among ALL survivors has evaluated this hypothesis.

A randomized, controlled trial of a diet and physical activity intervention in this population is urgently needed. ALL survivors are at very high risk for cardiometabolic disease, are typically sedentary, and do not adhere to dietary guidelines(24, 25). Also, small improvements in diet appear to be metabolically beneficial for these survivors(26). Yet, it remains unknown whether a diet and physical activity intervention can be successful in this population. To our knowledge, few prior studies have attempted to improve physical activity among adult survivors of childhood ALL, and no prior weight loss intervention study among ALL survivors has included a dietary intervention. In preliminary analysis from the ALLIFE Study, (R01 CA100474, PI: Oeffinger) long-term ALL survivors randomized to a physical activity intervention showed trends towards increased physical activity (measured by activity sensor), improved cardiorespiratory fitness (measured by maximum O₂ consumed on fitness testing) improved body mass index, and lower leptin to adiponectin ratio, but none of these changes was statistically significant, possibly due to small sample size.(**Table 1**) Of note, insulin resistance did show statistically significant improvement, indicating that physical activity has the potential to be metabolically impactful in this setting. Among breast cancer survivors, a secondary analysis of the WHEL trial suggested a significant survival advantage among participants who exercised 30 minutes, 6 days/week AND consumed at least 5

servings/day of fruits and vegetables; no advantage was seen in women who achieved only one of these goals(29). Therefore, a weight loss intervention trial among long-term ALL survivors is not only necessary, it should include a larger number of participants and target both diet and physical activity.

Table 1. Preliminary intervention effects for ALLIFE Participants randomized to a physical activity intervention compared to controls (N=46).			
Difference in Means			
	INT-CTRL*	(95% CI)	P value**
Body mass index (kg/m ²)	-1.1	(-2.3, 0.2)	0.08
Physical activity energy expenditure (Kcal/kg/day)	2.1	(-0.7, 4.9)	0.1
Maximum O ₂ consumed (ml/kg/min)	1.1	(-1.1, 3.3)	0.3
Insulin resistance (HOMA-IR)	-1.5	(-2.5, 0.4)	0.001
High-sensitivity C reactive protein (hsCRP)	0.2	(-1.8, 2.2)	0.9
Leptin to Adiponectin ratio	-0.8	(-1.5, 0.1)	0.06
Triglycerides	-25.4	(-53, 2.2)	0.8

*Difference in mean result among intervention group (INT) compared to control group (CTRL) at the end of the study period; **P value by ANCOVA

Prior intervention studies among CCSS participants have targeted smoking cessation, breast cancer screening, and screening for cardiomyopathy. As outlined in a paper from CCSS leaders(30), cardiometabolic disease among ALL survivors could be positively affected by healthy lifestyle practices such as eating a low-fat diet and maintaining a physically active lifestyle. The authors state:

The CCSS has developed an infrastructure capable of supporting the rigorous testing of interventions, has an extensive track record of successful collaborations with independent investigators, and has served as a resource for numerous investigator-initiated, externally supported studies.... There are few comparable resources that offer such an established infrastructure and a diverse cohort of survivors to allow the completion of adequately powered intervention trials aimed at encouraging health lifestyle behaviors(30)

In sum, an intervention that would enhance healthy diet and physical activity has been strongly encouraged. Thus far, this call for a diet and physical activity intervention trial among ALL survivors has gone unanswered.

Table 2. Weight loss goals and behavioral recommendations for the intervention group

Weight loss goal	Minimum 5% weight loss
Behavioral recommendations	
Total calorie recommendation	1200 kcal/day if ≤ 170 lb 1500 kcal/day if > 170 lb and ≤ 220 lb 1800 kcal/day if > 220 lb and ≤ 270 lb 2200 kcal/day if > 270 lb
Dietary recommendation	7-12 services of fruits & vegetables 2-3 services of low fat dairy reduced sodium $\leq 25\%$ of calories from fat
Physical activity goal	Build to ≥ 180 minutes/week of moderate intensity
Website log-in	At least weekly
Online feedback based on self monitoring	After each weight log in
Email feedback based on self monitoring	Monthly feedback, re-engagement reminders
Self-monitoring recommendations: Achieved weight loss $< 5\%$	
Weight	Weekly
Food record	Daily
Calorie counting	3 times per week
Physical activity	Daily
Mode	Online behavioral tracking of above behaviors
Self-monitoring recommendations: Achieved weight loss $\geq 5\%$	
Weight	Daily
Food record	3 times per week
Calorie counting	3 times per week
Physical activity	Daily
Mode	Online behavioral tracking of above behaviors

To reach a nationwide population of ALL survivors, a distance intervention is required.

Numerous weight loss studies, including those conducted by the investigative team, have demonstrated the efficacy of in-person behavioral counseling for weight loss among overweight or obese adults(31-33). The time, expense, and personnel required for an in-person intervention is not feasible among a nationwide sample of overweight or obese ALL survivors, however. Furthermore, based on the recent results of the POWER trial, conducted by Appel, Clark and colleagues, an in-person intervention is not necessary to achieve meaningful and significant weight loss(34). In the POWER trial, non-cancer obese participants were randomized to one of three arms: (1) remote, call center-delivered weight loss support delivered via telephone, a web hub, and email, and provided by *Healthways at Hopkins*; (2) in-person support group and individual sessions in addition to the telephone, email, and web hub forms of support, and (3) self-directed weight loss support via a fixed website with links to advice on healthy eating and physical activity. Details of the diet and physical activity intervention (used to guide both active intervention arms) are in **Table 2** and **Table 3**.

In the first three months of the intervention, participants were contacted by their *Healthways at Hopkins* counselor on a weekly basis; strategies to achieve a healthy weight were encouraged and barriers were explored. As the intervention proceeded and weight loss goals were met, contacts decreased in frequency. Participants entered diet diaries, physical activity records, and self-measured weight via a web-based hub; the web hub facilitated communication between the participants and counselors and reinforced behavior change through displays such as weight loss

over time and calories consumed. Screenshots from the *Healthways at Hopkins* intervention website are viewable in **Appendix B**.

At 24 months, the mean weight loss was 0.8kg in the self-directed group, 5.1kg in the in-person support group ($P<0.001$ for the comparison with the control group) and 4.6kg in the group receiving call center-directed support only ($P<0.001$ for the comparison with the control group)(34). The change in weight did not differ significantly between the two intervention groups. In sum, a remote intervention delivered by *Healthways at Hopkins* provided clinically significant weight loss at 24 months that was not different from weight loss achieved with in-person counseling(34).

The proposed intervention study will be conducted via the same program of behavioral counselors and web hub provided by *Healthways at Hopkins* and successfully tested in the POWER trial. The *Healthways at Hopkins* program provides the opportunity to address the cardiometabolic disease facing a nationwide sample of ALL survivors in a scientifically rigorous manner. In collaboration with *Healthways at Hopkins*, Dr. Clark at Johns Hopkins University, and the CCSS, we now have the ability to test, effectively and appropriately, a call center-directed diet and physical activity intervention among a nationwide population of ALL survivors in the CCSS.

Table 3. Intervention contacts by arm

	Self-Directed	Call Center Directed
Time 0	Introduction following randomization	
Months 1-3	Mailed healthy living materials	Weekly telephone calls or emails
Months 4-6	None	Monthly telephone calls or emails
Months 7-24	Mailed healthy living materials	Every other month calls or emails

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The EQUAL Study is a 24-month intervention trial among 400 overweight and obese adult survivors of childhood leukemia from the Childhood Cancer Survivor Study. Participants will be recruited from among the estimated 2,349 overweight and obese ALL survivors enrolled in the CCSS. Following completion of informed consent and the baseline questionnaire, participants will be randomized to the diet and physical activity intervention group (N=200) or the control group (N=200). The primary outcome is weight loss at 24 months.

4.2 Intervention

All participants:

All participants (N=400) will complete questionnaires found in **Appendix C** regarding health, physical activity, and diet, along with a fasting blood draw (2 tubes, approximately 20cc) and measurement of height, weight, waist circumference, and blood pressure during three approximate time periods: at baseline, and at 12 and 24 months.

Control group participants:

ALL survivors randomized to the control group (N=200) will receive general information brochures on healthy living and weight loss (**Appendix D**). The control group, also referred to as Group B in

the Informed Consent Form, will not have access to the *Healthways at Hopkins* website or counselors.

Controls will receive the following brochures during the first 18 months of the study:

- “Facts About Healthy Weight” was created by the National Heart, Lung, and Blood Institute. This brochure gives information on classifications of overweight and obese, how to determine the risk of these, setting weight loss goals, creating a healthy eating plan, and participating in physical activity. The brochure also points readers to more information via the website and telephone number of the National Heart, Lung, and Blood Institute.
- “Rethink Your Drink” was created by the Centers for Disease Control and Prevention, within the Department of Health and Human Services. This brochure gives information on different drinks and their calories, how to read nutritional labels of packaged juice and soda, and healthier alternatives.
- “Physical Activity and Your Heart,” created by the National Heart, Lung, and Blood Institute. This brochure defines the different types of physical activity, as well as gives recommendations for physical activity, and describes physical activity’s benefits.
- “How to Avoid Portion Size Pitfalls to Help Manage Your Weight,” created by the Centers for Disease Control and Prevention, with the Department of Health and Human Services. This brochure creates awareness on portion size, and helps people make informed decisions on portion control. The brochure also gives links to websites with more information on portion size, and nutrition labels.

Intervention group participants:

ALL survivors randomized to the intervention group (N=200) will be enrolled in a weight loss intervention run by *Healthways at Hopkins*. Details of the *Healthways at Hopkins* program for weight loss were introduced in Section 3.0, above. Briefly, the 200 participants enrolled in the intervention arm of the EQUAL study will be assigned an individual diet and physical activity counselor through *Healthways at Hopkins*. This counselor will stay with the participant for the 24 month duration of the intervention. The primary communication with the counselor will be via website and email. Participants who decline or drop out of the intervention program will remain on-study doing home visits and questionnaires.

Diet: Intervention participants will be encouraged to consume a low-calorie, low-salt diet with 7-12 daily servings of fruits and vegetables and low-fat dairy products. Calorie goals are based upon weight at study entry and whether or not the weight loss goal has been met.

Physical Activity: Intervention participants will gradually build to ≥ 180 minutes of moderate to vigorous physical activity per week, using the activity of their own choosing and gradually adding bouts of ≥ 10 minutes in length.

Monitoring and Counselor Contacts: For the first three months of the intervention, intervention group participants are encouraged to log into the web hub on a daily basis to record weight, food intake, and physical activity (see **Tables 2 and 3, above**). Contacts with the counselor, who can view the web hub data and give direct feedback to the participant, are initially every week. Prior studies have demonstrated that personal contacts with an interventionist can improve physical activity and promote self-monitoring, which is relevant for initial weight loss and maintenance(35, 36). As the trial proceeds and the weight loss goal is achieved, contacts are reduced in frequency. Participants will be sent reminder emails and/or called by telephone if they have not logged into the web hub on schedule.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

The EQUAL Study will recruit 400 adult survivors of childhood acute lymphoblastic leukemia (ALL) who are participants in the Childhood Cancer Survivor Study (CCSS) and meet the eligibility criteria. Eligibility will be confirmed via the CCSS-based medical record and by a series of questions on the EQUAL website, prior to consent.

5.1 Subject Inclusion Criteria

- 1) Participation in the CCSS cohort
- 2) Diagnosed with acute lymphoblastic leukemia < 18 years of age
- 3) Cancer free at time of study enrollment
- 4) Current age ≥ 18 years
- 5) A body mass index (BMI) ≥ 25 kg/m² (overweight or obese), as determined by self-reported height and weight on the most recent CCSS questionnaire
- 6) Internet access and a personal email account
- 7) Able to read and comprehend informed consent

5.2 Subject Exclusion Criteria

- 1) Prior history of congestive heart failure, coronary artery disease, myocardial infarction, stroke, or unstable angina;
- 2) Medical condition for which weight loss might be contraindicated or which would cause weight loss, such as pregnancy, anorexia or bulimia;
- 3) Use of prescription weight loss medication within the previous 6 months
- 4) History of total body irradiation (TBI)

6.0 RECRUITMENT PLAN

Eligible participants will be identified using the CCSS database. CCSS participants include an original cohort (participants diagnosed between 1970 and 1986) and an expansion cohort (participants diagnosed between 1987 and 1999). Based on self-reported height and weight from the most recent CCSS questionnaires, we have identified 1,098 obese ALL survivors and 1,251 overweight survivors (total potentially eligible CCSS participants = 2,349).

An introductory packet including an introduction letter (**Appendix A**), a copy of the informed consent, the study brochure (**Appendix E**), an EQUAL magnet (**Appendix K**), and a stamped, return envelope will be mailed to potential participants. The letter will include a URL link with instructions for logging on to the CCSS maintained study website describing the study goals, objectives, methods, and eligibility criteria. Upon providing a valid email address, completing the questionnaire, and confirming eligibility, the potential participant will be able to view the informed consent document. After reading the document, the website will require clicking on a check box to document "signing" the informed consent. If the potential participant clicks "Yes," the DatStat system will log the consent. This process will result in an enrollment form that is generated at the CCSS Coordinating Center, where staff will complete an eligibility checklist, link the consent to the CCSS Study ID already in existence for the participant, and email to the MSKCC study staff, who will then submit these documents to the MSKCC Protocol Participant Registration office for registration and randomization. For readability and convenience, the baseline questionnaire will be presented prior to the informed consent on the study website. However, questionnaires from potential participants who do not consent will not be registered and will be electronically discarded. Importantly, potential participants will not be given the option of a telephone or paper enrollment, as the study intervention requires a valid, active email address and the ability to complete study materials online.

Potential participants who do not respond to the introduction letter may be contacted by a study representative from the CCSS approximately four weeks later. These potential participants will be invited by telephone to log on to the study website to read more about the study and to provide a valid email address, if interested. The CCSS study personnel may attempt to call potential participants up to three times.

Following each visit by EMSI (approximately 0, 12, and 24 months following randomization), participants will receive a \$50 gift card. Additionally, participants will receive token items such as a pen, magnet, or key chain with the EQUAL logo. Study participants will also receive a birthday card (Appendix L) on their birthday month, along with a promotional item, such as a pen light, with the study logo.

There will be full consideration for inclusion of minorities in this study. About 13% of the original Childhood Cancer Survivor Study cohort is of minority race or ethnicity; as the expansion cohort has been enriched for minority participants, it can be expected to have a higher prevalence of minorities, although preliminary demographic data is not yet available.

7.0 ASSESSMENT/EVALUATION PLAN

Implementation, Control Group

Following randomization, MSKCC study personnel will be informed of the participant contact information and the randomization arm (call center-directed or self-directed weight loss). Participants in the control group will be given materials offering recommendations for healthy eating, drinking, and physical activity.

Implementation, Intervention Group

Following randomization, participants in the intervention group will be registered to *Healthways at Hopkins* by MSKCC study staff.

Participants randomized to the call center-directed (CCD) weight loss arm will initiate a telephone and web-based diet and physical activity intervention modeled on the successful POWER trial and run by *Healthways at Hopkins*. A weight loss counselor will be assigned to participants in the CCD arm, and contacts will occur via telephone, email, and the web hub (see **Appendix B** for screen shots from the *Healthways at Hopkins* program). Participants will sign into the web hub to enter diet diaries, physical activity records, and self-reported weight. Links to personalized summary data such as weight over time and total calories per day are available. The health counselor will also be able to see this data, and direct the participant to relevant goals and achievements. As employed in the successful POWER trial, the *Healthways at Hopkins* program uses established behavioral techniques to accomplish weight loss: frequent contacts, self-monitoring of weight and physical activity, use of food records, and accountability.

Implementation, All Participants

At the time of randomization, the MSKCC study RSA will coordinate with the phlebotomy vendor (EMSI) and the participant to schedule a baseline visit which will include 1) blood pressure, height, weight, and waist circumference; 2) a blood sample, to be performed by a medical technologist using standard venipuncture technique. Participants will be instructed to fast for twelve hours prior to the visit. Following the visit, a site visit report (**Appendix F**) including blood pressure, height, and weight data will be faxed by the technologist to the MSK study fax (646-888-4923). A copy of the site visit report will be retained by EMSI, and the hard copy will be mailed to KryoCal, the study's blood storage facility, via US mail.

Blood Pressure (BP) will be determined by the OMRON 907 or similar device which records BP using an oscillometric technique. BP will be obtained by trained and certified data collectors according to a standard protocol, adapted from that used in the OmniHeart trial. Three measurements will be obtained at each visit on the right arm of participants after they rest quietly in the seated position for at least 5 minutes. A cuff of appropriate size will be identified at the initial visit and used thereafter at all subsequent visits.

Weight will be measured three times at each in-person visit. Weight in light indoor clothes without shoes will be recorded. Duplicate measurements will be made to ensure accuracy. Weight will be measured in pounds for ease of interpretation by the participants and subsequently converted to kilograms for data analysis. Scales will be calibrated annually by the Bureau of Weights and Standards and quarterly by EMSI personnel using standard weights.

Height to the nearest 0.1 cm will be measured three times using a calibrated stadiometer. The participant stands shoeless on a firm, level surface, with his/her head in the horizontal (Frankfort) plane.

Waist circumference to the nearest 0.1cm will be measured three times at each in-person visit. With the participant standing in light indoor clothing, the waist at the level of the iliac crest will be measured and recorded.

Labs: A venipuncture kit and tubes for each sample will be prepared in advance by the phlebotomy vendor. The kit will include: 1 pair Vinyl P/F Medium Gloves, 1 Gauze 2x2, 1 Latex-Free Tourniquet, 1 Alcohol Prep Pad, 1 band-aid, 1 24-gauge butterfly needle, 2 10cc red top tubes, one 1 vacutainer transfer device, 20 cryovials (2cc each), one lab pack for mailing, two gel ice packs, and one air bill or shipping label. The blood sample will be drawn by the vendor medical technologist using standard venipuncture technique. The medical technologist will prepare the sample in the following manner: each red top tube will be centrifuged at 3000 rpm for 8-10 minutes; the tube will be opened and the serum will be drawn off the pellet and deposited into secondary tubes, i.e. 2cc cryovials. Samples will be labeled with the study participant's ID number, and the date they were collected. The samples will be placed within the lab pack mailing box, resting between two gel ice packs; the air bill or shipping label will be applied to the lab pack mailing box; the package will be shipped via FedEx to KryoCal, the sample storage vendor, in North Carolina. Samples will be shipped to 4222 Empire Boulevard, Suite 300, Durham, NC 27703. Upon receipt at the KryoCal facility, KryoCal standard operating procedures regarding processing and storage of the specimens will be followed. Samples will be tracked internally on a MSK Access database, located in a restricted access folder on the MSK network.

Questionnaires: Participants will complete behavioral questionnaires and diet and physical activity assessments (**Appendix C**) through the CCSS-based study website.

1. Physical activity will be assessed using the physical activity questionnaire from the Behavioral Risk Factor Surveillance System(5) Time in each intensity category (mild, moderate, or vigorous intensity) is summed based on self-reported activity, intensity, and duration. To examine whether different intensity levels of physical activity are differentially associated with weight loss and the three key metabolic biomarkers, three categories of physical intensity level will be created: 1) meeting vigorous physical activity guidelines (at least 75 minutes per week of vigorous-intensity physical activity, ≥ 6 METS); 2) meeting moderate intensity guidelines (at least 150 minutes per week of moderate intensity activity, 3-5.9 METS); and 3) meeting neither moderate nor vigorous physical activity guidelines.(38)
2. Dietary habits will be collected using the Diet History Questionnaire (DHQ) II for eating habits in the month prior, developed by the NIH. The DHQ II is accompanied by free nutritional component analysis software (<http://appliedresearch.cancer.gov/dhq2/dietcalc/>) Whole food consumption, as

- categorized and classified by MSKCC study staff will be used to calculate the Mediterranean Diet Score, as described in section 11.0 below.(26, 39)
3. Self-efficacy, perceived norms, and risk perception will be assessed as in prior nutritional and physical activity research in the general population and within cancer survivorship. Based on our clinical experience, we anticipate that even apparently motivated participants may struggle with weight loss; these questions will try to elucidate these reasons (if applicable). Self-efficacy is the belief or conviction that one can perform a specific task. Self-efficacy for exercise and eating behavior will each be measured with four questions using a 5-point Likert scale (1=Sure I could do it; 5=Sure I could NOT do it). Lower scores indicate higher self-efficacy. Weight loss in a cancer survivor may be viewed as worrisome or distressing for survivor family and peers. Therefore, we will capture subjective norms to describe the environment of support (or opposition) to weight loss among participants. Four questions will be rated 1 (people think I should eat healthy, for example) to 7 (people think I should not eat healthy). Lower scores will indicate that healthy behaviors are supported and considered normal. Finally, risk perception embodies the level of concern or worry about health effects of obesity. Perceived risk of diabetes and heart disease will be evaluated through 5 questions each, rated on a scale of 1 (strongly agree) to 5 (strongly disagree). Answers will be scored by MSKCC study staff. The first two questions under perceived risk will require reverse coding; lower scores will indicate higher perceived risk. For questions 3 through 5, higher scores will indicate higher perceived risk. A higher overall score will indicate higher perceived risk for diabetes or heart disease. Importantly, this portion of the questionnaire is based on a long history of behavioral research.(40-49)

Repeat visits: Following the baseline assessment, visits will be repeated at approximately 12 months and 24 months (study conclusion) for all participants. Repeat visits will also be requested of participants whose sample cannot be utilized due to shipping or laboratory error.

Study participants will also be offered the option of personally reporting their height, weight, and waist measurements if scheduling with EMSI is not feasible. In these cases, an electronic scale and batteries will be mailed to the patient to improve accuracy of this self-report. An introduction to the scale has been added to Appendix J.

Study staff may contact participants by phone to get follow-up and feedback on the EQUAL study experience.

8.0 TOXICITIES/SIDE EFFECTS

The benefits of weight loss, either self-directed or call center-directed, are myriad, although some risks do exist. Rarely, cardiovascular events can occur as a result of physical activity. Examples of these events include arrhythmias, myocardial infarction, and sudden cardiac death. The risk of these events is related to the baseline fitness level, medical disease, and the intensity of the activity. *Healthways at Hopkins* weight-loss counselors are trained to assess baseline fitness and to advise a stepwise approach to increasing physical activity in 10-minute intervals. Any suggestion of ill effect will result in a referral to a local physician or emergency room. Participants who are known to have coronary artery disease, congestive heart failure, a history of an MI, or other medical contraindications will not be eligible to participate.

A small risk to venipuncture can be anticipated. This includes bruising at the site of venipuncture, pain, or a small amount of bleeding.

9.0 PRIMARY OUTCOMES

Tests and measures for the EQUAL Study are described under Section 7.0, above.

Primary outcome:

Weight loss at 24 months

Secondary outcomes:

Three pre-specified biomarkers:

Fasting insulin

Leptin:adiponectin ratio

Small, dense LDL

Diet goal: 3.5 servings of vegetables per day

Physical activity goal: ≥ 180 minutes of moderate to vigorous physical activity per week

Modifying factors:

Diet quality, assessed with the Mediterranean Diet Score

Physical activity, assessed via 7-day Physical Activity Recall

Self-efficacy, perceived norms, and risk perception (see questionnaire, **Appendix C**)

10.0 CRITERIA FOR REMOVAL FROM STUDY

Participants can stop being in the study at any time. Participants may also be removed from the study at the discretion of the study team.

11.0 BIOSTATISTICS

Overview

This study is a randomized trial to determine the efficacy of the remotely-delivered weight loss intervention among ALL survivors who are at increased risk of late occurring cardiometabolic morbidity and mortality. The intervention components are described in section 4.0. Following enrollment into the study and completion of the informed consent form, participants will be randomized to the intervention group or the control group. A description of the analytic approach follows.

Analytic Plan

Aim 1: Determine the efficacy of the remotely-delivered diet and physical activity intervention, compared with a standard control

The primary outcome is weight loss at 24 months after randomization. Weight loss will be evaluated in an intent-to-treat analysis with a linear mixed effects model with robust standard errors and an unstructured covariance matrix(50) using weight measured at each time points (0, 12 months and 24 months after randomization) as the outcome modeled as a function of time, randomization arm, a history of CRT, gender, age, and race together with interaction terms between time and randomization arm. By using an unstructured covariance matrix with data where measurements are taken at fixed time points, our model essentially reduces to the classical multivariable regression model and eliminates the need to specifically model random effects(51). The test of the difference in weight loss between the two arms at 24 months will be evaluated

after the model has been fit. For the primary aim our underlying model assumes that weight satisfies

$$weight_{ij}(t) = \begin{cases} \beta_{10} + \beta_{11}visit + \beta_2CRT + \beta_3age + \beta_4race + \epsilon_i & \text{in the Intervention group} \\ \beta_{C0} + \beta_{C1}visit + \beta_2CRT + \beta_3age + \beta_4race + \epsilon_i & \text{in the Control group} \end{cases}$$

where $visit = 0, 12, 24$. The primary endpoint, the average difference at 24 months, can be written as $(\beta_{10} - \beta_{C0}) - 24(\beta_{11} - \beta_{C1})$. The test of whether this difference is significantly different from 0 will be carried out with an F -test.

We will evaluate the fitted mixed effects model to ensure that the underlying distributional assumptions, including whether the random error is normally distributed and whether the within-group errors are independent and identically distributed, are satisfied. Diagnostic plots such as individual boxplots for each participant, plots of standardized residuals and observed versus fitted values of weight from the model will be assessed(52).

Aim 2: Calculate the effect of the diet and physical activity intervention, compared to self-directed weight loss, on three key metabolic biomarkers

For Aim 2, the three outcomes are fasting insulin, leptin:adioponectin ratio, and small, dense LDL. The metabolic biomarkers will be measured with a blood draw at baseline, and then again at 12 months and 24 months after randomization. The differences in endpoints at 24 months will be the main outcome. Mixed effects models, described under Aim 1 will be used to analyze these outcomes (separately for each metabolic biomarker), as a function of time, randomization arm, CRT history, gender, age, and race together with interaction terms between time and randomization arm.

Aim 3: Calculate the relative contribution of diet and physical activity to weight loss and the three key metabolic biomarkers

In Aim 3, the four outcomes are weight and each of the three key metabolic biomarkers. Physical activity will be measured via a validated questionnaire, the 7-Day Physical Activity Recall, as described above. To examine whether different intensity levels of physical activity are differentially associated with weight loss and the three key metabolic biomarkers, three categories of physical intensity level will be created: 1) meeting vigorous physical activity guidelines (at least 75 minutes per week of vigorous-intensity physical activity, ≥ 6 METS); 2) meeting moderate intensity guidelines (at least 150 minutes per week of moderate intensity activity, 3-5.9 METS); and 3) meeting neither moderate nor vigorous physical activity guidelines.(38)

As in our prior work with ALL survivors, the quality of diet will be assessed using the Mediterranean Diet Score.(26) Briefly, recorded consumption of whole foods is divided into positive components (fruits, vegetables, fish, cereals, legumes, olive oil) and negative components (meat and dairy). Median intake of each component is calculated. Using DHQ II responses, this categorization will be completed by Nidha Mubdi, MPH, as performed in our prior work. Subject score points by being at or above the median intake of positive components and below the median intake of negative components. Subjects can score a single point for intake of alcohol within a specified range (one to six drinks per day for men and $\frac{1}{2}$ to three drinks per day for women). A subject who is adherent to a Mediterranean Diet pattern on all components would score 8, while a subject who was non-adherent to a Mediterranean Diet pattern on all components would score 0.

Mixed effects models, as described above, will be used to analyze the impact of these measures on the four outcomes (initially with separate models for diet and physical activity), as a function of time, measurements, CRT history, gender, age, and race together with interaction terms between time and diet or physical activity measurements. Separate models by randomization arm will be performed.

Aim 4: Assess the roles of self-efficacy and risk perception on meeting diet and physical activity goals.

In an effort to understand what influences diet and physical activity in adult survivors of childhood ALL, we will compare participants who achieve dietary (3.5 servings of vegetables per day)(26) or physical activity (180 minutes per week) goals to those who do not.(34) Importantly, our preliminary work suggests that these goals are both achievable and likely to be metabolically beneficial. Prior work among survivors of adult cancer suggests that perceived behavioral control (i.e. their sense of self-efficacy) and risk perception are relevant to behavioral and nutritional change(40, 44, 53-56). Subjects with high self-efficacy and with high levels of perceived risk will be most likely to make behavioral changes (in physical activity and nutrition). Perceived risk will be assessed by measuring perceived risk of developing heart problems or diabetes in comparison with others of their age and sex using 5-point Likert type items(57-59). Self-efficacy will be measured as outlined by Sallis(60).

Totals, or “scores,” for self-efficacy and risk perception will be calculated by adding together responses. Median, mean, and mode will be calculated, and scores will be examined for outliers and normal distribution. This type of calculation has been described and validated for nutritional research in different populations, including cancer survivors.(40-49) As described previously, mixed effect models will be used to explore the impact of these measures on diet and physical activity goals as a function of the score, time, gender, age, and race together with interaction terms between time and scores. Separate models by randomization arm will be performed.

Missing data

Despite our efforts to encourage all participants to remain in the study, it is likely that some will drop out of the study at different points in time. It is for this reason that the primary analytic method we will use is a mixed effects model. The mixed effects model produces valid estimates of the treatment effect as long as data are missing at random (that is, missing data are independent of unobserved measurements conditional on the observed data), allows participants with incomplete data to contribute information to the estimated treatment effect, and is consistent with the intent-to-treat principle(61). We will evaluate the missing data mechanism by modeling the drop out process and the data simultaneously and testing whether the dropout depends on unobserved weight measurements.

Non-participation

To assess the generalizability of our results, we will assess non-participant bias. Socio-demographic characteristics and previous cancer therapy will be compared between participants and non-participants to determine if a particular subgroup is underrepresented in the study. These data are available through the CCSS cohort dataset. Importantly, every effort will be made to measure a final (24 month) weight for every participant. The POWER study was able to measure final (24 month) weight for 94.5% of participants.

Sample size and power

Based on body mass index $\geq 25\text{kg/m}^2$ at the most recent survey, we expect approximately 2349 ALL survivors enrolled in the CCSS to be eligible for this study. We plan to enroll 200 ALL survivors in the control arms and 200 ALL survivors in the intervention arm for a total of 400 subjects.

Difference in average weight loss between arms (kg)	Power for overall comparison
2.50	79%
2.75	87%
3.00	91%
3.25	94%
3.50	97%
3.75	98%
4.00	99%
4.25	>99%

Aim 1: In the most recent data available on the ALL survivors in the CCSS who will be eligible for this study (N=2349), the mean weight was 88.6 kg with a standard deviation (σ) of approximately 19. Based on prior weight loss studies including the POWER trial, we assume the correlation between longitudinal measurements of BMI will be 0.85(33, 34). In the POWER trial, the average weight loss in the self-directed (control) arm from baseline to the 24 month assessment was 0.8 kg. Assuming a baseline weight of 88.6 kg (σ =19) in both arms of our proposed study and that we observe a similar weight loss of 0.8 in the self-directed arm, with 200 participants in each arm we will have 87% power to detect a clinically meaningful difference in weight loss of 2.75 kg between the two groups at 24 months (corresponding to approximate 24 month measurements of 87.8 kg vs. 85.05 kg) using a two-sided 0.05 level test. The tested intervention (CCD) in this trial is run by *Healthways at Hopkins* and was previously tested in the POWER trial.(34) Among obese participants in POWER, the mean weight reduction from baseline to 24 months was 4.6kg in the CCD group and 0.8kg in the control (self-directed) group, and other behavioral intervention studies have met or exceeded this level of weight loss.

Aim 2: In our preliminary work among 118 ALL survivors (Table 4), we found standard deviations of 10.2 for fasting insulin, 2.0 for the leptin:adiponectin ratio, and 20.0 for small dense LDL across all participants. Assuming similar variation in our data, using two-sided 0.0125 level tests for each of the 3 outcomes, we have 90% power to detect a difference between the intervention and control groups for each outcome separately if the true difference between groups in (a) fasting insulin is 3.89, (b)

leptin:adiponectin ratio is 0.76, and (c) small dense LDL is 7.62.

Hormone and fat measures in 118 childhood ALL survivors

	All N=118		CRT N=39		No CRT N=77	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Leptin:adiponectin	1.7	2.0	2.6	2.5	1.2	1.5
Insulin	18.5	10.2	22.1	12.4	16.7	8.4
Glucose	97.4	14.9	95.7	23.0	89.3	7.3
HOMA-IR	4.2	2.6	5.3	3.3	3.7	2.0
HsCRP	3.6	4.4	5.1	4.4	2.8	4.2
Weight (kg)	77.1	19.2	78.5	22.5	76.4	17
Height (cm)	166.5	10.3	161.2	11.2	169.3	8.7
BMI	27.9	7.0	30.2	8.2	26.7	5.9
Small dense LDL ₃₊₄	50.9	20.0	57.7	19.8	48.0	19.4

Aim 3: Assuming the same standard deviations for the three metabolic parameters as listed above and a standard deviation of 19 kg for weight, using a two-sided 0.0125 level test there is a 90% probability that we will detect an association between each independent variable, the

dietary characteristics and physical activity, separately for each arm, with (a) weight loss if the true change in weight loss is 5.14 units per one standard deviation change in the independent variable (b) fasting insulin if the true change in fasting insulin is 2.76 units per one standard deviation change in the independent variable, (c) the leptin:adeponectin ratio if the true change in the ratio is 0.54 units per one standard deviation change in the independent variable, and (d) small dense LDL if the true change in small dense LDL is 5.41 units per one standard deviation change in the independent variable

Aim 4: There is an 80% probability that the study will detect a relationship between the self-efficacy or perceived risk and meeting the dietary goal, within each randomized arm, at a two-sided 0.05 significance level if the true change in the dietary intake is 0.199 standard deviations per one standard deviation change in self-efficacy or perceived risk. We have the same probability of finding a relationship between these independent variables and meeting the physical activity goal.

A timeline for the EQUAL Study implementation is provided below. All testing and questionnaires should be performed within four weeks of the intended measurement.

Project Year	PY1		PY2		PY3		PY4		PY5	
Months	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun

Calendar Year	2014	2015	2015	2016	2016	2017	2017	2018	2018	2019
Protocol development	x									
Intervention piloting	x									
Recruitment		x	x	x						
Randomization		x	x	x						
Intervention		x	x	x	x	x	x	x	x	
Home visits, questionnaires		0		12		24				
Data analysis, publication									x	x
Dissemination										x

12.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000 and OCR_PPR/OCR@MSKCC.ORG. The completed signature page of the electronic consent/RA, a completed Eligibility Checklist and other relevant documents will be emailed to MSK research staff by CCSS staff within 48 hours of patient consent. MSK staff will then register the patient with PPR via the PPR Electronic Registration System (<http://ppr/>).

12.2 Randomization

Patients will be randomized with a 1:1 ratio to either the intervention arm or the control arm stratifying on a history of cranial radiation therapy. After they have been registered to the PPR, participants will be randomized using the Clinical Research Database (CRDB) by calling the MSKCC PPR Office at 646-735-8000 between the hours of 8:30 AM and 5:30 PM, Monday-Friday. Randomization will be accomplished by the method of random permuted block. Participants will not be blinded to their treatment group assignments.

13.0 DATA MANAGEMENT ISSUES

The CCSS, the MSKCC laboratory, and the *Healthways at Hopkins* teams will convey data to the MSKCC biostatistics team, led by Chaya S. Moskowitz, PhD (Co-Investigator), who will collate and integrate data appropriately. The database will be created using the existing platform of the MSKCC Clinical Research Database (CRDB), an institutionally supported database for clinical research data. All participants will be registered into CRDB at the time of randomization, after providing informed consent. Throughout the study, the CCSS ID number will be used to identify participants.

13.1 Quality Assurance

The Survivorship research team comprising of a CRM, CRC, RPC, and RSAs will be assigned to manage the data on this study. The responsibilities of the research staff will include project compliance, ensuring complete data collection and entry, problem resolution, and coordination of all study activities. The research team will meet with the Principal Investigator regularly to review study progress, reconcile data, and to manage any difficulties.

13.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: <http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://inside2.clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation.

13.3 Regulatory Documentation for Participating Sites

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB of Record.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB membership
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae/biosketch and medical license (if applicable) for each investigator
- Documentation of Human Subject Research Certification for investigators and key staff members

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with the study.

13.3.1 Amendments

Each change to the protocol document must be organized and documented by MSK and approved first by the MSK IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating site. All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.

Each participating site must obtain IRB approval for all amendments within 90 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, participating sites will not be permitted to continuing enrolling new participants until site IRB approval of the revised protocol documents is granted and submitted to MSK.

13.3.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment.

Deviations

A protocol deviation on this study is defined as any incident involving non-adherence to an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events should be reported according to section 14.2.

Deviations that do not adversely affect the rights and/or welfare of the participant or the scientific validity of the study and are related to protocol scheduling changes outside of the allowed window due to a holiday (e.g., New Year's, Thanksgiving, etc.) and/or inclement weather or other natural event do not require reporting to the MSK IRB/PB. However, they must be clearly documented in the patient's medical record.

Prospective Deviations

Deviations to the research protocol that involve patient eligibility, an informed consent procedure change, and/or treatment/pharmacy alterations that are not allowed by the protocol require prospective approval from the MSK IRB/PB prior to the change being carried out. Participating sites should contact the MSK PI who will in turn seek approval from the MSK IRB/PB.

Retrospective Deviations

Deviations that include a change or departure from the research protocol without prior approval from the MSK IRB/PB are considered retrospective deviations. Retrospective deviations should be reported to the MSK PI as soon as possible, who will in turn report the deviation to the MSK IRB/PB as per MSK guidelines.

Participating Site IRB Reporting

Participating sites should report all deviations to their institution's IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations should be submitted to MSK upon receipt.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

13.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified. The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the investigator will maintain all source documents, study related documents and CRFs for 3 years.

13.4 Noncompliance

If a participating site is found to be noncompliant with the study protocol, study involvement may be suspended and/or contract payments may be withheld (if applicable), until the outstanding issues have been resolved.

14.0 PROTECTION OF HUMAN SUBJECTS

Subjects will be treated with respect and sensitivity. All information will be labeled with unique study identification numbers and stored in password-protected computerized databases. Study files will be kept in locked cabinets and access restricted to study staff. No data will be sent over the internet unless it is encrypted. Only key personnel will have access to the information in the database on an as-needed basis. Key personnel may not alter the data in the database or directly view all of it without specific cause and approval of the PI. All email with subject-identifiable information will be password protected. Findings will be presented in aggregate form only with no references made to the individual participant's data. Confidentiality of each participant's data will be protected with utmost care with all questionnaire data identified solely by a code number. A list matching participants' names and code numbers will be maintained on an Excel sheet on MSKCC secure servers, with limited access.

Costs: Participants will not be charged for protocol-related costs. As a token of appreciation for their time and effort, participants will be compensated \$50 gift card upon completion of each of the study measurements (0, 12-months, and 24 months; maximum total of \$150 per participant), as well as trinkets (pen, magnet or keychain) with the study logo.

Alternatives: Participants will be informed of their right to withdraw from the study at any time.

Risks and Associated Support Services: Over time, the CCSS has developed the infrastructure and trained personnel to assist CCSS participants with information needs, facilitate community referrals, and provide crisis management for the small number of distraught survivors. A full-time master-level trained oncology nurse responds to calls from the CCSS 1-800 telephone number and works closely with the CCSS Project Director (Armstrong). Institutional PIs are also called upon to expedite community referrals for health services.

14.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

14.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

14.2.1

Not applicable.

15.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, potential participants will be informed of the full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Survivors will be informed that participation is voluntary and will not affect their continued participation in other aspects of CCSS. Participants will also be informed that they are free to withdraw from the study at any time. The randomized study design will be described in detail, with particular attention given to ensuring that participants are willing to be assigned to either the active intervention or attention control group. The CCSS Principal Investigator (Gregory Armstrong, MD), as well, as the staff at the CCSS Coordinating Center, will be available to respond to questions or concerns of the survivor. All participants will be consented online via a secure website managed at the CCSS Coordinating Center. A copy of the informed consent will be automatically printed out, and mailed or emailed to the participant for their records. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study.
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

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17.0 APPENDICES

Appendix A: Introduction Letter
Appendix B: Healthways at Hopkins Screen Shots
Appendix C: Baseline Questionnaires
Appendix D: Control Group Brochures
Appendix E: Study Brochure
Appendix F: EMSI Site Contact Report Form
Appendix G: Letter to Participant with gift card
Appendix H: Letters to Control Group
Appendix I: Letter to Participant with Trinket
Appendix J: Verbal and email scripts
Appendix K: EQUAL magnet
Appendix L: Birthday Card