CHILDHOOD CANCER SURVIVOR STUDY Analysis Concept Proposal
March 25, 2021

1. **STUDY TITLE**: Incidence and Risk Factors for Late Total Joint Arthroplasty in Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

2. **WORKING GROUP AND INVESTIGATORS:**
Primary CCSS Working Group: Chronic Disease Working Group

Proposed Investigators Include:

Wayne Cohen-Levy: wayneblevy@gmail.com (Current affiliation: Massachusetts General Hospital Orthopaedic Arthroplasty Fellow, Boston, MA.)

Jamie Shoag: JamieShoag@gmail.com (Current affiliation: University of Miami/Jackson Memorial Pediatric Hematology and Oncology Fellow, Miami, FL)

Eric Chow: ericchow@uw.edu

Christopher Weldon: Christopher.Weldon@childrens.harvard.edu

Andrew Murphy: Andrew.Murphy@STJUDE.ORG

Kiri Ness: Kiri.Ness@STJUDE.ORG

Duncan Ramsey: DCRamsey@mgh.harvard.edu

Greg Armstrong: greg.armstrong@stjude.org

Stephanie Dixon: Stephanie.Dixon@STJUDE.ORG

Kerri Becktell: kbecktell@mcw.edu

Wendy Leisenring: wleisenr@fredhutch.org

Rebecca Howell: rhowell@mdanderson.org

Yutaka Yasui: yutaka.yasui@stjude.org

Yan Yuan: yyuan@ualberta.ca

Kevin Raskin: KRaskin@mgh.harvard.edu

Brent Weil: Brent.Weil@childrens.harvard.edu

3. **BACKGROUND AND RATIONALE:**

With advancements in therapies for pediatric malignancies, long-term survivors of childhood and adolescent cancers represent a growing population[1]. Adult survivors of childhood cancer have a high burden of chronic health conditions including total joint arthroplasty (TJA)[2]. In 2006, Oeffinger et al. described a dramatic increase in risk of requiring TJA in the Childhood Cancer Survivor Study (CCSS) original cohort, diagnosed 1970-1986, with a 54 times higher risk of requiring TJA in cancer survivors compared to sibling controls[2]. At the time of this study, the mean age in childhood cancer survivors was 26.6±6.1 years old and for sibling controls was 29.2±7.3 years old[2], far younger than the average age for requiring TJA in the general population of 68.9 years[3]. In fact, despite the high relative risk of people who undergo TJA, the prevalence of TJA was relatively low amongst survivors and siblings (1.61% and 0.03% respectively).

The increased risk of TJA in survivors of childhood cancer may be attributed to osteonecrosis (ON), a well-described sequelae of many cancer therapies[4-7]. In 2008, Kadan-Lottick et al. reported a relative risk of osteonecrosis amongst survivors in the CCSS cohort to be 6.2 times that of sibling controls (cumulative incidence of 0.43% vs 0.03% respectively)[4]. A novel finding of this study was that the cumulative incidence of ON increased over time from treatment, contrary to previous studies in which ON was thought to be an acute toxicity of therapy[4,5,8]. While this study did not report treatments of ON[4], a population-based study of the Finnish and Danish registries estimated a cumulative incidence of severe ON necessitating TJA in survivors of childhood hematological malignancies ranged from 0.4%-4.5%[6]. However, this study only looked at patients requiring orthopedic intervention before 40 years of age[6], potentially missing a large group of survivors who may require TJA later in life.

The association of corticosteroids and subsequent ON is well documented[9,10]. McAvoy et al. demonstrated that the cumulative dose of corticosteroid correlated to the risk of subsequent ON in patients undergoing hematopoietic cell transplantation[11]. These results are supported by animal model studies demonstrating a dose-dependent response of the articular cartilage and subchondral bone to variable levels of dexamethasone[12].

Despite advancements in treatment of pediatric sarcomas specifically, many survivors are limited in the long term due to impaired functional abilities[13]. In fact, survivors of primary bone malignancies and soft tissue sarcomas had higher rates of major joint replacement as compared to other survivors of other childhood cancers[2]. Of 167 major joint replacements listed, 93 were among bone tumor survivors (affecting 8% of bone tumor survivors) and remainder (n=74) were in other cancers, with leukemia (0.7% of leukemia survivors) the most common. These sequelae may be a consequence of radiation treatment given for sarcomas as it has been shown to result in fibrosis, bone growth abnormalities and impaired function[14]. A previous analysis of survivors of Ewing's Sarcoma in the CCSS cohort demonstrated significantly higher rates of chronic health conditions, which includes arthritis, in survivors as compared to sibling controls[15].

Several chemotherapeutic agents have demonstrated toxicity to the skeletal growth plate. Etoposide[16], Cyclophosphamide[16], 5-Flourouracil[17] and Methotrexate[18,19] have all been found to have deleterious effects on the growth plate in animal models. Previous use of folic acid

antagonists was associated with growth arrest lines on radiographs indicating periods of slowed longitudinal growth[19].

Radiation therapy in children can also have significant musculoskeletal implications including rickets, slipped capital femoral epiphysis, and osteonecrosis[20]. Open growth plates in skeletally immature children can lead to angular deformities and limb length discrepancy[21,22]. Van Dijk et al. found that radiation therapy to the flank or abdomen in Wilms tumor survivors was an independent predictor of adverse orthopaedic events such as limb length discrepancy, short stature and pain[23].

Alterations to the skeleton during childhood alter normal joint kinematics and loading which can lead to abnormal contact stresses thus predisposing to osteoarthritis. Furthermore, while the proximal femoral physis is only responsible for approximately 25% of longitudinal growth of the femur, alterations in the growth plate can change the neck-shaft angle (the angle formed between the femoral head and neck and the femoral shaft). Such alterations can similarly lead to altered gait mechanics, contact stresses and cartilage degeneration. Lastly, chronic kidney disease has been shown to impact bone turnover, bone mineral density and longitudinal growth.[2425]

TJA is indicated to treat end stage arthritis of various joints. It is commonly performed on the hip, knee and shoulder but replacement of the elbow, wrist and ankle are increasing in popularity. Similarly, obesity has been shown to be a risk factor for requiring TJA at an earlier age[26]. Lastly, osteonecrosis has also been shown to be a risk factor for undergoing TJA at an earlier[27]. While surgical techniques and implants have improved, joint replacements at younger ages increase the risk of requiring a revision surgery. This is due to a combination of wear on the prosthetic materials and generally increased activity in the younger population as compared to a more elderly and sedentary cohort.

Previous studies have shown that survivors of childhood cancer are at increased risk for functional and physical limitations later in life [2829]. Previous literature using the CCSS population has demonstrated that ON is a risk factor for lower functional scores as compared to controls [30]. The authors also found that survivors who had surgery to treat their ON fared even worse from a functional standpoint as compared with their counterparts who had not undergone surgical treatment[30]. To the best of our knowledge, a comparison of functional outcomes has not been performed when comparing specifically those survivors who had joint replacement surgery as compared to those who did not.

Although childhood cancer survivors have been shown to have a significantly higher risk of TJA in early CCSS cohort surveys, the literature is very limited and *longer follow-up among the original CCSS cohort and the addition of an expanded cohort will allow us to study the risk of requiring a TJA later in life in greater depth*. This will be the first comprehensive assessment of the incidence, treatment and disease related risk factors for needing a joint replacement in survivors of childhood cancer using the CCSS cohort. Furthermore, we aim to evaluate the need for joint replacement by anatomic location which has not been done in the CCSS population. We will also investigate the correlation between ON in earlier surveys and TJA on subsequent follow-up. These results will provide valuable information on an aging CCSS cohort for which the risk of needing TJA may not have been fully appreciated in earlier years with a younger

survivor and sibling cohort. We believe that these results will provide meaningful information for screening and management in the CCSS cohort and for future childhood cancer survivors.

4. **SPECIFIC AIMS / OBJECTIVES / RESEARCH HYPOTHESES**:

1. **Aim 1:** Determine the cumulative incidence and mean age of late TJA (i.e., total hip arthroplasty, total knee arthroplasty, total shoulder arthroplasty and other joint arthroplasty >5 years from diagnosis) amongst non-bone tumor childhood cancer survivors compared with sibling controls.
   Hypothesis: Survivors of non-primary bone tumor childhood cancers will undergo TJA at an increased rate and at a younger mean age relative to sibling controls.

2. **Aim 2:** Determine the cumulative incidence and mean age of late TJA (i.e., total hip arthroplasty, total knee arthroplasty, total shoulder arthroplasty and other joint arthroplasty >5 years from diagnosis) amongst primary bone tumor childhood cancer survivors compared with non-bone tumor survivors and with sibling controls.
   Hypothesis: Survivors of bone tumors will undergo TJA at an increased rate and at a younger mean age relative to non-bone tumor survivors and relative to sibling controls.

3. **Aim 3:** Determine which demographic factors, cancer diagnoses, and cancer treatment-related exposures are associated with risk for requiring TJA among childhood cancer survivors.
   Hypothesis 1: Frequency of TJA will vary amongst survivors by age at diagnosis, cancer diagnosis, and treatment modalities. Specifically, among non-bone tumor survivors: 1. Those who were diagnosed at younger ages when growth plates are highly vascularized, will be more sensitive to the toxic effects of chemotherapy. 2. Those whose have joints involved in a radiation field will be more likely to require TJA. 3. Those who receive stem cell transplant will undergo more TJA
   Hypothesis 2: Frequency of TJA will vary amongst survivors by age at diagnosis, cancer diagnosis, and treatment modalities. Specifically, among bone tumor survivors: 1. Those who were diagnosed at younger ages when growth plates are highly vascularized, will be more sensitive to the toxic effects of chemotherapy. 2. Those whose have joints involved in a radiation field will be more likely to require TJA

4. **Aim 4:** Compare long term functional outcomes between survivors who underwent TJA, survivors who did not undergo TJA and sibling controls who underwent TJA.
   Sub-aim 4-1: Among survivors who have undergone TJA, determine the impact of cancer diagnosis, cancer treatment exposures, age at TJA and joint replaced (IE shoulder vs. hip vs. knee) on functional outcome scores.
   Hypothesis 1: Sibling controls will report the highest functional scores. Survivors who required TJA will report the lowest functional scores.
   Hypothesis 2: Age of TJA, cancer diagnosis and joint replaced will significantly correlate with long term function. Those survivors who required TJA at a relatively young age, survivors with primary bone or CNS malignancies and those who had their shoulder replaced will have lower functional scores as compared to others.

5. **ANALYSIS FRAMEWORK**:

Subject Population:

The study sample will consist of childhood cancer survivors and a sibling comparison group enrolled in the CCSS cohort who responded to the baseline or expansion baseline questionnaires. A stratified analysis of two populations will be analyzed consistent with the aims listed above. Bone tumors will be defined as Ewing's Sarcoma, Osteosarcoma and all other tumors that arise from bone, cartilage or periosteum. The non-bone tumor cohort will include all other childhood malignancies including leukemias (all subtypes), lymphomas (all subtypes), soft tissue sarcomas (e.g., rhabdomyosarcoma), neuroblastoma, Wilms Tumor, and CNS malignancies (e.g., astrocytoma, medulloblastoma). *The reason for separating the two cohorts is that primary bone tumors commonly require joint replacement, amputation or other limb salvage surgery as part of the primary treatment of sarcoma, which we hypothesize will increase their risk of subsequent later TJA.* In order to separate those survivors who may have had these treatments we will use a stratified analysis approach.

Outcomes of Interest:

Survivors and siblings will be defined as having undergone a TJA if they responded "yes" to question on the 4th or 5th follow-up questionnaires. Age and joint replaced will be queried from the free text follow-up question.

- Total joint replacements (Baseline [both original & expansion cohort]- I.5, FU4 (2007) and FU5 (2014) survivor and sibling surveys - J5), as well as age at replacement, and specific joint replaced.
- Physical Performance: Scored by adding the answers to a series of 6 questions about participant's performance of particular physical activities during the past 2 years. Functional status was assessed on the Original Baseline N14 a-f, Expansion Baseline O20 a-f, FU4(2007) N26 a-f and FU5 (2014) N29 a-f. Scores of 1 to 3 are assigned to each of the 6 questions. A lower score indicates a greater degree of limitation[28,31]. This outcome will be calculated as a continuous score. In addition, patients will be categorized as impaired in Physical Performance if their cutoff score is below the 10th percentile of the distribution of the sibling group[30]. As previously studied [28], participation restrictions will also be evaluated in three separate categories based on yes vs no questions Original Baseline N10-12, Expansion Baseline O16-18, FU4(2007) N22-24 and FU5 (2014) N25-27. Responses will be evaluated as a percentage of respondents who respond "Yes" to each question individually. Respondents will be censored at their last completed functional outcome response.
- A preliminary query of the available data was performed. A total of 642 late TJAs were performed amongst 25658 survivors (2.50%). Of that total, when considering only survivors of non-primary bone malignancies, 307 survivors required TJA out of a total of 23663 (1.3%). In contrast, 29 siblings required TJA out of a total of 5051 (0.57%).

Exploratory Variables:

A. Sociodemographic Variables:

- Age (BL, FU 2014 & birth date)
- Sex (BL- A2)
- Race/ ethnicity (BL- A4)

B. Disease / Treatment Variables:
Treatment related variables will be analyzed to investigate if any association can be established between treatment exposures and an increased risk of long term TJA. Exposure to radiation as part of the survivors' index treatment will be included as a potential risk factor. The thought is that either the radiation treatment or scatter could affect the physis of an adjacent joint (IE chest radiation scatter potentially affecting the physis of the proximal humerus, pelvic radiation scatter potentially affecting the physis of the proximal femur). If the physis is affected, skeletal growth and development could be altered which could lead to alterations in joint development and biomechanics.

- Cancer diagnosis
    - Leukemia (ALL, AML, other)
    - Lymphoma (HL, NHL)
    - CNS tumors (Astrocytoma, Medulloblastoma/PNET, other CNS)
    - Non-CNS/Sarcoma Solid Tumor (Neuroblastoma, Wilms tumor)
    - Primary Bone Sarcoma (Ewing's Sarcoma, Osteosarcoma)
    - Soft Tissue Sarcoma (Rhabdomyosarcoma, Nonrhabdomyosarcoma soft tissue sarcoma)
- Era of diagnosis
    - 1970s
    - 1980s
    - 1990s
- Age at diagnosis
- Chemotherapy vs. steroids vs. surgery vs. radiation vs. stem cell transplant vs. combination
- If "yes" to chemotherapy, then
    - Vinca alkaloid
    - Alkylating agent (with cumulative dose expressed as cyclophosphamide equivalent dose)
    - Platinum agent
    - Antimetabolites: 6-mercaptopurine, 5-fluorouracil, gemcitabine, cytarabine, methotrexate
    - Anthracycline (with cumulative dose expressed as doxorubicin equivalent dose)
    - Topoisomerase: etoposide
    - We will first explore individual chemotherapeutic agent exposure as a binary (Y/N) and then, for those agents where cumulative doses are known, we will consider dose relationships in tertiles (or other categories) if the sample sizes permit
- If "yes" to steroids, then
    - Prednisone only
    - Any Dexamethasone
    - As steroid doses are not available, we will consider the variable as a binary term
- If "yes" to radiation, then
    - Any radiation exposure to a field that includes the shoulder
        - If upper extremity directly treated, maximum target dose
        - If extremity not treated
            - High Stray
            - Low Stray

- Any radiation exposure to a field that includes the hip
  - If pelvis directly treated, maximum target dose
  - If pelvis not treated
    - High stray
    - low stray
- Any radiation exposure to a field that includes the knee
  - If upper extremity directly treated, maximum target dose
  - If extremity not treated
    - High Stray
    - Low Stray

D. Associated/preceding symptoms and diseases:

- Osteonecrosis (FU2 [2003] – P4, P5, P6) – Due to the fact that only the original CCSS cohort completed this survey and these data are not captured elsewhere, we acknowledge that information about osteonecrosis may not be available for a sizeable portion of the population. Therefore, osteonecrosis will be treated as an exploratory variable.
- Body mass index (BMI; all questionnaires)
  - Based on participants answers to height and weight questions, body mass index will be analyzed as a continuous variable.
  - We will use the BMI value prior to age of first TJA. However, we recognize that BMI may not be available for all participants as some individuals may have had TJA prior to their first reported BMI value.
    - Based on participants' answers to height and weight questions, BMI will be calculated and categorized according to the CDC guidelines as underweight (BMI < 18.5), normal (BMI between 18.5 and 25), overweight (BMI between 25 and 30) and obese (BMI above 30). For survivors or siblings with joint replacement prior to age 21, BMI will be calculated based on z-score unless the absolute BMI value meets adult overweight and obese thresholds, in which case they would default to that adult BMI category.
- Chronic kidney disease [Stage 3] – as defined by chronic disease matrix.

Data Analysis Plan:

***Aim 1*:** Determine the incidence and average age of TJA in survivors of non-bone tumor childhood cancers compared with sibling matched controls. Within this analysis determine the incidence and average age of total hip arthroplasty, total knee arthroplasty, total shoulder arthroplasty and other joint arthroplasty in survivors of childhood cancer, as compared with sibling controls.

We will tabulate the characteristics (sex, race, BMI) for survivors of non-bone tumor childhood cancers and all sibling controls stratified by TJA. Age at TJA, last follow up, or death, whichever is the earliest will be summarized. Cumulative incidences of TJA, overall as well as the rates of knee, hip, shoulder and other joint arthroplasty, will be estimated for survivors and siblings over their follow-up period. Secondary neoplasms will be treated as a competing risk and last follow up will be treated as a censoring event. To estimate the rate ratio comparing survivors with siblings, piecewise exponential regression model will be developed adjusting for sex, attained age, race and BMI.

- See proposed Figure 1a, Figure 1b, Table 3, Table 4

***Aim 2*:** Determine the incidence and average age of TJA in survivors of childhood bone tumors compared with non-bone tumor survivors and with all sibling controls. Within this analysis determine the incidence and average age of total hip arthroplasty, total knee arthroplasty, total shoulder arthroplasty and other joint arthroplasty in survivors of childhood bone tumors as compared with the two comparison groups.
We will tabulate the characteristics (sex, race, BMI) for survivors of childhood bone tumors and sibling controls stratified by TJA. Age at TJA, last follow up, or death, whichever is the earliest will be summarized. Cumulative incidences of TJA, overall and the four component of TJAs, will be estimated for survivors and siblings over their follow-up period. Death will be treated as a competing risk and last follow up will be treated as a censoring event. To estimate the rate ratio comparing survivors with siblings, piecewise exponential regression model will be developed adjusting for sex, attained age, race and BMI.

- See proposed Figure 1a, Figure 1b, Table 3, Table 4

Aim 3: Amongst all childhood cancer survivors, determine if the incidence of TJA and age at which TJA occurs is impacted by age at cancer diagnosis, cancer type, chemotherapy exposure (including steroids), radiation, site of radiation, stem cell transplantation, and diagnosis osteonecrosis on 2003 questionnaire using univariate and multivariable logistic regression. As with previous aims, survivors will be grouped as either primary bone tumors or other cancers and analyzed separately within that grouping. Within this analysis, determine the incidence of total hip arthroplasty, total knee arthroplasty, total shoulder arthroplasty and other joint arthroplasty in survivors by the above factors.
To estimate the rate ratio of various risk factors, we will develop piecewise exponential regression models for non-bone and bone tumor survivors separately for each outcome of interest (TJA- hip, knee, shoulder and other) wherever the number of events allows. Attained age, sex, race and BMI will be adjusted for. Separate treatment and cancer diagnosis models will be built to avoid the potential collinearity issue.

- See proposed Table 5, Table 6

Aim 4: Evaluate functional outcomes of survivors who underwent TJA as compared to survivors who did not undergo TJA and sibling controls who underwent TJA. To estimate functional limitations, a score will be calculated for each respondent based on the responses to 6 questions which will be scored from 1 to 3 (as defined above). Respondents will be censored based on the last questionnaire completed as functional scores were collected only Original Baseline, Expansion Baseline, FU4(2007) and FU5 (2014). Lower scores indicate a greater degree of limitation. Scores will be compared using the generalized estimation equation (GEE) for assessing the effect of TJA and being a survivor, adjusting for age at assessment and sex.
Sub-aim 4-1: To evaluate the impact of TJA and age at TJA on functional outcome, we use the Impaired Physical Performance status (yes / no) as the outcome. We will develop piecewise exponential regression models for survivors modelling TJA (shoulder, knee, hip and other) as time-varying variables. Age at TJA (possibly categorized) will be evaluate in the same model, adjusting for attained age and sex. Separate treatment and cancer diagnosis models will be built to avoid the potential collinearity issue.

- See proposed Table 7, Table 8

Table 1 - Cohort Demographics		
	Survivors	**Siblings**
Characteristic	**N (%)**	**N (%)**
Race/Ethnicity		
White (non-Hispanic)		
Black (non-Hispanic		
Hispanic		
Other		
Age at last follow up (mean, sd)		
Sex		
Male		
Female		
BMI (Baseline)		
Diagnosis		
Non-Bone Tumors		
ALL		
AML		
Other Leukemia (IE: CML, CLL)		
HL		
NHL		
Astrocytoma		
Medulloblastoma		
PNET		
Other CNS Malignancy		
Neuroblastoma		
Wilms tumor		
Rhabdomyoscarcoma		
Bone Tumors		
Ewing's Sarcoma		
Osteosarcoma		
Other primary bone tumors		
Age at diagnosis (years) (mean, sd)		
Treatments		
Chemotherapy		
Vinca alkaloid		
Alkylating agent		
Platinum agent		
Antimetabolites		
Anthracycline		
Topoisomerase		
Radiotherapy		

Radiation with potential impact to the hips		
Radiation with potential impact to shoulder		
Radiation with potential impact to the knee		
Bone Marrow Transplantation		
No		
Autologous (if known)		
Allogeneic (if known)		
Corticosteroids		
None		
Prednisone		
Any Dexamethasone		
Osteonecrosis		
Prior limb sparing surgery as part of cancer treatment		

Table 2 – Temporal Relationship of TJA to Cancer Diagnosis		
	TJA done within 5 years of diagnosis	TJA done greater than 5 years from year of diagnosis
Survivors with non-bone tumor primary diagnosis		
Survivors with primary bone tumor diagnosis		

Table 3- Cumulative Incidence of Late (> 5 years from diagnosis) TJA in Survivors of Childhood Cancers as Compared to Sibling Controls					
	Survivors with non-bone tumor primary diagnosis	Survivors with primary bone tumor diagnosis	All Sibling Controls (Cumulative Incidence)	Rate Ratio (95% CI)	P-value
All TJA					
Total hip arthroplasty					
Total knee arthroplasty					

Total shoulder arthroplasty					
Other total joint arthroplasty					

Table 4 - Mean Age of TJA in Survivors of Childhood Cancers as Compared to Sibling Controls (2-sample t-test)				
	Survivors with non-bone tumor primary diagnosis	Survivors with primary bone tumor diagnosis	Sibling Control	p-value
All TJA				
Total hip arthroplasty				
Total knee arthroplasty				
Total shoulder arthroplasty				
Other total joint arthroplasty				

Table 5 - Multivariable Logistic Regression Modeling for Rate Ratio of Late (> 5 years from diagnosis) TJA within Non-Bone Tumor Childhood Cancer Survivors					
	All TJA RR (95% CI) p-value	Total Hip Arthroplasty RR (95% CI) p-value	Total Knee Arthroplasty RR (95% CI) p-value	Total Shoulder Arthroplasty RR (95% CI) p-value	Other Joint Arthroplasty RR (95% CI) p-value
Race/Ethnicity					
White (non-Hispanic)					
Black (non-Hispanic					
Hispanic					

Other					
Age (years)					
Sex					
BMI					
Age at diagnosis (years)					
Era of diagnosis					
Treatments					
Chemotherapy					
Vinca alkaloid					
Alkylating agent					
Platinum agent					
Antimetabolites					
Anthracycline					
Topoisomerase					
Radiation					
Pelvic Radiation					
Maximum target dose if pelvis was irradiated					
High Stray					
Low Stray					
Shoulder radiation					
Maximum target dose if upper extremity was irradiated					
High Stray					
Low Stray					
Knee Radiation					
Maximum target dose if lower extremity was irradiated					
High Stray					
Low Stray					
Bone Marrow Transplantation					
No					
Autologous					
Allogeneic					
Corticosteroids					
None					
Prednisone					
Any Dexamethasone					
Osteonecrosis					

Table 6 - Multivariable Logistic Regression Modeling for Rate Ratio of Late (> 5 years from diagnosis) TJA within Bone Tumor Childhood Cancer Survivors					
	All TJA RR (95% CI) p-value	Total Hip Arthroplasty RR (95% CI) p-value	Total Knee Arthroplasty RR (95% CI) p-value	Total Shoulder Arthroplasty RR (95% CI) p-value	Other Joint Arthroplasty RR (95% CI) p-value
Race/Ethnicity					
White (non-Hispanic)					
Black (non-Hispanic					
Hispanic					
Other					
Age (years)					
Sex					
BMI					
Age at diagnosis (years, sd)					
Era of diagnosis					
Treatments					
Chemotherapy					
Vinca alkaloid					
Alkylating agent					
Platinum agent					
Antimetabolites					
Anthracycline					
Topoisomerase					
Radiation					
Pelvic Radiation					
Maximum target dose if pelvis was irradiated					
High Stray					
Low Stray					
Shoulder radiation					
Maximum target dose if upper extremity was irradiated					
High Stray					
Low Stray					
Knee Radiation					

Maximum target dose if lower extremity was irradiated					
High Stray					
Low Stray					
Corticosteroids					
None					
Prednisone					
Any Dexamethasone					
Osteonecrosis					
Prior limb sparing surgery as part of cancer treatment					

Table 7 – Functional Outcome scores		
	Mean Score (SD)	ANOVA
Survivors who previously underwent TJA		
Survivors who did not previously undergo TJA		
Sibling Controls		

Table 8 - Multivariable Logistic Regression Modeling for Functional Outcomes of Survivors who Previously Underwent TJA	
	All TJA RR (95% CI) p-value
Age (years)	
Sex	
BMI	
Age at diagnosis (years, sd)	
Joint Replaced (Shoulder, Hip, Knee, Other)	
Age at TJA (years, sd)	
Osteonecrosis	
Diagnosis	
Non-Bone Tumors	
ALL	
AML	

Other Leukemia (IE: CML, CLL)	
HL	
NHL	
Astrocytoma	
Medulloblastoma	
PNET	
Other CNS Malignancy	
Neuroblastoma	
Wilms tumor	
Rhabdomyoscarcoma	
Primary Bone Tumors	
Osteosarcoma	
Ewings Sarcoma	

Table 9 – Effect of TJA on Participation Restrictions				
	All TJA RR (95% CI) p-value	Total Hip Arthroplasty RR (95% CI) p-value	Total Knee Arthroplasty RR (95% CI) p-value	Total Shoulder Arthroplasty RR (95% CI) p-value
N25: Because of any impairment or health problems, do you need the help of other persons with personal care needs, such as eating, bathing, dressing, or getting around your home?				
N26: Because of any impairment or health problems, do you need the help of other persons in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?				
N27: Does any impairment or health problem				

keep you from holding a job or attending school?				

Figure 1

- 1a: Cumulative incidence curve for all total joint replacements, total hip replacement and total shoulder replacement in survivors stratified by primary bone tumor and non-bone tumor cohort
- 1b: Cumulative incidence curve for all total joint replacements, total hip replacement and total shoulder replacement in siblings

6. **SPECIAL CONSIDERATIONS**:

No special considerations exist for this proposal.

1. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 9 Registries, Nov 2019 Sub (1975-2017) - Linked To County Attributes - Time Dependent (1990-2017) Income/Rurality, 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2020, based on the November 2019 submission.

.

2. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355(15):1572-1582.
3. Oh C, Slover JD, Bosco JA, Iorio R, Gold HT. Time Trends in Characteristics of Patients Undergoing Primary Total Hip and Knee Arthroplasty in California, 2007-2010. *J Arthroplasty.* 2018;33(8):2376-2380.
4. Kadan-Lottick NS, Dinu I, Wasilewski-Masker K, et al. Osteonecrosis in adult survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol.* 2008;26(18):3038-3045.
5. Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol.* 2000;18(18):3262-3272.
6. Niinimaki R, Hansen LM, Niinimaki T, et al. Incidence of Severe Osteonecrosis Requiring Total Joint Arthroplasty in Children and Young Adults Treated for Leukemia or Lymphoma: A Nationwide, Register-Based Study in Finland and Denmark. *J Adolesc Young Adult Oncol.* 2013;2(4):138-144.
7. Rao SS, El Abiad JM, Puvanesarajah V, Levin AS, Jones LC, Morris CD. Osteonecrosis in pediatric cancer survivors: Epidemiology, risk factors, and treatment. *Surg Oncol.* 2019;28:214-221.
8. Burger B, Beier R, Zimmermann M, Beck JD, Reiter A, Schrappe M. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)--experiences from trial ALL-BFM 95. *Pediatr Blood Cancer.* 2005;44(3):220-225.

9. Zhu H, Cai X, Lin T, Shi Z, Yan S. Low-intensity pulsed ultrasound enhances bone repair in a rabbit model of steroid-associated osteonecrosis. *Clin Orthop Relat Res.* 2015;473(5):1830-1839.
10. Chan KL, Mok CC. Glucocorticoid-induced avascular bone necrosis: diagnosis and management. *Open Orthop J.* 2012;6:449-457.
11. McAvoy S, Baker KS, Mulrooney D, et al. Corticosteroid dose as a risk factor for avascular necrosis of the bone after hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2010;16(9):1231-1236.
12. Chen Y, Huang LF, Zhu JX. Dose-related histopathology and bone remodeling characteristics of the knee articular cartilage and subchondral bone induced by glucocorticoids in rats. *Exp Ther Med.* 2019;17(6):4492-4498.
13. Mansky P, Arai A, Stratton P, et al. Treatment late effects in long-term survivors of pediatric sarcoma. *Pediatr Blood Cancer.* 2007;48(2):192-199.
14. Paulino AC. Late effects of radiotherapy for pediatric extremity sarcomas. *Int J Radiat Oncol Biol Phys.* 2004;60(1):265-274.
15. Ginsberg JP, Goodman P, Leisenring W, et al. Long-term survivors of childhood Ewing sarcoma: report from the childhood cancer survivor study. *J Natl Cancer Inst.* 2010;102(16):1272-1283.
16. Xian CJ, Cool JC, van Gangelen J, Foster BK, Howarth GS. Effects of etoposide and cyclophosphamide acute chemotherapy on growth plate and metaphyseal bone in rats. *Cancer Biol Ther.* 2007;6(2):170-177.
17. Xian CJ, Howarth GS, Cool JC, Foster BK. Effects of acute 5-fluorouracil chemotherapy and insulin-like growth factor-I pretreatment on growth plate cartilage and metaphyseal bone in rats. *Bone.* 2004;35(3):739-749.
18. Xian CJ, Cool JC, Scherer MA, et al. Cellular mechanisms for methotrexate chemotherapy-induced bone growth defects. *Bone.* 2007;41(5):842-850.
19. van Leeuwen BL, Kamps WA, Jansen HW, Hoekstra HJ. The effect of chemotherapy on the growing skeleton. *Cancer Treat Rev.* 2000;26(5):363-376.
20. Gawade PL, Hudson MM, Kaste SC, et al. A systematic review of selected musculoskeletal late effects in survivors of childhood cancer. *Curr Pediatr Rev.* 2014;10(4):249-262.
21. Horton JA, Margulies BS, Strauss JA, et al. Restoration of growth plate function following radiotherapy is driven by increased proliferative and synthetic activity of expansions of chondrocytic clones. *J Orthop Res.* 2006;24(10):1945-1956.
22. Krasin MJ, Constine LS, Friedman DL, Marks LB. Radiation-related treatment effects across the age spectrum: differences and similarities or what the old and young can learn from each other. *Semin Radiat Oncol.* 2010;20(1):21-29.
23. van Dijk IW, Oldenburger F, Cardous-Ubbink MC, et al. Evaluation of late adverse events in long-term wilms' tumor survivors. *Int J Radiat Oncol Biol Phys.* 2010;78(2):370-378.
24. Bacchetta J, Harambat J, Cochat P, Salusky IB, Wesseling-Perry K. The consequences of chronic kidney disease on bone metabolism and growth in children. *Nephrol Dial Transplant.* 2012;27(8):3063-3071.
25. Wetzsteon RJ, Kalkwarf HJ, Shults J, et al. Volumetric bone mineral density and bone structure in childhood chronic kidney disease. *J Bone Miner Res.* 2011;26(9):2235-2244.

26. Clement ND, Deehan DJ. Overweight and Obese Patients Require Total Hip and Total Knee Arthroplasty at a Younger Age. *J Orthop Res.* 2020;38(2):348-355.
27. Pierce TP, Elmallah RK, Jauregui JJ, Verna DF, Mont MA. Outcomes of total hip arthroplasty in patients with osteonecrosis of the femoral head-a current review. *Curr Rev Musculoskelet Med.* 2015;8(3):246-251.
28. Ness KK, Mertens AC, Hudson MM, et al. Limitations on physical performance and daily activities among long-term survivors of childhood cancer. *Ann Intern Med.* 2005;143(9):639-647.
29. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer. *J Clin Oncol.* 2018;36(21):2181-2189.
30. DeFeo BM, Kaste SC, Li Z, et al. Long-Term Functional Outcomes Among Childhood Survivors of Cancer Who Have a History of Osteonecrosis. *Phys Ther.* 2020;100(3):509-522.
31. Hudson MM, Neglia JP, Woods WG, et al. Lessons from the past: opportunities to improve childhood cancer survivor care through outcomes investigations of historical therapeutic approaches for pediatric hematological malignancies. *Pediatr Blood Cancer.* 2012;58(3):334-343.