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Pain in Long-Term Survivors of Childhood Cancer: A Systematic Review of the Current State of Knowledge and a Call to Action from the Children's Oncology Group

Fiona Schulte, PhD^{1,2,*}, Michaela Patton, MSc^{1,*}, Nicole M. Alberts, PhD³, Alicia Kunin-Batson, PhD⁴, Barbara A. Olson-Bullis, MA⁵, Caitlin Forbes, MSc¹, K. Brooke Russell, MSc¹, Alexandra Neville, MSc¹, Lauren C. Heathcote, PhD⁶, Cynthia Karlson, PhD⁷, Nicole Racine, PhD¹, Courtney Charnock, BA¹, Matthew C. Hocking, PhD^{8,9}, Pia Banerjee, PhD⁵, Perri Tutelman, MSc¹⁰, Melanie Noel, PhD^{1,2}, Kevin R. Krull, PhD⁵

¹University of Calgary, Calgary, AB, Canada

²Alberta Children's Hospital, Calgary, AB, Canada

³St. Jude Children's Research Hospital, Memphis, TN, USA

⁴University of Minnesota, Minneapolis, MN, USA

⁵HealthPartners Institute, Minneapolis, MN, USA

⁶Stanford University, Stanford, CA, USA

⁷University of Mississippi Medical Center, Jackson, MS, USA

⁸Children's Hospital of Philadelphia, Philadelphia, PA, USA

⁹University of Pennsylvania, Philadelphia, PA, USA

¹⁰Dalhousie University, Halifax, NS, Canada

Abstract

Background: Survivors of childhood cancer may be at risk of experiencing pain; a systematic review would advance our understanding of pain in this population.

Purpose: To describe: (i) the prevalence of pain in survivors of childhood cancer; (ii) methods of pain measurement; (iii) associations between pain and biopsychosocial factors; iv) recommendations for future research.

Data Sources: Articles published from January 1990 to August 2019 identified in PubMed, PsycINFO, EMBASE, and Web of Science.

Corresponding Author: Fiona Schulte, University of Calgary, Oncology, 2202 2 St SW, Calgary, Alberta, T2S 3C3, Canada, Phone: 403-698-8103, fiona.schulte@albertahealthservices.ca.

*Shared First Authors

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Conflicts of Interest: None to declare.

Study Selection: Eligible studies included: 1) original research; 2) quantitative assessments of pain; 3) published in English; 4) a diagnosis of cancer between 0–21 years; 5) survivors at 5 years from diagnosis and/or 2 years from therapy completion; 6) sample size >20.

Data Extraction: Seventy-three articles were included in the final review. Risk of bias was considered using the Cochrane Risk of Bias Tool. Quality of evidence was evaluated according to the Grading of Recommendations Assessment Development and Evaluation criteria.

Data Synthesis: Common measures of pain were items created by the authors for the purpose of the study (45.2%) or health-related quality of life/ health status questionnaires (42.5%). Pain was present in 4.3–75% of survivors across studies. Three studies investigated chronic pain according to the definition by the International Classification of Diseases.

Conclusions: Survivors of childhood cancer are at higher risk of experiencing pain compared to controls. Fatigue was consistently associated with pain. Females report more pain than males. Other factors related to pain require stronger evidence. Theoretically grounded, multidimensional measurements of pain are absent from the literature.

Precis:

Survivors of childhood cancer are at higher risk of experiencing pain compared to controls. Future research is urgently needed to discern the true prevalence of pain among this vulnerable population and to develop interventions to enhance the quality of survivorship.

Keywords

neoplasms; pediatrics; pain; survivorship; psycho-oncology

Introduction

Currently, there are over 500,000 survivors of pediatric cancer in North America alone.¹ Given increasing survival rates for this population, it is imperative that we maximize long-term quality of life outcomes. There is emerging research documenting significant pain, including chronic pain (i.e., pain lasting > 3 months)² among survivors of pediatric cancer. Pain (e.g., musculoskeletal pain, headaches, generalized pain) has been noted to significantly impact quality of life,³ and psychosocial well-being. Survivors of pediatric cancer may have a unique relationship to pain, given the prominence of pain across multiple points of the cancer journey. In addition, given that pain in the general population has been linked to many negative health consequences, including poorer sleep and mental health, it is critical that pain be examined among survivors of childhood cancer as their risks for late effects may be compounded by the experience of pain.

Pain among children and adolescents has been conceptualized using a biopsychosocial framework.⁴ This framework proposes that there are bidirectional relationships among biological (e.g., sex), psychological (e.g., anxiety), and social (e.g., socioeconomic status) factors that contribute to the presence and impact of pain.^{5–7} More recently, Alberts and colleagues proposed a model of pain pathways specific to survivors of childhood cancer which considers the influence of a cancer diagnosis, disease- and treatment-related pain as

well as procedural pain in the development of chronic pain among survivors.⁸ Despite the availability of these conceptual models, the literature focused on pain in survivors of pediatric cancer has centered on biomedical risk factors. The research examining the biopsychosocial factors related to pain requires further elucidation.

Therefore, we aimed to evaluate the available evidence of pain in survivors of childhood cancer through a systematic review of the literature. The objectives of this review were to: (i) characterize the prevalence of pain (including chronic pain) in survivors of childhood cancer after completion of treatment; (ii) describe what methods are being used to measure pain; (iii) examine associations between pain and biological/physical and psychosocial factors; and (iv) make specific recommendations for more rigorous research of pain among long-term survivors of childhood cancer.

Methods

Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for completion of systematic reviews were followed.^{9,10} In March 2016, the Children's Oncology Group (COG) Guideline Task Force on Neurocognitive and Psychosocial late-effects performed an extensive review of the literature to identify updates for the COG LTFU Guidelines (version 5.0). This review was updated for the current manuscript.

Databases searched included PubMed (Web-based), PsycINFO (EBSCO), EMBASE (Ovid), and Web of Science (Thomson Reuters). Full PubMed search parameters are available in the online material (see Supplementary Table 1 in Online-Only Materials). Search strategies for PsycINFO, EMBASE, and Web of Science were adjusted for the syntax appropriate for each database using a combination of thesauri and text words. Relevant articles published from January 1990 to August 2019 were included. Narrative and systematic reviews and meta-analyses on this topic were also evaluated to identify relevant original manuscripts, but the reviews themselves were not included in the current analysis. Dissertations, books, book chapters, editorials, letters, case studies and conference proceedings/abstracts were excluded.

Inclusion and exclusion criteria were determined prior to manuscript selection. Eligible studies: 1) were original research; 2) included quantitative assessment of pain (including chronic pain); 3) were published in English; 4) included children diagnosed with cancer between 0–21 years of age; 5) described survivors of any age who were at least 5 years from diagnosis and/or 2 years from the completion of therapy; and 6) included a sample size > 20 (to avoid case studies). Studies that had a wide range of ages and/or intervals from diagnosis and treatment were retained only if the mean age and/or time interval included the aforementioned criteria.

Data extraction was completed according to the Late Effect Evidence Table (LEET) developed by the COG Late-Effects Guideline Task Force and included study design, median follow-up time, participation rate, and description of study objectives. Risk of bias was considered for each study using domains adapted from the Cochrane Risk of Bias

Tool¹⁰ including: selection/subject bias, attrition bias, instrumentation and missing data and reporting outcomes. Each category was labeled 'low risk of bias', 'high risk of bias' or 'unclear'.¹⁰ Quality of evidence and strength of recommendations according to criteria from the Grading of Recommendations Assessment Development and Evaluation (GRADE) was completed.¹¹ Specifically, evidence was graded according to three categories: 1) Level A, high level of evidence; 2) Level B, moderate to low level of evidence (e.g., risk factor is significant in >50% of studies); 2) Level C, very low level of evidence (e.g., risk factor is significant in <50% of studies). Data extraction and quality assessments were completed by one independent rater for each published study.

Results

Data Extraction

This review yielded 4,302 unique publications title/abstracts, of which 73 articles were included in the final review (Supplementary Figure 1). Disagreements were resolved in all cases through consensus. Reasons for further exclusion are presented in Supplementary Figure 1.

Quality Assessment

Quality assessment was completed for each study independently and by considering these four key criteria: 1) Selection/Subject bias; 2) Attrition; 3) Instrumentation and Missing data; and 4) Reporting Measurement outcomes (see Supplementary Table 2 in Online-Only Materials). Of the 73 studies reviewed, 36% reported low risk of bias with respect to selection/subject bias (n=26/73); 1% for attrition (n=1/73), 19% for instrumentation and missing outcomes (n=14/73) and 7% for reporting outcomes (n=5/73). GRADE assessments can be found in Table 1.

Data Synthesis

Descriptive Characteristics of Included Studies—Supplementary Table 2 in online-only materials provides descriptive characteristics of the studies included. Studies were largely observational, cross-sectional study designs (46.6% n=34) with the remainder categorized as observational, cohort (41.1%, n=30), observational, case control (11.0%, n=8) and finally non-experimental (1.3%, n=1). Three studies evaluated pain longitudinally (4.1%). Of all the studies reviewed, 32.9% (n=24) included a comparison group: healthy or population controls (n=10), siblings (n=13), and other cancer survivors (e.g., comparison of survivors with versus without meningioma, survivors with versus without chronic fatigue, and various diagnoses; n=3). The remaining 67.1% did not include any comparison sample. Sample size of studies ranged from 25 to 20,051 participants. Length of follow-up ranged from an average of 5.4 to 32.0 years after diagnosis. Among the current sample of studies reporting pain in their results, only 13 (17.8%) identified pain in their specific study objectives. Of these 13 studies, 3 utilized a comparison group in their analyses.

Objective 1: What is the Prevalence of Pain?—Only three studies investigated chronic pain according to its definition of pain lasting more than 3 months. The prevalence of chronic pain was identified in 11.0–43.9% of survivors.^{12–14} These three studies focused

specifically on survivors of acute lymphoblastic leukemia (ALL) and lymphoma and focused specifically on chronic headache,²² chronic hip pain and/or chronic back pain in ALL survivors,²¹ or any type of chronic pain in lymphoma survivors.²³ The study reporting on any type of chronic pain reported the highest prevalence. Only one of these studies included a control group.¹² The overall occurrence of any pain reported across studies was between 4.3–75%^{15,16}

Twenty-four studies included control groups. Of these, evidence suggested that survivors of childhood cancer are at higher risk of experiencing any occurrence of pain (GRADE Level B; 21/25 studies). Evidence from these studies generally suggests that survivors reported more pain compared to controls and population norms^{12,17–22} with the exception of five studies.^{23–27} Of these five studies, one found that survivors reported significantly less bodily pain than their healthy peers²⁵ while the other four studies showed survivors had no significant differences in pain compared to controls.^{23,24,26,27} Importantly, the one study showing less bodily pain in cancer survivors compared to health peers was a sample comprised of 45% females in the cancer survivor sample vs. 55% females in the healthy peers.

Objective 2: Methods for Measuring Pain—Specific measures for measuring pain varied and most were self- or parent-proxy report (see Table 2). The most commonly used measures of pain were items created by the authors for the purpose of the study (45.2%) or items derived from health-related quality of life or health status questionnaires (42.5%). The majority of author-created measures were limited to only one or two items. Examples of items created by authors include: “Does your child currently have pain as a result of his/her cancer, leukemia, tumor or similar illness, or its treatment?”^{28,29} Only a small minority of studies (9.0%) used independent pain measures that have been validated in other populations. One study³⁰ utilized an Algometer, a validated measurement of pain tolerance and pain sensitivity. However, this study only used the Algometer to measure pain sensitivity.

Objective 3: Factors Related to Pain—To conceptualize the factors related to pain, we considered an adapted theoretical model that incorporates the conceptual model of pain among survivors of childhood cancer developed by Alberts et al. as well as the biopsychosocial model of pain (see Figure 1). We have subsequently summarized the available literature according to these factors below. The evidence related to these factors as evaluated using the GRADE criteria can be found in Table 1.

Disease-Related Pain: Disease related pain factors explored in the literature included diagnosis, treatment and age at diagnosis. Six studies reported on diagnosis, where survivors of germ cell tumor, high-risk ALL, neuroblastoma, Hodgkin lymphoma, Wilms tumor and osteosarcoma reported more pain compared to population norms as did survivors who developed subsequent meningioma compared to those who did not.^{20,31–35}

Survivors of bone and soft tissue sarcomas were almost five times more likely to report cancer-related pain compared to survivors of leukemia in one study.³⁶ Another study found that brain tumor survivors reported experiencing more pain than those diagnosed with ALL

treated on a standard- or high-risk protocol, as well as those diagnosed with a solid tumor.³⁵ Finally, one study found that history of disease recurrence or progression was significantly related to pain.³⁷

There was conflicting evidence that age at diagnosis was related to pain where three studies found that younger age was significantly related to increased reports of pain^{19,38,39} and one study found no association between age at diagnosis with pain.⁴⁰

Treatment-Related Pain: Children diagnosed with Wilms tumor who had hemi-abdominal radiation, children with neuroblastoma treated with hematopoietic stem cell transplant (HSCT), children with osteosarcoma who had lower-extremity amputation, and children diagnosed with soft-tissue sarcomas who underwent abdominal radiation were all more likely to report more pain during survivorship compared to their survivor peers who did not receive these therapies.^{20,33,41}

Hsiao and colleagues³⁵ found that ALL survivors who were treated on a high-risk protocol reported experiencing significantly greater pain than survivors treated on a standard-risk protocol,³⁵ whereas Meeske and colleagues found no associations between pain with treatment in survivors of ALL.⁴⁰ Survivors who had undergone total knee replacement surgery were also more likely to report pain in their limbs than survivors who had undergone other surgical procedures.⁴² Additionally, radiation therapy was found to put survivors at increased risk for pain.³⁷ Another study explored small-fiber toxicity and pain sensitization in survivors of ALL and discovered survivors with increased pain sensitization suffered from at least two or three losses of quantitative sensory testing parameters.⁴³

Biological Factors: Biological factors explored in relation to pain included age and sex. There was robust evidence in the current literature to support that females report significantly more pain than males.^{12,14,19,26,37,41,44–46} Data supporting age at the time of study was inconsistent where one study found pain to be negatively associated with age²³ and other studies found pain to be positively associated with age.^{40,41,46} Recklitis and colleagues³⁷ separated survivors into three different age groups and found that survivors who were currently 13–17 years of age had a higher frequency of pain than those who were 18–22 years of age, but not those who were 23–31 years.³⁷ Interestingly, Cox et al.³⁸ found that younger age at diagnosis was associated with pain in male survivors, but not female survivors.³⁸

Psychological Factors: Psychological factors examined in the literature included sleep, fatigue, emotional distress, and quality of life. Fatigue and daytime sleepiness were consistently positively related to pain.^{14,30,36,40,47,48} Sleep difficulties were also found to be associated with increased reports of pain.^{47,49} With respect to emotional distress, one study found pain was associated with poorer body image and sports/physical activity-related self-confidence⁵⁰ and another found that headaches were associated with emotional symptoms affecting daily activities and work.¹⁴ Pain was positively associated with global emotional distress,^{51–53} anxiety,^{38,53} depression,^{40,51,53} and suicidal ideation.^{54,55} Finally, it was generally found that more pain was significantly related to decreased health related quality of life (HRQL).^{56,57} Importantly, survivors who reported experiencing cancer-related pain

were also more likely to report unmet information needs for managing pain as well as fear of cancer recurrence.³⁶

Social Factors: Only 5 studies examined social factors related to pain in the current sample. Survivors' with lower socioeconomic status (SES) had increased reports of pain^{33,46,53} as well as survivors' with lower educational attainment²⁵ or not completing high school.^{19,21} Other social factors related to increased pain included identifying as Hispanic or African American,¹⁹ single relationship status^{19,21} and being unemployed.¹⁹

Objective 4: Recommendations for future research in pain among survivors of childhood cancer—Based on the existing literature, and more specifically the gaps in the existing literature, the authors have considered areas for future research in pain among survivors of childhood cancer. These recommendations are summarized in Table 3.

Discussion

The aims of the current review were to characterize the prevalence of pain (including chronic pain) in survivors of childhood cancer, describe the measurement of pain, examine factors associated with pain and provide recommendations for future work in this field. The results of this study revealed significant gaps in the assessment of pain among survivors of childhood cancer, which has led to a wide range of prevalence rates reported among the literature, limiting our understanding of pain in this vulnerable population. The majority of the included studies reported pain outcomes based on a single item or very few items and not using theoretically-grounded, multidimensional measurements of pain. In addition, rigorous, high quality studies assessing pain among this population are limited.

Importantly, we have proposed a conceptual model that amalgamates two existing pain frameworks^{7,8} in an attempt to capture the complex contributions to pain among this unique population. Based on our review, with respect to the factors found to be related to pain, only a few factors emerged consistently in their relationship to pain. Females were more likely to report pain than males, which is consistent with chronic non-cancer pain populations. Fatigue was also a prominent comorbid concern alongside pain in survivors of childhood cancer. These findings have important implications for developing interventions that target pain and fatigue concurrently, which may also include components of sleep as well. The chronic non-cancer pain literature has demonstrated that pain may disrupt sleep and subsequently, lack of sleep may exacerbate pain, leading to a cycle that is hard to overcome.⁵⁸ The only other factor that demonstrated a moderate level of evidence in its relationship to pain was quality of life. The finding that quality of life is related to pain highlights that perhaps regardless of prevalence rates, pain among survivors of childhood cancer negatively impacts the quality of survivorship thereby warranting intervention.

Strong evidence supports the use of behavioral interventions for the management of procedural pain⁵⁹ in pediatric cancer patients and generally the most effective pain management approaches combine pharmacological approaches with psychosocial procedural preparation and intervention.^{60–62} There is little research that has been conducted with respect to interventions for chronic pain among survivors of childhood cancer, however,

considerable evidence also supports the use of behavioral interventions for the management of chronic pain among non-cancer populations.⁶³ Certainly, given increasing concerns regarding the use of opioids to manage pain, attention must now turn to research focused on behavioral interventions specific to survivors of childhood cancer.

The remaining factors reported in the literature reviewed were considered to have very low evidence for their relationship to pain reinforcing our call to action for more work in this field. Certainly, based on the current review, pain has not been a priority in the pediatric cancer survivor literature, as evidenced by the absence of pain as a primary outcome in the majority of studies, and the use of one or two items driving analyses around pain outcomes. Accordingly, we wish to advocate for a commitment to future research in this field within the domains of: our background theoretical understanding of pain; improved measurement; enhanced research design; factors related to pain; intervention; and clinical care.

This review was not without limitations. To begin, we intentionally left our definition of pain broad to capture the broad range of studies that have assessed pain among survivors, however this limited our ability to be more specific in describing outcomes. In addition, as part of our search we excluded qualitative papers. Despite this, we acknowledge the strength of qualitative research to better capture the context of one's experiences and provide greater perspective to quantitative findings. Finally, we acknowledge that within our review we did not take into account the era of treatment for studies reviewed. We are aware that treatment protocols have shifted significantly over the last several decades in favor of less toxic therapies and therefore we might expect differing prevalence rates of pain over time.

Conclusions

In summary, while there are a large number of studies that reported on pain in survivors of childhood cancer, the quality of pain assessment across these studies is quite poor, as evidenced by inconsistent findings and a large range of reported pain prevalence. Based on the results, it is important that future research on this topic utilize more comprehensive measures of pain as well as longitudinal designs in order to disentangle this complex, multidimensional construct. Deeper understanding of pain experienced by this population will inform future research into tailored interventions that address the complex and unique histories of survivors of childhood cancer. Clinically, greater attention to the experience of pain is warranted during regular follow-up appointments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
A conceptual model of factors associated with pain in survivors of childhood cancer

Table 1.

GRADE Assessment for factors related to pain

FACTOR ASSESSED	GRADE
DISEASE RELATED FACTORS	
Diagnosis	
Neuroblastoma	Level C (1/1 studies) ²⁰
Brain tumor	Level C (1/1 studies) ³⁵
High-risk acute lymphoblastic leukemia	Level C (1/1 studies) ³⁵
Hodgkin lymphoma	Level C (2/2 studies) ^{31,34}
Germ cell tumor	Level C (1/1 studies) ³⁴
Wilms' tumor	Level C (2/2 studies) ^{31,33}
Osteosarcoma	Level C (2/2 studies) ^{33,36}
Soft-tissue sarcoma	Level C (1/1 studies) ³⁶
Development of post-treatment meningioma	Level C (1/1 studies) ³²
History of disease recurrence or progression	Level C (1/1 studies) ³⁷
TREATMENT RELATED FACTORS	
Treatment	
Hemi-abdominal radiation in children with Wilms' tumor	Level C (1/1 studies) ³³
Hematopoietic stem cell transplant in children with neuroblastoma	Level C (1/1 studies) ²⁰
Lower-extremity amputation in children with osteosarcoma	Level C (1/1 studies) ³³
Abdominal radiation in children with soft-tissue sarcomas	Level C (1/1 studies) ⁴¹
Total knee replacement	Level C (1/1 studies) ⁴²
Radiation ^{33,37,64}	Level C (3/3 studies) ^{38,45,46}
BIOLOGICAL FACTORS	
Age	
There is some evidence that younger age at diagnosis is associated with increased pain	Level C (3/4 studies) ^{19,38–40}
There is some evidence to suggest that younger age at diagnosis is associated with increased pain in females but not males	Level C (1/1 studies) ³⁸
There is some evidence that age at time of study is associated with pain	Level C (4/5 studies) ^{23,37,40,41,46}
Sex	
There is evidence to suggest that females report more pain than males	Level A (9/9 studies) ^{12,14,19,26,37,41,44–46}
PSYCHOLOGICAL FACTORS	
Sleep	
Some evidence suggests that pain is associated with excessive daytime sleepiness	Level C (1/1 studies) ⁴⁷
Some evidence suggests that pain is associated with sleep difficulties	Level C (2/2 studies) ^{47,49}
Fatigue	
There is evidence to suggest that pain is associated with increased fatigue	Level A (6/6 studies) ^{14,30,36,40,47,48}
Psychological Distress	
Some evidence suggests that pain is associated with increased psychological distress	Level C (3/3 studies) ^{51–53}

FACTOR ASSESSED	GRADE
Body Image	
Some evidence suggests pain is associated with poorer body image	Level C (1/1 studies) ⁵⁰
Sports/Physical Activity-related Self-confidence	
Some evidence suggests pain is associated with decreased sports/physical activity-related self-confidence	Level C (1/1 studies) ⁵⁰
Anxiety	
Some evidence suggests pain is associated with increased anxiety	Level C (2/2 studies) ^{38,53}
Depression	
Some evidence suggests pain is associated with increased depression	Level C (3/3 studies) ^{40,51,53}
Suicidal Ideation	
Some evidence suggests that pain is associated with suicidal ideation	Level C (2/2 studies) ^{54,55}
Quality of Life	
Evidence suggests that pain is associated with reduced quality of life	Level B (3/3 studies) ^{37,56,57}
SOCIAL FACTORS	
SES	
Some evidence suggests lower SES is associated with increased pain	Level C (3/3 studies) ^{33,46,53}
Ethnic Background	
Some evidence suggests that individuals of Hispanic or African American background is associated with increased pain	Level C (1/1 studies) ¹⁹
Educational Level	
Some evidence suggests lower educational level and not completing high school is associated with increased pain	Level C (3/3 studies) ^{19,21,25}
Employment Status	
Some evidence suggests that current employment status is related to pain	Level C (1/1 studies) ⁴⁴
Relationship Status	
Some evidence suggests that single status is associated with increased pain	Level C (2/2 studies) ^{21,44}

Note: Level A = high level of evidence; Level B = moderate to low level of evidence (e.g., risk factor is significant in >50% of studies); Level C = very low level of evidence (e.g., risk factor is significant in <50% of studies)

Table 2.

Frequency of measures of pain included in studies.

Measure	# of studies using measure (%)
Author-created measures	33 (45.2%)
Health-related quality of life or health status measures	31 (42.5%)
Disease-specific measures	9 (12.3%)
Valid pain measures	7 (9.6%)
Chart review	2 (2.7%)
Unclear	2 (2.7%)

Table 3.

Directions for future research

Directions for Future Research		
Background	1	Adapt current models of pain to unique characteristics of cancer survivors
	2	Reach consensus on a consistent definition of pain to be applied to survivors of childhood cancer
Measurement	1	Identify theoretically, grounded, multidimensional measurements of pain for use as assessment including intensity, duration, frequency, location, affect, chronicity, and interference
	2	Determine reliability and validity of identified measures when applied among survivors of childhood cancer
	3	Identify potential screening tools that might be used in the context of clinical assessment
Research Design	1	Conduct epidemiological studies to clarify prevalence, severity, duration, location and interference of pain
	2	Conduct longitudinal studies to identify potential directionality of relationships among factors
Factors Related to Pain	1	Identify specific diagnoses (e.g., osteosarcoma, leukemia) and treatment exposures (e.g., vincristine, steroid use) related to the experience of pain
	2	Broaden exploration of psychological factors that might be related to pain including pain catastrophizing, intolerance of uncertainty, fear of cancer recurrence
	3	Consider social (e.g., SES), cultural factors (e.g., ethnicity) related to the experience of pain
	4	Consider factors that may be comorbid with pain including fatigue, sleep
Intervention	1	Assess the strength of evidence regarding pain management strategies among CCS.
	2	Develop and/or adapt interventions that may target pain in survivors of childhood cancer considering the possibility of multipronged approaches based on findings related to factors related to pain
	3	Test interventions for feasibility, acceptability among survivors of childhood cancer
	4	Conduct randomized control trials of interventions deemed to be feasible among this population
Clinical Care	1	Develop care coordination and communication methods, implementation standards and evaluation measures among multidisciplinary teams for surveillance and potential interventions for prevention and/or treatment