Childhood Cancer Survivor Study
Concept Proposal and Analytic Plan

1. **Study Title**
   Chronic Pain in Adult Survivors of Childhood Cancer: Utilization of the Childhood Cancer Survivor Study mHealth Platform in Assessing Pain and Wearable Sensor Technology

2. **Primary Working Group:** Psychology
   Secondary Working Group: Cancer Control

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Note: With the recent funding of the CCSS competitive renewal, a primary initiative in CCSS is the development of a new resource center for mHealth research within the cohort, now called the CCSS mHealth Technology Support Facility. Led by Jeff Olgin MD (UCSF), this center has developed a mHealth-based platform, called the Eureka platform, that can be deployed to all CCSS participants and allow for direct assessment of outcomes by survey-based, app-based, and sensor-based technologies. The Eureka platform will be ready for dissemination in early 2018 and the current study assessing chronic pain will be the first study available on the platform. The goal of the study will be to assess the prevalence and predictors of chronic pain in a sample of the CCSS population and to pilot sensor-based data collection of respiration (exploratory) with the goal of generating preliminary data for a future R01 intervention trial.

Chronic Pain

Chronic pain has been defined as pain that persists past normal healing time.[1] Pain is typically regarded as chronic when it lasts or recurs for more than 3 to 6 months.[2] Chronic pain is common and costly to individuals as well as society. According to the Institute of Medicine,[3] 116 million American adults experience some form of chronic pain. It has significant negative effects on health and quality of life as it is consistently associated with decreased activity,[4] sleep disturbance,[5] depression,[6] and disability.[3] Chronic pain is also increasingly expensive for the health care system and society. The estimated total cost of chronic pain to the U.S. economy ranges between $560 and $630 billion annually.[3] Chronic pain has recently been recognized as a global public health priority, with adequate pain treatment considered to be a human right and the duty of any health care system to provide.[7,8]

Chronic Pain in Adult Survivors of Childhood Cancer

Advances in treatment have dramatically improved pediatric cancer survival rates.[9] Nonetheless, by age 45, 95% of pediatric cancer survivors will have one or more late effects, with 81% having serious/disabling or life-threatening late-effects.[10] Research on survivorship in adult onset cancer and chronic pain more generally, suggests that several treatment, developmental, and health-related factors place survivors at risk for chronic pain. Treatment-related factors include, but are not limited to, amputation, radiation therapy, inadequate postoperative pain control, chemotherapy-induced peripheral neuropathy, and graft-versus-host disease.[11] Developmentally, chronic pain presents in childhood and adolescence and often continues into adulthood in individuals without cancer; [12,13] thus, chronic pain that emerges during childhood or adolescence as a result of cancer or cancer treatments could persist into adulthood. This is particularly concerning given that chronic pain has been observed in over 50% of children undergoing outpatient treatment for cancer.[14] With respect to health-related factors, several chronic health conditions (e.g., diabetes, obesity) as well as frailty[15] are associated with chronic pain. As a population already at increased risk for secondary malignancies,[9] chronic health conditions,[9] and frailty,[16] the potential compounded impact of chronic pain may have significant adverse implications for survivor health and health-related quality of life.

Despite these findings, little research has examined the prevalence and nature of chronic pain among pediatric survivors. In one study from the Childhood Cancer Survivor Study (CCSS), 12%, 16%, and 21% of survivors reported pain/abnormal sensations, migraines, and other frequent headaches, respectively.[17] In addition, history of non-Hodgkin lymphoma, Wilms tumor, or neuroblastoma were associated with greater risk of pain, while indirect (i.e. scatter) irradiation of the brain was associated with elevated risk for migraines and cancer-related pain.[17] More recently, estimates from the St. Jude Lifetime Cohort Study (SJLIFE) suggested that 36% to 59% of adult survivors of childhood cancer reported pain as still present.[18] However, both studies lacked validated measures of pain and failed to examine pain chronicity which may have resulted in an underestimate of the prevalence and nature of chronic pain. Both studies also utilized retrospective assessment of pain which can lead to recall bias since current pain and other factors significantly influence memory of past pain.[19,20]

Ecological momentary assessment (EMA) is one method for overcoming such problems with reliability. EMA refers to the collection of individuals' current experiences, behaviors, and mood as they occur in real time and in their real-world settings.[21] It has been used to assess a variety of constructs including smoking,[22] physical activity,[23] eating behaviors,[24] and chronic pain,[25] with assessment frequency ranging from once [26-30] to multiple times per day. [31,32] In recent years, the use of EMA methods has been facilitated by the pervasive availability and unobtrusive nature of mobile devices, including smartphone applications and platforms. There is an unprecedented opportunity to utilize these technologies, in combination with EMA methods, to assess and treat health problems and behaviors across large sections of the population. The current proposal will be the first study to utilize a mobile health (mHealth) platform and integrated smartphone application to gather health-related outcomes in the large CCSS cohort (>20,000 active participants).

Past examinations of chronic pain among adult survivors of pediatric cancer have also failed to consider cognitive-affective factors likely to influence the experience of chronic pain in survivors, such as fear of cancer recurrence, interpretation of pain as a sign of recurrence (cancer threat), and pain catastrophizing (i.e., an exaggerated negative cognitive response to

actual or anticipated pain experience).[33,34] The exclusion of such factors limits our understanding of variables that contribute to the development and maintenance of chronic pain in this population. Improved understanding of such factors is integral to the comprehensive assessment of chronic pain, identification of survivors at high risk for developing chronic pain, and the development of targeted and effective interventions for chronic pain among survivors.

Respiration, Pain, and Sensor Technology

Wearable devices, also known as *wearables*, are sensor-enabled technologies designed to be worn for health and fitness purposes, and to continuously track activities and physiological outcomes.[35] Wearables also use sensors designed for their specific targets, and are intended to be worn in a specified and consistent manner (e.g., on the wrist or clipped to the belt).[35] Given these features, they may provide data that is of significantly higher quality than that provided by smartphones, which are not designed specifically for health tracking.[35] Monitoring of respiration via wearables is of value among medical populations, and particularly among those with chronic pain, as respiration and pain are thought to be closely related processes with bidirectional influences, whereby by pain influences respiration by increasing its flow, frequency, and volume, and breathing interventions reduce pain.[36] However, no published studies have measured respiration via wearable technology or examined the effect of breathing on chronic pain among adult survivors of childhood cancer. Utilization of this technology would allow for the collection of real-time, high-quality, and comprehensive respiration data in the large, geographically diverse CCSS population.

The *Spire* device is a validated[37] wearable that measures respiration and infers respiratory effort by sensing relative changes in expansion and contraction of the torso. The device uses Bluetooth to connect to a smartphone app, which analyzes and categorizes breathing patterns. When a change in breathing is detected, a notification is sent to the device and the app. Following this notification, the individual can then alter their breathing based on the feedback provided. Initial studies involving *Spire* have provided evidence of its validity and reliability. For example, in one study participants wore both a gold-standard sensing apparatus (medical grade CPAP mask connected to digital flow meter) and the *Spire* device while performing various tasks such as reading and breath-holding.[37] Respiration metrics (i.e., minute-by-minute respiration rate, temporal location of the respiratory cycle) generated by the *Spire* device were compared to those generated by the flow meter. Results indicated that reliable respiratory data was generated via the *Spire* device across different work tasks. The impact of *Spire* on stress in the work environment has also been examined. In comparison to a control group of employees who did not receive the *Spire* device (n = 111), employees who used *Spire* for one month (n = 114) showed significant decreases in stress, anxiety, and negative affect from pre to post *Spire* intervention use.[38]

If shown to be feasible, longitudinal measurement of respiration (e.g., over 6-8 weeks) via *Spire* could be integrated into mHealth-based interventions for chronic pain among survivors. For example, respiration could be an examined outcome to monitor compliance with breathing techniques within a cognitive behavioral intervention. *Spire*'s ability to alert individuals of changes in their breathing, and to instruct them to change their behavior (e.g., utilize breathing techniques), could also be used as a primary component of the intervention itself.

4. **Specific Aims**

Aim 1: To estimate the prevalence and nature of chronic pain (defined as recurrent or persistent pain, lasting at least 3 months) and pain interference among long-term survivors of childhood cancer using an ecological momentary assessment design delivered in an integrated smartphone application.

Aim 2: To identify demographic, diagnostic, and treatment-related factors associated with chronic pain and pain interference in long-term survivors of childhood cancer.

Aim 3: To evaluate associations between chronic pain and pain interference and depression, anxiety, fear of cancer recurrence, pain catastrophizing, intolerance of uncertainty, and sleep among long-term survivors of childhood cancer.

Exploratory Aims

Exploratory Aim 1: To assess the feasibility (participant accrual, retention, ease of use of the device, participant receptions of use of the device, quality of data collected) of collecting respiration data using a validated wearable device (*Spire*) integrated within the mHealth platform, and to conduct a preliminary examination of the effect of the device on pain, depression, and anxiety.

Exploratory Aim 2: To examine the feasibility of implementing a novel mHealth platform and integrated smartphone application to measure pain and health related outcomes within a large cohort of long-term survivors of childhood cancer.

Exploratory Aim 3: To examine factors that increase participation in the overall study utilizing an integrated smartphone application within a large cohort of long-term survivors of childhood cancer. We will determine whether the addition of telephone calls, texts and in-app push notifications, increase participation and longitudinal engagement in the study. Please see the study flow diagram provided, which includes an overview of the notifications/reminders.

5. **Analysis Framework**

5.1 **Study Population:** Participants will be a sample of survivors (n = 4000), and siblings (n = 1000) from the CCSS cohort, and will be randomly selected to be representative of the larger cohort with respect to sex, race/ethnicity, diagnosis, current age, and age at diagnosis. Given an assumed participation rate of 70%, we expect to enroll approximately 2800 survivors. Participants within this representative sample will be invited to access the CCSS Eureka app to complete pain-related questions for the current study. Given the app-based nature of this study, it is possible to invite the full CCSS population. However, the rationale for sampling is to target a population for use of strategies to maximize participation rate (multiple mailings, phone follow-up) and minimize potential participation bias.

A subset of participants (n = 100) with chronic pain will be invited to participate in the *Spire* feasibility testing component of the study.

5.2 **Inclusion and Exclusion criteria:**

- **Inclusion for Baseline Phase:**
  - CCSS survivors ≥ 18 years of age at study baseline
  - Speak and read English

- Own a smartphone
- Access to data/Wi-Fi/Internet

- **Inclusion for Longitudinal Phase:**
  - Completion of Baseline Phase
  - Report persistent or recurrent pain for ≥ past 3 months
- **Exclusion from Baseline Phase:**
  - Unable/unwilling to complete daily questions for approximately 2 weeks
    - Assessed using the following question: Are you willing and able to complete some quick daily questions about how you feel for approximately 2 weeks?

5.3 **Outcomes:**

Outcomes are organized based on the stage of the study and/or method of assessment: baseline, daily diary, weekly diary, follow-up, and *Spire* feasibility testing. The progression of the study and the components included at each stage is outlined in the **study flow diagram provided**.

*****All participants will complete the baseline measures. The measures below with * will not be administered to participants who do not endorse chronic pain on the initial baseline question.

- ***Baseline (20 (+/- 5) minutes to complete):***
- **Chronic pain** will be assessed using the following survey questions:
  - Do you have any persistent or recurrent pain, more than aches and pains that are fleeting and minor?
    - This question is derived from the definition of chronic pain developed and recommended by the International Association for the Study of Pain (IASP).[2] This definition and the specific wording (i.e., "persistent," "recurrent") have been recommended for use in epidemiological studies of chronic pain.[39]
  - If so, how long have you been experiencing this pain (in months)?

  The baseline measures consist of 68 items. To decrease potential burden, participants will be given the option to complete all of the baseline measures at once, or to complete some measures, and return at a later time to finish all of the measures. As such, baseline measures will be open for completion for 2 days.
- **Pain location*** will be assessed by the following item:
  - Please indicate the **location** of your pain:
    - Response options will include: 1) Arm(s), 2) Leg(s), 3) Stomach, 4) Chest, 5) Lower Back, 6) Neck, 7) Head, 8) Pelvis 9) Feet, 10) Hands 11) Other (please specify)
    - *Note*: Participants will be able to select multiple locations. Option 11 will include an open field text.
- **Worst Pain Intensity*** will be assessed by an item adapted from the BPI and past research examining chronic pain, where participants will respond on an 11-point Likert scale ranging from 0 (no pain) to 10 (pain as bad as I can imagine):
  - Please rate your pain at its WORST during the **past week**.
- **Average Pain Intensity*** will be assessed by an item adapted from the Brief Pain Inventory (BPI) and past research examining chronic pain, where participants will

respond on an 11-point Likert scale ranging from 0 (no pain) to 10 (pain as bad as I can imagine):
    - Please rate your pain on AVERAGE during the **past week**.
- **Cause of pain*** will be assessed by the following item:
    - What do you think this pain was due to?
        - Response options will include: 1) Your childhood cancer treatments; 2) Medical procedures and tests you had during your childhood cancer; 3) Your cancer as a child; 4) Medical condition(s) other than your cancer (e.g., arthritis); 5) Past injury (e.g., back injury, muscle strain) 6) Not sure 7) Other (please specify)
        - *Note*: Option 7 will include an open text field.
- **Interpretation of pain as cancer threat*** will be assessed by the following items, where participants will indicate their response on a 5-point Likert Scale ranging from 0 (agree very little) to 4 (agree very much)
    - When I feel pain, I worry that the pain is caused by **my cancer coming back**.
    - When I feel pain, I worry that the pain is caused by **me having a new type of cancer**.
- **Pain interference*** will be assessed by the interference scale of the Brief Pain Inventory (BPI), a well-validated and widely used measure of pain interference.
- **Depression** will be assessed by the Patient Health Questionnaire – 8 item (PHQ-8), a well-validated and widely used measure of depression.
- **General anxiety** will be assessed by the Generalized Anxiety Disorder – 7 item (GAD-7), a well-validated and widely used measure of anxiety symptoms.
- **Sleep** will be assessed by the PROMIS Sleep Disturbance 4 – item (PROMIS-SD), a well-validated measure of sleep quality in adults with chronic health conditions including chronic pain.
- **Fear of cancer recurrence** will be assessed by the Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF), a well-validated measure of fear of cancer recurrence or progression among adult cancer survivors.
- **Pain catastrophizing*** will be assessed by the Pain Catastrophizing Scale (PCS), a widely-used measure of the magnification of the threat of, rumination about, and perceived inability to cope with pain.
- **Intolerance of uncertainty** will be assessed by the Intolerance of Uncertainty Scale (IUS-12), a widely-used and validated measure of responses to uncertainty, ambiguous situations, and the future.

- ***Longitudinal Phase: Daily Diary (Participants with chronic pain only and who have completed the Baseline assessment)***
  The daily diary will be completed 1x/day (end of day) for 14 days. It consists of 8 items. Completion of these items will take less than 3 minutes initially. The time it takes to complete the diary is expected to decrease as participants' familiarity with the diary and the app increases.
- **Pain** and **Pain Interference** will be assessed by the following diary items (adapted from the BPI), where participants respond on an 11-point Likert scale ranging from 0 (no pain) to 10 (pain as bad as I can imagine) and an 11-point Likert scale ranging from 0 (did not interfere) to 10 (completely interfered):
    - **Worst Pain Intensity:** What was your pain when it was at its WORST in the past 24 hours?
    - **Average Pain Intensity:** What was your pain, on AVERAGE, in the past 24 hours?

    - **Pain Interference:** How much did pain interfere with your general activities in the past 24 hours?
- **Mood (anxiety and depression)** will be assessed by the following diary items (adapted from the Patient Health Questionnaire – 4 Item), where participants respond on a 4-point Likert scale ranging from 0 (not at all) to (nearly all day):
    - Over the **past 24 hours**, how often have you been bothered by the following problems?
    - Feeling nervous, anxious or on edge?
    - Not being able to stop or control worrying.
    - Little interest or pleasure in doing things.
    - Feeling down, depressed, or hopeless.
- **Sleep quality** will be assessed via the daily diary using the following item (adapted from the Pittsburgh Sleep Quality Index), where participants respond on a 4-point Likert scale ranging from 0 (very good) to 3 (very bad):
    - For last night, how would you rate your sleep quality overall?

- ***Longitudinal Phase: Weekly Diary (Participants with chronic pain only)***
  The weekly diary will be completed at the end of the first and second week of the diary portion of the study. It consists of 4 items, with an estimated completion time of 1-2 minutes.
- **Pain management** will be assessed using the following items, which have been adapted from previous pain and EMA research:
    - Please tell us about the strategies you used to try to reduce your pain **during the past week.**
        - Response options will include: None, Non-prescription medication (Tylenol, Advil), Non-prescription cream or patch (e.g., Icy Hot), Prescription medication (e.g., gabapentin, morphine, Lyrica, Amitriptyline), Prescription medication not prescribed for you (e.g., a friend or family member's medication), Saw a healthcare provider (e.g., physical therapist, psychologist, chiropractor), Alcohol, Relaxation exercises (e.g., deep breathing, imagery), Marijuana/cannabis (e.g., oil, smoking, edibles), Distraction, Talking with friends/family, Rest/sleep, Prayer, Meditation, Heat/cold, and Massage/rubbing, Other (please specify).
        - *Note*: The "Other" response will include an open text field.
    - How helpful was this strategy(s)? (participants will rate all strategies endorsed)
        - Response options will include: Not helpful, a little helpful, somewhat helpful, very helpful, and don't know.
- **Interpretation of pain as cancer threat** will be assessed using the following items, where participants respond on a 5-point Likert scale ranging from 0 (agree very little) to 4 (agree very much):
    - When I felt pain **during the past week**, I worried that the pain was caused by **my cancer coming back**.
    - When I felt pain **during the past week**, I worried that the pain was caused by **me having a new type of cancer**.

Note: On Day 7, participants will complete the daily and weekly diary. On Day 15, following completion of the daily diary, they will complete the second weekly diary.

- ***Follow-Up***
- **Acceptability/feasibility** of the mHealth platform and smartphone-based symptom diary will be assessed via two methods:
    - 1) Participants will complete an acceptability measure adapted from the Acceptability E-Scale, which has been used in previous studies of usability and acceptability of mHealth applications for pain.
    - 2) We will *a priori* define participants as low, medium, or high app/diary engagers based on their completion of the daily and weekly diary assessments, and select 10 participants within each group based on maximum variation in demographic characteristics of interest, to invite for a brief follow-up telephone interview regarding likes/dislikes of the app/diary and barriers/facilitators of use. Approximately 5-7 participants will be interviewed within each engagement group, as sample sizes in this range have been shown to result in data saturation in qualitative studies focused on mHealth acceptability.[40,41]
- **Examination of Participant Engagement Methods**
    - To examine whether telephone calls increase completion of measures at each stage of the study, all participants will be randomized to the following groups: 1) Telephone reminder (texts, push notifications, telephone call reminder) or 2) No telephone reminder (texts, push notifications only)

Participants without chronic pain will complete a short version of the acceptability measure following completion of the baseline measures.

- ***Spire Feasibility Testing***
- Following completion of the follow-up activities, feasibility of the use of Spire as a wearable device will be assessed by deploying the device to participants with chronic pain. Outcomes such as uptake of the device, adherence to longitudinal, participant accrual and retention, participant perceptions of the device, as well as costs of delivering and returning the device and the quality of data received will be examined.

5.3.1 Primary cancer/diagnosis variables:

- Age at diagnosis
- Specific diagnosis
- Time since diagnosis

5.3.2 Treatment variables:

- Surgery yes/no
    - If yes, then major type (amputation, limb sparing, brain, thoracotomy, laparotomy)
    - If yes, then time since surgery
- Chemotherapy yes/no
    - If yes, then yes/no for all types of chemotherapy agents including:
    - Alkylating agent
    - Anthracycline
    - High-dose methotrexate
    - Prednisone
    - Dexamethasone
    - Vincristine
    - Bleomycin

- Cisplatin
- If yes, then dose for each type

- Radiation: yes/no
  - If yes, then yes/no for Cranial, Non-cranial
  - If yes, then cumulative dose of: 1) Cranial, 2) Neck, 3) Chest, 4) Abdomen, 5) Pelvis, and 6) Limb

5.3.3 Demographic variables: (from FU5 or most recent survey)

- Age
- Sex
- Race
- Household income
- Education
- Employment
- Marital status
- Assistance with routine needs

Note: If a participant has not completed a recent survey, we will have the ability to contact the participant through the Eureka platform via either text direct messaging within the app to obtain updated data.

5.4 **Covariates:** (from FU5 or most recent survey)

- Medications
  - Use of antidepressant medications
  - Use of opioid and non-opioid analgesic medications
- Chronic health conditions (from FU5 or most recent survey)
  - Conditions in which pain is commonly experienced will be examined, such as: joint replacement, diabetes, osteoporosis, cardiac and pulmonary conditions that could be interpreted as vague chest pain.
  - Grade/severity score (mild, moderate, severe, life-threatening or disabling) of each condition will be considered
  - Number of health conditions (multiple: ≥ 2, ≥ 3)

6. Analytic Approach

Aim 1: To estimate the prevalence and nature of chronic pain (defined as recurrent or persistent pain, lasting at least 3 months) and pain interference among long-term survivors of childhood cancer using an ecological momentary assessment design delivered in an integrated smartphone application.

For aim 1, we will generate prevalence estimates of chronic pain, using report of chronic pain at the outset of the study. Chronic pain will be defined as persistent or recurrent pain for ≥ the past 3 months. Prevalence estimates of chronic pain will also be generated for each diagnostic group (e.g., osteosarcoma, Ewing sarcoma, acute lymphoblastic leukemia). Prevalence for additional subgroups may be reported based on the factors in Aim 2 that are identified as important predictors of chronic pain (e.g., time since diagnosis, current age). Among participants with chronic pain, we will examine the nature of the chronic pain by reporting total and individual items scores pertaining to pain interference, location(s) of the pain, and average and worst pain ratings. These estimates will be reported as proportions (e.g., the proportion

of survivors with chronic pain who endorse pain interference). All prevalence and proportion estimates will be reported with their associated 95% confidence intervals.

Aim 2: To identify demographic, diagnostic, and treatment-related factors associated with chronic pain and pain interference in long-term survivors of childhood cancer.

For aim 2, we will utilize multivariable logistic, log-binomial or linear regression modelling to examine associations between chronic pain and pain interference and demographic, diagnostic, and treatment-related variables. Separate multivariable models will be run for diagnostic and treatment-related variables to control for confounding. All models will be adjusted for sex and marital relationship based on a priori information. Each of the candidate variables (see Table 3) will be examined in univariable models and those with p-values <.02 will be examined together in a multivariable model. Care will be taken to ensure that multiple variables used as covariates are not on a causal pathway for each outcomes (e.g. cranial radiation > depression > sleep > chronic pain). When such potential pathways are identified, sensitivity analyses will be conducted with and without specific variables, and mediation analyses will be considered. Step up and step down modelling will be used to determine the best model for each outcome. For chronic pain, as we expect the prevalence of chronic pain to be ≥10%, we plan to directly model and report relative risk estimates and corresponding 95% confidence intervals using a log-binomial (or modified Poisson) model. As pain interference is a continuous variable we will utilize linear regression modeling for this outcome. The same model building approach will be used with pain interference, and these analyses will be among only those individuals with chronic pain.

Aim 3: To evaluate associations between chronic pain and pain interference outcomes and depression, anxiety, fear of cancer recurrence, pain catastrophizing, intolerance of uncertainty, and sleep among long-term survivors of childhood cancer.

For aim 3, we will utilize multivariable logistic, log-binomial or linear regression modelling to examine associations between our primary outcomes of interest, chronic pain and pain interference, with our exposures of interest including depression, anxiety, fear of cancer recurrence, pain catastrophizing, perceived cause of pain, interpretation of pain as cancer threat, intolerance of uncertainty, and sleep. We will first examine potential collinearity among our exposures and will adjust for relevant demographic, treatment, and clinical factors to reduce potential confounding bias among covariates. Again, care will be taken to ensure that multiple variables used as covariates are not on a causal pathway for each outcomes. When such potential pathways are identified, sensitivity analyses will be conducted with and without specific variables, and mediation analyses will be considered. Candidate variables for this analysis are outlined in Table 3.

Exploratory Aim 1: To assess the feasibility (participant accrual, retention, ease of use of the device, participant receptions of use of the device, quality of data collected) of collecting respiration data using a validated wearable device (*Spire*) integrated within the mHealth platform, and to conduct a preliminary examination of the effect of the device on pain, depression, and anxiety.

For exploratory aim 1, we will examine the number and percent of participants who successfully connect the device, use it in the way specified, and their perceptions of using this device. In regards to the latter, a modified version of the Acceptability E-Scale will be used to assess perceived likes/dislikes as well as barriers/facilitators of use of the device. We will also examine variables such as how many participants adhered to using the device for the time frame specified. An adherence rate of approximately 70% will be defined as acceptable and

indicative of feasibility. We will also characterize participants' patterns of use. We will calculate accrual and retention rates in the Spire component of the study as well as costs associated with delivery of the device and return of it to the study team. Rates will be compared to rates among siblings.

Exploratory Aim 2: To examine the feasibility of implementing a novel mHealth platform and integrated smartphone application to measure pain and health related outcomes within a large cohort of long-term survivors of childhood cancer.

For exploratory aim 2, we will examine study participation rate, compliance with the diary measures, and perceptions of the mHealth platform and smartphone application. A participation rate of 60 % will be defined as acceptable. Participant perceptions will be obtained via the Acceptability E-Scale and telephone interviews with participants. Compliance will be calculated as the total number of correctly completed assessments divided by the total number of scheduled diary assessments for each participant. Compliance will be calculated for all assessments combined and for each assessment separately (daily pain, daily mood, daily sleep, weekly pain management, weekly interpretation of pain). A compliance rate of approximately 70% will be defined as acceptable and indicative of feasibility.

Exploratory Aim 3: To examine factors that increase participation in the overall study utilizing an integrated smartphone application within a large cohort of long-term survivors of childhood cancer. We will determine whether the addition of telephone calls, texts and in-app push notifications, increase participation and longitudinal engagement in the study (see Study Flow diagram).

For exploratory aim 3, to examine whether calls increase completion of baseline measures, daily and weekly diaries, and follow-up measures, we will compare completion and compliance rates between the telephone-reminder and no telephone-reminder groups.

Table 1. Characteristics of study population (N =)

	M	SD
Age at evaluation		
Age at diagnosis		
Time since diagnosis		
	N	%
Sex		
Female		
Male		
Race/Ethnicity		
White/non-Hispanic		
Other		
Diagnosis		
Leukemia		
Bone tumors		
CNS tumor		
Hodgkin lymphoma		
Non-Hodgkin's lymphoma		
Wilms tumor		
Neuroblastoma		
Other cancer		
Marital Status		
Single, never married		
Married, living as married		
Widowed, divorced, separated		
Location		
Rural		
Non-rural		
Assistance with routine needs		
Yes		
No		
Physical health status		
Poor, fair		
Good, very good, excellent		
Radiation		
None		
Non-cranial		
Cumulative Cranial		
Cumulative Neck		
Cumulative Chest		
Cumulative Abdomen		
Cumulative Pelvis		
Cumulative Limb		
Chemotherapy		
Alkylating agent		
Anthracycline		
High-dose methotrexate		
Prednisone		
Dexamethasone		

- Vincristine
- Bleomycin
- Cisplatin
- Cumulative dose

Surgery

- Neurosurgery
- Amputation
- Limb-sparing
- Other
- None

Table 2. Duration, severity, location, and associated interference of chronic pain childhood cancer survivors.

	N	Prevalence/Proportion	95% CI
Duration of chronic pain			
At least 3 months but less than 1 year			
1 year or more			
Average pain intensity in the past week			
Mild (1-4)			
Moderate (5-6)			
Severe (7-10)			
Worst pain intensity in the past week			
Mild (1-4)			
Moderate (5-6)			
Severe (7-10)			
Location			
Arm(s)			
Leg(s)			
Stomach			
Chest			
Lower back			
Neck			
Head			
Pelvis			
Feet			
Hands			
Other			
Pain interference			
Total interference			
None/Mild (<2)			
Moderate (2-5)			
Severe (>5)			
Mood-related interference			
None/Mild (<2)			
Moderate (2-5)			
Severe (>5)			

Activity-related interference
None/Mild (<2)
Moderate (2-6)
Severe (>6)

Table 3. Planned candidate variables to be examined in univariable models.

Aim 2
Demographic
Race/Ethnicity
Current age
Diagnostic
Primary diagnosis
Age at diagnosis
Time since diagnosis
Treatment
Radiation
Chemotherapy
Surgery
Aim 3
Psychological
Depression
Anxiety
Sleep disturbance
Fear of cancer recurrence
Intolerance of uncertainty
Pain catastrophizing
Interpretation of pain as cancer threat
Interpretation of the cause of pain

Table 4. Relative risk ratios and 95% confidence intervals for predictors of chronic pain and pain interference in childhood cancer survivors.

	Chronic Pain			Pain Interference		
	RR	95% CI	*P*-value	RR	95% CI	*P*-value
Sex						
Male	1.0			1.0		
Female						
Race/Ethnicity						
White/non-Hispanic						
Other	1.0			1.0		
Diagnosis						
Leukemia						
Bone tumors						
CNS tumors	1.0			1.0		
Hodgkin lymphoma						
Non-Hodgkin's lymphoma						
Wilms tumor						
Neuroblastoma						
Other cancer						
Marital Status						
Single, never married						
Married, living as married	1.0			1.0		
Widowed, divorced, separated						
Physical health status						
Poor, fair						
Good, very good, excellent	1.0			1.0		
Radiation						
Non-cranial						
Cumulative Cranial						
Cumulative Neck						
Cumulative Chest						
Cumulative Abdomen						
Cumulative Pelvis						
Cumulative Limb						
None	1.0			1.0		
Chemotherapy						

Alkylating agent		
Anthracycline		
High-dose methotrexate		
Prednisone		
Dexamethasone		
Vincristine		
Bleomycin		
Cisplatin		
None	1.0	1.0
Surgery		
Neurosurgery		
Amputation		
Limb-sparing		
Other		
None	1.0	1.0
Depression		
Clinical		
Sub-clinical	1.0	1.0
Anxiety		
Clinical		
Sub-clinical	1.0	1.0
Sleep disturbance		
Clinical		
Sub-clinical	1.0	1.0
Fear of cancer recurrence		
Clinical		
Sub-clinical	1.0	1.0
Intolerance of uncertainty		
Clinical		
Sub-clinical	1.0	1.0
Pain catastrophizing		
Clinical		
Sub-clinical	1.0	1.0
Interpretation of pain as cancer threat		
Clinical		
Sub-clinical	1.0	1.0

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