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Project Requirements and Description

Requirements to submit AOI

Requirements to submit AOI (all answers must be "yes" to proceed)

A comprehensive review of previously published data has been completed	Yes
The specific aims are clear and focused	Yes
The investigator has appropriate experience and expertise to develop the concept proposal; if not, has identified a mentor or senior co-investigator.	Yes
The investigator agrees to develop an initial draft of the concept proposal within 6 weeks of approval of the AOI and to finalize the concept proposal within 6 months	Yes

Project Title

Longitudinal Chronic Prescription Medication Use and Polypharmacy Among Childhood Cancer Survivors

Planned research population (eligibility criteria)

Entire CCSS cohort (survivors and siblings) ≥18 years of age who completed the baseline survey and at least one follow-up survey that queried medication use (FU-1, FU-2, FU-4, FU-5, FU-7).

Proposed specific aims

Aim 1. Describe the timing and cumulative numbers of chronic medications prescribed to childhood cancer survivors as they age. We will assess the numbers of cumulative and active prescriptions that participants are reporting at longitudinal timepoints relative to participants' age, characterize active medications within previously defined categories of classifications used for prior studies (e.g., hypertension, diabetes, dyslipidemia, psychiatric, pain meds, opioids), and estimate the prevalence of polypharmacy (≥5 active chronic medications) among survivors.

Aim 2. Compare the cumulative numbers of chronic prescriptions among survivors across the lifespan with prescription use among sibling controls. Prescription medication use will be based on participants' self-report of "current use" in each applicable questionnaire. We anticipate this analysis would be performed with a GEE model to capture longitudinal trends in chronic medication use over time, and likelihood of developing polypharmacy.

- Exploratory Aim 2b. Compare cumulative numbers of prescriptions among survivors in the US to those living in countries with universal healthcare systems: Canada (CCSS) and Switzerland (Swiss CCSS), and

specifically among survivors with a greater number of chronic health conditions.

Aim 3. Assess factors associated with greater prescription medication use and/or polypharmacy. We will test associations between these outcomes of interest and social factors (insurance coverage, household income, area-based factors such as SVI, etc.), chronic health condition burden, treatment exposures, and health behaviors (tobacco, alcohol use).
- Exploratory Aim 3b. In a subanalysis of survivors who responded to FU-6 medium, we will also explore whether chronic prescription use and/or polypharmacy are associated with financial hardship scores, the behavioral financial hardship domain score (previously defined by Nathan et al, JCO 2020), whether a survivor had ever been sent to debt collections, and whether a survivor had ever filed for bankruptcy.

Will the project require non-CCSS funding to complete? No

If yes, what would be the anticipated source(s) and timeline(s) for securing funding?

Does this project require contact of CCSS study subjects for:

Additional self-reported information	No
Biological samples	No
Medical record data	No

If yes to any of the above, please briefly describe.

What CCSS Working Group(s) would likely be involved? (Select all that apply)

	Primary	Secondary
Second Malignancy		
Chronic Disease	✓	
Psychology/Neuropsychology		
Genetics		
Cancer Control		✓
Epidemiology/Biostatistics		✓

Outcomes or Correlative Factors

	Primary	Secondary	Correlative Factors
Late Mortality			✓
Second Malignancy			✓

Health Behaviors

	Primary	Secondary	Correlative Factors
Tobacco			✓
Alcohol			✓
Physical Activity			✓
Medical Screening			✓
Other			

If other, please specify

Psychosocial

	Primary	Secondary	Correlative Factors
Insurance			✓
Marriage			✓
Education			✓
Employment			✓
Other			

If other, please specify

Medical Conditions

	Primary	Secondary	Correlative Factors
Hearing/Vision/Speech			✓
Hormonal Systems			✓

	Primary	Secondary	Correlative Factors
Heart and Vascular			✓
Respiratory			✓
Digestive			✓
Surgical Procedures			✓
Brain and Nervous System			✓
Other			

If other, please specify

Medications

Describe medications

The primary outcome at each timepoint will be number of active medications to describe medication accumulation and define polypharmacy. Secondary outcomes may include medications within previously defined categories, for which no new coding would be needed: hypertension, diabetes, dyslipidemia, psychiatric, pain meds, opioids. These would be collected for purely descriptive purposes.

Psychologic/Quality of Life

	Primary	Secondary	Correlative Factors
BSI-18			
SF-36			✓
CCSS-NCQ			
PTS			
PTG			
Other			

If other, please specify

Other

	Primary	Secondary	Correlative Factors
Pregnancy and Offspring			
Family History			

	Primary	Secondary	Correlative Factors
Chronic Conditions (CTCAE v3)			✓
Health Status			

Demographic

	Primary	Secondary	Correlative Factors
Age			✓
Race			✓
Sex			✓
Other			✓

If other, please specify

Cancer Treatment

	Correlative Factors
Chemotherapy	✓
Radiation Therapy	✓
Surgery	✓

Anticipated Sources of Statistical Support

CCSS Statistical Center	Yes
Local Institutional Statistician	No

If local, please provide the name(s) and contact information of the statistician(s) to be involved.

Will this project utilize CCSS biologic samples?

No

If yes, which of the following?

If other, please explain

Other General Comments

In discussion of the data with the CCSS analytic team, medications have been carefully recorded and there is thought to be little misclassification beyond the limitations of self-report. Not all medications have been categorized into various groups. However, we can leverage the work of prior CCSS studies that documented and coded specific medications based on typical indications (e.g., psychiatric meds, opioids, hypertension meds), to incorporate these indications into the analysis--reporting medications by category would be purely descriptive. The specific comparative components at longitudinal timepoints will use numbers of active medications/polypharmacy only, which should facilitate a slightly more straightforward analysis. If possible, it might be helpful to establish a collaboration with a pharmacy representative(s) for concept development and analysis, to supplement biostatistical support.

The Swiss CCSS team (Drs. Severin Fankhauser and Christina Schindera) previously expressed interest in a joint project to concurrently characterize prescription utilization in a non-US cohort. We anticipate a US-European comparison could be interesting, either as part of this project (Exploratory Aim 2) or in parallel. However, careful consideration would need to be given to the methodologies used for identifying prescriptions in each cohort, to not attribute any identified differences in prescription use to artifacts of data capture/classification, rather than true differences in patterns. If there are concerns in methodology, purely descriptive results could be presented cautiously. A parallel comparison between US and Canadian participants in the CCSS could also supplement US-Europe comparisons, given consistency in the methods of prescription listing between US and Canadian participants in the CCSS.

As alluded to above, there have been isolated analyses and concepts examining the use of particular classes of medications among survivors. Tara Brinkman and other CCSS colleagues previously published two papers assessing use of psychoactive medications (PMID: 22848025, 23224753) in childhood cancer survivors. Opioid use has also been examined within the CCSS (PMID: 33134833). This proposal will distinguish itself by focusing on the longitudinal accumulation of prescriptions across the lifespan and polypharmacy, rather than specific indications themselves. Notably, an Application of Intent some overlapping interest in polypharmacy was approved in 2018 (C. Murphy); however, this never made it to the concept phase and our review did not identify other concepts or peer-reviewed studies outlining burden of prescriptions in general or polypharmacy in childhood cancer survivors.

Agree

I agree to share this information with St. Jude

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