A FEASIBILITY STUDY OF THREE TIMES WEEKLY SYMPTOM SCREENING FOR CHILDREN WITH CANCER

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BACKGROUND

There are approximately 1,500 children and adolescents diagnosed with cancer each year in Canada and there are currently over 10,000 children living with cancer nationally.[1] Over the last few decades, impressive gains in survival have been made and now, more than 82% of children with cancer will be cured.[2] These survival gains have been, in part, attributable to the provision of intensive therapies. However, as a result, most children suffer and experience severe and distressing treatment-related symptoms such as pain, fatigue and nausea.[3] In our recent cross-sectional study of 302 inpatients 8-18 years of age, 99% of children experienced at least one bothersome symptom and 60% experienced at least one *severely* bothersome symptom, including severe pain in 22% and severe fatigue in 33% when asked about yesterday or today.[4] Symptoms impact on quality of life (QoL), morbidity and future psychosocial functioning.[5]

We know from studies in adult cancer patients that routine collection of patient-reported outcomes (PROs), improves patient-clinician communication,[6] reduces distress[7] and improves QoL.[8,9] Furthermore, a recent randomized trial showed that routine PRO assessment may improve survival in adults with metastatic solid tumors.[10] Thus, the routine measurement of PROs is considered essential to high quality of care.[8] Challenges to the incorporation of PROs into clinical practice include lack of integration into clinical care work flow.[11] We also know that delivery of care consistent with evidence-based clinical practice guidelines (CPGs) can improve patient outcomes.[12] However, compliance with CPGs is generally poor.[13,14]

Consequently, in Canadian adult oncology practice, screening and assessment of symptoms and improving accessibility of supportive care CPGs are important priorities.[15-18] Efforts by Cancer Care Ontario have culminated in the wide-spread use of a symptom screening tool based upon the Edmonton Symptom Assessment Scale (ESAS).[19] The ESAS is a validated tool which asks adult patients to rate the severity of nine common symptoms including pain, anxiety and nausea. In a satisfaction survey of 2,921 patients, 87% of respondents thought the ESAS was an important tool for letting healthcare providers know how they feel.[20] Furthermore, through an initiative with Cancer Care Ontario and the Canadian Partnership against Cancer, evidence-based guidelines were developed to manage severe symptoms identified by the tool.[20] These efforts have continued to evolve and led to the development and implementation of the Interactive Symptom Assessment and Collection (ISAAC) tool, Your Symptoms Matter, which allows patients to assess and monitor their symptoms through an online computer program. Your Symptoms Matter is available at kiosks in 14 regional cancer centers and 28 hospitals across Ontario. More than 27,000 patients are screened every month through the system. Implementation of ISAAC in the adult cancer setting improved health outcomes,[19] led to decreased emergency room visits and triggered clinical action for those with higher symptom scores.[21,22] In contrast to these advances in adult cancer care, efforts in children are limited.[23] We used the Knowledge-to-Action cycle[24] as the conceptual framework to guide this research program.

Development of SSPedi and SPARK: Efforts in children to achieve routine symptom screening and enhance CPG compliance are limited.[23] We conducted a systematic review and identified the lack of appropriate symptom screening tools for children with cancer and that no study altered patient management based upon identified symptoms.[25]

SSPedi: Early in our program, we recognized the lack of an appropriate symptom screening tool for pediatric cancer patients and thus, developed the Symptom Screening in Pediatrics Tool (SSPedi).[26,27] It is a 15-item symptom screening tool for children receiving cancer treatments; recall period is yesterday or today. Items were generated using a nominal group technique among pediatric cancer clinicians and a patient advocate.[28] Next, based upon input from 50 children receiving cancer treatments and 20 parents of pediatric oncology patients, we refined the paper and electronic versions of SSPedi and confirmed content validity, understandability and ease of use.[28-30] The electronic version of SSPedi has an audio feature which allows specific questions or the entire instrument to be read

aloud. A help feature provides synonyms for each symptom; these were derived primarily from children themselves during cognitive interviewing.

Next, we conducted a multi-center study to evaluate the psychometric properties of SSPedi. Among 502 children 8-18 years of age receiving cancer treatments, all were able to complete SSPedi without difficulty. We confirmed that SSPedi is reliable, valid and responsive to change. More specifically, the intraclass correlation coefficients were 0.88 (95% confidence interval (CI) 0.82 to 0.92) for test re-test reliability, and 0.76 (95% CI 0.71 to 0.80) for inter-rater reliability between children and parents. Mean difference in total SSPedi scores between groups hypothesized to be more and less symptomatic was 7.8 (95% CI 6.4 to 9.2; P<0.001). Construct validity was demonstrated as all hypothesized relationships among measures were observed. SSPedi was responsive to change; those who reported they were much better or worse on a global symptom change scale had significantly changed from their baseline score (absolute mean difference 5.6, 95% CI 3.8 to 7.5; P<0.001).[4]

SSPedi is also available as a proxy-version that is reliable and valid.[31]

Mini-SSPedi: In order to address the needs of younger children, we developed a version of self-report SSPedi for children 4-7 years named mini-SSPedi using cognitive interviews with 100 young children. Development included decision making regarding questionnaire structure, recall period (today) and response option format (three-point Likert scale).[32] Mini-SSPedi has content validity and is easy to understand and complete. Mini-SSPedi is also available as a proxy-version.

SPARK: Supportive care Prioritization, Assessment and Recommendations for Kids (SPARK) is a web-based application which builds upon SSPedi and consists of two components: (1) a symptom screening component centered on SSPedi; and (2) a supportive care CPG component. CPGs contained within SPARK are those that meet rigorous development criteria established by the National Guideline Clearinghouse.[33] There are patient, family and healthcare provider portals in SPARK. This proposal focuses on the patient and provider portals of SPARK.

SPARK pages and function were developed and iteratively refined by performing cognitive interviews using the think aloud technique with 90 children receiving cancer treatment and 60 healthcare providers until the website was considered satisfactory for longitudinal evaluation.[34]

Next, in a pilot study conducted in preparation for a funded and currently ongoing randomized trial, we evaluated the feasibility of daily completion of SSPedi for five days among children who were either admitted to hospital or seen in clinic for five consecutive days. We defined feasibility as the completion of SSPedi within SPARK for at least 60% of on-study days in at least 75% of participants. In three months, we enrolled 20 participants of whom 18 completed assessments all 5 days. Two children missed one day each: one because of transfer to the intensive care unit due to a seizure and the second because she was seen in clinic only for blood work and was missed by the research team. Consequently, 100% of children met our *a priori* defined threshold for feasibility. All found completion of SSPedi via SPARK was easy and that SPARK was easy to navigate. They all thought daily completion was “about right” and not “too much” or “too little” for this population. All completely understood their own SPARK bar and line graphs.

Based upon this data, we designed and were funded by CIHR (Project Scheme, fall 2018) to conduct a multi-center study of daily symptom screening for patients anticipated to be in hospital or clinic daily for at least five days across seven Canadian centers.

OBJECTIVES

Primary Objective: Among children and adolescents 4-18 years of age with newly diagnosed or relapsed cancer, to determine the feasibility of three times weekly symptom reporting by guardians and children using the SPARK platform for 12 weeks. Feasibility will be evaluated by compliance with symptom screening and anticipated that at least 75% can achieve compliance with at least 60% of symptom evaluations.

Secondary Objectives: a) To describe symptom burden as measured by the total SSPedi or mini-SSPedi score, fatigue using PROMIS fatigue scale, pain using Faces Pain Scale-Revised (FPS-R), and

quality of life using the PedsQL 3.0 Acute Cancer Module.
b) To describe symptom documentation in the health records and intervention provision for symptom control
c) To describe emergency department visits and unplanned clinic visits and hospitalizations.

METHODS

This is an open label feasibility study enrolling newly diagnosed and relapsed patients to evaluate symptom screening and feedback. We anticipate that the majority of symptom screening will occur in the ambulatory setting. The study will only be conducted at The Hospital for Sick Children.

We will include children with cancer who: (1) are 4-18 years of age at enrollment; (2) are English or Spanish or French-speaking (SSPedi is validated in these languages); (3) have any newly diagnosed or relapsed cancer; (4) have a plan for any chemotherapy, radiotherapy or surgery; and (5) enroll within 28 days after treatment initiation. Exclusion criteria will be cognitive disability or visual impairment (cannot see SPARK even with corrective lens). Respondents will be children themselves and one guardian. Participating guardian needs to be able to speak English, Spanish or French.

Potentially eligible families will be approached by the research team who will obtain informed consent and assent (if appropriate). Enrolled participants will be prompted to complete symptom screening three times weekly via SPARK with corresponding feedback sent to healthcare providers with each completed assessment. Symptom reports will contain links to CPGs for symptom management. Active intervention will last for 12 weeks starting from the date of enrollment.

Potential participants will be identified by the clinical staff and recruited from the inpatient ward and outpatient clinics. Informed consent and assent will be obtained from each participant/guardian as appropriate. Demographic information including age, sex, race, ethnicity, diagnosis, cancer stage, family socioeconomic information and treatment plan will be collected at enrollment. For all participants, the following PROs will be obtained by trained research staff at baseline, and weeks 4, 8 and 12: SSPedi, PROMIS Fatigue, FPS-R and the PedsQL 3.0 Acute Cancer Module. Data from health records will be abstracted for all enrolled participants to evaluate symptom documentation and intervention provision at times symptom screening is completed as well as emergency room visits, clinic visits and hospitalizations.

Symptom screening using SPARK will be prompted three times weekly for 12 weeks. The three times weekly frequency was chosen based upon our data showing that symptoms can change rapidly in children with cancer. For example, among 282 inpatient children 8-18 years of age who provided two SSPedi scores three days apart, 68.8% had a change in overall symptoms as measured by a 5-point global symptom change scale.[4] In terms of fatigue scores specifically, about half had a change in the degree of bothersome fatigue.[35] Participants will be set up to use their own smart phone, tablet or computer to perform symptom screening. If participants do not have a device, one will be loaned to them for the study duration. Participants will receive reminders on their device three times weekly to complete symptom screening; this reminder mechanism was found to be effective in our pilot study. We will also provide text or email reminders depending on the participants' preferences.

Each time the participant completes symptom screening, the primary healthcare team will receive an email with the symptom report as an attached pdf. "A lot" or "extremely" bothersome symptoms will be highlighted in the body of the email. The specific recipients of the email will be dictated by each team's preferences. For example, teams may choose to have emails sent to attending physicians, nurse practitioners or contact nurses, or specific combinations of these or other recipients (all of whom must be in the patient's circle of care). The emails and reports have been developed, tested and approved for use at SickKids and are being used in our current randomized trial. Reports will contain Quick Response codes for easy access to SPARK-housed CPGs. Qualitative feedback from providers receiving these reports in our pilot study has been positive.

Primary and Secondary Outcome Measures: The primary endpoint is feasibility, defined as at least 75% achieving compliance with at least 60% of symptom evaluations among guardian and self-report populations separately.

Secondary endpoints are potential endpoints for the randomized trials. They will include:
a) Total SSPedi symptom or Mini-SSPedi score, which is the sum of each of the 15 SSPedi item's Likert scores, resulting in a total score that ranges from 0 (no bothersome symptoms) to 60 (worst

bothersome symptoms). The recall period is yesterday or today (SSPedi) or today (mini-SSPedi). The total SSPedi score is reliable, valid and responsive to change in children with cancer 8-18 years of age.[4]

b) Fatigue will be measured using PROMIS. The recall period is the last 7 days. It is reliable and valid in children 5-18 years of age with cancer.[36]
c) QoL will be measured using the PedsQL 3.0 Acute Cancer Module.[37] The 7 day recall version will be used. This measure is a multidimensional instrument that is reliable and valid in children with cancer.[37] It assesses pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance and communication.
d) FPS-R. The FPS-R consists of a series of horizontal faces that depict a neutral facial expression of "no pain" at the left and "most pain possible" expression at the right. It has 6 faces and may be scored on a 0-10 scale.[38] FPS-R is psychometrically sound and feasible for children 4-18 years of age.[39]
e) Symptom documentation and intervention provision at each time point in which symptom assessment is performed.
f) Emergency department visits and unplanned clinic visits and hospitalizations.

All questionnaires including SSPedi will be administered at baseline, week 4 (±1 week), week 8 (±1 week) and week 12 at an in-person visit during a hospitalization or clinic visit (preferred), or will be obtained remotely. At these visits a member of the study team will ask the patient or guardian if the patient has had any visits to the emergency department, unplanned clinic visits or any unplanned hospital admissions since enrollment or the last assessment. A member of the study team will coordinate with the family to identify the preferred place and location to obtain these outcomes.

Endpoints to be abstracted from the health record are documentation of symptoms, provision of interventions for symptoms and emergency department visits and unplanned clinic visits and hospitalizations. Documentation of symptoms and intervention provision for symptom control will be abstracted from the patients' health records using the procedures our team previously developed. [40] The number of interventions for each symptom at each reporting period will be recorded and categorized as any intervention provided vs. no intervention provided. Both documentation of symptoms and interventions for these symptoms will be described for each specific symptom at each time point. These outcomes will be obtained on each day that a week 4, 8 or 12 SSPedi/mini-SSPedi assessment was obtained with a one-day window before and after these assessments. In other words, if the participant completed SSPedi on a Tuesday, we would accept documentation of that symptom (or provision of an intervention for that symptom) if it were recorded in the health records on Monday, Tuesday or Wednesday. A comprehensive and field-tested list of synonyms for symptoms and interventions is available for each of the 15 symptoms in SSPedi/mini-SSPedi.[40] We found study data could be abstracted with minimal training and effort. Emergency department visits, clinic visits and hospitalizations will be abstracted from the health record; the study team will adjudicate whether clinic visits and hospitalizations were unplanned or planned, blinded to that patient's SSPedi or mini-SSPedi scores.

A future project will be to link the data from this trial with a pediatric cancer national database named Cancer in Young People-Canada (CYP-C). CYP-C has been collecting detailed demographic, cancer-related, and treatment data on all children with cancer in Canada since 2001 and it currently includes > 13,000 patients. The consent form for this application will allow future linking to CYP-C such that we can identify patient and institutional factors associated with high symptom scores and we can evaluate survival outcomes for those with uncontrolled symptoms.

Data Protection and Security: Please refer to Appendix that describes how data are protected in this study.

Statistics and Sample Size: All statistics are descriptive. As our primary outcome is feasibility, sample size justification will focus on having sufficient number of guardians and children to optimize study processes and to describe the number of completed symptom assessments. We will enroll 20-30 guardians and children for each of SSPedi and mini-SSPedi and anticipate we can enroll this number

over one year. The 95% confidence intervals assuming 60% compliance will be 36-81% and 41-77% for 20 and 30 participants respectively; this precision is adequate for our purposes.

SIGNIFICANCE AND FUTURE PLANS

This study will be the critical foundation upon which to develop a future randomized trial of symptom screening and symptom feedback for newly diagnosed and relapsed children with cancer. It is thus an important step toward optimizing symptom control and quality of life in pediatric cancer patients.

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