Symptom Screening Linked to Care Pathways for Pediatric Patients with Cancer: a Cluster Randomized Trial

This supplement contains the following items:

Protocol Title: Symptom Screening Linked to Care Pathways for Children with Cancer: a Cluster Randomized Trial

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BACKGROUND

Over the last few decades, impressive gains in survival for children and adolescents with cancer have been made and now, more than 82% of children with cancer will be cured.[1] 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.[2] In our cross-sectional study of 302 inpatients 8-18 years of age, when asked about yesterday or today, 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%.[3] Symptoms are important; we previously demonstrated a strong correlation between increasing symptom burden and worse quality of life (QoL) in children receiving cancer treatments.[3] Given excellent survival outcomes, we now need to focus more attention on symptom control.

To gain insight into why symptoms are uncontrolled, we evaluated 168 children and described the extent to which symptoms self-reported as severely bothersome were documented in the health record and for which any interventions were provided.[4] We created a standard operating procedure and a list of synonyms that met criteria for documentation of symptoms. For example, “tired”, “feel weak”, “low energy”, and “sluggish” were all considered adequate documentation for fatigue. We also created a list of possible interventions for each symptom. For most of the symptoms measured (12/15), severely bothersome symptoms were documented in the health record less than 60% of the time. The most infrequently documented severely bothersome symptoms were problems with thinking or remembering things (0%), changes in how your body or face look (4.8%), changes in taste (7.7%) and tingly or numb hands or feet (11.1%). Only two severely bothersome symptoms were documented at least 80% of the time, namely hurt or pain (92.6%) and throwing up or feeling like you might throw up (92.6%).

Provision of an intervention to address severely bothersome symptoms occurred less than 60% of the time for 10 of 15 symptoms. The most infrequently treated severely bothersome symptoms were thinking or remembering things (0%), changes in how your body or face look (0%), tingly or numb hands or feet (0%), changes in taste (0%), diarrhea (0%) and feeling tired (1.6%). Intervention provision was most common for hurt or pain (96.3%), headache (89.5%), throwing up or feeling like you might throw up (88.9%) and constipation (84.2%). However, even when interventions were provided, they were often not prescribed specifically for that symptom (for example, acetaminophen for fever rather than pain).

Within the adult oncology setting, screening and assessment of symptoms through patient self-report has been identified as an important priority.[5-8] In adult cancer patients, routine collection of patient-reported outcomes (PROs) improves patient-clinician communication[9], reduces distress[10] and improves QoL.[11,12] Furthermore, a recent randomized trial showed that routine PRO assessment may improve survival in adult patients with metastatic solid tumors.[13] Among participants that were randomized to symptom screening vs. standard of care, median overall survival was 31.2 months (95% confidence interval (CI) 24.5 to 39.6) in the symptom screening group vs. 26.0 months (95% CI 22.1 to 30.9) in the standard of care group (P=0.03). Consequently, routine assessment of PROs is now considered essential to high quality care.[11] It is also known that delivery of care consistent with clinical practice guidelines (CPGs) can improve patient outcomes. For example, timely administration of CPG-consistent antibiotics to adult patients with fever and neutropenia resulted in significantly lower mortality compared to patients who did not receive CPG-consistent antibiotics.[14] However, adherence to CPGs is generally poor.[15,16]

In contrast to these accomplishments in adults, efforts in children are limited.[17] To help address this gap, we developed SSPedi (Symptom Screening in Pediatrics Tool; Appendix 1)[18,19] and SPARK (Supportive care Prioritization, Assessment and Recommendations for Kids; Appendix 2). SSPedi is a self-reported 15-item symptom screening tool for children receiving cancer treatments. SSPedi consists of the following 15 items: disappointed or sad, scared or worried, cranky or angry, problems thinking, body or face changes, tiredness, mouth sores,

headache, other pain, tingling or numbness, throwing up, hunger changes, taste changes, constipation and diarrhea. We developed SSPedi because our previous work concluded that then-available pediatric cancer symptom assessment tools were not appropriate for clinical use due to length or content.[20] Items were generated using a nominal group technique among pediatric cancer clinicians and a patient advocate.[20] 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.[20-22] The electronic version of SSPedi has an audio feature that allows specific questions or the entire instrument to be read aloud. A help feature provides synonyms for each symptom; these were derived from children themselves during cognitive interviews.

Next, we conducted a multi-center study in the US and Canada to evaluate the psychometric properties of SSPedi. SSPedi was shown to be reliable (internal consistency and test re-test and inter-rater reliability), valid (construct validity) and responsive to change in 502 English-speaking children 8-18 years of age receiving cancer therapies.[3] More specifically, the intraclass correlation coefficients (ICC) were 0.88 (95% 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 SSPedi scores between groups hypothesized to be more and less symptomatic was 7.8 (95% CI 6.4 to 9.2; P<0.001).[3] 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 (mean absolute difference 5.6, 95% CI 3.8 to 7.5; P<0.001). This instrument has been translated into Spanish; the translated version is satisfactory to use in the US and Canada based on understandability and cultural relevance.

Building upon SSPedi, SPARK is a web-based application that consists of two components: (1) a symptom screening component centered on SSPedi; and (2) a supportive care CPG component. While SSPedi asks children about symptoms, SPARK facilitates access to SSPedi, encourages symptom screening, generates reports and allows children to track their symptoms. In addition, when used by healthcare providers, SPARK links the symptoms identified using SSPedi with CPGs to manage them. CPGs contained within SPARK are those endorsed by the Children's Oncology Group (COG) and thereby meet minimum specific criteria with respect to methodological rigor and relevance to pediatric oncology.[23]

AIMS

Aims 1 and 2: Among children with newly diagnosed cancer, to determine if symptom screening and feedback to healthcare providers at least three times weekly and locally-adapted symptom management care pathways, when compared to usual care:

> Aim 1. Improves overall self-reported symptom scores (total SSPedi score), fatigue (PROMIS–Fatigue) and cancer-specific QoL (PedsQL 3.0 Acute Cancer Module) over 8 weeks
>
> *Hypothesis: Symptom screening and care pathways will improve symptoms, fatigue and QoL*
>
> Aim 2. Improves symptom documentation, increases provision of interventions for symptoms, and reduces emergency department visits and unplanned clinic visits and hospitalizations over 8 weeks
>
> *Hypotheses: Symptom screening and care pathways will increase symptom documentation and provision of interventions for symptoms, and will reduce healthcare utilization.*

Aim 3: As an exploratory aim, we will evaluate key elements of the intervention related to the external validity and generalizability of the intervention effects using the RE-AIM framework.

METHODS

Overall Strategy

This is a cluster randomized trial including 20 pediatric oncology sites. The coordinating center is The Hospital for Sick Children in Toronto, Canada. Sites will be randomized to either systematic symptom screening via SPARK with provision of symptom reports to healthcare providers containing links to care pathways for symptom management (intervention) or usual care (control).

Research Methods

Eligibility: We will include children with cancer who: (1) are 8-18 years of age at enrollment (SSPedi is validated in this age range); (2) are English or Spanish-speaking (all PROs are validated in these languages in this age range); (3) have any newly diagnosed cancer; (4) have a plan for any chemotherapy, radiotherapy or surgery; (5) have a plan to be followed by or receive care from the study institution for ≥ 50% of the 8-week study period and expected to be available on site or virtually for the week 8 assessment and (6) enroll within 28 days after diagnosis or treatment initiation, whichever occurs later. Exclusion criteria will be cognitive disability (attending lower than second grade or equivalent) or visual impairment (cannot see SPARK even with corrective lens).

Procedures: In this cluster randomized trial, we will randomize sites to either intervention or control groups. At both intervention and control sites, we will enroll participants within 28 days after diagnosis or treatment initiation, whichever occurs later. Eligible participants will be identified by site personnel and the study will be explained to them by trained research team members. Participant capacity to consent will be assessed by the clinical or research team according to institutional standards. After the study has been explained and sufficient time has been provided to ensure all questions have been answered, informed consent and assent will be obtained from participants and guardians as appropriate. For those who decline to contribute PROs, they will be given the option to only participate in a retrospective chart review to evaluate symptom documentation, intervention provision and healthcare utilization. Careful tracking of all newly diagnosed patients by site research personnel will occur to determine how many patients are approached and consented, and where possible, reasons for declining participation.

For all enrolled participants who will be contributing PROs (excluding those only involved in the retrospective chart review), a personal SPARK account will be created to allow SSPedi to be completed and symptom results to be recorded. At the 10 intervention sites, site-specific symptom management care pathways will be adapted from template care pathways for each of the 15 symptoms included in SSPedi. Enrolled participants will be prompted by text or email to complete symptom screening three times weekly via SPARK with corresponding feedback sent to their healthcare providers. Participants may be contacted in person, by email, text, or over the phone to ensure there are no technical barriers to completing SSPedi. Symptom reports will contain links to care pathways for symptom management. Active intervention will last for eight weeks starting from the date of enrollment. At the 10 control sites, participants will complete SSPedi to obtain the primary outcome at weeks 0, 4 and 8 but the scores will not be revealed to providers and will not be linked to care pathways. Usual care will be provided to participants at control sites and thus, there will be no study-requested routine, systematic symptom screening, symptom feedback to providers, or linkage to care pathways. If sites already routinely perform systematic symptom screening or use care pathways for symptom management, these may be continued but their use will be recorded.

At both intervention and control sites, demographic information including age, sex, race, ethnicity, diagnosis, cancer stage, family socioeconomic information and treatment plan will be collected at enrollment. The following PROs will be obtained by trained research staff at baseline, week 4 and week 8 for all participants: SSPedi, PROMIS Fatigue and the PedsQL 3.0 Acute Cancer Module (Aim 1). We will contact participants ahead of time to coordinate the week

4 and 8 PROs so that they can be completed in person during hospitalizations or clinic visits. If unable to arrange completion of these PROs in person, we will use their contact information to complete the questionnaires by email, text or over the phone. Data from health records (Aim 2) will be abstracted for all enrolled participants. Relapse and cancer treatment received information will be collected at the end of the study.

Procedures at Intervention and Control Sites**:**

Procedures at Intervention Sites**:** Participants enrolled at intervention sites will be prompted to complete symptom screening three times weekly via SPARK with corresponding feedback and links to symptom management care pathways sent to their healthcare providers.

a) Symptom Screening using SPARK: Symptom screening using SPARK can be performed at any time and as often as desired, but screening will be prompted three times weekly for eight weeks. In our pilot studies, the mean time for SSPedi completion using the identical SPARK platform was 1.0 (SD=1.5) minutes and in over 1,000 children who have completed SSPedi, no child has ever stated that SSPedi completion was distressing. The ideal frequency of symptom screening is not known; the need to identify change in symptoms as soon as possible must be balanced against the burden of frequent screening to children and healthcare providers. In order to identify the ideal frequency of symptom screening reminders, we surveyed site investigators at participating sites. The most commonly suggested frequency was three times weekly (n=15, range 2-5 times weekly). However, it is important to stress that three times weekly is the frequency in which we will remind participants to complete SSPedi; participants can complete SSPedi as often as they wish including daily or more often.

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. Text message reminders will be sent from SPARK using a HIPPA-compliant third party vendor to route the text messages. Email reminders will be sent from SPARK using the institutional email domain or other institutionally-approved approaches where required.

b) Symptom Reports to Healthcare Providers: Each day the participant completes symptom screening (whether prompted or unprompted) and has at least one severely bothersome symptom, the primary healthcare team will receive an email summarizing the symptom report and highlighting symptoms that are “a lot” or “extremely” bothersome. Emails will include links to the site-specific care pathways for symptom management. Patient name and date of SSPedi completion are included in the email to ensure correct identification of the patient. Thus, patient name will exist within the SPARK database but the system is configured such that no other site including The Hospital for Sick Children can access it. These approaches have been approved by The Hospital for Sick Children’s Privacy Office and IRB, and all IRBs of institutions that have participated in other SPARK studies. In terms of email communication, each hospital’s policies will be followed. At some hospitals, emails sent internally within the hospital are considered secure. In this case, SPARK emails will be generated from that hospital’s email domain if possible. Some hospitals may require encrypted emails; these will be used where required. Other approaches will be instituted where required.

Qualitative feedback from providers receiving these reports in our pilot study has been positive. When specifically asked, receiving these reports was not considered burdensome. In fact, providers found reports helpful to communicate symptom experience and to initiate or escalate symptom management interventions.

c) Creation of Local Care Pathways for Symptom Management: Care pathway templates for symptom management have been drafted for each of the 15 items included in SSPedi. These are primarily based on COG-endorsed CPGs and other CPGs that were developed using appropriate methodology. To supplement SSPedi symptom care pathway templates for which

CPGs exist and to address SSPedi symptoms for which CPGs do not exist, templates are also based on "good practice statements"[24]. In brief, "good practice statements" are guidance statements regarding the provision of care where to provide care in any other way would be considered unethical or absurd. Guideline experts have explicitly acknowledged their necessity and have published guidance for how and when to use such statements.[24] Upon study activation, we will work with each of the 10 intervention sites to develop site-specific, adapted care pathways that consider relevant work flows, institutional culture and available resources (laboratory tests, medications and personnel); this process will require three months to complete. The finalized local care pathways will contain explicit direction for how to prevent and manage symptoms at each site. The process for creating local care pathways will be based upon a procedure we developed for CPG adaptation, will require local inter-professional input and will be finalized at an in-person or video-conference meeting at the site.[25] This process incorporates activities known to promote practice change and enhance implementation. Activities include appreciation of local resources and values, identification of local barriers and facilitators, stakeholder participation in decision making, education of healthcare professionals and creation of implementation tools. It is expected that across the 10 sites, the care pathways could differ substantially in some areas, such as which profession or specialty should be consulted and choice of specific medications to treat a symptom, but that there should be similarities across all 10 local care pathways since they have a common evidence base. Annually, we will assess how the initial adaptations have changed to gain insight into the adaptation process over the course of the study and to evaluate how the process might inform future implementation of care pathways. Adaptations will be summarized and will be made available to all intervention sites during the study, and will be widely available to all sites following study completion as part of knowledge translation, and as a component of the RE-AIM implementation evaluation.

d) Training: From a patient participant perspective, training on how to use SPARK and how to interpret SPARK symptom reports will be provided at enrollment. From a healthcare provider perspective, training on how to interpret SPARK symptom reports, CPGs and care pathways will be provided to each site during the in-person or video-conference meeting to adapt symptom management care pathways and via a webinar at study activation and regularly throughout the study to educate new staff and to re-enforce knowledge for existing staff. Different aspects of training also will be highlighted during the site calls every two weeks. Stories of successful implementation at a particular site will be shared so that all sites can benefit. Technical assistance and support will be available to providers throughout the study from The Hospital for Sick Children where SPARK is located.

***Procedures at Control Sites*:** At control sites, usual care will be provided, which may or may not include symptom screening, access to CPGs or care pathways. Participants will complete SSPedi to obtain the primary outcome at weeks 0, 4 and 8 but the scores will not be revealed to providers and will not be linked to care pathways.

Describing Site Characteristics (both Intervention and Control Sites): In order to describe supportive care practices that could impact on intervention effectiveness and to gain insight into future implementation (adoption), the site PIs will complete a short questionnaire at study activation (baseline prior to randomization) and annually while participants are being enrolled. Questions will include demographic characteristics of patients and providers (only at baseline), psychosocial resources available for pediatric cancer patients and current approaches to systematic symptom screening, symptom management CPG availability and care pathway existence for SSPedi symptoms. CPG availability will be defined as either the posting of CPGs themselves or links to CPGs on an institutional website or drive that is available to all oncology providers (not an individual clinician's computer only). Care pathway use will be defined as a written set of instructions for the management of a symptom that is available to all oncology providers at that site. Site characteristics were also measured using the inner setting measures

from the Consolidated Framework for Implementation Research (CFIR).[26,27]

Site Monitoring, Quality Control and Intervention Site Auditing: Quality control will be maintained with calls every two weeks among participating site PIs and clinical research personnel. Separate calls will be held with intervention and control sites to reduce the risk of contamination. On those calls, we will summarize enrollments at each site and review the proportion of eligible patients enrolled. We will also review identified issues with respect to missing data and data quality identified during routine data checks.

For intervention sites, fidelity to the symptom screening approach will also be monitored. Each intervention site will be audited at least once (4-6 months after site activation) to assess adherence to the process of symptom screening, namely documentation of participant training in the health records, completion of SSPedi at least three times weekly, and delivery of symptom reports to providers. Accessibility of local care pathways will also be examined. These will be evaluated as part of the implementation dimension of RE-AIM.[28] Audits may be conducted in person or remotely.

Proposed Practical Arrangements for Allocating Sites: The allocation sequence will be computer generated. Sites will be randomized 1:1 and will be stratified by two site characteristics ≥ or < median: (1) anticipated number of cancer patients 8-18 years of age who speak English or Spanish per year, and (2) percentage of patients with private insurance vs. other payment types. Block size is not disclosed in this protocol. Assignment will be communicated by email to the site PI and clinical research personnel following randomization.

Proposed Methods for Protecting against Sources of Bias: Given the cluster randomized nature of the study, a potential source of bias is that allocation will be known, which could lead to selection bias during participant enrollment. To address this potential, efforts will be made to both identify all potentially eligible participants and maximize enrollment. We will describe those not approached and those who decline to participate in the intervention and control sites. We will describe these groups by sex, age, race, ethnicity, cancer type and institution.

Primary, Secondary and Exploratory Outcome Measures: Endpoints for Aim 1 are PROs; all PROs are self-report. The primary endpoint is the total SSPedi symptom 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. The total SSPedi score is reliable, valid and responsive to change in children with cancer 8-18 years of age.[3] Secondary endpoints include fatigue and QoL. Fatigue will be measured using PROMIS. The recall period is the last 7 days. It is reliable and valid in children 8-18 years of age with cancer.[29] QoL will be measured using the PedsQL 3.0 Acute Cancer Module.[30] The 7 day recall version will be used. This measure is a multidimensional instrument that is reliable and valid in children with cancer.[30] It assesses pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance and communication. All PROs are validated for use in English and Spanish for children 8-18 years of age.

For both groups, all questionnaires including SSPedi will be administered at baseline, week 4 (±1 week) and week 8 (±1 week) at an in-person visit during a hospitalization or clinic visit (preferred), or will be obtained remotely. The approach will be identical for intervention and control sites.

Endpoints for Aim 2 will be abstracted from the health record and are: documentation of symptoms, provision of interventions for symptoms and emergency department visits and unplanned clinic visits and hospitalizations. Guardians will also be asked about healthcare visits to ensure encounters outside the primary institution are captured. Documentation of symptoms and intervention provision for symptom control will be abstracted from the patients' health records using the procedures our team previously developed.[4] The number of interventions for each symptom at each reporting period will be recorded and categorized as any intervention

provided vs. no intervention provided. Interventions included in the local care pathway will be noted. 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 or 8 SSPedi assessment was obtained (as measured in conjunction with the other PROs) with a one day window before and after these assessments. For example, 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.[4] We found study data could be abstracted with minimal training and effort. De-identified source documentation will be sent to the coordinating center for quality assurance.

Exploratory endpoints for Aim 3 will be RE-AIM characteristics to measure reach, effectiveness, adoption and implementation. For reach, we propose to describe the baseline demographic characteristics of eligible patients who participate and who do not participate. We will describe site attributes using the inner setting measures from the CFIR as measured at baseline.[26,27] These attributes include culture, culture stress, culture effort, implementation climate, learning climate, leadership engagement and available resources. Effectiveness will be evaluated through primary and secondary outcomes and also by comparisons of the percentages of patients with severely bothersome symptoms within intervention and control sites. We will characterize adoption at intervention sites by describing characteristics of sites and providers at those sites. Site characteristics will include pediatric vs. mixed adult and pediatric, number of pediatric cancer patients diagnosed annually, and percentage of patients anticipated to have private, public or no insurance. Healthcare provider characteristics will include number of physician and nurse practitioner full-time equivalents and median years in practice. Adoption will be assessed through the number of SSPedi per participant completed at intervention institutions; this analysis will use duration of time on protocol therapy as an offset. Further, we will dichotomize each participant as a high or low SSPedi completer, with a high completer being defined as one who completed 15 or more SSPedi. This analysis will use those who complete protocol therapy as planned as the denominator. In addition, we will count the number of times the institutional care pathways were clicked at intervention sites. We will describe the total number of clicks overall and by specific care pathway, access route (email link or QR code) and device (iPad, iPhone, Mac, Windows or unknown). Implementation outcomes will capture the percentages of intervention patients who came off protocol therapy early and the number of all participants who came off study early, both overall and stratified by intervention or control group.

Off Protocol and Off Study Criteria

Off protocol criteria only apply to intervention sites. When off protocol criteria are met, the reminders to complete symptom screening via SPARK will be discontinued but the collection of PROs will continue until off study criteria are met.

Off protocol criteria:

a) Refusal to continue with study intervention
b) Physician determines it is in the patient's best interest
c) Death
d) Completion of planned study intervention
e) Other, describe

Off study criteria:

a) Withdrawal of consent for further data submission
b) Physician determines it is in the patient's best interest
c) Death
d) Completion of planned study observations (Up to 10 weeks after enrollment to allow window around week 8 assessment and to allow ability to abstract health records

outcomes accurately)
e) Other, describe

ANALYTIC PLAN

Power Calculations

The primary endpoint is the total self-reported SSPedi score at eight weeks. We used data from our SSPedi validation study for power calculation.[3] In that study, we recruited 302 children across nine sites who were hospitalized and expected to be in hospital or in clinic three days later. Children completed SSPedi on days 1 and 4 and a 5-point global symptom change scale on day 4. The average absolute change in total SSPedi scores for those who reported they were a little better or a little worse (1-point change) was 2.7 while the average absolute change in total SSPedi scores for those who reported they were much better or much worse (2-point change) was 5.6. Thus, the minimum plausible clinically important difference is likely approximately 3.0 but may be higher. The intracluster correlation coefficient (ICC), a measure of the degree of clustering, was 0.021 (95% CI 0 to 0.123). In power calculations for the proposed study, we used ICC=0.021 but show sensitivity analyses to ICCs at the extremes of the 95% CI (which are unlikely). Among the 20 sites in the proposed trial, we anticipate that four will each contribute eight patients, four will each contribute 32 patients, and the remaining 12 will each contribute 20 patients, for a total of 400 patients. With these cluster sizes, Table 1 shows power for combinations of these ICCs and clinically important differences, at a 2-sided alpha of 0.05 and assuming a within-cluster standard deviation of 8.8 (derived from the SSPedi validation study[3]). Power for each combination in the table was calculated through simulation of 4000 trials; each one was analyzed with a linear mixed effects model clustering by site and the percentage with a significant P value was taken as the estimate of power. If there is a baseline characteristic, such as age, that explains 20% of the variance in 8-week scores, including that variable in analyses increases power to the value shown in the far right column. Table 1 shows that assuming a minimal clinically important difference of 3.0 and with inclusion of age as a covariate in the analysis, there is 85% power with ICC=0.021. Assuming that 10% of patients have missing final scores, we will inflate the sample size to 444.

Table 1: Power Assuming 400 Patients, Alpha=0.05 and Standard Deviation=8.8

ICC	Difference	Power	
		Without baseline predictor	With age as baseline predictor
0.000	2.5	71.0	81.4
	3.0	86.7	94.2
	3.5	95.9	98.9
0.021	2.5	59.5	70.1
	3.0	**75.7**	**85.2**
	3.5	86.5	94.2
0.123	2.5	26.6	32.6
	3.0	38.2	45.3
	3.5	47.7	57.0

Baseline Characteristics: Summary statistics on baseline characteristics will be calculated within each study arm and presented in a table – means and standard deviations (SDs) for variables treated as continuous, counts and percentages for categorical variables, along with total numbers with missing data.

Outcomes: Similar tables will be created for all study outcomes. Individual SSPedi symptom scores will be summarized by the percentages of participants with scores of 3 or 4, the two most bothersome categories.

Comparative Analyses: The primary analysis will use the patient-level 8-week total SSPedi score as the outcome in a mixed linear regression model with a random effect for cluster, fixed effects for treatment assignment, child age and diagnosis group (leukemia/lymphoma, solid tumor and central nervous system tumor), and two binary fixed effects at the cluster level for stratification variables (above or below the average anticipated yearly number of English or Spanish-speaking cancer patients 8-18 years of age, and above or below the average anticipated percentage of patients with private insurance vs. other payment types). Child age and diagnosis group will be included as they are known to be associated with total SSPedi scores; this will reduce residual variance in scores. We do not plan to adjust the model for baseline SSPedi score because some of the care pathway interventions (that are prophylactic) will affect symptoms prior to enrollment and the baseline score may already reflect some benefit of the cluster's treatment assignment. The treatment effect will be the covariate-adjusted mean difference between study groups in 8-week SSPedi, presented with a 95% CI and a two-sided p-value for a test of no treatment effect. If we find the residuals from the mixed model fitted to the 8-week total SSPedi score deviate substantially from normality, we will conduct sensitivity analyses, one using normalizing transformations of the outcome and another using an ordinal regression model. To account for potential differential enrollment of surgery only patients (who might not be cared for by oncology teams) between intervention vs. control sites, we will also conduct a sensitivity analysis restricted to patients that received systemic chemotherapy.

Secondary outcomes will be analyzed as follows:

1. **Self-reported individual symptoms at weeks 4 and 8 on the SSPedi instrument**: For each of the 15 ordinal outcomes representing symptoms (scored 0-4), a mixed effects proportional odds model will be fitted using treatment assignment and stratification factors as fixed effects covariates and with a random effect for site. As some individual symptoms may be uncommon, to avoid specifying models that may be overfitted for those symptoms, these models will use only this minimal set of three covariates. The estimated odds ratio for the intervention (representing the odds of having a higher vs. lower score in the intervention group) will be estimated and presented along with a 95% CI.
2. **PROMIS Fatigue Scale**: This scale will be treated as a continuous variable and analyzed using a linear mixed effects model in the same way as the primary SSPedi outcome.
3. **PedsQL 3.0 Acute Cancer Module domain scores**: Each of these 8 scores will be treated as continuous variables and analyzed using a linear mixed effects model in the same way as the primary SSPedi outcome.
4. **Documentation of symptoms on weeks 4 and 8 (± 1 day):** Analyses will involve three analyses for each symptom class. Each analysis will fit a mixed effects logistic regression model to estimate the odds ratio for documentation (on weeks 4 and 8) comparing intervention groups, adjusting for stratification factors. It is possible that there will be too few documentation events to reliably fit this mixed model to all 15 symptoms. If this model cannot be fitted to some symptoms (likely because the random effects variance cannot be estimated), we will fit a fixed effects logistic regression model to just those symptoms. Three cohorts will be defined:
    a. Each participant will be classed as having the symptom documented or not. All participants are included in the analytic sample for each symptom.
    b. The analytic sample will be limited to those participants who self-report the symptom on weeks 4 and 8 (symptom score > 0).

    c. The analytic sample will be limited to those participants who have the most bothersome self-report of the symptom on the weeks 4 and 8 SSPedi (symptom score ≥ 3).
5. **Interventions for symptoms**: Analyses will follow a similar flow to the analyses of documentation of symptoms. For each of the 15 symptoms, each participant will be classified as having an intervention at weeks 4 and 8 (±1 days). Also collected is whether interventions were administered specifically for the specific symptoms. For example, acetaminophen may be administered for fever or pain. As interventions are expected to be more uncommon than symptoms, all treatment effects will be estimated by simple differences in the proportions with interventions (i.e., ignoring clustering), p-values will be computed from the Fisher exact test, and 95% CI for differences in proportions will use the Newcombe method. Three cohorts will be defined:
    a. Each participant will be classed as having an intervention for the symptom or not. All participants are included in the analytic sample for each intervention-symptom pair.
    b. The analytic sample will be limited to those participants who self-report the symptom on the weeks 4 and 8 SSPedi (symptom score > 0).
    c. The analytic sample will be limited to those participants who have the most bothersome self-report of the symptom on the weeks 4 and 8 SSPedi (symptom score ≥ 3).
6. **Unplanned encounters:** For each of the secondary endpoints of unplanned health services utilization (emergency, clinic visits, hospitalizations, and the total across categories), the number of events per child will be counted over the 8-week period and compared between randomized groups using a mixed-effects Poisson or negative binomial regression analysis (with zero-inflation if necessary), with a random effect for site and fixed effects for the two stratification factors. If a child has less than 8 weeks of follow-up, the model will include an offset equal to the logarithm of each child's follow-up time.

Exploratory outcomes will be analyzed as follows:

1. **Reach**: we will describe the baseline demographic characteristics (sex, age or age group and diagnosis group) of eligible patients who participate and who do not participate using means and standard deviations for continuous variables and counts and percentages for categorical variables. We will also summarize CFIR inner setting attributes as counts and percentages.
2. **Effectiveness**: In addition to the analyses of primary and secondary outcomes detailed above, we will also carry out analyses that dichotomize each of the 15 SSPedi symptoms as being severely bothersome (3 or 4) or not. Percentages for each symptom will be tabulated and compared between intervention groups using mixed effects binary logistic regression. We will also assess between-site variation in the odds of having a severely bothersome symptom (after adjusting for intervention and stratification factors) by plotting the random effects associated with each site and by calculating the median odds ratio (MOR). This is an alternative measure of clustering (or between-cluster variability); it is the estimated median of the ratio of the odds of a bothersome symptom for a participant at one site to the odds of a bothersome symptom for an otherwise identical participant at another site. The MOR is always defined with the higher odds in the numerator. One appealing aspect of the MOR is that it is on the same scale as the odds ratio for treatment, aiding interpretation of both the OR for intervention and the MOR for variation in the outcome.
3. **Adoption**: We will characterize adoption at intervention sites by summarizing the following:
    a. characteristics of sites and their providers
    b. number of SSPedis completed per enrolled participant
    c. proportion of participants that are high or low SSPedi completers
    d. number of times the institutional care pathways were clicked.

Site and provider attributes will be described by using means and standard deviations for continuous variables and counts and percentages for categorical variables. Site characteristics will include pediatric vs. mixed adult and pediatric, number of pediatric cancer patients diagnosed annually, and percentage of patients anticipated to have private, public or no insurance. Healthcare provider characteristics will include number of physician and nurse practitioner full-time equivalents and median years in practice. CFIR attributes will also be described.

The dependence of the number of SSPedi completed by a participant on participant, guardian and site characteristics will be assessed using a mixed effects Poisson or negative binomial regression model, with a random effect for site. Participant characteristics will include sex, age/age group, race, ethnicity, preferred language, and cancer diagnosis group. Guardian characteristics will include marital status, guardian employment and highest education, and high annual household income. Site characteristics will be those included above. The dependence of the odds of being a high responder on these same characteristics will be assessed using mixed effects logistic regression adjusting for stratification factors.

The number of recorded clicks is available on aggregate for each site, so we will summarize this as a set of 10 rates, clicks per enrolled participant, and assess whether there is site-to-site variability by fitting a random effects Poisson or negative binomial model with clicks as the outcome and the logarithm of the number of patients as an offset. A summary rate will be estimated from this model and the median rate ratio (analogous to the MOR above) will be calculated.

4. Implementation will calculate the percentage of patients who enrolled but came off protocol therapy early (intervention only) or off study early (all participants), overall and stratified by intervention or control group. Counts and percentages will be shown, with no inferential statistics.

Missing Data: The PedsQL will be scored according to its scoring guide, which includes rules for scoring in the presence of missing elements on each domain modules. No other deterministic rule-based method will be used to deal with missing data.

If more than 10% of participants are missing the primary outcome or secondary patient-reported outcomes, the analysis will use multiple imputation based on previous SSPedi assessments (weeks 0 and 4), group and site. In addition, we will conduct sensitivity analysis assuming that missing scores are from children with high total SSPedi scores and from children with low total SSPedi scores (randomly drawn from the highest and lowest quartile). A set of 20 complete datasets will be generated using separate within-treatment-group imputation models. These models will include all the study outcomes listed just above, and the key covariates that appear in our adjusted models (age, diagnosis group and stratification factors). The models will be fitted in each imputed dataset and the pooled estimate of the treatment effect and its standard error will be computed using Rubin's rules.

Analyses of documentation and interventions will not use any imputation. There can be no missing data for these outcomes: if a symptom is not documented in the health record and there is no record of an intervention being used, then this constitutes a 'no' for the outcome. While it is possible that the SSPedi symptom score needed for the identification of the analytic datasets in analyses (4b, 4c, 5b, and 5c) is missing for some participants, the more exploratory nature of these analyses led us to the decision to use only observed data for these outcomes.

FEASIBILITY AND POTENTIAL BENEFITS/RISKS

Feasibility and Recruitment Rate

Among the 20 sites that have agreed to participate, there are expected to be 60 patients/

month who are newly diagnosed with cancer 8-18 years of age and who speak English or Spanish. Assuming that 60% meet eligibility criteria (for example, some patients will not receive treatment for cancer such as those with low grade brain tumors and some centers provide consultation only services for newly diagnosed patients), and 75% agree to participate (conservative estimate based upon other SPARK studies), we anticipate enrollment of 27 patients/month. Thus, to reach the target sample size of 444 patients, enrollment is anticipated to be complete within 2 to 2.5 years (this allows for periods of slow enrollment such as holidays or when research personnel have limited availability). In terms of timelines, start-up activities will require 12 months, enrollment and follow-up of the last patient will require 24 to 36 months, data analysis will require nine months and knowledge dissemination will be completed within three months. Thus, the entire study will require five years to complete.

The time commitment of participants, providers and research staff is expected to be similar to other supportive care and SPARK trials and we do not anticipate barriers with respect to effort required. Abstraction of symptom documentation and intervention provision will be done over a short time frame (3 days for each of two time points (weeks 4 and 8)); pilot work at The Hospital for Sick Children has shown this workload to be modest. The PROs at weeks 4 and 8 will require <5-10 minutes to complete and can be completed electronically.

Potential Benefits and Risks to Study Participation

For participants at intervention sites, potential benefits include increased awareness of experienced symptoms and increased guideline-concordant care to prevent and manage symptoms. Consequently, participants may have better symptom control and QoL by participating in this study. Even for those who decline participation in the study, establishment of care pathways for symptom management may improve symptom control for all patients at that site. For participants at control sites, participants may gain increased self-awareness of symptoms by completion of PROs at weeks 0, 4 and 8.

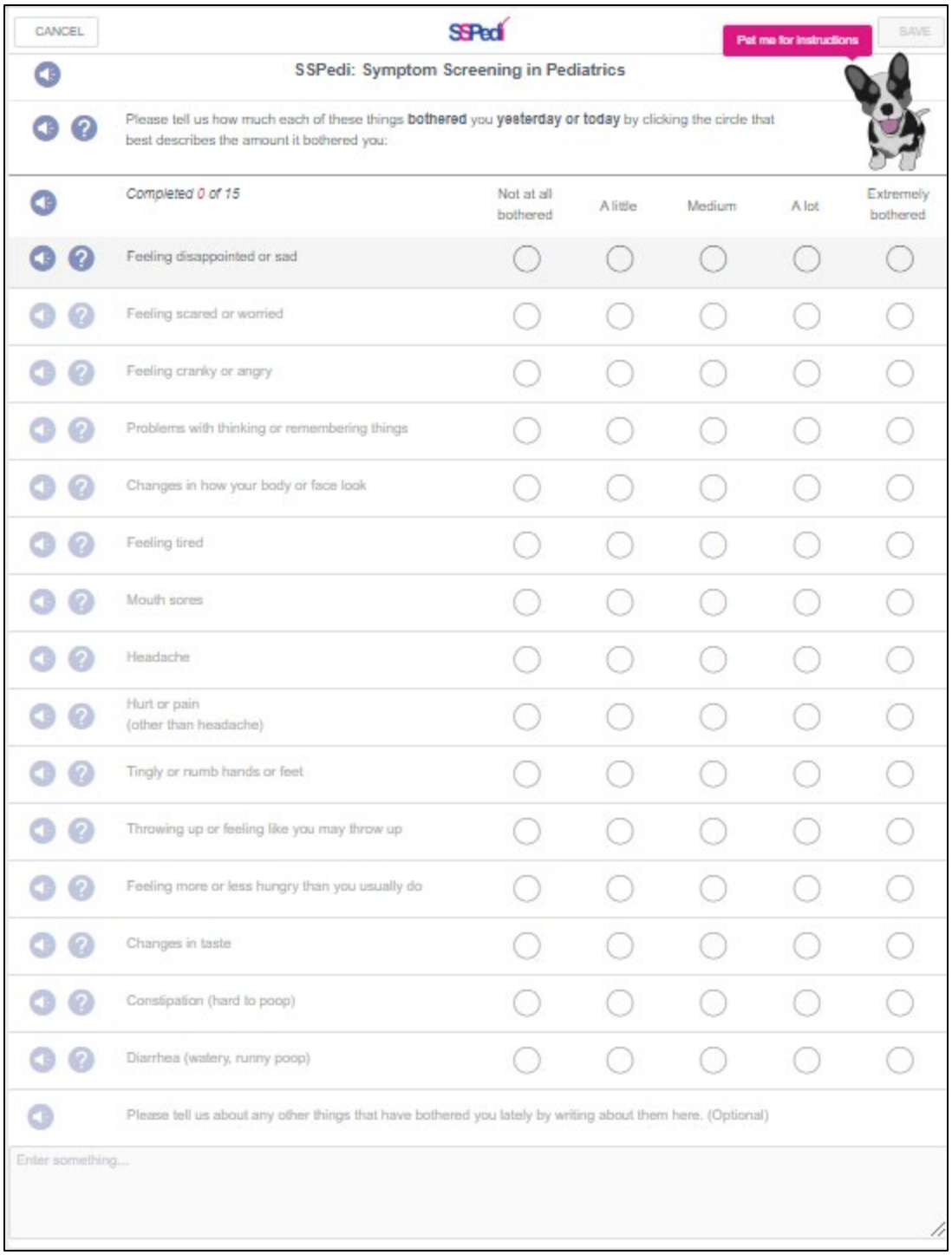
Risks include the potential for inadvertent disclosure of personal health information although risks should be low given the precautions instituted. Although there is a risk of distress with symptom assessment, such an occurrence has not been observed in SSPedi studies to date. Study participation also entails time commitment and some inconvenience to schedule the weeks 4 and 8 PRO assessments.

REFERENCES

1. Canadian Cancer Society's Steering Committee on Cancer Statistics: Canadian Cancer Statistics. Toronto, ON, Canadian Cancer Society, 2011
2. Baggott C, Dodd M, Kennedy C, et al: Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy. J Pediatr Oncol Nurs 27:307-15, 2010
3. Dupuis LL, Johnston DL, Baggott C, et al: Validation of the Symptom Screening in Pediatrics Tool in Children Receiving Cancer Treatments. J Natl Cancer Inst, 2017
4. Hyslop S, Davis H, Duong N, et al: Symptom Documentation and Intervention Provision for Symptom Control in Children Receiving Cancer Treatments. Submitted 2018
5. Carelle N, Piotto E, Bellanger A, et al: Changing patient perceptions of the side effects of cancer chemotherapy. Cancer 95:155-63, 2002
6. Coates A, Abraham S, Kaye SB, et al: On the receiving end--patient perception of the side-effects of cancer chemotherapy. Eur J Cancer 19:203-8, 1983
7. de Boer-Dennert M, de Wit R, Schmitz PI, et al: Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer 76:1055-61, 1997
8. Griffin AM, Butow PN, Coates AS, et al: On the receiving end. V: Patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 7:189-95, 1996
9. Yang LY, Manhas DS, Howard AF, et al: Patient-reported outcome use in oncology: a systematic review of the impact on patient-clinician communication. Support Care Cancer 26:41-60, 2018
10. Berry DL, Hong F, Halpenny B, et al: Electronic self-report assessment for cancer and self-care support: results of a multicenter randomized trial. J Clin Oncol 32:199-205, 2014
11. Mooney K, Berry DL, Whisenant M, et al: Improving Cancer Care Through the Patient Experience: How to Use Patient-Reported Outcomes in Clinical Practice. Am Soc Clin Oncol Educ Book 37:695-704, 2017
12. Basch E, Deal AM, Kris MG, et al: Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol 34:557-65, 2016
13. Basch E, Deal AM, Dueck AC, et al: Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA, 2017
14. Wright JD, Neugut AI, Ananth CV, et al: Deviations from guideline-based therapy for febrile neutropenia in cancer patients and their effect on outcomes. JAMA Intern Med 173:559-68, 2013
15. FitzGerald JM, Boulet LP, McIvor RA, et al: Asthma control in Canada remains suboptimal: the Reality of Asthma Control (TRAC) study. Can Respir J 13:253-9, 2006
16. Grimshaw J, Eccles M, Thomas R, et al: Toward evidence-based quality improvement. Evidence (and its limitations) of the effectiveness of guideline dissemination and implementation strategies 1966-1998. J Gen Intern Med 21 Suppl 2:S14-20, 2006
17. Wolfe J, Orellana L, Cook EF, et al: Improving the care of children with advanced cancer by using an electronic patient-reported feedback intervention: results from the PediQUEST randomized controlled trial. J Clin Oncol 32:1119-26, 2014
18. O'Sullivan C, Dupuis LL, Gibson P, et al: Refinement of the symptom screening in pediatrics tool (SSPedi). Br J Cancer 111:1262-8, 2014
19. O'Sullivan C, Dupuis LL, Gibson P, et al: Evaluation of the electronic self-report Symptom Screening in Pediatrics Tool (SSPedi). BMJ Support Palliat Care, 2016
20. Tomlinson D, Dupuis LL, Gibson P, et al: Initial development of the Symptom Screening in Pediatrics Tool (SSPedi). Support Care Cancer 22:71-5, 2014

21. Soman D: The Last Mile: Creating Social and Economic Value from Behavioural Insights, University of Toronto Press, 2015
22. O'Sullivan C, Dupuis LL, Gibson P, et al: Refinement of the symptom screening in pediatrics tool (SSPedi). British Journal of Cancer 111:1262-8, 2014
23. National Guideline Clearinghouse: Inclusion Criteria. http://www.guideline.gov/about/inclusion-criteria.aspx, 2014
24. Guyatt GH, Schunemann HJ, Djulbegovic B, et al: Guideline panels should not GRADE good practice statements. J Clin Epidemiol 68:597-600, 2015
25. Koo A, Li C, Liu LL, et al: Successful adaptation of fever and neutropenia clinical practice guideline in China. . Applied Cancer Research, In Press, 2018
26. Damschroder LJ, Aron DC, Keith RE, et al: Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 4:50, 2009
27. Fernandez ME, Walker TJ, Weiner BJ, et al: Developing measures to assess constructs from the Inner Setting domain of the Consolidated Framework for Implementation Research. Implement Sci 13:52, 2018
28. Glasgow RE, Harden SM, Gaglio B, et al: RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. Front Public Health 7:64, 2019
29. Hinds PS, Nuss SL, Ruccione KS, et al: PROMIS pediatric measures in pediatric oncology: valid and clinically feasible indicators of patient-reported outcomes. Pediatr Blood Cancer 60:402-8, 2013
30. Varni JW, Burwinkle TM, Katz ER, et al: The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer 94:2090-2106, 2002

Appendix 1: Symptom Screening in Pediatrics Tool (SSPedi)



CANCEL

SSPedi

Pet me for instructions

SAVE

SSPedi: Symptom Screening in Pediatrics

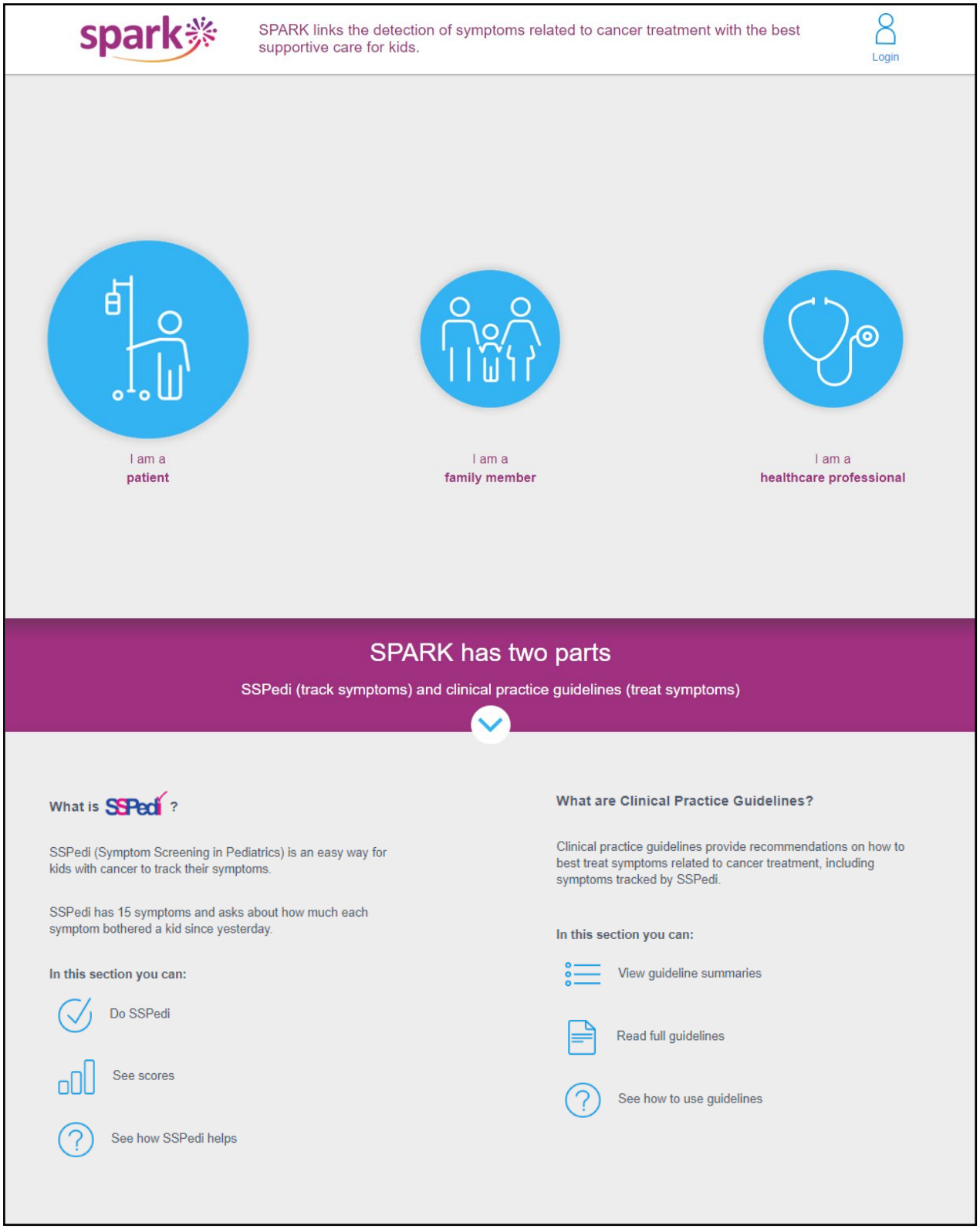
Please tell us how much each of these things **bothered** you **yesterday or today** by clicking the circle that best describes the amount it bothered you:

Completed 0 of 15	Not at all bothered	A little	Medium	A lot	Extremely bothered
Feeling disappointed or sad	○	○	○	○	○
Feeling scared or worried	○	○	○	○	○
Feeling cranky or angry	○	○	○	○	○
Problems with thinking or remembering things	○	○	○	○	○
Changes in how your body or face look	○	○	○	○	○
Feeling tired	○	○	○	○	○
Mouth sores	○	○	○	○	○
Headache	○	○	○	○	○
Hurt or pain (other than headache)	○	○	○	○	○
Tingly or numb hands or feet	○	○	○	○	○
Throwing up or feeling like you may throw up	○	○	○	○	○
Feeling more or less hungry than you usually do	○	○	○	○	○
Changes in taste	○	○	○	○	○
Constipation (hard to poop)	○	○	○	○	○
Diarrhea (watery, runny poop)	○	○	○	○	○

Please tell us about any other things that have bothered you lately by writing about them here. (Optional)

Enter something...

Appendix 2: SPARK Landing Page



Symptom Screening Linked to Care Pathways for Children with Cancer: a Cluster Randomized Trial
Study Protocol

BACKGROUND

Over the last few decades, impressive gains in survival for children and adolescents with cancer have been made and now, more than 82% of children with cancer will be cured.[1] 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.[2] In our cross-sectional study of 302 inpatients 8-18 years of age, when asked about yesterday or today, 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%.[3] Symptoms are important; we previously demonstrated a strong correlation between increasing symptom burden and worse quality of life (QoL) in children receiving cancer treatments.[3] Given excellent survival outcomes, we now need to focus more attention on symptom control.

To gain insight into why symptoms are uncontrolled, we evaluated 168 children and described the extent to which symptoms self-reported as severely bothersome were documented in the health record and for which any interventions were provided.[4] We created a standard operating procedure and a list of synonyms that met criteria for documentation of symptoms. For example, "tired", "feel weak", "low energy", and "sluggish" were all considered adequate documentation for fatigue. We also created a list of possible interventions for each symptom. For most of the symptoms measured (12/15), severely bothersome symptoms were documented in the health record less than 60% of the time. The most infrequently documented severely bothersome symptoms were problems with thinking or remembering things (0%), changes in how your body or face look (4.8%), changes in taste (7.7%) and tingly or numb hands or feet (11.1%). Only two severely bothersome symptoms were documented at least 80% of the time, namely hurt or pain (92.6%) and throwing up or feeling like you might throw up (92.6%).

Provision of an intervention to address severely bothersome symptoms occurred less than 60% of the time for 10 of 15 symptoms. The most infrequently treated severely bothersome symptoms were thinking or remembering things (0%), changes in how your body or face look (0%), tingly or numb hands or feet (0%), changes in taste (0%), diarrhea (0%) and feeling tired (1.6%). Intervention provision was most common for hurt or pain (96.3%), headache (89.5%), throwing up or feeling like you might throw up (88.9%) and constipation (84.2%). However, even when interventions were provided, they were often not prescribed specifically for that symptom (for example, acetaminophen for fever rather than pain).

Within the adult oncology setting, screening and assessment of symptoms through patient self-report has been identified as an important priority.[5-8] In adult cancer patients, routine collection of patient-reported outcomes (PROs) improves patient-clinician communication[9], reduces distress[10] and improves QoL.[11,12] Furthermore, a recent randomized trial showed that routine PRO assessment may improve survival in adult patients with metastatic solid tumors.[13] Among participants that were randomized to symptom screening vs. standard of care, median overall survival was 31.2 months (95% confidence interval (CI) 24.5 to 39.6) in the symptom screening group vs. 26.0 months (95% CI 22.1 to 30.9) in the standard of care group (P=0.03). Consequently, routine assessment of PROs is now considered essential to high quality care.[11] It is also known that delivery of care consistent with CPGs can improve patient outcomes. For example, timely administration of CPG-consistent antibiotics to adult patients with fever and neutropenia resulted in significantly lower mortality compared to patients who did not receive CPG-consistent antibiotics.[14] However, adherence to CPGs is generally poor.[15,16]

In contrast to these accomplishments in adults, efforts in children are limited.[17] To help address this gap, we developed SSPedi (Symptom Screening in Pediatrics Tool; Appendix 1)[18,19] and SPARK (Supportive care Prioritization, Assessment and Recommendations for Kids; Appendix 2). SSPedi is a self-reported 15-item symptom screening tool for children receiving cancer treatments. SSPedi consists of the following 15 items: disappointed or sad, scared or worried, cranky or angry, problems thinking, body or face changes, tiredness, mouth sores, headache, other pain, tingling or numbness, throwing up, hunger changes, taste changes, constipation and diarrhea. We developed SSPedi because our previous work concluded that then-available pediatric cancer symptom assessment tools were not appropriate for clinical use due to length or content.[20] Items were generated using a nominal group technique among pediatric cancer clinicians and a patient advocate.[20] 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.[20-22] The electronic version of SSPedi has an audio feature that allows specific questions or the entire instrument to be read aloud. A help feature provides synonyms for each symptom; these were derived from children themselves during cognitive interviews.

Next, we conducted a multi-center study in the US and Canada to evaluate the psychometric properties of SSPedi. SSPedi was shown to be reliable (internal consistency and test re-test and inter-rater reliability), valid (construct validity) and responsive to change in 502 English-speaking children 8-18 years of age receiving cancer therapies.[3] More specifically, the intraclass correlation coefficients (ICC) were 0.88 (95% 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 SSPedi scores between groups hypothesized to be more and less symptomatic was 7.8 (95% CI 6.4 to 9.2; P<0.001).[3] 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 (mean absolute difference 5.6, 95% CI 3.8 to 7.5; P<0.001). This instrument has been translated into Spanish; the translated version is satisfactory to use in the US and Canada based on understandability and cultural relevance.

Building upon SSPedi, SPARK is a web-based application that consists of two components: (1) a symptom screening component centered on SSPedi; and (2) a supportive care CPG component. While SSPedi asks children about symptoms, SPARK facilitates access to SSPedi, encourages symptom screening, generates reports and allows children to track their symptoms. In addition, when used by healthcare providers, SPARK links the symptoms identified using SSPedi with CPGs to manage them. CPGs contained within SPARK are those endorsed by the Children's Oncology Group (COG) and thereby meet minimum specific criteria with respect to methodological rigor and relevance to pediatric oncology.[23]

AIMS

Aims 1 and 2: Among children with newly diagnosed cancer, determine if symptom feedback to healthcare providers given at least three times weekly using SPARK and locally-adapted symptom management care pathways based on CPGs, when compared with usual care:

Aim 1. Improves overall self-reported symptom scores (total SSPedi score), fatigue (PROMIS–Fatigue) and cancer-specific QoL (PedsQL 3.0 Acute Cancer Module) over 8 weeks

Hypothesis: Symptom screening and care pathways will improve symptoms, fatigue and QoL

Aim 2. Improves symptom documentation, increases provision of interventions for symptoms, and reduces emergency department visits and unplanned clinic visits and hospitalizations over 8 weeks

Hypotheses: Symptom screening and care pathways will increase symptom documentation and provision of interventions for symptoms, and will reduce healthcare utilization.

Aim 3: As an exploratory aim, we will evaluate key elements of the intervention related to the external validity and generalizability of the intervention effects using the RE-AIM framework.

METHODS

Overall Strategy

This is a cluster randomized trial including 20 pediatric oncology sites, each with a history of excellent accrual to supportive care trials, with geographic variation and representativeness among ethnic minority groups. Sites will be randomized to either systematic symptom screening via SPARK with provision of symptom reports to healthcare providers containing links to care pathways for symptom management (intervention) vs. usual care (control).

Research Methods

Eligibility: We will include children with cancer who: (1) are 8-18 years of age at enrollment (SSPedi is validated in this age range); (2) are English or Spanish-speaking (all PROs are validated in these languages in this age range); (3) have any newly diagnosed 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 (attending minimum second grade or equivalent) or visual impairment (cannot see SPARK even with corrective lens).

Procedures: In this cluster randomized trial, we will randomize participating sites to either intervention or

control groups. We will enroll participants within 28 days after treatment initiation. 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. Careful tracking of all newly diagnosed patients by site clinical research associates will occur to determine how many patients are approached and consented, and where possible, reasons for declining participation.

At the 10 intervention sites, site-specific symptom management care pathways will be adapted from template care pathways based upon COG-endorsed CPGs for each of the 15 symptoms included in SSPedi. Enrolled participants will be prompted to complete symptom screening three times weekly via SPARK with corresponding feedback sent to healthcare providers. Symptom reports will contain links to care pathways for symptom management. Active intervention will last for eight weeks starting from the date of enrollment. At the 10 control sites, participants will complete SSPedi to obtain the primary outcome at weeks 0, 4 and 8 but the scores will not be revealed to providers and will not be linked to care pathways. Usual care will be provided to participants at control sites and thus, there will be no study-requested routine, systematic symptom screening, symptom feedback to providers, or linkage to care pathways. If sites already routinely perform systematic symptom screening or use care pathways for symptom management, these may be continued but their use will be recorded. We will contact participants to time the week 4 and 8 PROs with hospital or clinic visits. If unable to arrange, we will use their contact information to complete the questionnaires by email, text or over the phone.

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, week 4 and week 8: SSPedi, PROMIS Fatigue and the PedsQL 3.0 Acute Cancer Module (Aim 1). Data from health records (Aim 2) will be abstracted for all enrolled participants.

Procedures at Intervention and Control Sites**:**

Procedures at Intervention Sites**:** Participants enrolled at intervention sites will be prompted to complete symptom screening three times weekly via SPARK with corresponding feedback and links to symptom management care pathways sent to their healthcare providers.

a) Symptom Screening using SPARK and Timing Justifications: Symptom screening using SPARK can be performed at any time and as often as desired, but screening will be prompted three times weekly for eight weeks. In our pilot studies, the mean time for SSPedi completion using the identical SPARK platform was 1.0 (SD=1.5) minutes and in over 1,000 children who have completed SSPedi, no child has ever stated that SSPedi completion was distressing. The ideal frequency of symptom screening is not known; the need to identify change in symptoms as soon as possible must be balanced against the burden of frequent screening to children and healthcare providers. In a trial of adult oncology patients demonstrating that routine symptom screening improved QoL, weekly email reminders were sent.[17] In order to identify the ideal frequency of symptom screening reminders, we surveyed site investigators at participating sites. The most commonly suggested frequency was three times weekly (n=15, range 2-5 times weekly). However, it is important to stress that three times weekly is the frequency in which we will remind participants to complete SSPedi; participants can complete SSPedi as often as they wish including daily or more often.

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.

b) Symptom Reports to Healthcare Providers: Each day the participant completes symptom screening (whether prompted or unprompted), the primary healthcare team will receive an email summarizing the symptom report and highlighting of symptoms that are “a lot” or “extremely” bothersome. Emails will include links to the site-specific care pathways for symptom management. Patient name and date of SSPedi completion are included in the email to ensure correct identification of the patient. Thus, patient name will exist within the SPARK database but the system is configured such that no other site including SickKids can access it. These approaches have been approved by the SickKids Privacy Office and IRB, and all IRBs outside of SickKids that have participated in other SPARK studies. In terms of email communication, each hospital’s policies will be followed. For example, at all institutions currently participating in other SPARK studies, emails sent within that hospital’s system are considered secure and that approach is being used to transmit symptom reports with these emails being generated from the hospital’s email domain. Some hospitals may require

encrypted emails; these will be used where required.

Qualitative feedback from providers receiving these reports in our pilot study has been positive. When specifically asked, receiving these reports was not considered burdensome. In fact, providers found reports helpful to communicate symptom experience and to initiate or escalate symptom management interventions.

c) Creation of Local Care Pathways for Symptom Management: Care pathway templates for symptom management have been drafted for each of the 15 items included in SSPedi. These are primarily based on COG-endorsed CPGs. To supplement SSPedi symptom care pathway templates for which COG-endorsed CPGs exist and to address SSPedi symptoms for which COG-endorsed CPGs do not exist, templates are also based on "good practice statements"[35]. In brief, "good practice statements" are guidance statements regarding the provision of care where to provide care in any other way would be considered unethical or absurd. Guideline experts have explicitly acknowledged their necessity and have published guidance for how and when to use such statements.[35] Upon study activation, we will work with each of the 10 intervention sites to develop site-specific, adapted care pathways that consider relevant work flows, institutional culture and available resources (laboratory tests, medications and personnel); this process will require three months to complete. The finalized local care pathways will contain explicit direction for how to prevent and manage symptoms at each site. The process for creating local care pathways will be based upon a procedure we developed for CPG adaptation, will require local inter-professional input and will be finalized at an in-person meeting at the site.[26] This process incorporates activities known to promote practice change and enhance implementation. Activities include appreciation of local resources and values, identification of local barriers and facilitators, stakeholder participation in decision making, education of healthcare professionals and creation of implementation tools. It is expected that across the 10 sites, the care pathways could differ substantially in some areas, such as which profession or specialty should be consulted and choice of specific medications to treat a symptom, but that there should be similarities across all 10 local care pathways since they have a common evidence base. Each care pathway will contain links to the healthcare provider SPARK portal so that providers can view the source CPG summary or full guideline document upon which the care pathway was based. Annually, we will assess how the initial adaptations have changed to gain insight into the adaptation process over the course of the study and to evaluate how the process might inform future implementation of care pathways. Adaptations will be summarized and will be made available to all intervention sites during the study, and will be widely available to all sites following study completion as part of knowledge translation, and as a component of the RE-AIM implementation evaluation.

d) Training: From a patient participant perspective, training on how to use SPARK and how to interpret SPARK symptom reports will be provided at enrollment. From a healthcare provider perspective, training on how to interpret SPARK symptom reports, CPGs and care pathways will be provided to each site during the in-person meeting to adapt symptom management care pathways and via a webinar at study activation and regularly throughout the study to educate new staff and to re-enforce knowledge for existing staff. Different aspects of training also will be highlighted during the site calls every two weeks. Stories of successful implementation at a particular site will be shared so that all sites can benefit. Technical assistance and support will be available to providers throughout the study from SickKids where SPARK is located.

***Procedures at Control Sites*:** At control sites, usual care will be provided, which may or may not include symptom screening, access to CPGs or care pathways. Participants will complete SSPedi to obtain the primary outcome at weeks 0, 4 and 8 but the scores will not be revealed to providers and will not be linked to care pathways.

Describing Site Characteristics (both Intervention and Control Sites): In order to describe supportive care practices that could impact on intervention effectiveness and to gain insight into future implementation (adoption), the site PIs will complete a short questionnaire at study activation (baseline prior to randomization) and annually while participants are being enrolled. Questions will include demographic characteristics of patients and providers (only at baseline), psychosocial resources available for pediatric cancer patients and current approaches to systematic symptom screening, symptom management CPG availability and care pathway existence for SSPedi symptoms. CPG availability will be defined as either the posting of CPGs themselves or links to CPGs on an institutional website or drive that is available to all oncology providers (not an individual clinician's computer only). Care pathway use will be defined as a written set of instructions for the management of a symptom that is available to all oncology providers at that site. At intervention sites,

questions will pertain to patients not enrolled.

Site Monitoring, Quality Control and Intervention Site Auditing: Quality control will be maintained with calls every two weeks among participating site PIs and clinical research associates. Separate calls will be held with intervention and control sites to reduce the risk of contamination. On those calls, we will summarize enrollments at each site and review the proportion of eligible patients enrolled. We will also review identified issues with respect to missing data and data quality identified during routine data checks.

For intervention sites, fidelity to the symptom screening approach will also be monitored. Each intervention site will be audited at least once (4-6 months after site activation) to assess adherence to the process of symptom screening, namely documentation of participant training in the health records, completion of SSPedi at least three times weekly, and delivery of symptom reports to providers. Accessibility of local care pathways will also be examined. These will be evaluated as part of the implementation dimension of RE-AIM.[36]

Proposed Practical Arrangements for Allocating Sites: The allocation sequence will be computer generated. Sites will be randomized 1:1 and will be stratified by two site characteristics ≥ or < median: (1) anticipated number of cancer patients 8-18 years of age who speak English or Spanish per year, and (2) percentage of patients with private insurance vs. other payment types. Block size is not disclosed in this protocol. Randomization will be performed using an internet-based randomization service. Assignment will be communicated by email to the site PI and clinical research associate following randomization.

Proposed Methods for Protecting against Sources of Bias: Given the cluster randomized nature of the study, a potential source of bias is that allocation will be known, which could lead to selection bias during participant enrollment. To address this potential, efforts will be made to both identify all potentially eligible participants and maximize enrollment. We will describe those not approached and those who decline to participate in the intervention and control sites. We will describe these groups by sex, age, race, ethnicity, cancer type and institution.

Primary, Secondary and Exploratory Outcome Measures: Endpoints for Aim 1 are PROs; all PROs are self-report. The primary endpoint is the total SSPedi symptom 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. The total SSPedi score is reliable, valid and responsive to change in children with cancer 8-18 years of age.[3] Secondary endpoints include fatigue and QoL. Fatigue will be measured using PROMIS. The recall period is the last 7 days. It is reliable and valid in children 8-18 years of age with cancer.[37] QoL will be measured using the PedsQL 3.0 Acute Cancer Module.[38] The 7 day recall version will be used. This measure is a multidimensional instrument that is reliable and valid in children with cancer.[38] It assesses pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance and communication. All PROs are validated for use in English and Spanish for children 8-18 years of age.

For both groups, all questionnaires including SSPedi will be administered at baseline, week 4 (±1 week) and week 8 (±1 week) at an in-person visit during a hospitalization or clinic visit (preferred), or will be obtained remotely. The approach will be identical for intervention and control sites.

Endpoints for Aim 2 will be abstracted from the health record and are: documentation of symptoms, provision of interventions for symptoms and emergency department visits and unplanned clinic visits and hospitalizations. Guardians will also be asked about healthcare visits to ensure encounters outside the primary institution are captured. Documentation of symptoms and intervention provision for symptom control will be abstracted from the patients' health records using the procedures our team previously developed.[4] The number of interventions for each symptom at each reporting period will be recorded and categorized as any intervention provided vs. no intervention provided. Interventions included in the local care pathway will be noted. 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 or 8 SSPedi assessment was obtained (as measured in conjunction with the other PROs) with a one day window before and after these assessments. For example, 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.[4] We found study data could be abstracted with minimal training and effort. De-identified source documentation will be sent to the

coordinating center for quality assurance.

Exploratory endpoints for Aim 3 will be RE-AIM characteristics to measure reach, effectiveness, adoption and implementation. Sufficient understanding of the contextual factors in SPARK implementation is critical to ensuring future scale-up of the intervention. An important aspect of dissemination is estimating the reach and representativeness of participants. Therefore, we propose to describe the baseline sociodemographic characteristics of eligible patients who participate and who do not participate (where possible). Effectiveness will be evaluated through primary and secondary outcomes. In addition, we will describe the percentage of patients without any severely bothersome symptoms within intervention and control sites. We will estimate adoption of the intervention by describing characteristics of sites that participate and providers at those sites. We will describe adherence with symptom screening and care pathways at intervention sites. Adoption can also be assessed through metrics that the SPARK website itself tracks such as the number of clicks within the symptom screening and CPG components and specific sections clicked. Implementation will focus on care pathway adaptations and number of patients who use SPARK as intended.

Statistical Analyses, Power Calculations and Data Management

The primary endpoint is the total self-reported SSPedi score at eight weeks. We used data from our SSPedi validation study for power calculation.[3] In that study, we recruited 302 children across nine sites who were hospitalized and expected to be in hospital or in clinic three days later. Children completed SSPedi on days 1 and 4 and a 5-point global symptom change scale on day 4. The average absolute change in total SSPedi scores for those who reported they were a little better or a little worse (1-point change) was 2.7 while the average absolute change in total SSPedi scores for those who reported they were much better or much worse (2-point change) was 5.6. Thus, the minimum plausible clinically important difference is likely approximately 3.0 but may be higher. The intracluster correlation coefficient (ICC), a measure of the degree of clustering, was 0.021 (95% CI 0 to 0.123). In power calculations for the proposed study, we used ICC=0.021 but show sensitivity analyses to ICCs at the extremes of the 95% CI (which are unlikely). Among the 20 sites in the proposed trial, we anticipate that four will each contribute eight patients, four will each contribute 32 patients, and the remaining 12 will each contribute 20 patients, for a total of 400 patients. With these cluster sizes, Table 1 shows power for combinations of these ICCs and clinically important differences, at a 2-sided alpha of 0.05 and assuming a within-cluster standard deviation of 8.8 (derived from the SSPedi validation study[3]). Power for each combination in the table was calculated through simulation of 4000 trials; each one was analyzed with a linear mixed effects model clustering by site and the percentage with a significant P value was taken as the estimate of power. If there is a baseline characteristic, such as age, that explains 20% of the variance in 8-week scores, including that variable in analyses increases power to the value shown in the far right column. Table 1 shows that assuming a minimal clinically important difference of 3.0 and with inclusion of age as a covariate in the analysis, there is 85% power with ICC=0.021. Assuming that 10% of patients have missing final scores, we will inflate the sample size to 444.

Table 1: Power Assuming 400 Patients, Alpha=0.05 and Standard Deviation=8.8

ICC	Difference	Power	
		Without baseline predictor	With age as baseline predictor
0.000	2.5	71.0	81.4
	3.0	86.7	94.2
	3.5	95.9	98.9
0.021	2.5	59.5	70.1
	3.0	**75.7**	**85.2**
	3.5	86.5	94.2
0.123	2.5	26.6	32.6
	3.0	38.2	45.3
	3.5	47.7	57.0

The primary analysis will use the patient-level 8-week total SSPedi score as the outcome in a mixed linear regression model with a random effect for cluster, a fixed effect for child age, and fixed effects at the cluster level for stratification variables and treatment assignment. Child age will be included as it is known to be associated with higher total SSPedi scores[39]; this will reduce residual variance in scores. We do not plan to adjust the model for baseline SSPedi score because some of the care pathway interventions (that are

prophylactic) will affect symptoms prior to enrollment and this baseline score may already reflect some benefit of the cluster's treatment assignment. All attempts to avoid missing data will be made and, given the short duration of this study, we anticipate a low dropout rate by week 8. However, if more than 10% of participants are missing the primary outcome, the primary analysis will use multiple imputation based on previous SSPedi assessments (weeks 0 and 4), group and site. In addition, we will conduct sensitivity analysis assuming that missing scores are from children with high total SSPedi scores and from children with low total SSPedi scores (randomly drawn from the highest and lowest quartile).

The secondary endpoints of self-reported fatigue and QoL will be compared between randomized groups using the methods for the primary analysis (with inclusion of child age in the model). Presence of documented severely bothersome symptoms (SSPedi score of 3 or 4) and any intervention for severely bothersome symptoms at weeks 4 and 8 will be compared between groups for each symptom using mixed-effects logistic regression analysis that takes cluster effects into account. For the secondary endpoint of unplanned health services utilization (emergency and clinic visits and hospitalizations), the number of visits or unplanned admissions per child will be counted over the 8-week period and compared between randomized groups using a mixed-effects Poisson or negative binomial regression analysis (with zero-inflation if necessary), accounting for site.

Child sex, race, ethnicity, diagnosis (leukemia/lymphoma, solid tumor vs brain tumor), cancer stage, socioeconomic status and guardian education will be described. If a covariate is found, blinded to group treatment assignment, to be associated with the 8-week total SSPedi scores, it will be included in each of the regression analyses described above for primary and secondary outcomes. In addition, psychosocial resources and characteristics of the usual care provided by each site (e.g. routine systematic symptom screening, availability of CPGs and care pathways for symptom management) will be described and accounted for in exploratory regression and stratified analysis. For sex in particular, we also will determine if the impact of the intervention is moderated by sex by including an interaction term in the model and we will explore stratified analysis by sex.

For the exploratory aim, we propose to describe key elements related to the external validity and generalizability of the intervention effects using the RE-AIM framework. These analyses will be descriptive.

In terms of data management, SPARK data are stored on the SickKids server each time SSPedi is completed. This process was used in SSPedi and other SPARK multi-institutional trials; processes met institutional privacy and IRB requirements to maintain personal health information. Data outside of SSPedi scores including demographics, non-SSPedi outcomes and covariates will be maintained in a REDCap database. The database will have data validation checks to maximize data quality at data entry. Data will be downloaded and evaluated quarterly to identify missing data and perform additional data validation checks.

Feasibility and Recruitment Rate

Among the 20 sites that have agreed to participate, there are expected to be 60 patients/ month who are newly diagnosed with cancer 8-18 years of age and who speak English or Spanish. Assuming that 60% meet eligibility criteria (for example, some patients will not receive treatment for cancer such as those with low grade brain tumors and some centers provide consultation only services for newly diagnosed patients), and 75% agree to participate (conservative estimate based upon other SPARK studies), we anticipate enrollment of 27 patients/month. Thus, to reach the target sample size of 444 patients, enrollment is anticipated to be complete within 2 to 2.5 years (this allows for periods of slow enrollment such as holidays or when research personnel have limited availability). In terms of timelines, start-up activities will require 12 months, enrollment and follow-up of the last patient will require 24 to 36 months, data analysis will require nine months and knowledge dissemination will be completed within three months. Thus, the entire study will require five years to complete.

The time commitment of participants, providers and research staff is expected to be similar to other supportive care and SPARK trials and we do not anticipate barriers with respect to effort required. Abstraction of symptom documentation and intervention provision will be done over a short time frame (3 days for each of two time points (weeks 4 and 8)); pilot work at SickKids has shown this workload to be modest. The PROs at weeks 4 and 8 will require <5-10 minutes to complete and can be completed electronically.

Knowledge Translation and Exchange

The targets of our KTE efforts are patients, families, healthcare providers and decision makers including hospital and governmental administrators.

Integrated KTE*:* To increase awareness and to engage with a variety of stakeholders, we will create an Advisory Panel. The Panel will include two childhood cancer survivors, one parent of a child with cancer,

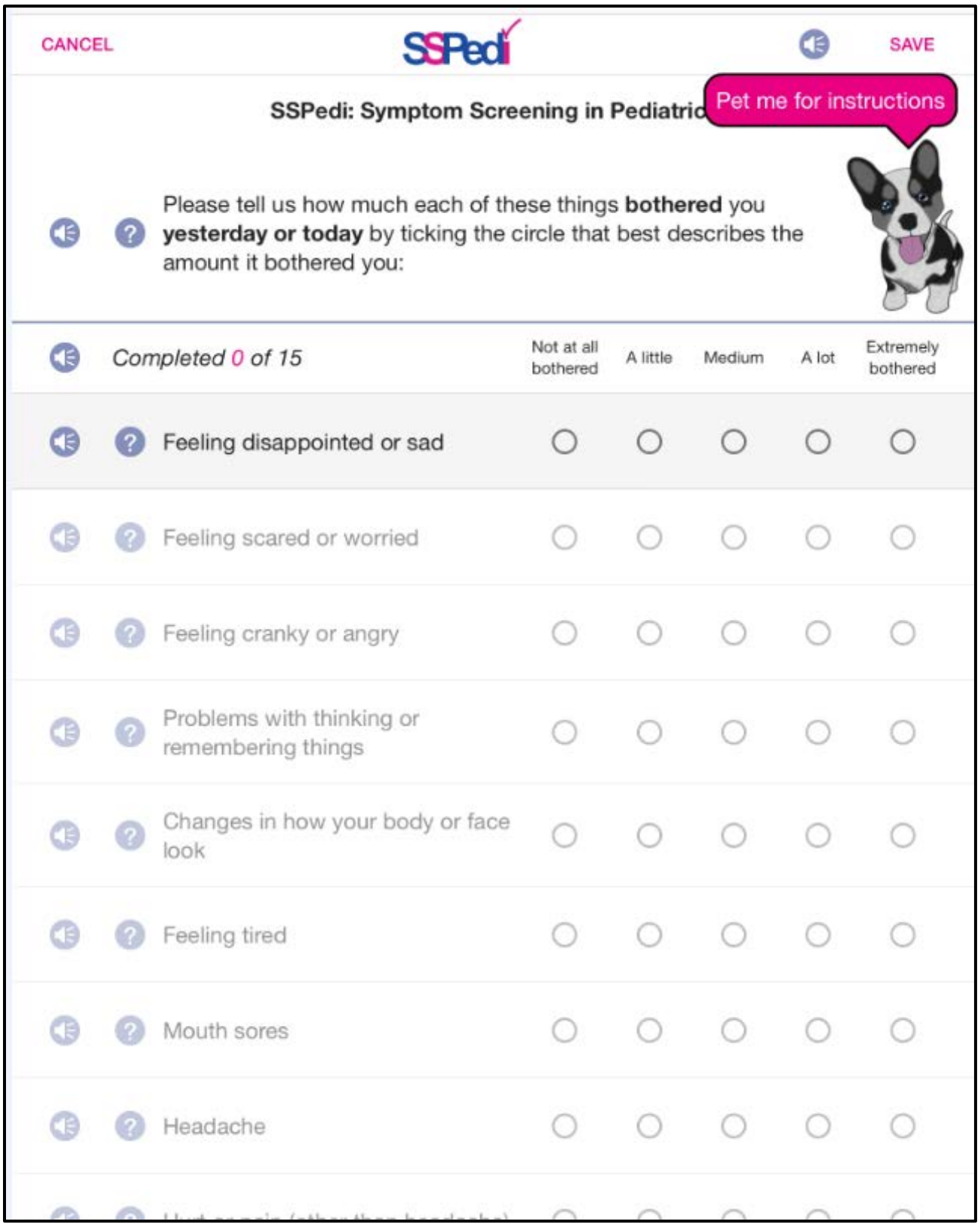
healthcare providers and hospital administrators. We will meet face-to-face or by teleconference at least annually to discuss progress and identify opportunities for KTE.
End of Grant KTE*:* We will publish the results of this study in peer-reviewed journals (minimum of 3 mid to high impact journals) and support attendance at national and international conferences. We plan to distribute plain language summaries throughout the COG, the C17 Research Network (represents the 17 centers in Canada) and the Pediatric Oncology Group of Ontario (represents the 5 centers in Ontario). We also plan to hold regular webinars and podcasts. The SickKids Industry, Partnerships and Commercialization office will help promote SPARK as a no cost web-portal for hospital use. In order to further enhance KTE, we will create an end-of-grant report that summarizes the processes refined to achieve symptom screening and feedback, and to adapt local care pathways for symptom management. This report will include the steps taken, challenges encountered and solutions to those challenges. This report will help other institutions to implement the approach expeditiously.

REFERENCES

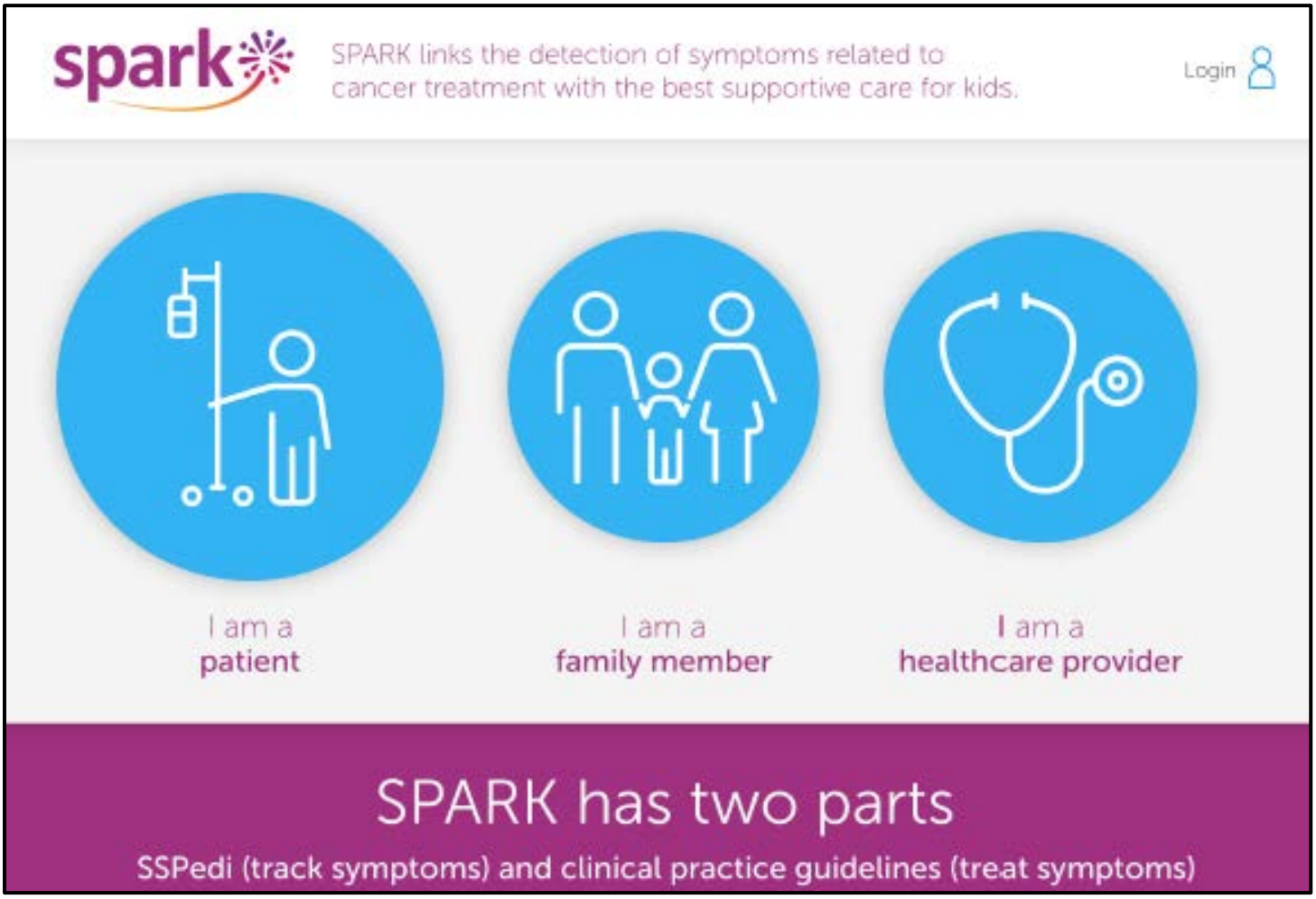
1. Canadian Cancer Society's Steering Committee on Cancer Statistics: Canadian Cancer Statistics. Toronto, ON, Canadian Cancer Society, 2011
2. Baggott C, Dodd M, Kennedy C, et al: Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy. J Pediatr Oncol Nurs 27:307-15, 2010
3. Dupuis LL, Johnston DL, Baggott C, et al: Validation of the Symptom Screening in Pediatrics Tool in Children Receiving Cancer Treatments. J Natl Cancer Inst, 2017
4. Hyslop S, Davis H, Duong N, et al: Symptom Documentation and Intervention Provision for Symptom Control in Children Receiving Cancer Treatments. Submitted 2018
5. Carelle N, Piotto E, Bellanger A, et al: Changing patient perceptions of the side effects of cancer chemotherapy. Cancer 95:155-63, 2002
6. Coates A, Abraham S, Kaye SB, et al: On the receiving end--patient perception of the side-effects of cancer chemotherapy. Eur J Cancer 19:203-8, 1983
7. de Boer-Dennert M, de Wit R, Schmitz PI, et al: Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer 76:1055-61, 1997
8. Griffin AM, Butow PN, Coates AS, et al: On the receiving end. V: Patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 7:189-95, 1996
9. Yang LY, Manhas DS, Howard AF, et al: Patient-reported outcome use in oncology: a systematic review of the impact on patient-clinician communication. Support Care Cancer 26:41-60, 2018
10. Berry DL, Hong F, Halpenny B, et al: Electronic self-report assessment for cancer and self-care support: results of a multicenter randomized trial. J Clin Oncol 32:199-205, 2014
11. Mooney K, Berry DL, Whisenant M, et al: Improving Cancer Care Through the Patient Experience: How to Use Patient-Reported Outcomes in Clinical Practice. Am Soc Clin Oncol Educ Book 37:695-704, 2017
12. Basch E, Deal AM, Kris MG, et al: Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol 34:557-65, 2016
13. Basch E, Deal AM, Dueck AC, et al: Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA, 2017
14. Wright JD, Neugut AI, Ananth CV, et al: Deviations from guideline-based therapy for febrile neutropenia in cancer patients and their effect on outcomes. JAMA Intern Med 173:559-68, 2013
15. FitzGerald JM, Boulet LP, McIvor RA, et al: Asthma control in Canada remains suboptimal: the Reality of Asthma Control (TRAC) study. Can Respir J 13:253-9, 2006
16. Grimshaw J, Eccles M, Thomas R, et al: Toward evidence-based quality improvement. Evidence (and its limitations) of the effectiveness of guideline dissemination and implementation strategies 1966-1998. J Gen Intern Med 21 Suppl 2:S14-20, 2006
17. Wolfe J, Orellana L, Cook EF, et al: Improving the care of children with advanced cancer by using an electronic patient-reported feedback intervention: results from the PediQUEST randomized controlled trial. J Clin Oncol 32:1119-26, 2014
18. O'Sullivan C, Dupuis LL, Gibson P, et al: Refinement of the symptom screening in pediatrics tool (SSPedi). Br J Cancer 111:1262-8, 2014
19. O'Sullivan C, Dupuis LL, Gibson P, et al: Evaluation of the electronic self-report Symptom Screening in Pediatrics Tool (SSPedi). BMJ Support Palliat Care, 2016
20. Tomlinson D, Dupuis LL, Gibson P, et al: Initial development of the Symptom Screening in Pediatrics Tool (SSPedi). Support Care Cancer 22:71-5, 2014
21. Soman D: The Last Mile: Creating Social and Economic Value from Behavioural Insights, University of Toronto Press, 2015
22. O'Sullivan C, Dupuis LL, Gibson P, et al: Refinement of the symptom screening in pediatrics tool (SSPedi). British Journal of Cancer 111:1262-8, 2014
23. National Guideline Clearinghouse: Inclusion Criteria. http://www.guideline.gov/about/inclusion-criteria.aspx, 2014
24. Forman J, Heisler M, Damschroder LJ, et al: Development and application of the RE-AIM QuEST mixed methods framework for program evaluation. Prev Med Rep 6:322-328, 2017
25. Graham ID, Logan J, Harrison MB, et al: Lost in knowledge translation: time for a map? J Contin Educ Health Prof 26:13-24, 2006

26. Koo A, Li C, Liu LL, et al: Successful adaptation of fever and neutropenia clinical practice guideline in China. . Applied Cancer Research, In Press, 2018
27. Altman M, Huang TTK, Breland JY: Design Thinking in Health Care. Prev Chronic Dis 15:E117, 2018
28. Thaler RH, Sunstein CR: Nudge improving decisions about health, wealth, and happiness. New Haven, Yale University Press,, 2008, pp 1 online resource (x, 293 p.)
29. Patel MS, Volpp KG, Asch DA: Nudge Units to Improve the Delivery of Health Care. N Engl J Med 378:214-216, 2018
30. Vettese E, Cook S, Soman D, et al: Longitudinal evaluation of Supportive care Prioritization, Assessment and Recommendations for Kids (SPARK), a symptom screening and management application. BMC Cancer 19:458, 2019
31. Allanson ER, Tuncalp O, Vogel JP, et al: Implementation of effective practices in health facilities: a systematic review of cluster randomised trials. BMJ Glob Health 2:e000266, 2017
32. Shoup JA, Gaglio B, Varda D, et al: Network analysis of RE-AIM framework: chronology of the field and the connectivity of its contributors. Translational Behavioral Medicine 5:216-32, 2015
33. Glasgow RE, Chambers D: Developing robust, sustainable, implementation systems using rigorous, rapid and relevant science. Cts-Clinical and Translational Science 5:48-55, 2012
34. Vanhoff D, Hesser T, Kelly KP, et al: Facilitating accrual to cancer control and supportive care trials: the clinical research associate perspective. BMC Med Res Methodol 13:154, 2013
35. Guyatt GH, Schunemann HJ, Djulbegovic B, et al: Guideline panels should not GRADE good practice statements. J Clin Epidemiol 68:597-600, 2015
36. Glasgow RE, Harden SM, Gaglio B, et al: RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. Front Public Health 7:64, 2019
37. Hinds PS, Nuss SL, Ruccione KS, et al: PROMIS pediatric measures in pediatric oncology: valid and clinically feasible indicators of patient-reported outcomes. Pediatr Blood Cancer 60:402-8, 2013
38. Varni JW, Burwinkle TM, Katz ER, et al: The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer 94:2090-2106, 2002
39. Johnston DL, Hyslop S, Tomlinson D, et al: Describing symptoms using the Symptom Screening in Pediatrics Tool in hospitalized children with cancer and hematopoietic stem cell transplant recipients. Cancer Med 7:1750-1755, 2018
40. Wild D, Grove A, Martin M, et al: Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health 8:94-104, 2005
41. Cook S, Vettese E, Soman D, et al: Initial Development of Supportive Care Assessment, Prioritization and Recommendations for Kids (SPARK), a symptom screening and management application. Submitted 2018

Appendix 1: Symptom Screening in Pediatrics Tool (SSPedi)



Appendix 2: SPARK Landing Page



PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History of Initial Approvals, Amendments and Statistical Plan

Version Date	Timeline	Date
N/A	Data sent to biostiatistician	15Dec2023
21Nov2023	Statistical Analysis Plan Uploaded to ClinicalTrials.gov	13Dec2023
21Nov2023	Amendment #2-4 – statistical edits	Nov 23, 2023 July 19, 2023 April 18, 2023
21Dec2021	Amendment #1 – modified eligibility criteria and ability to contact	March 2, 2022
26Feb2020	Initial protocol approved by SickKids Research Ethics Board	April 15, 2020

Amendment #2-4 (version date 21Nov2023)

Protocol Section	Major Modifications	Reason for Amendment
Statistical Analysis, Power Calculations and Data Management	Modifications to match the final statistical analytical plan uploaded to clinicaltrials.gov	To match the final statistical analytical plan uploaded to clinicaltrials.gov

Amendment #1 (version date 21Dec2021)

Protocol Section	Major Modifications	Reason for Amendment
Eligibility Criteria	Added: (5) have a plan to be followed by or receive care from the study institution for ≥ 50% of the 8-week study period and expected to be available on site or virtually for the week 8 assessment and (6) enroll within 28 days after diagnosis or treatment initiation, whichever occurs later.	Changes made to study eligibility to ensure there is a healthcare team at the participating site to receive the reports and have the ability to act on them if required for the on-study period, and to account for patients that receive initial treatment prior to a confirmed cancer diagnosis.
Procedures	Added that participants may be contacted in person, by email, text, or over the phone to ensure there are no technical barriers to completing SSPedi.	Changes made to procedures since we have identified technical issues preventing receipt of reminders to complete SSPedi. This allows us to identify and address those issues if needed.

Statistical Analytic Plan for Symptom Screening Linked to Care Pathways for Children with Cancer: A Cluster Randomized Trial

Study Title: Symptom Screening Linked to Care Pathways for Children with Cancer: A Cluster Randomized Trial

NCT Number: NCT04614662

Document Date: November 21, 2023

Objectives

Aims 1 and 2: Among children with newly diagnosed cancer, to determine if symptom screening and feedback to healthcare providers at least three times weekly and locally-adapted symptom management care pathways, when compared to usual care:

Aim 1. Improves overall self-reported symptom scores (total SSPedi score), fatigue (PROMIS–Fatigue) and cancer-specific quality of life (QoL) (PedsQL 3.0 Acute Cancer Module) over 8 weeks.

Hypothesis: Symptom screening and care pathways will improve symptoms, fatigue and QoL

Aim 2. Improves symptom documentation, increases provision of interventions for symptoms, and reduces emergency department visits and unplanned clinic visits and hospitalizations over 8 weeks.

Hypotheses: Symptom screening and care pathways will increase symptom documentation and provision of interventions for symptoms, and will reduce healthcare utilization.

Aim 3: As an exploratory aim, we will evaluate key elements of the intervention related to the external validity and generalizability of the intervention effects using the RE-AIM framework.

Sample Size Justification

The primary endpoint is the total self-reported SSPedi score at eight weeks. We used data from our SSPedi validation study for power calculation. In that study, we recruited 302 children across nine sites who were hospitalized and expected to be in hospital or in clinic three days later. Children completed SSPedi on days 1 and 4 and a 5-point global symptom change scale on day 4. The average absolute change in total SSPedi scores for those who reported they were a little better or a little worse on this global change scale (a 1-point change) was 2.7 while the average absolute change in total SSPedi scores for those who reported they were much better or much worse (a 2-point change) was 5.6. Thus, the minimum plausible clinically important difference is likely approximately 3.0 but may be higher. The intracluster correlation coefficient (ICC), a measure of the degree of clustering, was 0.021 (95% confidence interval (CI) 0 to 0.123). In power calculations for the proposed study, we used ICC=0.021 but show sensitivity analyses to ICCs at the extremes of the 95% CI (which are unlikely). Among the 20 sites in the proposed trial, we anticipate that four will each contribute eight patients, four will each contribute 32 patients, and the remaining 12 will each contribute 20 patients, for a total of 400 patients. With these cluster sizes, Table 1 shows power for combinations of these ICCs and clinically important differences, at a 2-sided alpha of 0.05 and assuming a within-cluster standard deviation of 8.8 (derived from the SSPedi validation study). Power for each combination in the table was calculated through simulation of 4000 trials. Each one was analyzed with a linear mixed effects model clustering by site and the percentage with a significant P value was taken as the estimate of power. If there is a baseline characteristic, such as age, that explains 20% of the variance in 8-week scores, including that variable in analyses increases power to the value shown in the far right column. Table 1 shows that assuming a minimal clinically important difference of 3.0 and with inclusion of age as a covariate in the analysis, there is 85% power with ICC=0.021. Assuming that 10% of patients have missing final

scores, we inflated the sample size to 444.

Table 1: Power With 400 Patients, Alpha=0.05 and Standard Deviation=8.8			
ICC	Difference	Power (%)	
		Without baseline predictor	With age as baseline predictor
0.000	2.5	71.0	81.4
	3.0	86.7	94.2
	3.5	95.9	98.9
0.021	2.5	59.5	70.1
	3.0	**75.7**	**85.2**
	3.5	86.5	94.2
0.123	2.5	26.6	32.6
	3.0	38.2	45.3
	3.5	47.7	57.0

Analytic Datasets

All analyses will follow the intention-to-treat principle. See below (Missing Data) for details on how those with missing data will be included in the analysis.

Study Outcomes

Questionnaires including the primary outcome and secondary patient-reported outcomes are obtained at weeks 4 and 8 from enrollment.

1. Primary outcome: The primary outcome is the total SSPedi symptom 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 designated week 4 or 8 SSPedi score will be taken on the day the other patient-reported outcomes were obtained or were planned to be obtained. This assures that the SSPedi score was collected as an outcome rather than as an intervention.
2. Secondary outcomes:
    a. Individual SSPedi symptom scores, which consist of each of the 15 symptoms scored as 0, 1, 2, 3 or 4.
    b. Fatigue will be measured using PROMIS. The raw score is translated to a T-score for each participant, where in the general population, the average T-score is 50 and the standard deviation is 10. The recall period is the last seven days. A higher T-score represents more fatigue, or worse health.
    c. PedsQL 3.0 Acute Cancer Module (scored according to https://www.pedsql.org/PedsQL-Scoring.pdf), which produces 8 domain scores on a 0-100 scale. The domains are (1) pain and hurt; (2) nausea; (3) procedural anxiety; (4) treatment anxiety; (5) worry; (6) cognitive problems; (7) perceived physical appearance; and (8) communication. The recall period is the last seven days. Higher scores indicate better QoL.

d. Documentation of symptoms (mapped onto the 15 SSPedi symptoms) in the participant's heath record; these are a set of 15 binary outcomes (assessed at weeks 4 and 8). For each, the window is a 3-day period extending from one day before to one day after the week 4 and 8 SSPedi time point.
e. SSPedi symptom-specific intervention performed; these are a set of 15 binary outcomes (assessed at weeks 4 and 8). For each, the window is a 3-day period extending from one day before to one day after the week 4 and 8 SSPedi time point.
f. Healthcare encounters including emergency department visits, unplanned clinic visits and unplanned hospitalizations over the 8-week period. The number of encounters in each category and the total across categories will each be a separate secondary outcome.

3. Exploratory outcomes: These are RE-AIM characteristics to measure reach, effectiveness, adoption and implementation.
    a. For reach, we propose to describe the baseline demographic characteristics of eligible patients who participate and who do not participate. We will also describe site attributes using the inner setting measures from the Consolidated Framework for Implementation Research (CFIR) as measured at baseline.(18, 19) This conceptual framework includes factors that may impact on intervention implementation. These attributes include culture, culture stress, culture effort, implementation climate, learning climate, leadership engagement and available resources.
    b. Effectiveness will be evaluated through primary and secondary outcomes as described in list items 1 and 2 above and also by comparisons of the percentages of patients with severely bothersome symptoms within intervention and control sites. We will characterize adoption at intervention sites by describing characteristics of sites and providers at those sites. Site characteristics will include pediatric vs. mixed adult and pediatric, number of pediatric cancer patients diagnosed annually, and percentage of patients anticipated to have private, public or no insurance. Healthcare professional characteristics will include number of physician and nurse practitioner full-time equivalents and median years in practice.
    c. Adoption will be assessed through the number of SSPedis per participant completed at intervention institutions; this analysis will use duration of time on protocol therapy as an offset. Further, we will dichotomize each participant as a high or low SSPedi completer, with a high completer being defined as one who completed 15 or more SSPedis. This analysis will use those who complete protocol therapy as planned as the denominator. In addition, we will count the number of times the institutional care pathways were clicked at intervention sites. We will describe the total number of clicks overall and by specific care pathway, access route (email link or QR code) and device (iPad, iPhone, Mac, Windows or unknown).
    d. Implementation outcomes will capture the percentages of intervention patients who came off protocol therapy early and the number of all participants who

came off study early, both overall and stratified by intervention or control group.

Descriptive Statistics

Baseline characteristics: Summary statistics on baseline characteristics will be calculated within each study arm and presented in a table – means and standard deviations (SDs) for variables treated as continuous, counts and percentages for categorical variables, along with total numbers with missing data.

Outcomes: Similar tables will be created for all study outcomes. Individual SSPedi symptom scores will be summarized by the percentages of participants with scores of 3 or 4, the two most bothersome categories.

Comparative Analyses

Primary Outcome

The primary analysis will use the patient-level 8-week total SSPedi score as the outcome in a mixed linear regression model with a random effect for cluster, fixed effects for treatment assignment, child age and diagnosis group (leukemia/lymphoma, solid tumor and central nervous system tumor), and two binary fixed effects at the cluster level for stratification variables (above or below the average anticipated yearly number of English or Spanish-speaking cancer patients 8-18 years of age, and above or below the average anticipated percentage of patients with private insurance vs. other payment types). Child age and diagnosis group will be included as they are known to be associated with total SSPedi scores; this will reduce residual variance in scores. We do not plan to adjust the model for baseline SSPedi score because some of the care pathway interventions (that are prophylactic) will affect symptoms prior to enrollment and the baseline score may already reflect some benefit of the cluster's treatment assignment. The treatment effect will be the covariate-adjusted mean difference between study groups in 8-week SSPedi, presented with a 95% CI and a two-sided p-value for a test of no treatment effect. If we find the residuals from the mixed model fitted to the 8-week total SSPedi score deviate substantially from normality, we will conduct sensitivity analyses, one using normalizing transformations of the outcome and another using an ordinal regression model.

To account for potential differential enrollment of surgery only patients (who might not be cared for by oncology teams) between intervention vs. control sites, we will also conduct a sensitivity analysis restricted to patients that received systemic chemotherapy.

Secondary Outcomes

1. **Self-reported individual symptoms at weeks 4 and 8 on the SSPedi instrument**: For each of the 15 ordinal outcomes representing symptoms (scored 0-4), a mixed effects proportional odds model will be fitted using treatment assignment and stratification factors as fixed effects covariates and with a random effect for site. As some individual symptoms may be uncommon, to avoid specifying models that may be overfitted for those symptoms, these models will use only this minimal set of three covariates. The estimated odds ratio for the intervention (representing the odds of having a higher vs. lower score in the intervention group) will be estimated and presented along with a 95%

CI. Two figures will be generated to present these results graphically: (a) to display the raw outcome data, a set of 15 pairs of stacked barplots will be created; within each pair, the stacked barplot will show the percentages of participants with scores of 0-4 in the control and intervention groups; (b) a forest-plot type figure will be created showing the estimated odds ratios with 95% CIs for each of the 15 symptoms.

2. **PROMIS Fatigue Scale**: This scale will be treated as a continuous variable and analyzed using a linear mixed effects model in the same way as the primary SSPedi outcome.
3. **PedsQL 3.0 Acute Cancer Module domain scores**: Each of these 8 scores will be treated as continuous variables and analyzed using a linear mixed effects model in the same way as the primary SSPedi outcome. A forest-plot type figure will be created showing the estimated treatment effects with 95% CIs for each of the 8 domains.
4. **Documentation of symptoms on weeks 4 and 8 (± 1 day):** Analyses will involve three analyses for each symptom class. Each analysis will fit a mixed effects logistic regression model to estimate the odds ratio for documentation (on weeks 4 and 8) comparing intervention groups, adjusting for stratification factors. It is possible that there will be too few documentation events to reliably fit this mixed model to all 15 symptoms. If this model cannot be fitted to some symptoms (likely because the random effects variance cannot be estimated), we will fit a fixed effects logistic regression model to just those symptoms. Three cohorts will be defined:
    a. Each participant will be classed as having the symptom documented or not. All participants are included in the analytic sample for each symptom.
    b. The analytic sample will be limited to those participants who self-report the symptom on weeks 4 and 8 (symptom score > 0).
    c. The analytic sample will be limited to those participants who have the most bothersome self-report of the symptom on the weeks 4 and 8 SSPedi (symptom score ≥ 3).
5. **Interventions for symptoms**: Analyses will follow a similar flow to the analyses of documentation of symptoms. For each of the 15 symptoms, each participant will be classified as having an intervention at weeks 4 and 8 (±1 days). Also collected is whether interventions were administered specifically for the specific symptoms. For example, acetaminophen may be administered for fever or pain. As interventions are expected to be more uncommon than symptoms, all treatment effects will be estimated by simple differences in the proportions with interventions (i.e., ignoring clustering), p-values will be computed from the Fisher exact test, and 95% CI for differences in proportions will use the Newcombe method. Three cohorts will be defined:
    a. Each participant will be classed as having an intervention for the symptom or not. All participants are included in the analytic sample for each intervention-symptom pair.
    b. The analytic sample will be limited to those participants who self-report the symptom on the weeks 4 and 8 SSPedi (symptom score > 0).
    c. The analytic sample will be limited to those participants who have the most bothersome self-report of the symptom on the weeks 4 and 8 SSPedi (symptom score ≥ 3).

6. **Unplanned encounters:** For each of the secondary endpoints of unplanned health services utilization (emergency, clinic visits, hospitalizations, and the total across categories), the number of events per child will be counted over the 8-week period and compared between randomized groups using a mixed-effects Poisson or negative binomial regression analysis (with zero-inflation if necessary), with a random effect for site and fixed effects for the two stratification factors. If a child has less than 8 weeks of follow-up, the model will include an offset equal to the logarithm of each child's follow-up time.

Exploratory Outcomes

1. **Reach**: we will describe the baseline demographic characteristics (sex, age or age group and diagnosis group) of eligible patients who participate and who do not participate using means and standard deviations for continuous variables and counts and percentages for categorical variables. The difference between participants and non-participants will be summarized two ways: numerically by the standardized mean difference and graphically by side-by-side barplots for categorical variables and by side-by side beeswarm plots for continuous variables. We will also summarize CFIR inner setting attributes as counts and percentages.
2. **Effectiveness**: In addition to the analyses of primary and secondary outcomes detailed above, we will also carry out analyses that dichotomize each of the 15 SSPedi symptoms as being severely bothersome (3 or 4) or not. Percentages for each symptom will be tabulated and compared between intervention groups using mixed effects binary logistic regression. We will also assess between-site variation in the odds of having a severely bothersome symptom (after adjusting for intervention and stratification factors) by plotting the random effects associated with each site and by calculating the median odds ratio (MOR). This is an alternative measure of clustering (or between-cluster variability); it is the estimated median of the ratio of the odds of a bothersome symptom for a participant at one site to the odds of a bothersome symptom for an otherwise identical participant at another site. The MOR is always defined with the higher odds in the numerator. One appealing aspect of the MOR is that it is on the same scale as the odds ratio for treatment, aiding interpretation of both the OR for intervention and the MOR for variation in the outcome.
3. **Adoption**: We will characterize adoption at intervention sites by summarizing the following:
    a. characteristics of sites and their providers
    b. number of SSPedis completed per enrolled participant
    c. proportion of participants that are high or low SSPedi completers
    d. number of times the institutional care pathways were clicked.

    Site and provider attributes will be described by using means and standard deviations for continuous variables and counts and percentages for categorical variables. Site characteristics will include pediatric vs. mixed adult and pediatric, number of pediatric cancer patients diagnosed annually, and percentage of patients anticipated to have private, public or no insurance. Healthcare professional characteristics will

include number of physician and nurse practitioner full-time equivalents and median years in practice. CFIR attributes will also be described.

The dependence of the number of SSPedis completed by a participant on participant, guardian and site characteristics will be assessed using a mixed effects Poisson or negative binomial regression model, with a random effect for site. Participant characteristics will include sex, age/age group, race, ethnicity, preferred language, and cancer diagnosis group. Guardian characteristics will include marital status, guardian employment and highest education, and high annual household income. Site characteristics will be those included above. The dependence of the odds of being a high responders on these same characteristics will be assessed using mixed effects logistic regression adjusting for stratification factors.

The number of recorded clicks is available on aggregate for each site, so we will summarize this as a set of 10 rates, clicks per enrolled participant, and assess whether there is site-to-site variability by fitting a random effects Poisson or negative binomial model with clicks as the outcome and the logarithm of the number of patients as an offset. A summary rate will be estimated from this model and the median rate ratio (analogous to the MOR above) will be calculated.

4. Implementation will calculate the percentage of patients who enrolled but came off protocol therapy early (intervention only) or off study early (all participants), overall and stratified by intervention or control group. Counts and percentages will be shown, with no inferential statistics.

Missing Data

Rule-based methods: The PedsQL will be scored according to its scoring guide, which includes rules for scoring in the presence of missing elements on each domain modules. No other deterministic rule-based method will be used to deal with missing data.

Multiple imputation: If more than 10% of participants are missing the primary outcome or secondary patient-reported outcomes, the analysis will use multiple imputation based on previous SSPedi assessments (weeks 0 and 4), group and site. In addition, we will conduct sensitivity analysis assuming that missing scores are from children with high total SSPedi scores and from children with low total SSPedi scores (randomly drawn from the highest and lowest quartile). A set of 20 complete datasets will be generated using separate within-treatment-group imputation models. These models will include all the study outcomes listed just above, and the key covariates that appear in our adjusted models (age, diagnosis group and stratification factors). The models will be fitted in each imputed dataset and the pooled estimate of the treatment effect and its standard error will be computed using Rubin's rules.

Analyses of documentation and interventions will not use any imputation. There can be no missing data for these outcomes: if a symptom is not documented in the health record and there is no record of an intervention being used, then this constitutes a 'no' for the outcome. While it is possible that the SSPedi symptom score needed for the identification of the analytic datasets in analyses (4b, 4c, 5b, and 5c) is missing for some participants, the more exploratory nature of these analyses led us to the decision to use only observed data for these outcomes.

Software

All analyses will use R 4.3.0 with these specific packages:

- base R for general programming and fitting linear and logistic regression models.
- the tidyverse and lubridate packages for data “wrangling”.
- the rms package for the proportional odds model.
- the mice package for multiple imputation.
- the ggplot2 package for graphs.
- the tableone package for summary descriptive tables.
- glmer for linear and logistic mixed effects regression models
- ordinal for proportional odds mixed effects regression models

Planned Tables

Planned tables are below.

Table 1: Participant Demographic Characteristics

Characteristics	All Patients	Symptom Screening	Usual Care
Male			
Median Age in Years (range)			
Age Group in Years			
8-10			
11-14			
15-18			
Race			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Other Pacific Islander			
White			
Unknown			
Ethnicity			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown			
Diagnosis			
Leukemia			
Lymphoma			
Solid tumor			
Brain tumor			
Other			
Metastatic Disease			
Median Days from Diagnosis (range)			
Planned or Received Treatment			
Chemotherapy			
Radiotherapy			
Surgery			
Median Days from Treatment Start (range)			
Inpatient at Enrollment			
First language English or Spanish			
Preferred Language for Patient Reported Outcomes			
English			
Spanish			
Not applicable (chart review only)			
Family Composition - Married			
Guardian Employment Full or Part Time			
Guardian Education College or Higher			
Annual Household Income ≥ $60,000			

Table 2: SSPedi Outcomes by Assessment Timepoint and Group

	Baseline		Week 4		Week 8		Treatment Effect Estimate; 95% CI; p-value	
	Symptom Screening	Usual Care	Symptom Screening	Usual Care	Symptom Screening	Usual Care	Unadjusted	Adjusted
Primary Outcome							Mean Difference	
SSPedi Score (mean, SD)								
							Odds Ratio	
Secondary Outcomes								
Severely Bothersome, n (%)*								
Feeling disappointed or sad								
Feeling scared or worried								
Feeling cranky or angry								
Problems with thinking or remembering things								
Changes in how your body or face look								
Feeling tired								
Mouth sores								
Headache								
Hurt or pain (other than headache)								
Tingly or numb hands or feet								
Throwing up or feeling like you may throw up								
Feeling more or less hungry than you usually do								
Changes in taste								
Constipation (hard to poop)								
Diarrhea (watery, runny poop)								

Table 3: Non-SSPedi Patient-reported Outcomes by Assessment Timepoint and Group

	Baseline				**Week 8**		**Treatment Effect Estimate; 95% CI; p-value**	
	Symptom Screening (n=175)	Usual Care (n=169)			Symptom Screening (n=168)	Usual Care (n=164)	Unadjusted	Adjusted
PROMIS Fatigue (Mean, SD)							Mean Difference	
Total PedsQL 3.0 Acute Cancer Module Score (Mean, SD)							Mean Difference	
Pain and hurt								
Nausea								
Procedural anxiety								
Treatment anxiety								
Worry								
Cognitive problems								
Perceived physical appearance								
Communication								

Table 4: Symptom Documentation and Intervention by Group for All Participants

	Symptom Screening	Usual Care	P value
Symptom Documentation (%)			
Feeling disappointed or sad			
Feeling scared or worried			
Feeling cranky or angry			
Problems with thinking or remembering things			
Changes in how your body or face look			
Feeling tired			
Mouth sores			
Headache			
Hurt or pain (other than headache)			
Tingly or numb hands or feet			
Throwing up or feeling like you may throw up			
Feeling more or less hungry than you usually do			
Changes in taste			
Constipation (hard to poop)			
Diarrhea (watery, runny poop)			
Any Symptom Intervention (%)			
Feeling disappointed or sad			
Feeling scared or worried			
Feeling cranky or angry			
Problems with thinking or remembering things			
Changes in how your body or face look			
Feeling tired			
Mouth sores			
Headache			
Hurt or pain (other than headache)			
Tingly or numb hands or feet			
Throwing up or feeling like you may throw up			
Feeling more or less hungry than you usually do			
Changes in taste			
Constipation (hard to poop)			
Diarrhea (watery, runny poop)			
Symptom Intervention Clearly			

for Symptom (%)			
Feeling disappointed or sad			
Feeling scared or worried			
Feeling cranky or angry			
Problems with thinking or remembering things			
Changes in how your body or face look			
Feeling tired			
Mouth sores			
Headache			
Hurt or pain (other than headache)			
Tingly or numb hands or feet			
Throwing up or feeling like you may throw up			
Feeling more or less hungry than you usually do			
Changes in taste			
Constipation (hard to poop)			
Diarrhea (watery, runny poop)			

Table 5: Number of Unplanned Healthcare Encounters by Group

Unplanned Encounter Type	Total	Symptom Screening	Control
		(n=xx)	(n=xx)
All unplanned encounters			
Rate per 100 patient-weeks			
Number of encounters (n, %)			
0			
1			
2			
3			
4			
5			
6 or more			
Emergency department visits			
Rate per 100 patient-weeks			
Number of encounters (n, %)			
0			
1			
2			
3			
4			
5			
6 or more			
Unplanned clinic visits			
Rate per 100 patient-weeks			
Number of encounters (n, %)			
0			
1			
2			
3			
4			
5			
6 or more			
Unplanned hospital admissions			
Rate per 100 patient-weeks			
Number of encounters (n, %)			
0			
1			
2			
3			
4			
5			
6 or more			