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The Pain Squad+ Smartphone App to Support Real-Time Pain Treatment for Adolescents with Cancer: Protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction. Pain negatively affects the health-related quality of life (HRQL) of adolescents with cancer. The Pain Squad+ smartphone-based app, has been developed to provide adolescents with real-time pain self-management support. The app uses a validated pain assessment and personalised pain treatment advice with centralised decision support via a registered nurse to enable real-time pain treatment in all settings. The algorithm informing pain treatment advice is evidence-based and expert-vetted. This trial will longitudinally evaluate the impact of Pain Squad+, with or without the addition of nurse support, on adolescent health and cost outcomes.

Methods and analysis. This will be a pragmatic, multi-centre, waitlist controlled, 3-arm parallel-group superiority randomised trial with 1:1:1 allocation enrolling 74 adolescents with cancer per arm from 9 cancer centres. Participants will be 12-18 years, English-speaking, and with ≥3/10 pain. Exclusion criteria are significant co-morbidities, end-of-life status, or enrollment in a concurrent pain study. The primary aim is to determine the effect of Pain Squad+, with and without nurse support, on pain intensity in adolescents with cancer, when compared to a waitlist control group. The secondary aims are to determine the immediate and sustained effect over time of using Pain Squad+, with and without nurse support, as per prospective outcome measurements of pain interference, HRQL, pain self-efficacy, and cost. Linear mixed models with baseline scores as a covariate will be used. Qualitative interviews with adolescents from all trial arms will be conducted and analysed.

Ethics and dissemination. This trial is approved by the Clinical Trials Ontario (CTO)-Qualified Research Ethics Board. Results will provide data to guide adolescents with cancer and healthcare teams in treating pain. Dissemination will occur through partnerships with stakeholder groups, scientific meetings, publications, mass media releases, and consumer detailing.

Trial registration. NCT03632343 *(ClinicalTrials.gov)*

Strengths and limitations of this study

- This study is a large trial evaluating an innovative method to address pain in adolescents with cancer, the most common and distressing symptom experienced by this group.
- This pragmatic design of the trial means that our approach to study eligibility criteria, intervention intensity, and participant adherence will determine intervention effect under real-world conditions.
- Former adolescent cancer patients are core members of this study team and have, and will continue to, guide and support study design, study conduct and results dissemination.
- Adolescents with cancer, their caregivers, and the study nurse will not be blinded to participant group as this is prohibited by the nature of the intervention.

Keywords

Pediatrics, cancer, pain, symptom treatment, smartphone app, supportive care, protocol, randomised controlled trial

INTRODUCTION

Adolescents with cancer report pain as the most commonly occurring and distressing cancer-related symptom experienced [1-3]. Pain negatively impacts health-related quality of life (HRQL) [4-6] represents a significant cost burden to patients, families and the health system [7] and is a major reason for cancer-related emergency health service use in adult patients [8-11]. However, the successful identification of pain, including in and outside of the hospital setting, does not equate to its adequate treatment and pain is often undertreated in adolescents [12-15].

Due to improvements in therapeutic regimes, supportive care, and changes in the health system, adolescents with cancer now spend less time in hospital and more time at home [16-18]. Thus, adolescents and their families are increasingly responsible for managing cancer-associated pain in environments with less supervision from healthcare professionals [13,19]. Adolescents are more vulnerable in these environments as they often lack the knowledge, skills, and self-efficacy needed to adequately react to symptoms and may ignore or inappropriately accept changes in pain [13,16,20,21]. Digital health technologies are widely used by adolescents [22] and can empower adolescents with cancer to engage in remote and real-time pain treatment in all of their natural environments (e.g., hospital, home, school). Studies have indicated that digital real-time symptom monitoring and treatment improves HRQL and decreases emergency service use and hospitalisation rates in adults with cancer [23,24], but no such research has been conducted with adolescents.

The Pain Squad+ smartphone-based real-time pain treatment application

Using a phased- and user-centred approach, our team has developed a smartphone app, called Pain Squad+, capable of providing adolescents with real-time pain treatment support (**Figure 1**) [25-31]. Pain Squad+ uses a truncated 8-item version of a valid and reliable automated

questionnaire to assess adolescent pain (severity, interference, location and capacity to self-manage pain) [12]. When pain is reported using Pain Squad+, self-management advice is presented to users in real-time according to a vetted and standardised clinical care algorithm [25,32]. Advice is based on a library of pharmacological (e.g., medication adherence reminders), psychological (e.g., distraction techniques), and physical (e.g., yoga instruction) advice that aligns with typical recommendations provided to adolescents by their healthcare teams [33]. Three consecutive moderate to severe reports of pain intensity (i.e., ≥3/10 [34]) trigger an email to be sent to a paediatric oncology-trained registered nurse. The nurse then contacts the adolescent and/or their healthcare team to discuss the case and initiate healthcare professional-driven intervention, which may be outside of the scope of the self-management algorithm (e.g., adjusting a prescribed medication regime). To encourage engagement with Pain Squad+, the app is "gamified" with users playing the role of superheroes who receive rewards for adherence to pain assessment and treatment recommendation completion [19].

The most recently completed phase of Pain Squad+ testing was a 1-group, baseline-poststudy pilot that demonstrated the feasibility (i.e., intervention fidelity, outcome measure completion, adherence, acceptability) of evaluating the app in a randomised controlled trial (RCT) , as well as small to moderate effect sizes (Cohen's d: 0.23-0.67) [35]. This protocol details the methods to be used in the next phase of Pain Squad+ testing: a RCT aimed at longitudinally evaluating the impact of Pain Squad+, with or without the addition of nurse support, on adolescent health and cost outcomes.

Specific objectives

Primary objective and hypothesis. To examine the effect of 4 weeks of Pain Squad+ app use, with and without nurse support, on pain intensity in adolescents with cancer, when compared to a

waitlist control group. We hypothesise that 4 weeks of Pain Squad+ use, with or without nurse support, will result in improved pain intensity scores, compared to a waitlist control group.

Secondary objectives and hypotheses as appropriate.

Objective related to the effect of Pain Squad+ on health outcomes overtime.

To examine the effect of each of 2, 4, and 8 weeks of Pain Squad+ app use, with and without nurse support, on each of pain intensity, pain interference, HRQL, and pain management self-efficacy in adolescents with cancer, when compared to a waitlist control group. We hypothesise that Pain Squad+ use, with or without nurse support, for 2, 4, and 8 weeks will result in improved pain intensity, pain interference, HRQL, and self-efficacy scores, compared to a waitlist control group.

Objective related to maintenance of potential therapeutic gains from Pain Squad+ use.

- To examine the effect of the Pain Squad+ app, with and without nurse support, on each of pain intensity, pain interference, HRQL, and pain management self-efficacy in adolescents with cancer compared to a waitlist control group, when assessed after intervention use has ceased (i.e., 8 weeks post-use of the intervention). We hypothesise that improvements in pain intensity, pain interference, HRQL, and self-efficacy scores related Pain Squad+ use, with or without nurse support, will be sustained when assessed after intervention use has ceased.

Objective related to the effect of Pain Squad+ on health system and societal costs.

- To examine the cost-effectiveness and cost utility of the Pain Squad+ app, with and without nurse support as compared to standard care from both a health system and societal perspective.

Objective related to treatment arm satisfaction.

- To explore adolescent with cancer-rated acceptability (including engagement with pain treatment strategies) of the Pain Squad+ app and the study following participation.

METHODS

Trial design

This will be a pragmatic, multi-centre, waitlist group-controlled, investigator and analyst-blinded, 3-arm parallel-group superiority RCT with 1:1:1 allocation (**Figure 2**). Randomisation will be stratified by recruitment site to account for differences in care across centres [36] with block sizes of 6 and 9 within each stratum. Reporting of this protocol is in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [37] (See Additional Files for SPIRIT checklist).

Study setting

Adolescent and caregiver recruitment will occur across 9 Canadian paediatric oncology programs that treat a diversity of paediatric cancers (often based on the same standardised protocols). All of these programs are located in tertiary care centres that serve paediatric populations with considerable racial, ethnic, and socioeconomic diversity. The lead study site is the Hospital for Sick Children (SickKids).

Eligibility criteria

The eligibility criteria for this study, with the rationale for each criterion and the sources of associated data collection, are shown in **Table 1**. No restrictions will be placed on analgesia use or hospitalisations, however data related to medication and other pain treatment strategy use, as well as in-patient stays (i.e., reason, duration, pain-related treatment received), will be collected during the study.

Table 1. Pain Squad+ RCT participation eligibility criteria

Criterion	Rationale	Source
Inclusion criteria		
12-18 years of age	Study restricted to AWC	Medical chart
Diagnosed with cancer (all disease types) and receiving cancer-directed therapy	Study restricted to AWC	Medical chart
English-speaking and reading	Pain Squad+ app currently available in English only	AWC self-report
Average pain score of ≥3/10 over the preceding week	Value describes moderate-severe pain in adolescents [34] and RCTs of similar interventions in adults with cancer pain [38,39]. In our pilot, 75% of AWC reported average pain of ≥3/10 in the week prior to enrollment.	AWC self-report measured using an 11-point numerical rating scale (NRS)
English-speaking and reading caregiver who is willing and able to complete outcome measures related to healthcare encounters	English-speaking caregivers required to complete outcome measure related healthcare utilisation and associated costs.	AWC or caregiver self-report
Exclusion criteria		
Significant cognitive impairments or co-morbid illnesses	Would limit interaction with Pain Squad+ or outcome measure assessment	Healthcare team report
Currently participating in other pain treatment studies	Concomitant intervention represents a threat to internal validity	AWC or caregiver self-report
Not expected to survive past 16 weeks	Terminal data collection point is at 16 weeks post-randomisation	Healthcare team report

Interventions

Experimental Group A. The deployment of the Pain Squad+ app to adolescent's personal phones will be done through the Apple App Store and Google Play store. The research team will loan an iPhone or Android phone to those without a smartphone. All adolescents will be trained to use Pain Squad+ using a standardised procedure. Three repeated audible smartphone alerts

over a 30-minute window will signal each adolescent to complete the 8-item pain assessment using Pain Squad+ every morning and evening for 8 weeks. The timing of morning and evening pain assessments will be individualised according to participant's daily and weekly schedules. An automated 30-minute window within which each assessment must be completed will be set, or the assessment will be registered as "missed". Adolescents will also have the option of completing *ad hoc* pain assessments anytime between the automated alert times. Algorithm-driven pain self-management advice will be issued in response to pain, providing real-time decision support (**Supplementary Appendix A**). One hour after a recommendation is made, the app will alert adolescents to complete a pain reassessment and additional advice will be offered as appropriate. All pain assessment and treatment advice data logged will be encrypted and wirelessly transferred to a secure server at SickKids for storage. Email alerts related to 3 consecutive reports of pain >3/10 will be sent to the study nurse who will log into the Analytics Platform to Evaluate Effective Engagement (APEEE) platform [38] to review the adolescent's pain report history. The nurse may liaise with the adolescent's healthcare team regarding the case and will contact the adolescent within 12 hours of receiving the alert, including on weekends. The time of nurse contact and the details of the pain treatment conversation will be recorded. A research coordinator will provide telephone-based technical assistance (weekdays 0900 – 1700 EST) to participants if required.

Experimental Group B. Adolescents randomised to this group will complete pain assessments and receive the same smartphone-based algorithm-driven pain treatment advice as in Experimental Group A but will not receive nurse-initiated pain support.

Waitlist Control Group. Adolescents randomised to this group will be waitlisted to receive the Experimental Group B condition within 1 month of completing all post-study outcome measures.

All study groups. Regardless of study group, adolescents will continue to receive standard medical care from their treating healthcare teams. All groups will be reminded to pursue help using the usual channels (calling oncology clinic, 'on-call' team, or 911) should any medical emergencies arise during the study.

Outcomes

All outcome measures have demonstrated validity and reliability in 12-18-year-olds with cancer and will be assessed according to the schedule shown in **Figure 3**. A 1-week recall period will be used for all health-related outcomes.

Primary outcome. The primary outcome is average pain intensity, measured using Brief Pain Inventory (BPI). The BPI assesses current pain and 'worst', 'least', and 'average' pain in the preceding week using an 11-point numerical rating scale (NRS) with verbal anchors 'no pain' at 0 and 'pain as bad as you can imagine' at 10 [39,40]. Item scores may also be averaged to give a Pain Intensity Summary Score [41].

Secondary outcomes.

(a) ***Pain interference*** will be assessed using the Patient Reported Outcomes Measurement Information System (PROMIS) Pediatric Pain Interference Short-form Scale. The PROMIS instrument is a valid 8-item scale assessing the impact of pain on function [42,43]. Higher scores represent greater interference with function.

(b) ***HRQL*** will be assessed using the Pediatric Quality of Life Inventory (PedsQL) 4.0. The PedsQL 4.0 is a valid and reliable 23-item instrument not specific to pain [2,44]. It is comprised of 4 subscales (physical functioning, emotional functioning, social functioning and school functioning), which are summed to provide a total score. Higher scores represent better quality of life.

(c) ***Pain management self-efficacy*** will be assessed with Porter's scale which assesses self-efficacy for managing pain, symptoms, and function in cancer patients [45,46]. This 16-item scale includes a valid and reliable 5-item subscale assessing cancer pain management self-efficacy with higher scores indicating more certainty and is adapted from a scale that has been successfully administered to adolescents [21,47].

(d) ***Cost effectiveness and cost utility*** analyses will determine the incremental costs (or savings) of the Pain Squad+ app, with and without nurse support, when compared to a waitlist control group in reducing pain over the study. Quality-adjusted life years (QALYs) will be calculated using data from the valid and reliable Health Utility Index Mark 2/3 (HUI2/3) [48] completed by adolescents. Direct healthcare costs will include the intervention costs as well as costs for health service utilization during the trial. Family out-of-pocket expenses, indirect costs due to lost productivity, and health service use will be ascertained using standardized customized data collection forms completed by caregiver report.

(e) ***Satisfaction with treatment*** will be assessed using qualitative interviews with a subset of participating adolescents. These interviews will specifically be used to explore the perceptions of adolescents with cancer as they relate to the acceptability (including engagement with pain treatment strategies) of Pain Squad+, with and without nurse support, or the waitlist control condition.

Socio-demographic- and disease-related data baseline. Adolescent age, sex, ethnicity, school grade, diagnosis, stage/risk, relapse-status, treatment-type, date of diagnosis, co-morbid conditions and medications, pain history; as well as caregiver age, sex, ethnicity, educational attainment, and financial characteristics; adolescent ownership and use of smartphones; and adolescent expectation about treatment effectiveness (assessed using a valid NRS scale with

verbal anchors ‘don’t think it will help at all’ at 0 and ‘think it will help a lot’ at 10).

Participant timeline

An 8-week treatment period will be used (**Figure 3**). The primary outcome, and health-related secondary outcomes will be assessed at baseline and 2, 4, 8, and 16 weeks post-randomisation. Cost-related outcomes will be assessed at baseline, 8, and 16 weeks post-randomisation. The primary endpoint will be at 4 weeks post-randomisation selected as our primary endpoint because, based on our pilot, it is feasible to administer the intervention for this period and significant pain improvements are observed at 4-weeks [35]. To examine whether duration of Pain Squad+ use changes the magnitude or direction of outcome changes, adolescents in the experimental groups will continue to use the app until 8 weeks post-randomisation and outcomes will be assessed at 2 and 8 weeks (specifically examining the effect of shortening or extending intervention use on health quality). A longer-term follow-up (16 weeks) will be used to examine the maintenance of any Pain Squad+ therapeutic gains after discontinuation of the intervention. Qualitative interviews will be conducted at study completion or withdrawal.

Sample size

The sample size is calculated based on detecting a difference of 1.1 points between any two treatment groups in the primary outcome, average pain intensity reported on the BPI, at 4 weeks post-randomisation. This difference in pain intensity represents one of minimal clinical significance (the smallest difference that patients perceive as beneficial) for pain intensity improvement on a 0-10 scale in adolescents [49]. Our pilot study showed that the effect size for a 1.1-point change in pain intensity in adolescents following Pain Squad+ was 0.52 [35]. We have used a conservative approach which accounts for the 1-group design of our pilot and have powered this RCT to detect a primary outcome effect size of 0.5. Using a sample size calculation

for analysis of covariance (ANCOVA) models and controlling for baseline pain intensity [50], sample sizes of 63 per group, or 189 in total, will be required to achieve 80% power to detect an effect size of 0.5 between any two treatment groups. This calculation assumes an overall Type I error set at 0.05 allowing for Bonferroni-corrected pairwise comparisons of treatment arms, and a conservative correlation between baseline and follow-up measurements of 0.5. To account for the 5% drop out and 10% loss to follow-up rates observed in the pilot study [35], we will recruit 222 (i.e., 189/0.85) adolescents into the study, or 74 per group.

Recruitment

Each site research assistant (RA) will coordinate with the clinic healthcare team to determine eligibility. Identified eligible potential participants will be recruited via telephone call (following a mailed or emailed study information letter) or in-person at the hospital. Recruitment will begin in November 2019 and is projected to end April 2022.

Allocation and blinding

A centrally controlled, online randomisation service will be used to assign adolescent to each study group using a 1:1:1 allocation model. When an adolescent is ready to be randomised, the lead site RA will enter a unique identification number and information about the stratification variable (recruitment site) into the online program. Group allocation will be assigned with block sizes of 6 and 9 within each stratum. The RA, who has no role in allocation sequence generation, will then inform the adolescent of their group assignment and instruct them on the procedures to be followed. The investigators, including data analysts, will be blind to group allocation. Treatment allocation may be unblinded only by the principal investigators when knowledge of the actual treatment is essential for further treatment of the patient [51], as determined by the adolescent's treating oncologist.

Data collection methods

Pre-randomisation procedures. Eligible adolescents who are hospital inpatients or have a scheduled clinic appointment during the recruitment period will be invited to participate. Site RAs will obtain informed consent from adolescents and one of their primary caregivers. The research coordinator will track the number of eligible adolescents approached and reasons for refusal on an investigator-developed form. The lead site RA will obtain baseline data on adolescents (socio-demographic- and disease-related characteristics) from their medical records and administer online pre-intervention measures on the secure password-protected Research Electronic Data Capture (REDCap) site.

Post-randomisation procedures. At 2, 4, 8, and 16 weeks post-randomisation, the lead site RA will contact adolescents and caregivers up to three times by text message, email and/or telephone and ask them to complete all outcome measures. To do so, participants will log into REDCap using an Internet-enabled device and their unique identifier. Outcome measure data will be time-stamped by REDCap when entered and participants will be encouraged to complete measures immediately after contact with the RA. The RA will provide telephone troubleshooting in the case of REDCap or questionnaire problems. Adolescents will receive a gift certificate for each outcome assessment completed in recognition of their time and effort. Loaned phones will be returned. All data will be exported from REDCap to SAS Statistics [52] on the secure server at SickKids for analysis. Qualitative interviews will be conducted with a subset of adolescents from each trial arm. Adolescents who vary across age, sex, diagnosis, and study engagement will be recruited. Interviews will be conducted until data saturation (i.e., no new data generated in an interview). We anticipate conducting a total of 45 interviews. A semi-structured interview guide that is based on the guide used in our pilot [25-31] and has been refined by former adolescent

cancer patients will be used. Interviews will be audio-recorded and may be conducted in-person or over the telephone. Field notes will be taken by the interviewer.

Data management and confidentiality

All outcome data will be collected online using REDCap and the associated database will be regularly backed up by SickKids. All data files (including back-ups) will be kept in a secured environment in Canada and are available for recovery. The secure digital platform Analytics Platform to Evaluate Effective Engagement (APEEE) will be used to collect adolescent-entered pain assessment and treatment data, as well as data related to app engagement, for each of the intervention groups. Data will be accessible only by the study team and staff. Any hardcopy documentation (e.g., consent forms) will be stored in locked cabinets in locked offices at study sites, separate from the stored data. All staff will be provided with training on the use of REDCap and APEEE and maintaining participant confidentiality.

Data analyses methods

Health outcome analyses. Pain intensity, pain interference, HRQL, and self-efficacy data will be analyzed using an intent-to-treat approach [53]. Background variable data collected at baseline will be described using measures of central tendency and variance. If outcome data meet the requirements for parametric statistics (e.g., approximate normality, linear distribution), linear mixed models will be used to assess the effects of the intervention on primary and secondary outcomes with baseline scores used as covariates. Regarding our HRQL outcome, as with our pilot, we will separately analyze the physical, emotional, social and school subscales of the PedsQL, as well as the total scale score. . To explore the effects of demographic, disease-related variables, and pain treatment strategies used on outcomes, separate linear mixed models with these variables as covariates will be used. A significance level of 0.05 will be used for all

outcomes (with adjustment made for serial analyses).

Economic analyses. Cost effectiveness and cost utility analyses will be conducted using both a health system and societal perspective. Cost effectiveness and cost utility will be expressed as incremental cost effectiveness ratios (ICERs), calculated by dividing the incremental costs between treatment arms by the incremental difference in average pain intensity or the incremental change in utility scores, measured by the HUI2/3. Multiple ICERS will be calculated comparing each of the three study groups in a pairwise fashion for both the cost effectiveness and cost utility analyses. Deterministic and probabilistic sensitivity analysis will be performed to evaluate the robustness of the results. A 95% confidence interval for incremental costs, incremental effects, and the ICER will be calculated from study data.

Qualitative interview analyses. Audio-recorded interviews will be transcribed verbatim. Transcribed data will be managed using NVivo 12.0 software (QRS International). Data analysis will occur shortly after each interview is conducted so that identified issues can be used to inform subsequent interview content. Data will be read several times by the study team for overall understanding and to identify data codes. Data will then be coded using a line-by-line approach according to study objective. Codes will be grouped into categories based on between-code relationships. Category development will occur until all data can be classified under the existing categories. Categories will then be grouped into themes. Field notes and relevant sociodemographic and disease characteristics will be integrated into the analysis process to illustrate or clarify emerging categories and themes.

Patient and public involvement statement

Adolescents with cancer have been directly and actively involved in all stages of the development and evaluation of the Pain Squad+ app, including determining the feasibility of this

study, evaluating any potential burden on adolescent participants, and in the development of this research protocol. An adolescent with cancer advisory committee has been established to guide trial conduct and results interpretation and dissemination from a patient perspective and will report to the principal investigators. This advisory committee will meet regularly with the lead investigators to ensure the trial is guided by the priorities and experiences of adolescents with cancer.

ETHICS AND DISSEMINATION

Trial steering and data safety and monitoring committees (DSMC)

The trial steering committee consists of the lead study team. Virtual progress meetings with all steering committee members will be routinely collected to ensure the smooth running of the study. A DSMC guided by a prepared charter of roles and responsibilities (available from corresponding author) and consisting of a statistical expert, a paediatric oncology nurse scientist, and a paediatric anesthesiologist who are independent of the research team has been established. The DSMC will meet biannually to review recruitment, accumulating study data and adverse events, and will provide guidance to the study team regarding any needed action.

Safety appraisal and protocol amendment reporting

Based on our pilot [35] and similar studies conducted by our group [12], there are no known risks to adolescents enrolled in the experimental or control groups. Any adverse events reported by adolescents, their healthcare teams, or the study nurse will be tracked on a critical incident form and reported to treating oncologists as soon as possible. Site ethics boards and the DSMC will also be contacted as soon as possible after the occurrence of any adverse event. Any major amendments to the protocol that may impact the conduct of the study or participant benefits or

harms will be agreed upon by the trial steering committee, as well as the adolescent with cancer advisory committee, and approved by all site ethics boards before they are instituted. These amendments will also be communicated with study participants as soon as possible by site RAs.

Dissemination and knowledge translation plan

We have and will continue to involve patient, healthcare professional, policy-making, and research stakeholders in all stages of the research process. We will present research findings at international oncology and paediatric conferences and publish in leading journals. Our knowledge translation strategy will also include: a 1-page brochure for distribution to oncology healthcare professionals, a ~3-minute video for adolescents with cancer, which will be posted on websites such as YouTube, media releases (i.e., for newspaper, magazines), posting on partner organization, hospital, and university websites, and supporting adolescents and caregivers in translating results into fact sheets to support these key stakeholders in educating their healthcare professionals about results (i.e., consumer detailing).

List of abbreviations

ANCOVA, analysis of covariance
APEEE, Analytics Platform to Evaluate Effective Engagement
BPI, Brief Pain Inventory
C^{17}, C^{17}: Children's Cancer and Blood Disorders
DSMC, data safety and monitoring committee
HRQL, health-related quality of life
HUI2/3, Health Utility Index Mark 2/3
ICER, Incremental Cost Effectiveness Ratio
NRS, numerical rating scale
OPACC, Ontario Parents Advocating for Children with Cancer
PedsQL, Pediatric Quality of Life Inventory
POGO, Pediatric Oncology Group of Ontario
PROMIS, Patient Reported Outcomes Measurement Information System
QALY, Quality-Adjusted Life Year
RA, research assistant
RCT, randomised controlled trial
REDCap, Research Electronic Data Capture
SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials

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Author contributions

LAJ and JNS conceived of this trial and designed and developed the Pain Squad+ intervention. All authors contributed to the design of the trial from a methodological standpoint. JCV and MM designed the data analyses plans. LAJ drafted the manuscript and all authors refined and approved of it.

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Competing interests

The authors have no competing interests, financial or otherwise, to declare.

Availability of data and material

The datasets used and/or analysed during the current study will be available from the corresponding author on reasonable request, where legally and ethically possible.

Consent for publication

Not applicable.

Ethics approval

Ethics approval for this study has been obtained from the Clinical Trials Ontario (CTO)-Qualified Research Ethics Board.

Figure Legends

Figure 1. Pain Squad+ smartphone application screenshots of the application landing screen (A), a visual analogue slider scale for pain assessment (B), and a portion of the library of pain self-management advice.

Figure 2. Flowchart of *Pain Squad*+ trial protocol

Figure 3. *Pain Squad*+ schedule of enrolment, interventions, and assessments.

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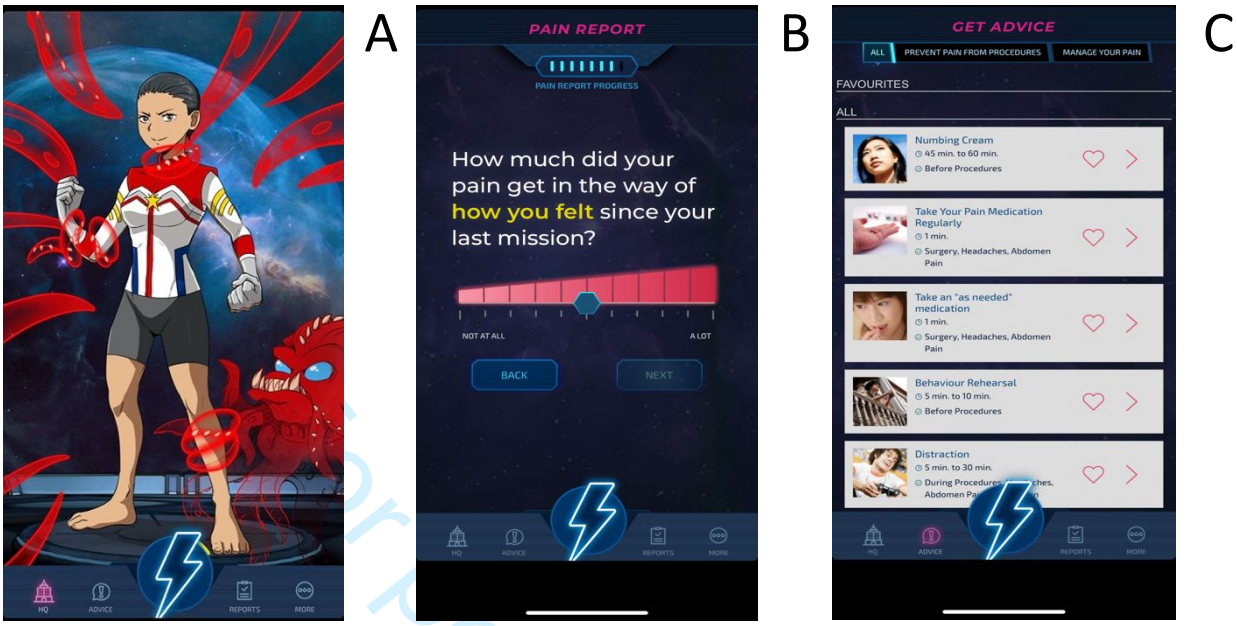

Figure 1. Pain Squad+ smartphone application screenshots of the application landing screen (A), a visual analogue slider scale for pain assessment (B), and a portion of the library of pain self-management advice.

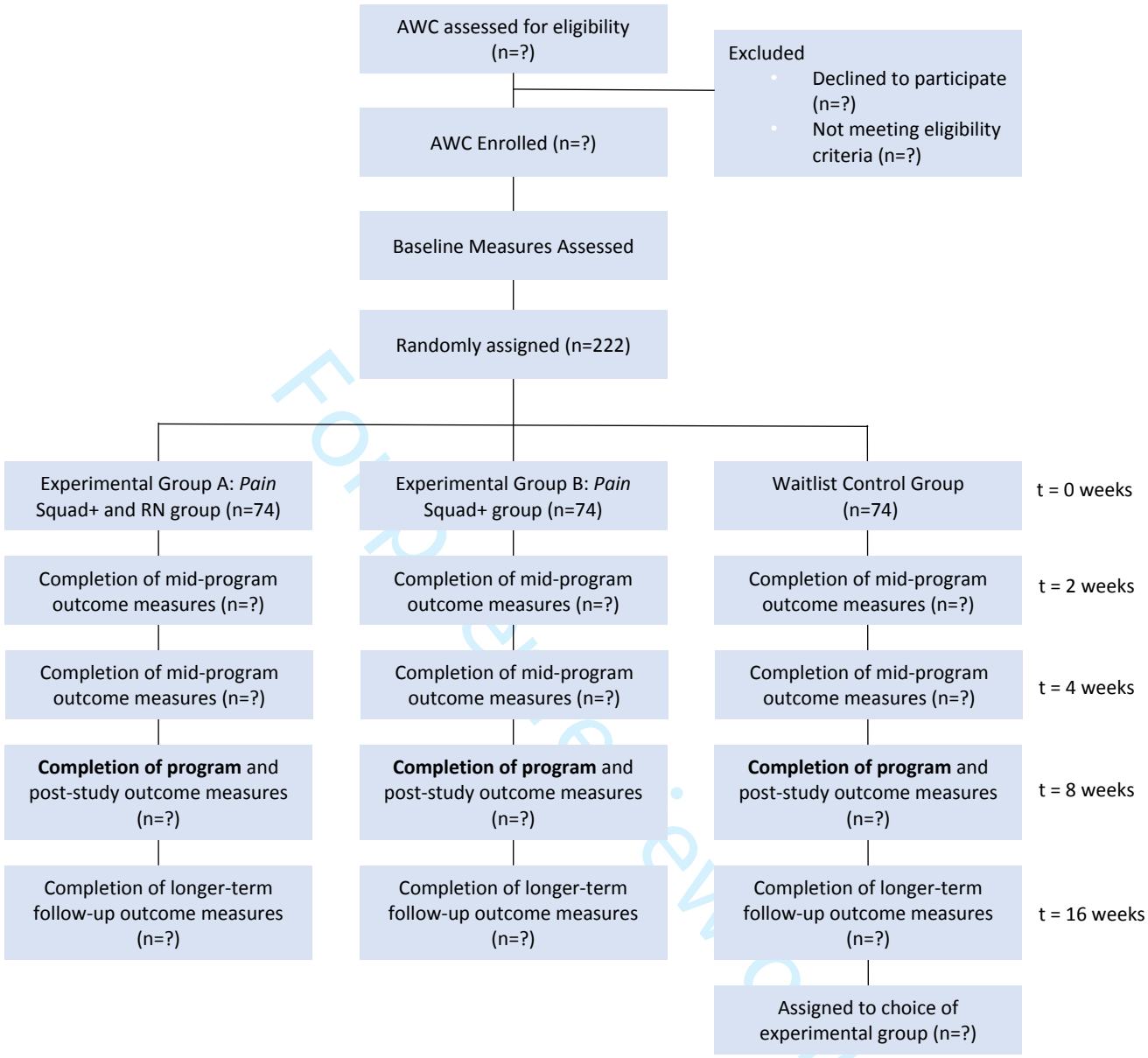

Figure 2. Flowchart of *Pain Squad*+ trial protocol

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT**	$-t_1$	0	t_1 (2 weeks)	t_2 (4 weeks)	t_3 (8 weeks)	t_4 (16 weeks)
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Experimental Group A Standard care + *Pain Squad*+ smartphone app + RN support			←	—	→	
Experimental Group B Standard care + *Pain Squad*+ smartphone app			←	—	→	
Waitlist Control Group Standard care						
ASSESSMENTS:						
Baseline Variables • Adolescent with cancer socio-economic, demographic, pain, and cancer-related characteristics • Adolescent ownership and use of smartphones • Adolescent expectation about treatment effectiveness • Caregiver demographics	X	X				
Health Quality Variables • Pain intensity [BPI] • Pain interference [PROMIS] • Quality of life [PedsQL 4.0] • Pain self-efficacy [Porter's scale])		X	X	X	X	X
Cost Variables • Cost effectiveness and utility [HUI2/3])		X			X	X

Figure 3. *Pain Squad*+ schedule of enrolment, interventions, and assessments.

Table 2. Details of pharmacological, psychological, and physical pain treatment advice provided to adolescents with cancer.

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
PHARMACOLOGICAL:					
Scrolling Page	Numbing Cream	45 - 60 minutes	Before Procedures	Remember to apply a pain numbing cream (topical anesthetic) 45-60 minutes before the procedure if your healthcare team has said it's okay.	*N/A (This advice only has one screen)*
Scrolling Page	Take Your Pain Medications Regularly	1 minute	Surgery, Headaches Abdomen Pain	Make sure you are sticking to the medication schedule your doctor recommends. If taking your medications is difficult, you can speak to your pharmacist about useful options such as setting reminders on a cell phone or using post-it notes. Make sure to talk to your doctor, nurse, or pharmacist if you're having trouble taking your medications, if they are not working or if you're having side effects from them.	*N/A (This advice only has one screen)*
Scrolling Page	Take an "as needed" medication	1 minute	Surgery, Headaches, Abdomen Pain	If your doctor has given you a medication for break-through pain AND it is time to take it, consider taking it now. You can talk to your parents or healthcare team if you're not sure about when and how to take these medications.	*N/A (This advice only has one screen)*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
				Make sure to talk to your doctor, nurse, or pharmacist if you're having trouble taking your medications, if they are not working or if you're having side effects from them.	
PSYCHOLOGICAL:					
Step-by-Step Slider	Behaviour Rehearsal	5-10 minutes	Before Procedures	Behaviour rehearsal helps you to prepare for an event that you think will be stressful before it even happens, like a painful procedure. What you need to do is break the situation into parts that you can imagine.	**Step 1** Rehearse what you are going to do to relax, stay calm, and get through the procedure. **Step 2** Relax your muscles, breathe deeply, stay calm and use positive thoughts like 'I can do this'. **Step 3** Imagine how you will relax during each part of the procedure. **Step 4** When you've made it through the procedure, make sure you have a plan to celebrate your success! You might not be able to cope exactly the way you wanted, but you still made it through!
Scrolling Page	Distraction	5-30 minutes	During Procedures, Headaches, Abdomen Pain, Muscle Pain	By turning your attention to something else, you can block out unpleasant or stressful thoughts. Make sure to choose pleasant things to focus your attention on. You can do things like listen to music, play video games or concentrate on your breathing.	*N/A (This advice only has one screen)*
Drill Down Table	Mental games	5-10 minutes	During Procedures, Headaches, Abdomen Pain, Muscle Pain	Mental games turn your attention away from pain and keep your mind busy with another activity. As a result, your mind isn't available to think about pain.	**Alphabet Game** Think of any category of interest, such as sports, cars, teams, animals, or countries. Try to name as many as you can that start with the letter A. When you're done, move on to the letters B, C, and so on through to Z **Song Lyrics** Try to remember all the words to your favourite song

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
					Count the Tiles Count the number of tiles on the floor or dots on an area of the ceiling
Step-by-Step Slider	Mindfulness	5-30 minutes	Surgeries, Mouth Sores, Muscle Pain, Abdominal Pain, Headaches etc.	Imagery is like daydreaming except you are doing it on purpose. Some people find it easy to use their imagination to distract themselves. Others need more practice.	**Step 1** The audio meditation helps you find a new way to experience discomfort. Use this meditation to explore the thoughts, feelings, or sensations that come with being upset or feeling physical pain. Holding an ice cube in the palm of your hand, follow along with the meditation to explore any feelings of discomfort. Have a towel handy to clean up the melted ice once the meditation is finished. *[Audio File Play Button]*
					Step 2 This audio meditation helps you develop kindness and compassion towards yourself. Use this meditation to acknowledge your physical pain or unpleasant emotions without harshness or judgment. Follow along with the meditation, noticing your breath and recognizing unpleasant sensations as useful signals. *[Audio File Play Button]*
					Step 3 This audio meditation helps you soften towards discomfort. Instead of resisting uncomfortable experiences or distracting yourself when they arise, use this meditation to help you develop an attitude of tenderness towards your suffering. As you follow the meditation, take time to allow your discomfort to come and go. If you become too uncomfortable, bring yourself back to your breath. *[Audio File Play Button]*
					Step 4 This audio meditation helps you connect with joy. Use it when you'd like to take a break or when you're dealing with unwanted thoughts, physical sensations, or emotions. Follow along with the meditation, connecting with the natural rhythm of your breath and exploring a joyful memory. *[Audio File Play Button]*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
					Step 5 This audio meditation helps you connect to the present moment using your sense of sight, sound, touch, taste, and smell. Use this meditation when you want to ground yourself in the here and now or if you are having unwanted thoughts, feeling physical discomfort or uncomfortable emotions. Follow along. *[Audio File Play Button]*
					Step 6 This audio meditation helps you explore and bring comfort to an unwanted thought or an area of physical or emotional discomfort. Use this meditation when you are feeling overwhelmed or experiencing physical discomfort. Follow along focusing with kindness and curiosity on an uncomfortable area of your body. *[Audio File Play Button]*
Step-by-Step Slider	Imagery	5-30 minutes	During Procedures, Headaches, Abdomen Pain, Muscle Pain	Imagery is like daydreaming except you are doing it on purpose. Some people find it easy to use their imagination to distract themselves. Others need more practice.	**Step 1** Imagine being in a pleasant place, maybe on a beach or in a park with your family and friends. This is much more interesting to think about than pain!
					Step 2 This guided audio meditation helps you find a sense of stillness within yourself. Use it to find a place of stillness within your mind and body when you are feeling upset or agitated. Follow along with the meditation, taking time to visualize yourself as grounded and strong, like a mountain.
					Step 3 This audio meditation helps you visualize your pain. When you are struggling with pain, use this meditation to help discover a new way to experience and respond to it. Follow along with the meditation so you can move from resisting and feeling frustrated about your pain to being open and curious and exploring it in detail without judgment. *[Audio File Play Button]*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
Step-by-Step Slider	Mini-relaxation	5 minutes	During Procedures, Headaches, Abdomen Pain, Muscle	Mini-relaxation is a very quick and easy way to relax when you feel stressed or are feeling pain wherever you are.	**Step 1** Take a deep breath in through your nose. Feel your stomach rise as you take in the deep breath. **Step 2** Hold your breath for a few seconds while you count to 5. **Step 3** Roll your shoulders in a circle and then let them drop loose. Think "r-e-l-a-x." **Step 4** Breathe out through your mouth, slow and relaxed, as if you're softly whistling. Repeat steps and feel more relaxed each time.
PHYSICAL:					
Step-by-Step Slider	Doing enjoyable activities	15-20 minutes	Mouth Sores, Headaches, Abdomen Pain, Muscle Pain etc.	Sometimes when you are in pain doing something else, even if it is fun, may be the last thing on your mind. But we know that, over time, doing activities that you enjoy can: Improve your mood, help you feel less tired, help you begin to think more clearly.	**Step 1** Figuring out your enjoyable activities. Everybody has a different idea of what's enjoyable. For instance, you might enjoy things that your friends don't like – and that's ok! Finding enjoyable activities involves setting goals to do something that makes you feel good every day. **Step 2** When choosing your activities, aim for those that: are realistic for you right now, are fun, according to you, are achievable, do not increase your pain levels, do not rely on things that are not easily available to you. For instance, don't pick an activity that requires a car if you don't have access to one. **Step 3** Try an enjoyable activity and see how it works for you!
Scrolling Page	Applying Cold	15-20 minutes	Mouth Sores, Muscle Pain	Cold temperatures can help reduce pain. For instance, the cold sensation from popsicles and ice chips can be really helpful for mouth sores!	*N/A (This advice only has one screen)*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
				Apply a cold pack or other cold things like ice to the area you are feeling pain.	
Scrolling Page	Applying Heat	15-20 minutes	Abdomen Pain, Muscle Pain	Warm temperatures can help reduce pain. For instance, the warm temperature of a hot pack can reduce muscle aches! Apply a hot pack to the area you are feeling pain. Remember not to apply heat to wounds or stitches.	*N/A (This advice only has one screen)*
Step-by-Step Slider	Belly-breathing	5-30 minutes	During Procedures, Headaches, Abdomen Pain, Muscle Pain	Belly breathing is one of the best and easiest ways to relax. It can help you manage pain and also distract you from unpleasant situations.	**Step 1** Lie down, knees bent, place one hand on your chest and one hand just above your belly button. (For now, try this sitting comfortably in your chair. Once you are off the computer. You can try it lying down) **Step 2** Take a deep breath in through your nose, pushing your belly out. Feel your bottom hand, on your belly, move out. The top hand on your chest should stay still. Notice how long your inhaled breath is by counting. When your belly is all the way out, pause for a moment... **Step 3** …now breathe out slowly through puckered lips, to the same count you used to breathe in, letting your belly come down until it is flat. **Step 4** Repeat slowly a few times. Notice your body beginning to feel relaxed with each breath out. After you have practiced this exercise a few times, you can make the count longer to get an even deeper, more relaxing breath.

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
Step-by-Step Slider	Mental Relaxation	10 minutes	Surgeries, Headaches, Abdomen Pain, Muscle Pain	Mental relaxation is an effective way to help you cope with pain and stress.	**Step 1** Find a comfortable, quiet place to sit. **Step 2** When you hit play, an audio recording will start. The audio recording will lead you through the relaxation exercise. *[Audio File/Play Button]*
Step-by-Step Slider	Muscle Relaxation	15 minutes	Headaches, Abdomen Pain, Muscle Pain	Muscle relaxation is a way to relieve muscle tension and pain by tensing and then relaxing different groups of muscles in your body.	**Step 1** Find a comfortable, quiet place to sit. **Step 2** When you hit play, an audio recording will start. The audio recording will lead you through the relaxation exercise. *[Audio File/Play Button]*
Scrolling Page	Gentle exercise	10-40 minutes	Muscle Pain, Headache, Abdominal Pain, Surgeries	Try gentle exercising by going for a walk. Research shows that physical activity can help you manage symptoms like pain. It's important to talk to your health care provider and maybe a physiotherapist before you start adding physical activity to your routine. Some types of exercise may be risky depending on the type of cancer you have. Remember, stop right away if you experience sudden intense pain.	*N/A (This advice only has one screen)*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or States
Drill Down Table	Stretching (yoga)	10-40 minutes	Muscle Pain, Headache, Abdominal Pain, Surgeries	Yoga aims to restore the balance between one's body, mind, and spirit through a series of gentle exercises and breathing techniques. There are lots of poses you can do in yoga.	**Mountain (tadasana) pose** Stand with feet hip-width apart and your weight evenly balanced between them. Pull up through the top of your forehead and try to make your spine feel longer. Tilt your tailbone (bottom of your spine) under so it points towards the ground and relax your shoulders away from the ears. Breathe in and out smoothly. Mentally scan your body, releasing any tension. Relax your neck, face, jaw, and tongue. Tell yourself a positive phrase like "I am strong and brave". *[Image from TTC Website]* **Archer pose** While standing, step forward with your left leg so your legs are about 2.5 feet apart. Turn your right foot out at a 45-degree angle. Raise your left arm straight out in front, parallel to the ground, with your hand in a fist. Pull your right arm back as if it's pulling back on a bowstring. Both wrists form a straight line with your shoulders. Bend your left knee and squeeze your thighs together. Look at your left fist and feel like a strong warrior. *[Image from TTC Website]* **Tree pose** Stand upright and shift your weight to 1 foot. When you feel stable, place your other foot either at your ankle or inner thigh. Focus on a spot in front of you to help you balance. Breathe deeply and raise your arms and put your hands together in front of your chest. Hold for a few minutes and then switch legs. [*Image from TTC Website]*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or States
					Ego pose Sitting at the edge of the bed, raise your arms overhead in a V shape. Stretch your thumbs to the sky and curl your fingers onto the palms of your hand. Breathe in and out slowly. Hold for as long as you can, up to a minute. *[Image from TTC Website]*
					Life nerve stretch Sitting up, flex both feet back towards the head. Keeping a straight back, reach as far down your legs as you can – it might be your shins or your toes, or somewhere in between. Breathe long slow breaths. Continue for 1 minute. *[Image from TTC Website]*
					Bridge pose (setu bandhasana) In this video, you'll learn how to come into the bridge pose. Follow the written instructions below, or watch the video for a short demonstration. [*video file play button*] Starting out on your back, bend your knees so your heels are flat and firm on the mat. Place your arms by your side. Try to bring your legs as close as you can to your buttocks, so you can tickle the back of your feet with your fingertips. Using your hands as a support, inhale as you lift your hips up toward the ceiling, as high as you can comfortably. If you feel comfortable here, bring your arms underneath your back and interlace your fingers. Make sure to keep your hands on the mat. Lift your hips as high as you can comfortably and hold for 5 breaths. Tip your chin toward the ceiling to protect your cervical (upper) spine. When you are ready to come down, release your arms first and then use them as a support to slowly lower your hips down to the mat, inch by inch.

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or States
					Baby cobra pose (bhujangasana) In this video, you'll learn how to come into the baby cobra pose. Follow the written instructions below, or watch the video for a quick demonstration. [*video file play button*] To start off, lie down on your belly, with your arms by your side and your forehead touching the mat. Bring your arms in line with your ribs, with your palms facing the mat and your elbows in the air. Pushing down the tops of your feet, lift your kneecaps off the mat and activate your legs as you inhale. As you exhale, slowly peel your forehead and chest off the mat. There should be no weight on your palms as they should rise with your chest to a height of about 1 inch off the mat. Hold this position for 5 breaths. Maintain space between your shoulders and your ears, draw the shoulder blades back and down – this will also help open your chest. There should be no pinching in your lower back – think of a long spine! When you are ready to come down, inhale and as you exhale, slowly lower your chest back to the mat. Return to your original posture by lowering your arms back to your sides
					Downward dog (adho mukha) In this video, you'll learn how to come into the downward facing dog pose. Follow the written instructions below, or watch the video for a demonstration. [*video file play button*] Start off in the table pose on all fours, standing on your hands and knees. As you inhale, curl your toes down to the floor for support and lift your knees off the ground, extending your legs as you push your hips up, towards the ceiling, and back towards the back wall. It is ok if your heels do not fully touch the mat and to have a

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or States
					slight bend in your knees if you cannot straighten them. Direct your focus toward fully extending your shoulders, keeping your shoulder blades down and in line with your spine, and pressing your hands and toes into the mat. However, try to keep your neck relaxed and maintain space between your ears and your shoulders. Hold this pose for 5 breaths. Tips: Try to draw your belly button in and bring your thigh bones toward the back wall. If your legs are tight, "walk them out" by bending one knee while straightening the other, in time with your breaths as you hold the pose. Child's pose: If the downward facing dog pose becomes difficult to hold, bring your knees back to the mat, returning to the table pose, and sit back onto your heels with your toes uncurled. Allow your head to come down to the mat, with your arms relaxed in front of you. Focus on allowing your lower back to sink into your heels.
					Reclined twist In this video, you'll learn how to come into the reclined twist pose. Follow the written instructions below, or watch the video for a full demonstration. [*video file play button*] Start on your back, with your knees bent and the soles of your feet on the mat, inhale. As you exhale, draw your knees towards your chest, picking your feet up off the mat. Extend your arms straight out to your sides, like an airplane and inhale. As you exhale, let both of your knees fall toward your right side. If your knee cannot fall all the way to the ground, use your right arm to support your top knee. Hold this position in a relaxed way for 5 breaths. Switch sides, bringing your knees to the left, and hold that position for 5 breaths. Modifications to pose: place a pillow between your legs to provide support as you twist. This will also help

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
					if you find your shoulder is lifting off of the mat during the posture. For a deeper stretch, try crossing the legs, or straightening the top leg.
					Side plank (vasisthasana) In this video, you'll learn how to come into the side plank pose. Follow the written instructions below, or watch the video for a full demonstration. [*video file play button*] Starting in table pose, on all fours, extend your legs straight back, resting on your palms and toes (a.k.a the plank pose). Shift your left palm towards the center of the mat and shift your weight onto your right arm. Slowly shift your hips toward your right side, lifting your left palm off of the mat and extending it toward the ceiling as you turn your body to the side. Hold this pose for 5 breaths. Shift back into the plank pose and return to the table pose. Modifications to pose: You may choose to keep your legs stacked together in this pose, but you can also separate them if you choose. As a variation, while in the pose, bring your top leg in front of you, as though you were taking a step, keeping the top leg bent at the knee and your bottom leg straight. For a more challenging variation, while in the pose, lift your top leg straight up toward the ceiling and hold it there for as long as you can.
					Reclined bound angle pose (supta baddha konasana) In this video, you'll learn how to come into the reclined bound angle pose. Follow the written instructions below, or watch the video for a full demonstration. [*video file play button*] Starting on your back, with your knees bent and the soles of your feet on the mat, inhale through your nose.

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
					As you exhale, open your knees to either side of the mat, like a book, bringing your heels together. As you continue to breathe, allow your knees to fall closer to the mat with every exhale. When you have reached your comfort limit, hold this position for 5 breaths. Modifications to pose: As a variation, support your body by placing one hand on your chest and another on your belly button. You may also place both of your arms up and over your head or around your head. For the restorative variation of this posture, place a pillow under your head and back to support your spine as well as pillows/props (e.g. yoga block, rolled towel) under your knees on each side. When propping the spine and upper back, ensure that your lower back stays in a relatively neutral position.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Protocol face page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	NCT03632343
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	All pages
Funding	4	Sources and types of financial, material, and other support	Section: Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Protocol face page
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Section: Trial steering and data safety and monitoring committees (DSMC).
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Section: Introduction
	6b	Explanation for choice of comparators	n/a
Objectives	7	Specific objectives or hypotheses	Section: Introduction
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Section: Trial design

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Section: Study setting
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Section: Eligibility criteria and Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Section: Interventions and Supplementary Appendix A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Sections: **The Pain Squad+ smartphone-based real-time pain treatment application and Interventions**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Section: Interventions
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Section: Outcomes
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Section: Participant timeline and Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Section: Sample size
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Section: Recruitment
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Section: Allocation and blinding

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Section: Allocation and blinding
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Section: Allocation and blinding
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Section: Allocation and blinding
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Section: Allocation and blinding
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Section: Data collection methods
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Section: Data collection methods
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Section: Data management and confidentiality
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Section: Data analyses methods
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Section: Data analyses methods
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Section: Data analyses methods
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Section: Trial steering and data safety and monitoring committees (DSMC)

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Sections: Trial steering and data safety and monitoring committees (DSMC) and Safety appraisal and protocol amendment reporting
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Sections: Trial steering and data safety and monitoring committees (DSMC) and Safety appraisal and protocol amendment reporting
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Sections: Trial steering and data safety and monitoring committees (DSMC) and Safety appraisal and protocol amendment reporting
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Section: Ethics approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Sections: Safety appraisal and protocol amendment reporting

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Section: Data collection methods
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Section: Data management and confidentiality
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Section: Competing interests
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Section: Availability of data and material
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Section: Dissemination and knowledge translation plan
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Section: Availability of data and material
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available from study team by request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The Pain Squad+ Smartphone App to Support Real-Time Pain Treatment for Adolescents with Cancer: Protocol for a Randomised Controlled Trial

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The Pain Squad+ Smartphone App to Support Real-Time Pain Treatment for Adolescents with Cancer: Protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction. Pain negatively affects the health-related quality of life (HRQL) of adolescents with cancer. The Pain Squad+ smartphone-based app, has been developed to provide adolescents with real-time pain self-management support. The app uses a validated pain assessment and personalised pain treatment advice with centralised decision support via a registered nurse to enable real-time pain treatment in all settings. The algorithm informing pain treatment advice is evidence-based and expert-vetted. This trial will longitudinally evaluate the impact of Pain Squad+, with or without the addition of nurse support, on adolescent health and cost outcomes.

Methods and analysis. This will be a pragmatic, multi-centre, waitlist controlled, 3-arm parallel-group superiority randomised trial with 1:1:1 allocation enrolling 74 adolescents with cancer per arm from 9 cancer centres. Participants will be 12-18 years, English-speaking, and with ≥3/10 pain. Exclusion criteria are significant co-morbidities, end-of-life status, or enrollment in a concurrent pain study. The primary aim is to determine the effect of Pain Squad+, with and without nurse support, on pain intensity in adolescents with cancer, when compared to a waitlist control group. The secondary aims are to determine the immediate and sustained effect over time of using Pain Squad+, with and without nurse support, as per prospective outcome measurements of pain interference, HRQL, pain self-efficacy, and cost. Linear mixed models with baseline scores as a covariate will be used. Qualitative interviews with adolescents from all trial arms will be conducted and analysed.

Ethics and dissemination. This trial is approved by the Hospital for Sick Children Research Ethics Board. Results will provide data to guide adolescents with cancer and healthcare teams in treating pain. Dissemination will occur through partnerships with stakeholder groups, scientific meetings, publications, mass media releases, and consumer detailing.

Trial registration. NCT03632343 *(ClinicalTrials.gov)*

Strengths and limitations of this study

- This study is a large trial evaluating an innovative method to address pain in adolescents with cancer, the most common and distressing symptom experienced by this group.
- This pragmatic design of the trial means that our approach to study eligibility criteria, intervention intensity, and participant adherence will determine intervention effect under real-world conditions.
- Former adolescent cancer patients are core members of this study team and have, and will continue to, guide and support study design, study conduct and results dissemination.
- Adolescents with cancer, their caregivers, and the study nurse will not be blinded to participant group as this is prohibited by the nature of the intervention.

Keywords

Pediatrics, cancer, pain, symptom treatment, smartphone app, supportive care, protocol, randomised controlled trial

INTRODUCTION

Adolescents with cancer report pain as the most commonly occurring and distressing cancer-related symptom experienced [1-3]. Pain negatively impacts health-related quality of life (HRQL) [4-6] represents a significant cost burden to patients, families and the health system [7] and is a major reason for cancer-related emergency health service use in adult patients [8-11]. However, the successful identification of pain, including in and outside of the hospital setting, does not equate to its adequate treatment and pain is often undertreated in adolescents [12-15].

Due to improvements in therapeutic regimes, supportive care, and changes in the health system, adolescents with cancer now spend less time in hospital and more time at home [16-18]. Thus, adolescents and their families are increasingly responsible for managing cancer-associated pain in environments with less supervision from healthcare professionals [13,19]. Adolescents are more vulnerable in these environments as they often lack the knowledge, skills, and self-efficacy needed to adequately react to symptoms and may ignore or inappropriately accept changes in pain [13,16,20,21]. Digital health technologies are widely used by adolescents [22] and can empower adolescents with cancer to engage in remote and real-time pain treatment in all of their natural environments (e.g., hospital, home, school). Studies have indicated that digital real-time symptom monitoring and treatment improves HRQL and decreases emergency service use and hospitalisation rates in adults with cancer [23,24], but no such research has been conducted with adolescents.

The Pain Squad+ smartphone-based real-time pain treatment application

Using a phased- and user-centred approach, our team has developed a smartphone app, called Pain Squad+, capable of providing adolescents with real-time pain treatment support (**Figure 1**) [25-31]. Pain Squad+ uses a truncated 8-item version of a valid and reliable automated

questionnaire to assess adolescent pain (severity, interference, location and capacity to self-manage pain) [12]. When pain is reported using Pain Squad+, self-management advice is presented to users in real-time according to a vetted and standardised clinical care algorithm [25,32]. Advice is based on a library of pharmacological (e.g., medication adherence reminders), psychological (e.g., distraction techniques), and physical (e.g., yoga instruction) advice that aligns with typical recommendations provided to adolescents by their healthcare teams [33]. Three consecutive moderate to severe reports of pain intensity (i.e., ≥3/10 [34]) trigger an email to be sent to a paediatric oncology-trained registered nurse. The nurse then contacts the adolescent and/or their healthcare team to discuss the case and initiate healthcare professional-driven intervention, which may be outside of the scope of the self-management algorithm (e.g., adjusting a prescribed medication regime). To encourage engagement with Pain Squad+, the app is "gamified" with users playing the role of superheroes who receive rewards for adherence to pain assessment and treatment recommendation completion [19].

The most recently completed phase of Pain Squad+ testing was a 1-group, baseline-poststudy pilot that demonstrated the feasibility (i.e., intervention fidelity, outcome measure completion, adherence, acceptability) of evaluating the app in a randomised controlled trial (RCT) , as well as small to moderate effect sizes (Cohen's d: 0.23-0.67) [35]. This protocol details the methods to be used in the next phase of Pain Squad+ testing: a RCT aimed at longitudinally evaluating the impact of Pain Squad+, with or without the addition of nurse support, on adolescent health and cost outcomes.

Specific objectives

Primary objective and hypothesis. To examine the effect of 4 weeks of Pain Squad+ app use, with and without nurse support, on pain intensity in adolescents with cancer, when compared to a

waitlist control group. We hypothesise that 4 weeks of Pain Squad+ use, with or without nurse support, will result in improved pain intensity scores, compared to a waitlist control group.

Secondary objectives and hypotheses as appropriate.

Objective related to the effect of Pain Squad+ on health outcomes overtime.

To examine the effect of each of 2, 4, and 8 weeks of Pain Squad+ app use, with and without nurse support, on each of pain intensity, pain interference, HRQL, and pain management self-efficacy in adolescents with cancer, when compared to a waitlist control group. We hypothesise that Pain Squad+ use, with or without nurse support, for 2, 4, and 8 weeks will result in improved pain intensity, pain interference, HRQL, and self-efficacy scores, compared to a waitlist control group.

Objective related to maintenance of potential therapeutic gains from Pain Squad+ use.

- To examine the effect of the Pain Squad+ app, with and without nurse support, on each of pain intensity, pain interference, HRQL, and pain management self-efficacy in adolescents with cancer compared to a waitlist control group, when assessed after intervention use has ceased (i.e., 8 weeks post-use of the intervention). We hypothesise that improvements in pain intensity, pain interference, HRQL, and self-efficacy scores related Pain Squad+ use, with or without nurse support, will be sustained when assessed after intervention use has ceased.

Objective related to the effect of Pain Squad+ on health system and societal costs.

- To examine the cost-effectiveness and cost utility of the Pain Squad+ app, with and without nurse support as compared to standard care from both a health system and societal perspective.

Objective related to treatment arm satisfaction.

- To explore adolescent with cancer-rated acceptability (including engagement with pain treatment strategies) of the Pain Squad+ app and the study following participation.

METHODS

Trial design

This will be a pragmatic, multi-centre, waitlist group-controlled, investigator and analyst-blinded, 3-arm parallel-group superiority RCT with 1:1:1 allocation (**Figure 2**). Randomisation will be stratified by recruitment site to account for differences in care across centres [36] with block sizes of 6 and 9 within each stratum. Reporting of this protocol is in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [37] (See Additional Files for SPIRIT checklist).

Study setting

Adolescent and caregiver recruitment will occur across 9 Canadian paediatric oncology programs that treat a diversity of paediatric cancers (often based on the same standardised protocols). All of these programs are located in tertiary care centres that serve paediatric populations with considerable racial, ethnic, and socioeconomic diversity. The lead study site is the Hospital for Sick Children (SickKids).

Eligibility criteria

The eligibility criteria for this study, with the rationale for each criterion and the sources of associated data collection, are shown in **Table 1**. No restrictions will be placed on analgesia use or hospitalisations, however data related to medication and other pain treatment strategy use, as well as in-patient stays (i.e., reason, duration, pain-related treatment received), will be collected during the study.

Table 1. Pain Squad+ RCT participation eligibility criteria

Criterion	Rationale	Source
Inclusion criteria		
12-18 years of age	Study restricted to AWC	Medical chart
Diagnosed with cancer (all disease types) and receiving cancer-directed therapy	Study restricted to AWC	Medical chart
English-speaking and reading	Pain Squad+ app currently available in English only	AWC self-report
Average pain score of ≥3/10 over the preceding week	Value describes moderate-severe pain in adolescents [34] and RCTs of similar interventions in adults with cancer pain [38,39]. In our pilot, 75% of AWC reported average pain of ≥3/10 in the week prior to enrollment.	AWC self-report measured using an 11-point numerical rating scale (NRS)
English-speaking and reading caregiver who is willing and able to complete outcome measures related to healthcare encounters	English-speaking caregivers required to complete outcome measure related healthcare utilisation and associated costs.	AWC or caregiver self-report
Exclusion criteria		
Significant cognitive impairments or co-morbid illnesses	Would limit interaction with Pain Squad+ or outcome measure assessment	Healthcare team report
Currently participating in other pain treatment studies	Concomitant intervention represents a threat to internal validity	AWC or caregiver self-report
Not expected to survive past 16 weeks	Terminal data collection point is at 16 weeks post-randomisation	Healthcare team report

Interventions

Experimental Group A. The deployment of the Pain Squad+ app to adolescent's personal phones will be done through the Apple App Store and Google Play store. The research team will loan an iPhone or Android phone to those without a smartphone. All adolescents will be trained to use Pain Squad+ using a standardised procedure. Three repeated audible smartphone alerts

over a 30-minute window will signal each adolescent to complete the 8-item pain assessment using Pain Squad+ every morning and evening for 8 weeks. The timing of morning and evening pain assessments will be individualised according to participant's daily and weekly schedules. An automated 30-minute window within which each assessment must be completed will be set, or the assessment will be registered as "missed". Adolescents will also have the option of completing *ad hoc* pain assessments anytime between the automated alert times. Algorithm-driven pain self-management advice will be issued in response to pain, providing real-time decision support (**Supplementary Appendix A**). One hour after a recommendation is made, the app will alert adolescents to complete a pain reassessment and additional advice will be offered as appropriate. All pain assessment and treatment advice data logged will be encrypted and wirelessly transferred to a secure server at SickKids for storage. Email alerts related to 3 consecutive reports of pain >3/10 will be sent to the study nurse who will log into the Analytics Platform to Evaluate Effective Engagement (APEEE) platform [38] to review the adolescent's pain report history. The nurse may liaise with the adolescent's healthcare team regarding the case and will contact the adolescent within 12 hours of receiving the alert, including on weekends. The time of nurse contact and the details of the pain treatment conversation will be recorded. A research coordinator will provide telephone-based technical assistance (weekdays 0900 – 1700 EST) to participants if required.

Experimental Group B. Adolescents randomised to this group will complete pain assessments and receive the same smartphone-based algorithm-driven pain treatment advice as in Experimental Group A but will not receive nurse-initiated pain support.

Waitlist Control Group. Adolescents randomised to this group will be waitlisted to receive the Experimental Group B condition within 1 month of completing all post-study outcome measures.

All study groups. Regardless of study group, adolescents will continue to receive standard medical care from their treating healthcare teams. All groups will be reminded to pursue help using the usual channels (calling oncology clinic, 'on-call' team, or 911) should any medical emergencies arise during the study.

Outcomes

All outcome measures have demonstrated validity and reliability in 12-18-year-olds with cancer and will be assessed according to the schedule shown in **Figure 3**. A 1-week recall period will be used for all health-related outcomes.

Primary outcome. The primary outcome is average pain intensity, measured using Brief Pain Inventory (BPI). The BPI assesses current pain and 'worst', 'least', and 'average' pain in the preceding week using an 11-point numerical rating scale (NRS) with verbal anchors 'no pain' at 0 and 'pain as bad as you can imagine' at 10 [39,40]. Item scores may also be averaged to give a Pain Intensity Summary Score [41].

Secondary outcomes.

(a) ***Pain interference*** will be assessed using the Patient Reported Outcomes Measurement Information System (PROMIS) Pediatric Pain Interference Short-form Scale. The PROMIS instrument is a valid 8-item scale assessing the impact of pain on function [42,43]. Higher scores represent greater interference with function.

(b) ***HRQL*** will be assessed using the Pediatric Quality of Life Inventory (PedsQL) 4.0. The PedsQL 4.0 is a valid and reliable 23-item instrument not specific to pain [2,44]. It is comprised of 4 subscales (physical functioning, emotional functioning, social functioning and school functioning), which are summed to provide a total score. Higher scores represent better quality of life.

(c) ***Pain management self-efficacy*** will be assessed with Porter's scale which assesses self-efficacy for managing pain, symptoms, and function in cancer patients [45,46]. This 16-item scale includes a valid and reliable 5-item subscale assessing cancer pain management self-efficacy with higher scores indicating more certainty and is adapted from a scale that has been successfully administered to adolescents [21,47].

(d) ***Cost effectiveness and cost utility*** analyses will determine the incremental costs (or savings) of the Pain Squad+ app, with and without nurse support, when compared to a waitlist control group in reducing pain over the study. Quality-adjusted life years (QALYs) will be calculated using data from the valid and reliable Health Utility Index Mark 2/3 (HUI2/3) [48] completed by adolescents. Direct healthcare costs will include the intervention costs as well as costs for health service utilization during the trial. Family out-of-pocket expenses, indirect costs due to lost productivity, and health service use will be ascertained using standardized customized data collection forms completed by caregiver report.

(e) ***Satisfaction with treatment*** will be assessed using qualitative interviews with a subset of participating adolescents. These interviews will specifically be used to explore the perceptions of adolescents with cancer as they relate to the acceptability (including engagement with pain treatment strategies) of Pain Squad+, with and without nurse support, or the waitlist control condition.

Socio-demographic- and disease-related data baseline. Adolescent age, sex, ethnicity, school grade, diagnosis, stage/risk, relapse-status, treatment-type, date of diagnosis, co-morbid conditions and medications, pain history; as well as caregiver age, sex, ethnicity, educational attainment, and financial characteristics; adolescent ownership and use of smartphones; and adolescent expectation about treatment effectiveness (assessed using a valid NRS scale with

verbal anchors ‘don’t think it will help at all’ at 0 and ‘think it will help a lot’ at 10).

Participant timeline

An 8-week treatment period will be used (**Figure 3**). The primary outcome, and health-related secondary outcomes will be assessed at baseline and 2, 4, 8, and 16 weeks post-randomisation. Cost-related outcomes will be assessed at baseline, 8, and 16 weeks post-randomisation. The primary endpoint will be at 4 weeks post-randomisation selected as our primary endpoint because, based on our pilot, it is feasible to administer the intervention for this period and significant pain improvements are observed at 4-weeks [35]. To examine whether duration of Pain Squad+ use changes the magnitude or direction of outcome changes, adolescents in the experimental groups will continue to use the app until 8 weeks post-randomisation and outcomes will be assessed at 2 and 8 weeks (specifically examining the effect of shortening or extending intervention use on health quality). A longer-term follow-up (16 weeks) will be used to examine the maintenance of any Pain Squad+ therapeutic gains after discontinuation of the intervention. Qualitative interviews will be conducted at study completion or withdrawal.

Sample size

The sample size is calculated based on detecting a difference of 1.1 points between any two treatment groups in the primary outcome, average pain intensity reported on the BPI, at 4 weeks post-randomisation. This difference in pain intensity represents one of minimal clinical significance (the smallest difference that patients perceive as beneficial) for pain intensity improvement on a 0-10 scale in adolescents [49]. Our pilot study showed that the effect size for a 1.1-point change in pain intensity in adolescents following Pain Squad+ was 0.52 [35]. We have used a conservative approach which accounts for the 1-group design of our pilot and have powered this RCT to detect a primary outcome effect size of 0.5. Using a sample size calculation

for analysis of covariance (ANCOVA) models and controlling for baseline pain intensity [50], sample sizes of 63 per group, or 189 in total, will be required to achieve 80% power to detect an effect size of 0.5 between any two treatment groups. This calculation assumes an overall Type I error set at 0.05 allowing for Bonferroni-corrected pairwise comparisons of treatment arms, and a conservative correlation between baseline and follow-up measurements of 0.5. To account for the 5% drop out and 10% loss to follow-up rates observed in the pilot study [35], we will recruit 222 (i.e., 189/0.85) adolescents into the study, or 74 per group.

Recruitment

Each site research assistant (RA) will coordinate with the clinic healthcare team to determine eligibility. Identified eligible potential participants will be recruited via telephone call (following a mailed or emailed study information letter) or in-person at the hospital. Recruitment will begin in November 2019 and is projected to end April 2022.

Allocation and blinding

A centrally controlled, online randomisation service will be used to assign adolescent to each study group using a 1:1:1 allocation model. When an adolescent is ready to be randomised, the lead site RA will enter a unique identification number and information about the stratification variable (recruitment site) into the online program. Group allocation will be assigned with block sizes of 6 and 9 within each stratum. The RA, who has no role in allocation sequence generation, will then inform the adolescent of their group assignment and instruct them on the procedures to be followed. The investigators, including data analysts, will be blind to group allocation. Treatment allocation may be unblinded only by the principal investigators when knowledge of the actual treatment is essential for further treatment of the patient [51], as determined by the adolescent's treating oncologist.

Data collection methods

Pre-randomisation procedures. Eligible adolescents who are hospital inpatients or have a scheduled clinic appointment during the recruitment period will be invited to participate. Site RAs will obtain informed consent from adolescents and one of their primary caregivers. The research coordinator will track the number of eligible adolescents approached and reasons for refusal on an investigator-developed form. The lead site RA will obtain baseline data on adolescents (socio-demographic- and disease-related characteristics) from their medical records and administer online pre-intervention measures on the secure password-protected Research Electronic Data Capture (REDCap) site.

Post-randomisation procedures. At 2, 4, 8, and 16 weeks post-randomisation, the lead site RA will contact adolescents and caregivers up to three times by text message, email and/or telephone and ask them to complete all outcome measures. To do so, participants will log into REDCap using an Internet-enabled device and their unique identifier. Outcome measure data will be time-stamped by REDCap when entered and participants will be encouraged to complete measures immediately after contact with the RA. The RA will provide telephone troubleshooting in the case of REDCap or questionnaire problems. Adolescents will receive a gift certificate for each outcome assessment completed in recognition of their time and effort. Loaned phones will be returned. All data will be exported from REDCap to SAS Statistics [52] on the secure server at SickKids for analysis. Qualitative interviews will be conducted with a subset of adolescents from each trial arm. Adolescents who vary across age, sex, diagnosis, and study engagement will be recruited. Interviews will be conducted until data saturation (i.e., no new data generated in an interview). We anticipate conducting a total of 45 interviews. A semi-structured interview guide that is based on the guide used in our pilot [25-31] and has been refined by former adolescent

cancer patients will be used. Interviews will be audio-recorded and may be conducted in-person or over the telephone. Field notes will be taken by the interviewer.

Data management and confidentiality

All outcome data will be collected online using REDCap and the associated database will be regularly backed up by SickKids. All data files (including back-ups) will be kept in a secured environment in Canada and are available for recovery. The secure digital platform APEEE will be used to collect adolescent-entered pain assessment and treatment data, as well as data related to app engagement, for each of the intervention groups. Data will be accessible only by the study team and staff. Any hardcopy documentation (e.g., consent forms) will be stored in locked cabinets in locked offices at study sites, separate from the stored data. All staff will be provided with training on the use of REDCap and APEEE and maintaining participant confidentiality.

Data analyses methods

Health outcome analyses. Pain intensity, pain interference, HRQL, and self-efficacy data will be analyzed using an intent-to-treat approach [53]. Background variable data collected at baseline will be described using measures of central tendency and variance. If outcome data meet the requirements for parametric statistics (e.g., approximate normality, linear distribution), linear mixed models will be used to assess the effects of the intervention on primary and secondary outcomes with baseline scores used as covariates. Regarding our HRQL outcome, as with our pilot, we will separately analyze the physical, emotional, social and school subscales of the PedsQL, as well as the total scale score. To explore the effects of demographic, disease-related variables, and pain treatment strategies used on outcomes, separate linear mixed models with these variables as covariates will be used. A significance level of 0.05 will be used for all outcomes (with adjustment made for serial analyses).

Economic analyses. Cost effectiveness and cost utility analyses will be conducted using both a health system and societal perspective. Cost effectiveness and cost utility will be expressed as incremental cost effectiveness ratios (ICERs), calculated by dividing the incremental costs between treatment arms by the incremental difference in average pain intensity or the incremental change in utility scores, measured by the HUI2/3. Multiple ICERS will be calculated comparing each of the three study groups in a pairwise fashion for both the cost effectiveness and cost utility analyses. Deterministic and probabilistic sensitivity analysis will be performed to evaluate the robustness of the results. A 95% confidence interval for incremental costs, incremental effects, and the ICER will be calculated from study data.

Qualitative interview analyses. Audio-recorded interviews will be transcribed verbatim. Transcribed data will be managed using NVivo 12.0 software (QRS International). Data analysis will occur shortly after each interview is conducted so that identified issues can be used to inform subsequent interview content. Data will be read several times by the study team for overall understanding and to identify data codes. Data will then be coded using a line-by-line approach according to study objective. Codes will be grouped into categories based on between-code relationships. Category development will occur until all data can be classified under the existing categories. Categories will then be grouped into themes. Field notes and relevant sociodemographic and disease characteristics will be integrated into the analysis process to illustrate or clarify emerging categories and themes.

Patient and public involvement statement

Adolescents with cancer have been directly and actively involved in all stages of the development and evaluation of the Pain Squad+ app, including determining the feasibility of this study, evaluating any potential burden on adolescent participants, and in the development of this

research protocol. An adolescent with cancer advisory committee has been established to guide trial conduct and results interpretation and dissemination from a patient perspective and will report to the principal investigators. This advisory committee will meet regularly with the lead investigators to ensure the trial is guided by the priorities and experiences of adolescents with cancer.

ETHICS AND DISSEMINATION

Trial steering and data safety and monitoring committees (DSMC)

The trial steering committee consists of the lead study team. Virtual progress meetings with all steering committee members will be routinely collected to ensure the smooth running of the study. A DSMC guided by a prepared charter of roles and responsibilities (available from corresponding author) and consisting of a statistical expert, a paediatric oncology nurse scientist, and a paediatric anesthesiologist who are independent of the research team has been established. The DSMC will meet biannually to review recruitment, accumulating study data and adverse events, and will provide guidance to the study team regarding any needed action.

Safety appraisal and protocol amendment reporting

Based on our pilot [35] and similar studies conducted by our group [12], there are no known risks to adolescents enrolled in the experimental or control groups. Any adverse events reported by adolescents, their healthcare teams, or the study nurse will be tracked on a critical incident form and reported to treating oncologists as soon as possible. Site ethics boards and the DSMC will also be contacted as soon as possible after the occurrence of any adverse event. Any major amendments to the protocol that may impact the conduct of the study or participant benefits or harms will be agreed upon by the trial steering committee, as well as the adolescent with cancer

advisory committee, and approved by all site ethics boards before they are instituted. These amendments will also be communicated with study participants as soon as possible by site RAs.

Dissemination and knowledge translation plan

We have and will continue to involve patient, healthcare professional, policy-making, and research stakeholders in all stages of the research process. We will present research findings at international oncology and paediatric conferences and publish in leading journals. Our knowledge translation strategy will also include: a 1-page brochure for distribution to oncology healthcare professionals, a ~3-minute video for adolescents with cancer, which will be posted on websites such as YouTube, media releases (i.e., for newspaper, magazines), posting on partner organization, hospital, and university websites, and supporting adolescents and caregivers in translating results into fact sheets to support these key stakeholders in educating their healthcare professionals about results (i.e., consumer detailing).

List of abbreviations

ANCOVA, analysis of covariance
APEEE, Analytics Platform to Evaluate Effective Engagement
BPI, Brief Pain Inventory
C^{17}, C^{17}: Children's Cancer and Blood Disorders
DSMC, data safety and monitoring committee
HRQL, health-related quality of life
HUI2/3, Health Utility Index Mark 2/3
ICER, Incremental Cost Effectiveness Ratio
NRS, numerical rating scale
OPACC, Ontario Parents Advocating for Children with Cancer
PedsQL, Pediatric Quality of Life Inventory
POGO, Pediatric Oncology Group of Ontario
PROMIS, Patient Reported Outcomes Measurement Information System
QALY, Quality-Adjusted Life Year
RA, research assistant
RCT, randomised controlled trial
REDCap, Research Electronic Data Capture
SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials

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Author contributions

LAJ and JNS conceived of this trial and designed and developed the Pain Squad+ intervention. LAJ, PCN, VB, CVF, DLJ, VL, SM, SP, CSa, CSt, JCV, MEM, CN, AH, CS, GER, HI, RH, GF, SK, and JNS contributed to the design of the trial from a methodological standpoint, including design of the data analyses plans (JCV and MEM). LAJ drafted the manuscript and PCN, VB, CVF, DLJ, VL, SM, SP, CSa, CSt, JCV, MEM, CN, AH, CS, GER, HI, RH, GF, SK, and JNS read or revised and approved the final version.

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Competing interests

The authors have no competing interests, financial or otherwise, to declare.

Availability of data and material

The datasets used and/or analysed during the current study will be available from the corresponding author on reasonable request, where legally and ethically possible.

Consent for publication

Not applicable.

Ethics approval

Ethics approval for this study has been obtained from the Hospital for Sick Children Research Ethics Board.

Figure Legends

Figure 1. Pain Squad+ smartphone application screenshots of the application landing screen (A), a visual analogue slider scale for pain assessment (B), and a portion of the library of pain self-management advice. Photos used in this figure are stock photos and are under license from the copyright owners.

Figure 2. Flowchart of *Pain Squad*+ trial protocol

Figure 3. *Pain Squad*+ schedule of enrolment, interventions, and assessments.

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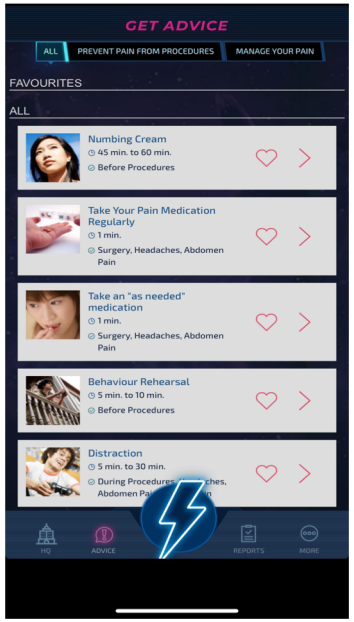
A

B



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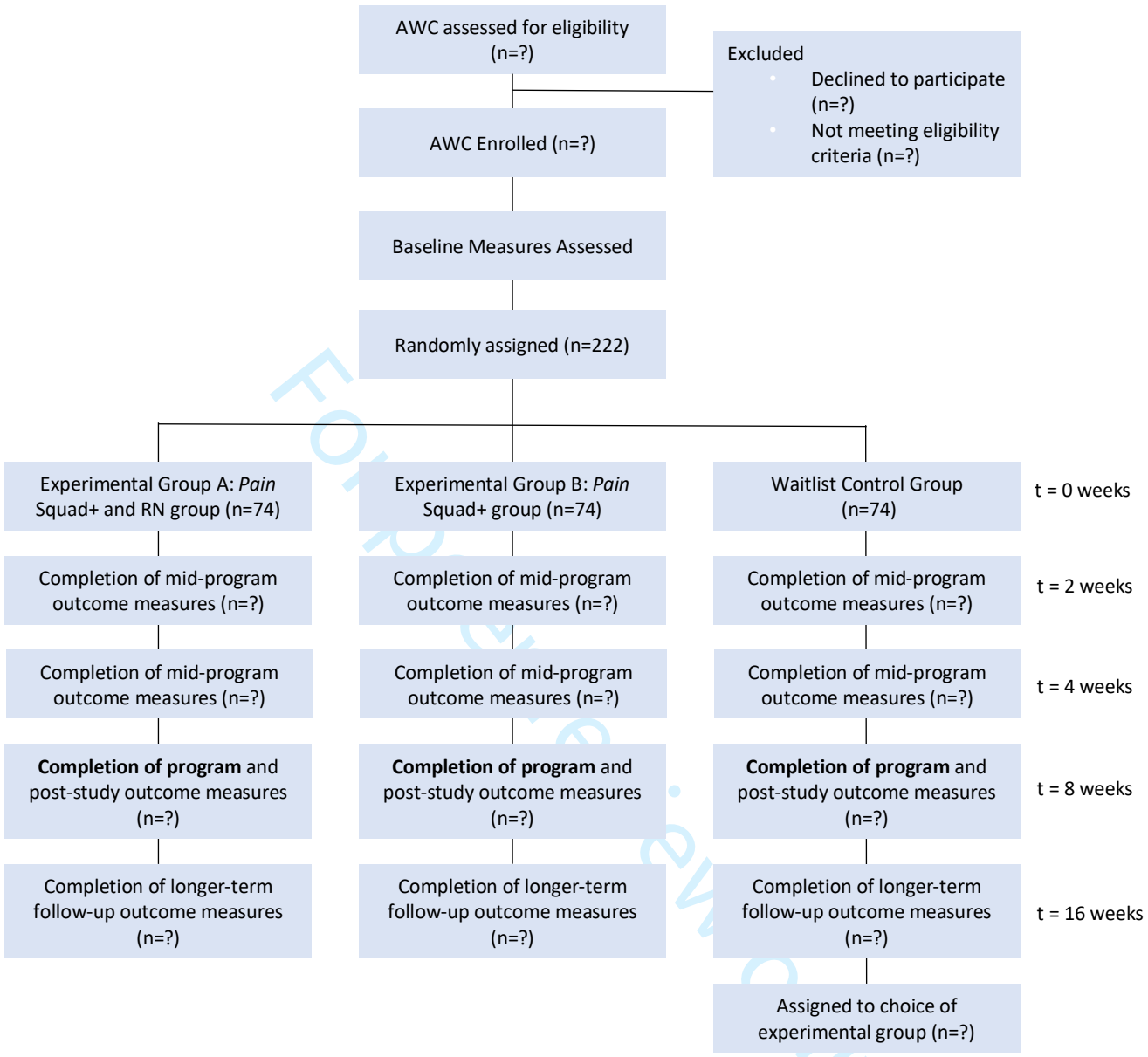

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT**	***-t_1***	**0**	***t_1 (2 weeks)***	***t_2 (4 weeks)***	***t_3 (8 weeks)***	***t_4 (16 weeks)***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Experimental Group A Standard care + *Pain Squad*+ smartphone app + RN support			←	—	→	
Experimental Group B Standard care + *Pain Squad*+ smartphone app			←	—	→	
Waitlist Control Group Standard care						
ASSESSMENTS:						
Baseline Variables • Adolescent with cancer socio-economic, demographic, pain, and cancer-related characteristics • Adolescent ownership and use of smartphones • Adolescent expectation about treatment effectiveness • Caregiver demographics	X	X				
Health Quality Variables • Pain intensity [BPI] • Pain interference [PROMIS] • Quality of life [PedsQL 4.0] • Pain self-efficacy [Porter's scale])		X	X	X	X	X
Cost Variables • Cost effectiveness and utility [HUI2/3])		X			X	X

Supplementary Appendix A. Details of pharmacological, psychological, and physical pain treatment advice provided to adolescents with cancer.

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
PHARMACOLOGICAL:					
Scrolling Page	Numbing Cream	45 - 60 minutes	Before Procedures	Remember to apply a pain numbing cream (topical anesthetic) 45-60 minutes before the procedure if your healthcare team has said it's okay.	*N/A (This advice only has one screen)*
Scrolling Page	Take Your Pain Medications Regularly	1 minute	Surgery, Headaches Abdomen Pain	Make sure you are sticking to the medication schedule your doctor recommends. If taking your medications is difficult, you can speak to your pharmacist about useful options such as setting reminders on a cell phone or using post-it notes. Make sure to talk to your doctor, nurse, or pharmacist if you're having trouble taking your medications, if they are not working or if you're having side effects from them.	*N/A (This advice only has one screen)*
Scrolling Page	Take an "as needed" medication	1 minute	Surgery, Headaches, Abdomen Pain	If your doctor has given you a medication for break-through pain AND it is time to take it, consider taking it now. You can talk to your parents or healthcare team if you're not sure about when and how to take these medications.	*N/A (This advice only has one screen)*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
				Make sure to talk to your doctor, nurse, or pharmacist if you're having trouble taking your medications, if they are not working or if you're having side effects from them.	
PSYCHOLOGICAL:					
Step-by-Step Slider	Behaviour Rehearsal	5-10 minutes	Before Procedures	Behaviour rehearsal helps you to prepare for an event that you think will be stressful before it even happens, like a painful procedure. What you need to do is break the situation into parts that you can imagine.	**Step 1** Rehearse what you are going to do to relax, stay calm, and get through the procedure. **Step 2** Relax your muscles, breathe deeply, stay calm and use positive thoughts like 'I can do this'. **Step 3** Imagine how you will relax during each part of the procedure. **Step 4** When you've made it through the procedure, make sure you have a plan to celebrate your success! You might not be able to cope exactly the way you wanted, but you still made it through!
Scrolling Page	Distraction	5-30 minutes	During Procedures, Headaches, Abdomen Pain, Muscle Pain	By turning your attention to something else, you can block out unpleasant or stressful thoughts. Make sure to choose pleasant things to focus your attention on. You can do things like listen to music, play video games or concentrate on your breathing.	*N/A (This advice only has one screen)*
Drill Down Table	Mental games	5-10 minutes	During Procedures, Headaches, Abdomen Pain, Muscle Pain	Mental games turn your attention away from pain and keep your mind busy with another activity. As a result, your mind isn't available to think about pain.	**Alphabet Game** Think of any category of interest, such as sports, cars, teams, animals, or countries. Try to name as many as you can that start with the letter A. When you're done, move on to the letters B, C, and so on through to Z **Song Lyrics** Try to remember all the words to your favourite song

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
					Count the Tiles Count the number of tiles in the floor or dots on an area of the ceiling
Step-by-Step Slider	Mindfulness	5-30 minutes	Surgeries, Mouth Sores, Muscle Pain, Abdominal Pain, Headaches etc.	Imagery is like daydreaming except you are doing it on purpose. Some people find it easy to use their imagination to distract themselves. Others need more practice.	**Step 1** The audio meditation helps you find a new way to experience discomfort. Use this meditation to explore the thoughts, feelings, and sensations that come with being upset or feeling physical pain. Holding an ice cube in the palm of your hand, follow along with the meditation to explore any feelings of discomfort. Have a towel handy to clean up the melted ice once the meditation is finished. *[Audio File Play Button]*
					Step 2 This audio meditation helps you develop kindness and compassion towards yourself. Use this meditation to acknowledge your physical pain or unpleasant emotions without harshness or judgment. Follow along with the meditation, noticing your breath and recognizing unpleasant sensations as useful signals. *[Audio File Play Button]*
					Step 3 This audio meditation helps you soften towards discomfort. Instead of resisting uncomfortable experiences or distracting yourself when they arise, use this meditation to help you develop an attitude of tenderness towards your suffering. As you follow the meditation, take time to allow your discomfort to come and go. If you become too uncomfortable, bring yourself back to your breath. *[Audio File Play Button]*
					Step 4 This audio meditation helps you connect with joy. Use it when you'd like to take a break or when you're dealing with unwanted thoughts, physical sensations, or emotions. Follow along with the meditation, connecting with the natural rhythm of your breath and exploring a joyful memory. *[Audio File Play Button]*

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Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
					Step 5 This audio meditation helps you connect to the present moment using your sense of sight, sound, touch, taste, and smell. Use this meditation when you want to ground yourself in the here and now or if you are having unwanted thoughts, feeling physical discomfort or uncomfortable emotions. Follow along. *[Audio File Play Button]*
					Step 6 This audio meditation helps you explore and bring comfort to an unwanted thought or an area of physical or emotional discomfort. Use this meditation when you are feeling overwhelmed or experiencing physical discomfort. Follow along focusing with kindness and curiosity on an uncomfortable area of your body. *[Audio File Play Button]*
Step-by-Step Slider	Imagery	5-30 minutes	During Procedures, Headaches, Abdomen Pain, Muscle Pain	Imagery is like daydreaming except you are doing it on purpose. Some people find it easy to use their imagination to distract themselves. Others need more practice.	**Step 1** Imagine being in a pleasant place, maybe on a beach or in a park with your family and friends. This is much more interesting to think about than pain!
					Step 2 This guided audio meditation helps you find a sense of stillness within yourself. Use it to find a place of stillness within your mind and body when you are feeling upset or agitated. Follow along with the meditation, taking time to visualize yourself as grounded and strong, like a mountain.
					Step 3 This audio meditation helps you visualize your pain. When you are struggling with pain, use this meditation to help discover a new way to experience and respond to it. Follow along with the meditation so you can move from resisting and feeling frustrated about your pain to being open and curious and exploring it in detail without judgment. *[Audio File Play Button]*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
Step-by-Step Slider	Mini-relaxation	5 minutes	During Procedures, Headaches, Abdomen Pain, Muscle	Mini-relaxation is a very quick and easy way to relax when you feel stressed or are feeling pain wherever you are.	**Step 1** Take a deep breath in through your nose. Feel your stomach rise as you take in the deep breath. **Step 2** Hold your breath for a few seconds while you count to 5. **Step 3** Roll your shoulders in a circle and then let them drop loose. Think "r-r-r." **Step 4** Breathe out through your mouth, slow and relaxed, as if you're softly whistling. Repeat steps and feel more relaxed each time.
PHYSICAL:					
Step-by-Step Slider	Doing enjoyable activities	15-20 minutes	Mouth Sores, Headaches, Abdomen Pain, Muscle Pain etc.	Sometimes when you are in pain doing something else, even if it is fun, may be the last thing on your mind. But we know that, over time, doing activities that you enjoy can: Improve your mood, help you feel less tired, help you begin to think more clearly.	**Step 1** Figuring out your enjoyable activities. Everybody has a different idea of what's enjoyable. For instance, you might enjoy things that your friends don't like – and that's ok! Finding enjoyable activities involves setting goals to do something that makes you feel good every day. **Step 2** When choosing your activities, aim for those that: are realistic for you right now, are fun, according to you, are achievable, do not increase your pain levels, do not rely on things that are not easily available to you. For instance, don't pick an activity that requires a car if you don't have access to one. **Step 3** Try an enjoyable activity and see how it works for you!
Scrolling Page	Applying Cold	15-20 minutes	Mouth Sores, Muscle Pain	Cold temperatures can help reduce pain. For instance, the cold sensation from popsicles and ice chips can be really helpful for mouth sores!	*N/A (This advice only has one screen)*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
				Apply a cold pack or other cold things like ice to the area you are feeling pain.	
Scrolling Page	Applying Heat	15-20 minutes	Abdomen Pain, Muscle Pain	Warm temperatures can help reduce pain. For instance, the warm temperature of a hot pack can reduce muscle aches! Apply a hot pack to the area you are feeling pain. Remember not to apply heat to wounds or stitches.	*N/A (This advice only has one screen)*
Step-by-Step Slider	Belly-breathing	5-30 minutes	During Procedures, Headaches, Abdomen Pain, Muscle Pain	Belly breathing is one of the best and easiest ways to relax. It can help you manage pain and also distract you from unpleasant situations.	**Step 1** Lie down, knees bent, place one hand on your chest and one hand just above your belly button. (For now, try this sitting comfortably in your chair. Once you are off the computer. You can try it lying down) **Step 2** Take a deep breath in through your nose, pushing your belly out. Feel your bottom hand, on your belly, move out. The top hand on your chest should stay still. Notice how long your inhaled breath is by counting. When your belly is all the way out, pause for a moment... **Step 3** …now breathe out slowly, through puckered lips, to the same count you used to breathe in, letting your belly come down until it is flat. **Step 4** Repeat slowly a few times. Notice your body beginning to feel relaxed with each breath out. After you have practiced this exercise a few times, you can make the count longer to get an even deeper, more relaxing breath.

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
Step-by-Step Slider	Mental Relaxation	10 minutes	Surgeries, Headaches, Abdomen Pain, Muscle Pain	Mental relaxation is an effective way to help you cope with pain and stress.	**Step 1** Find a comfortable, quiet place to sit. **Step 2** When you hit play, an audio recording will start. The audio recording will lead you through the relaxation exercise. *[Audio File/Play Button]*
Step-by-Step Slider	Muscle Relaxation	15 minutes	Headaches, Abdomen Pain, Muscle Pain	Muscle relaxation is a way to relieve muscle tension and pain by tensing and then relaxing different groups of muscles in your body.	**Step 1** Find a comfortable, quiet place to sit. **Step 2** When you hit play, an audio recording will start. The audio recording will lead you through the relaxation exercise. *[Audio File/Play Button]*
Scrolling Page	Gentle exercise	10-40 minutes	Muscle Pain, Headache, Abdominal Pain, Surgeries	Try gentle exercising by going for a walk. Research shows that physical activity can help you manage symptoms like pain. It's important to talk to your health care provider and maybe a physiotherapist before you start adding physical activity to your routine. Some types of exercise may be risky depending on the type of cancer you have. Remember, stop right away if you experience sudden intense pain.	*N/A (This advice only has one screen)*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or States
Drill Down Table	Stretching (yoga)	10-40 minutes	Muscle Pain, Headache, Abdominal Pain, Surgeries	Yoga aims to restore the balance between one's body, mind, and spirit through a series of gentle exercises and breathing techniques. There are lots of poses you can do in yoga.	**Mountain (tadasana) pose** Stand with feet hip-width apart and your weight evenly balanced between them. Pull up through the top of your forehead and try to make your spine feel longer. Tilt your tailbone (bottom of your spine) under so it points towards the ground and relax your shoulders away from the ears. Breathe in and out smoothly. Mentally scan your body, releasing any tension. Relax your neck, face, jaw, and tongue. Tell yourself a positive phrase like "I am strong and brave". *[Image from TTC Website]* **Archer pose** While standing, step forward with your left leg so your legs are about 2.5 feet apart. Turn your right foot out at a 45-degree angle. Raise your left arm straight out in front, parallel to the ground, with your hand in a fist. Pull your right arm back as if it's pulling back on a bowstring. Both wrists form a straight line with your shoulders. Bend your left knee and squeeze your thighs together. Look at your left fist and feel like a strong warrior. *[Image from TTC Website]* **Tree pose** Stand upright and shift your weight to 1 foot. When you feel stable, place your other foot either at your ankle or inner thigh. Focus on a spot in front of you to help you balance. Breathe deeply and raise your arms and put your hands together in front of your chest. Hold for a few minutes and then switch legs. [*Image from TTC Website]*

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
					Ego pose Sitting at the edge of the bed, raise your arms overhead in a V shape. Stretch your thumbs to the sky and curl your fingers onto the palms of your hand. Breathe in and out slowly. Hold for as long as you can, up to a minute. *[Image from TTC Website]*
					Life nerve stretch Sitting up, flex both feet back towards the head. Keeping a straight back, reach as far down your legs as you can – it might be your shins or your toes, or somewhere in between. Breathe long slow breaths. Continue for 1 minute. *[Image from TTC Website]*
					Bridge pose (setu bandhasana) In this video, you'll learn how to come into the bridge pose. Follow the written instructions below, or watch the video for a short demonstration. [*video file play button*] Starting out on your back, bend your knees so your heels are flat and firm on the mat. Place your arms by your side. Try to bring your legs as close as you can to your buttocks, so you can tickle the back of your feet with your fingertips. Using your hands as a support, inhale as you lift your hips up toward the ceiling, as high as you can comfortably. If you feel comfortable here, bring your arms underneath your back and interlace your fingers. Make sure to keep your hands on the mat. Lift your hips as high as you can comfortably and hold for breaths. Tip your chin toward the ceiling to protect your cervical (upper) spine. When you are ready to come down, release your arms first and then use them as a support to slowly lower your hips down to the mat, inch by inch.

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
					Baby cobra pose (bhujangasana) In this video, you'll learn how to come into the baby cobra pose. Follow the written instructions below, or watch the video for a quick demonstration. [*video file play button*] To start off, lie down on your belly, with your arms by your side and your forehead touching the mat. Bring your arms in line with your ribs, with your palms facing the mat and your elbows in the air. Pushing down the tops of your feet, lift your kneecaps off the mat and activate your legs as you inhale. As you exhale, slowly peel your forehead and chest off the mat. There should be no weight on your palms as they should rise with your chest to a height of about 1 inch off the mat. Hold this position for 5 breaths. Maintain space between your shoulders and your ears, draw the shoulder blades back and down – this will also help open your chest. There should be no pinching in your lower back – think of a long spine! When you are ready to come down, inhale and as you exhale, slowly lower your chest back to the mat. Return to your original posture by lowering your arms back to your sides
					Downward dog (adho mukha) In this video, you'll learn how to come into the downward facing dog pose. Follow the written instructions below, or watch the video for a demonstration. [*video file play button*] Start off in the table pose on all fours, standing on your hands and knees. As you inhale, curl your toes down to the floor for support and lift your knees off the ground, extending your legs as you push your hips up, towards the ceiling, and back towards the back wall. It is ok if your heels do not fully touch the mat and to have a

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or Slides
					slight bend in your knees if you cannot straighten them. Direct your focus toward fully extending your shoulders, keeping your shoulder blades down and in line with your spine, and pressing your hands and toes into the mat. However, try to keep your neck relaxed and maintain space between your ears and your shoulders. Hold this pose for 5 breaths. Tips: Try to draw your belly button in and bring your thigh bones toward the back wall. If your legs are tight, "walk them out" by bending one knee while straightening the other, in time with your breath, as you hold the pose. Child's pose: If the downward facing dog pose becomes difficult to hold, bring your knees back to the mat, returning to the table pose and sit back onto your heels with your toes uncurled. Allow your head to come down to the mat, with your arms relaxed in front of you. Focus on allowing your lower back to sink into your heels.
					Reclined twist In this video, you'll learn how to come into the reclined twist pose. Follow the written instructions below, or watch the video for a full demonstration. [*video file play button*] Start on your back, with your knees bent and the soles of your feet on the mat, inhale. As you exhale, draw your knees towards your chest, picking your feet up off the mat. Extend your arms straight out to your sides, like an airplane and inhale. As you exhale, let both of your knees fall toward your right side. If your knee cannot fall all the way to the ground, use your right arm to support your top knee. Hold this position in a relaxed way for 5 breaths. Switch sides, bringing your knees to the left, and hold that position for 5 breaths. Modifications to pose: place a pillow between your legs to provide support as you twist. This will also help

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Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or States
					if you find your shoulder is lifting off of the mat during the posture. For a deeper stretch, try crossing the legs, or straightening the top leg.
					Side plank (vasisthasana) In this video, you'll learn how to come into the side plank pose. Follow the written instructions below, or watch the video for a full demonstration. [*video file play button*] Starting in table pose, on all fours, extend your legs straight back, resting on your palms and toes (a.k.a the plank pose). Shift your left palm towards the center of the mat and shift your weight onto your right arm. Slowly shift your hips toward your right side, lifting your left palm off of the mat and extending it toward the ceiling as you turn your body to the side. Hold this pose for 5 breaths. Shift back into the plank pose and return to the table pose. Modifications to pose: You may choose to keep your legs stacked together in this pose, but you can also separate them if you choose. As a variation, while in the pose, bring your top leg in front of you, as though you were taking a step, keeping the top leg bent at the knee and your bottom leg straight. For a more challenging variation, while in the pose, lift your top leg straight up toward the ceiling and hold it there for as long as you can.
					Reclined bound angle pose (supta baddha konasana) In this video, you'll learn how to come into the reclined bound angle pose. Follow the written instructions below, or watch the video for a full demonstration. [*video file play button*] Starting on your back, with your knees bent and the soles of your feet on the mat, inhale through your nose.

Wireframe Template	Name of Advice	Duration	Most Effective For	Overview Page	Additional Screens or States
					As you exhale, open your knees to either side of the mat, like a book, bringing your heels together. As you continue to breathe, allow your knees to fall closer to the mat with every exhale. When you have reached your comfort limit, hold this position for 5 breaths. Modifications to pose: As a variation, support your body by placing one hand on your chest and another on your belly button. You may also place both of your arms up and over your head or around your head. For the restorative variation of this posture, place a pillow under your head and back to support your spine as well as pillows/props (e.g. yoga block, rolled towel) under your knees on each side. When propping the spine and upper back, ensure that your lower back stays in a relatively neutral position.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Protocol face page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	NCT03632343
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	All pages
Funding	4	Sources and types of financial, material, and other support	Section: Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Protocol face page
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Section: Trial steering and data safety and monitoring committees (DSMC).
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Section: Introduction
	6b	Explanation for choice of comparators	n/a
Objectives	7	Specific objectives or hypotheses	Section: Introduction
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Section: Trial design

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Section: Study setting
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Section: Eligibility criteria and Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Section: Interventions and Supplementary Appendix A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Sections: **The Pain Squad+ smartphone-based real-time pain treatment application and Interventions**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Section: Interventions
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Section: Outcomes
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Section: Participant timeline and Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Section: Sample size
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Section: Recruitment
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Section: Allocation and blinding

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Section: Allocation and blinding
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Section: Allocation and blinding
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Section: Allocation and blinding
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Section: Allocation and blinding
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Section: Data collection methods
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Section: Data collection methods
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Section: Data management and confidentiality
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Section: Data analyses methods
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Section: Data analyses methods
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Section: Data analyses methods
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Section: Trial steering and data safety and monitoring committees (DSMC)

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Sections: Trial steering and data safety and monitoring committees (DSMC) and Safety appraisal and protocol amendment reporting
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Sections: Trial steering and data safety and monitoring committees (DSMC) and Safety appraisal and protocol amendment reporting
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Sections: Trial steering and data safety and monitoring committees (DSMC) and Safety appraisal and protocol amendment reporting
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Section: Ethics approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Sections: Safety appraisal and protocol amendment reporting

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Section: Data collection methods
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Section: Data management and confidentiality
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Section: Competing interests
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Section: Availability of data and material
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Section: Dissemination and knowledge translation plan
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Section: Availability of data and material
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available from study team by request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.