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Abstract

Introduction Following the treatment of patients with soft tissue sarcomas (STS) that are not metastatic at presentation, the high risk for local and systemic disease recurrence necessitates post-treatment surveillance. Systemic recurrence is most often detected in the lungs. The most appropriate surveillance frequency and modality remain unknown and, as such, clinical practice is highly varied. We plan to assess the feasibility of conducting a multi-centre randomised controlled trial (RCT) that will evaluate the effect on overall five-year survival of two different surveillance frequencies and imaging modalities in patients with STS who undergo surgical excision with curative intent.

Methods and analysis The SAFETY trial will be a multi-centre 2X2 factorial randomized controlled trial. Patients with non-metastatic primary Grade II or III STS treated with excision will be allocated to one of four treatment arms: (1) chest radiograph (CXR) every three months for two years; (2) CXR every six months for two years; (3) chest computed tomography (CT) every three months for two years; or (4) chest CT every six months for two years. The primary outcome of the pilot phase is the feasibility of a definitive RCT based on a composite of feasibility endpoints. Secondary outcomes for the feasibility study include the primary outcome of the definitive trial (overall five-year survival), patient-reported outcomes on anxiety, satisfaction and quality of life, local recurrence-free survival, metastasis-free survival, treatment-related complications, and net healthcare costs related to surveillance.

Ethics and dissemination This trial received *Pro Tempore* ethics approval from the McMaster / Hamilton Health Sciences Research Ethics Board. Final ethics approval will be obtained prior to commencing patient recruitment. Once feasibility has been established and the definitive protocol is finalized, the study will transition to the definitive phase.

Article summary

Article focus

Surveillance AFter Extremity Tumour surgerY (SAFETY) is a pragmatic 2x2 factorial international multi-centre randomised controlled trial that aims to understand the impact of surveillance frequency and imaging on overall 5-year survival in patients with soft tissue sarcomas who underwent surgical resection. A pilot study assessing the feasibility of the definitive phase will be undertaken first.

Strengths and limitations of this study

- The SAFETY trial will be an international multi-centre 2X2 factorial randomized controlled trial
- The trial will answer a high priority question for sarcoma surgeons
- The SAFETY trial will build on the international collaboration and experience of the PARITY trial
- The feasibility pilot study is essential before undertaking this large multi-centre trial
- The success of the pilot study is dependent on the ability of clinical sites to recruit patients, comply with the protocol, and complete high quality follow-up data

Keywords: surveillance; soft tissue sarcoma; study protocol; randomized controlled trial; pilot study

Background

Magnitude of the problem

Sarcomas are malignancies of connective tissue that most commonly occur in the extremities. Sarcomas can arise within bone (bone sarcoma) or soft-tissue (soft-tissue sarcoma [STS]). Chemotherapy is not curative for the vast majority of patients with STS(1); therefore, surgery is the standard treatment for STS, with radiation considered important for local disease control.

Following treatment for a STS that is not metastatic at presentation, the risk for local and systemic disease recurrence necessitates careful post-operative surveillance. Between 40% and 50% of all sarcoma patients will develop a local or distant recurrence; however, the risk of recurrence is greatest in the first few years, with 68% occurring by two years and 90% by five years(2-4). Metastasis to the lung is the most frequent single location of disease recurrence in sarcoma patients, occurring in the majority of patients with metastases(4-7). Therefore, routine follow-up after completing sarcoma treatment is standard practice in the first five years after surgery. These visits typically include a clinical history, physical examination, and imaging of the lungs (chest radiograph [CXR], or computed tomography [CT] scan of the lungs).

Surveillance strategies for long-term follow-up of sarcoma patients have not been well researched and current guidelines are based on expert opinion, not on high quality evidence(8, 9). As such, current clinical practice is highly varied, with survey data of musculoskeletal oncologists showing that the number of clinic visits ranges from two to 12, the number of CXRs obtained ranges from zero to 13, and the number of CT scans ranges from one to eight in the first year of surveillance(10-12).

Best evidence for surveillance strategies

In order to assess the available evidence, we completed a systematic review of the available randomized controlled trial (RCT) evidence for surveillance in sarcoma management(13). A single

study (published separately with early and longer-term follow-up) was identified(14, 15). The authors of this single-centre study found that three-year overall and disease-free survival was not worse in sarcoma patients who had less intensive surveillance (CXRs) than those with more intensive surveillance (CT scans)(14). Due to the sample size, this trial could not conclusively demonstrate non-inferiority in overall or disease-free survival for a six-monthly interval of follow-up visits against three-monthly interval (both were 64% and 69%, respectively)(14).

A follow-up study on the same patient cohort with five-year survival outcomes confirmed that more frequent follow-up did not improve survival and that, although CT scans detected pulmonary metastasis earlier, they did not lead to better survival compared with CXRs(15). However, this was a single-centre study with relatively small numbers and, therefore, confidence in the results and generalizability of the data to other centres is limited. In addition, a relatively small proportion of screened patients (42%) that were eligible for the trial were included due to the exclusion of patients unlikely to follow-up, thus possibly introducing selection bias(14). Furthermore, low-grade sarcomas were eligible and included in this study, even though they have little metastatic potential and tumour-related mortality; their inclusion may have diminished the magnitude of the effects of the interventions(14). Finally, the majority of the included patients were bone sarcoma patients, thereby limiting the interpretation to STS patients(14).

Risks and benefits of intensive surveillance

Regular, intensive surveillance is more likely to identify recurrent disease earlier than would less intensive surveillance. This type of surveillance may provide reassurance to patients and clinicians; however, the adverse effects of intensive surveillance practices are also noteworthy. The costs that healthcare systems incur as a result of sarcoma surveillance are substantial and could be in excess

of USD $20,000 for high-grade sarcomas(16). Furthermore, intensive surveillance can threaten the financial security of patients, due in part to the direct (including travel, accommodation, personal care, and homemaking) and indirect costs (including lost wages for patients and their caregivers) incurred as a result of follow-up appointments(17). As a result, patients' health and quality of life can be dramatically impacted(17-19).

Secondary investigations and earlier knowledge of disease recurrence can also induce anxiety and impact the psychosocial wellbeing for those whose mortality risk cannot be significantly reduced by further medical interventions(20). Overcrowded clinics and long wait times may constitute other important factors that affect patients' psychosocial wellbeing(21). Finally, the use of CT has raised concerns over unnecessary radiation exposure compared to radiographs, although lower dose CT scans may mitigate some of these concerns(22).

Surveillance research as a priority in orthopedic oncology

We recently published a modified Delphi study in which we aimed to identify a clinically relevant consensus-based research agenda in the sarcoma field(23). From this Delphi process that included 80 orthopaedic oncologists and patient representation (with participation from 18 countries), we identified critical research priorities in the field of orthopaedic oncology and determined the top four feasible and important research questions that will directly inform patient care and enhance clinical practice. This study identified the evaluation of post-operative surveillance strategies as the highest-ranking research priority in the sarcoma field(23).

Study design

We plan to assess the feasibility of conducting the pragmatic international multi-centre 2X2 factorial Surveillance AFter Extremity Tumour surgerY (SAFETY) RCT that answers the following question: In extremity STS patients who undergo surgical resection with curative intent, what is the impact of surveillance frequency (every three vs. every six months) and surveillance imaging modality (CXR vs. CT scan) on overall survival at five years? To assess feasibility, we will conduct a pilot study. Study participants will be randomized to one of four possible treatment arms (see Study Interventions below). Randomization will occur at the end of active treatment (surgery ± systemic treatment ± local radiation). Following the two-year intervention phase, study participants will continue to be assessed at regular intervals for an additional three years. Details of the flow of each study arm are outlined in Figure 1. We anticipate the duration of the pilot phase to be three years in order to collect intervention phase data on all participants and preliminary post-intervention phase data. The primary outcome of the pilot phase is the feasibility of a definitive RCT based on a composite of feasibility endpoints.

Objectives

Primary Feasibility Research Objectives

The primary objective of the pilot study will be to determine whether it is feasible to conduct a large multi-centre RCT that will evaluate the impact of surveillance strategies on patient survival following extremity STS surgery. To do so, we will assess our ability to:

A) Recruit patients across multiple participating clinical sites;

B) Ensure compliance with the study protocol, including the application of eligibility criteria, timing of intervention phase and post-intervention phase visits and imaging modality;

C) Maintain completeness of follow-up data;

D) Maintain completeness of cost analysis data; and

E) Maintain data quality.

Secondary Feasibility Research Objectives

The secondary objectives of the pilot study will include assessing the impact of either surveillance frequency (every three vs. every six months) or imaging modality (CXR vs. CT scan) on:

A) Overall five-year survival;

B) Patient anxiety, satisfaction and quality of life;

C) Local recurrence-free survival and metastasis-free survival;

D) Treatment-related complications; and

E) Net direct healthcare costs and net costs of treatment and treatment-related complications once metastases are detected.

Hypothesis

Pilot Study

We hypothesize that the SAFETY trial will be feasible due to: A) its pragmatic design; B) our established international collaborative research network; C) our qualified, multi-disciplinary study team; D) our existing trial infrastructure; and E) the priority of the study question.

Definitive Study

We hypothesize that more frequent post-operative surveillance (compared to less frequent post-operative surveillance) and the use of post-operative CT scans (compared to CXR) in the first two years following the surgical excision of a STS will improve survival over five years.

Study setting

This study will be coordinated by the Methods Centre within the Centre for Evidence-Based Orthopaedics (CEO) at McMaster University (Hamilton, ON, Canada). For the pilot phase, we expect that patients will be enrolled from ten clinical sites across four continents. Clinical sites will be carefully screened prior to participation in the study. The clinical site inclusion criteria are: I) adequate research personnel and infrastructure to manage the study; II) sufficiently high extremity STS volume to complete enrollment within the study timeline (defined as greater than or equal to (≥) 20 patients per year); III) commitment from all or most orthopaedic oncologists to participate in the trial; and IV) access to the two imaging modalities. The exclusion criteria are: I) a lack of interest in the trial; II) anticipated challenges with protocol compliance; III) conflicting studies, in the judgment of the Principal Investigator, that would inhibit patient participation; and IV) financial or contract constraints.

Patient eligibility criteria

Inclusion criteria

Patients who meet all of the following criteria will be included:

1) Age of 18 years or older;
2) Diagnosed with a primary extremity grade II or III STS;
3) Undergone surgical resection of the tumour with curative intent and grossly negative margins;
4) Completed neoadjuvant or adjuvant radiation and / or chemotherapy, if applicable;
5) The tumour size is greater than or equal to (≥) five centimeters according to the pathology report or pre-treatment MRI if neoadjuvant radiation and / or chemotherapy are given; and
6) Provision of informed consent.

Exclusion criteria

Patients who meet any of the following criteria will be excluded:

1) Metastatic disease at initial presentation based on thoracic imaging (a second CT scan may be required to confirm that indeterminate nodules are false positives before the patient can be enrolled provided that the second CT scan shows no evidence of metastatic disease);
2) Undergone surgical excision of a local recurrence;
3) Diagnosis of one of the special sub-types: myxoid / round cell liposarcoma or extra-skeletal Ewing's sarcoma (These sarcomas have different metastatic patterns, which necessitate different surveillance protocols);
4) Previous diagnosis of a genetic syndrome with an elevated risk of malignancy, such as Li-Fraumeni Syndrome (such individuals appear to be at an elevated risk for radiation-induced cancers, so the use of CT scans should be limited);
5) Previous diagnosis with a co-morbid condition that has a life expectancy of less than one year;
6) The site-specific surveillance protocol for the patient's disease is not compatible with the study protocol (i.e., regular planned whole-body imaging with positron emission tomography [PET] scans);
7) Diagnosed with another malignancy within the past five years*;*
8) Likely problems, in the judgment of the investigator, with maintaining follow-up; and
9) Currently enrolled in a study that does not permit co-enrollment.

Recruitment and screening

Each participating clinical site will have a locally responsible investigator who will oversee the local administration of the trial, screen STS patients for eligibility, and develop a site-specific patient enrollment plan. A Screening Form will be completed for all STS patients aged 18 years or older, irrespective of whether they are eligible to participate in the study or not. Patients will become eligible, will be screened and consented during the first clinic visit at which all treatment is complete, the surgical wound has healed, and the plan for post-treatment surveillance is discussed with the patient. The process of obtaining and documenting informed consent will be completed in accordance with local Good Clinical Practice recommendations. Consent procedures will comply with the appropriate ethics committee and the Health Insurance Portability and Accountability Act (where applicable).

Randomization and allocation of patients to study groups

A centralized and automated internet-based randomisation system using random variable block sizes will assign participants to the study groups. Study personnel at each participating site will complete this task. Randomisation will occur only after eligibility is confirmed and consent to participate has been obtained. Participants will be stratified based on clinical site and peri-operative chemotherapy.

Study interventions

Participants will be randomised to one of four treatment groups:

1) CXR every three months for two years;

2) CXR every six months for two years;

3) Chest CT every three months for two years; or

4) Chest CT every six months for two years.

Following completion of the intervention phase, participants will continue to be followed in the study for an additional three years. During this three-year post-intervention phase, participants will be followed at least every six months as per National Comprehensive Cancer Network (NCCN) guidelines(24). If possible, thoracic imaging will continue at each scheduled post-intervention phase visit according to the participants' original allocations.

Relapse

Local imaging and clinical assessment of the primary tumour site will be carried out as per the standard protocol at each participating clinical site. Further diagnostic tests will be performed in the presence of clinical symptoms or radiologic findings suggestive of disease relapse. Recurrence will be radiologically or histologically confirmed and classified as local or systemic (metastasis) recurrence. The first modality suggesting disease relapse in participants with confirmed local or systemic recurrence will be recorded as responsible for its detection.

Outcome measures

Primary outcome

To evaluate feasibility, we will assess the number of patients screened and recruited at each participating clinical site, participant retention, and maintenance of data quality. In addition, we will evaluate the utilization of an internet-based centralized randomisation system focusing on the accuracy of data entry, appropriate stratification of participants and the minimization of randomisation errors. Finally, we will evaluate investigator and participant compliance with the

study protocol, including the application of eligibility criteria, compliance with the surveillance imaging and frequency regimens, frequency of crossover and timing of post-intervention phase visits. The a priori criteria for the success of the pilot phase are listed below.

Recruitment Measure: We will consider our recruitment strategy feasible if we are able to enroll the pilot sample of 195 patients (approximately 20 patients from each clinical site participating in the pilot phase) within two years. See sample size determination below.

Protocol Adherence Measure: During the pilot phase of the PARITY trial, we were able to maintain an overall protocol adherence rate in excess of 90%(25). Recent reports prepared for the PARITY Data and Safety Monitoring Board (DSMB) indicate a similar protocol adherence rate. However, given the greater complexity and longer duration of the SAFETY trial interventions, we will consider our protocol adherence strategies feasible if there is adherence of 85% or greater to the visit windows and imaging modality prescribed by the protocol.

Participant Retention Measure: While 20% loss-to-follow-up has traditionally been considered acceptable in clinical research, evidence from other orthopaedic trials suggests that bias begins to affect study results at even lower rates of loss-to-follow-up(26). Therefore, we will consider our participant retention strategies feasible if no more than 15% of participants are lost-to-follow-up.

Maintenance of Data Quality Measure: We obtained a data completeness rate of approximately 90% in the PARITY trial pilot phase(25). Therefore, we will consider our data quality strategies feasible if we are able to maintain 95% or greater completeness of participant follow-up data for

the definitive primary outcome. We will also consider our data quality strategies feasible if we are able to maintain 85% or greater completeness of participant follow-up data for the secondary outcomes.

Secondary outcomes

The main secondary outcome for the feasibility study will be the primary outcome of the definitive trial, which is overall five-year survival. The outcome measure will be death from any cause. Data on secondary outcomes for the definitive trial, which are listed below, will also be collected.

Patient-reported outcome measures: The validated Patient-Reported Outcomes Measurement Information System (PROMIS)® Cancer-Anxiety questionnaire, PROMIS® Satisfaction with Social Roles and Activities questionnaire, and the EuroQol-5 Dimension (EQ-5D) will be used to assess patient anxiety, satisfaction and quality of life, respectively. These questionnaires will be administered at the baseline visit, as well as the 6-month, 12-month, 18-month and 24-month intervention phase, as well as 36-month, 48-month and 60-month post-intervention phase visits.

Local recurrence-free survival (LRFS) outcome measure: LRFS will be defined as the length of time from randomization that the participant survives with no detection of recurrent disease at the initial tumor site or operative field.

Metastasis-free survival (*MFS) outcome measure:* MFS will be defined as the length of time from randomization that the participant survives with no detection of systemic disease recurrence at any anatomic location.

Treatment-related complications outcome measures: Treatment-related complications will include both chemotherapy-related complications, such as febrile neutropenia, fungal infections or sepsis, and thoracotomy-related complications, such as pneumothorax, or surgical site infections.

Net healthcare costs outcome measures: We will perform an incremental cost analysis of net costs of surveillance and costs incurred from metastasis treatment and metastasis treatment related complications. Unit costs for all resources used by trial participants will be obtained from regional statistics and from centers participating in the trial. These unit costs will be combined with the resource volumes to obtain a net cost per participant over their time in the trial.

Protecting against sources of bias

Adjudication of outcomes

An independent Central Adjudication Committee (CAC) will review all situations where eligibility is in doubt, as well as all reported instances of disease relapse, treatment-related complications, and death to determine whether a study event has occurred. The SAFETY CAC will be comprised of two orthopaedic oncologists, one medical oncologist, and one radiologist. All participating clinical sites will submit digital imaging and relevant hospital records to the Methods Centre via a web-based platform for events that require adjudication.

Blinding

The local clinical team, site study personnel and participants cannot be blinded to the treatment allocation. The CAC will be blinded to surveillance frequency. The data analysts will, however, remain blinded during the trial's analysis.

Maximization of follow-up

We anticipate only minimal losses to follow-up in our musculoskeletal oncology population. Nonetheless, the following procedures will be implemented to minimize losses:

- Individuals likely to present problems with compliance to the study protocol or maintaining follow-up will be excluded;
- At the time of randomization, participants will be asked to provide their contact information, as well as the contact information of their family physician and three alternate contacts;
- Participants who refuse to return for a study assessment will be asked if they are willing to provide follow-up data via telephone;
- If a participant cannot be reached, their status regarding the primary study outcome will be assessed by reviewing their medical records;
- Study personnel will remind participants of upcoming clinic visits;
- To assuage possible concerns related to less frequent follow-up, participants will be encouraged to schedule an ad hoc visit anytime they are concerned, even if it breaks the surveillance protocol to which they were assigned;
- Participants will be provided with access to educational content, such as a video that demonstrates how to self-examine for a local recurrence of their STS; and
- Parking and travel vouchers will be provided to participants, where possible, to alleviate the costs associated with the study.

Minimization of crossovers of surveillance interventions

Crossovers are unlikely for either surveillance intervention as investigators will be requesting the imaging modality during surveillance visits. Any deviation with regards to frequency or imaging modality will be documented. In the event of disease recurrence or progression, the following standardized management protocols will be adopted:

- Local Recurrence: the participant will have a lung CT scan to confirm no progression of their systemic disease before continuing with the study protocol.
- Metastases: the participant will no longer be followed as per the study protocol, but per the appropriate follow-up for the interventions required for the treatment of metastases; however, the participant will continue to be followed in the trial.

For both events, the specific imaging modality used to detect either the local recurrence or the metastases will be documented.

Sample size determination

Feasibility Sample Size

The confidence interval approach was used to calculate the required sample size for the pilot study(27). We determined *a priori* that the definitive trial would only be feasible if our protocol adherence rate was at least 85%. Using a 95% confidence level and a 5% margin of error, we calculated a required sample size of 195 patients.

Definitive Sample Size

Our best estimate of the control group overall five-year survival for both the surveillance frequency and imaging modality is 55%(15). A 10% absolute increase in overall five-year survival associated with both more frequent surveillance and the use of CT scans represents a clinically important difference, as outlined by the American Society of Clinical Oncology's statement on clinically meaningful outcomes in cancer trials(28). Therefore, the definitive trial will be powered to detect an absolute difference of 10% in overall five-year survival.

With a desired power of 0.80, 396 participants per study arm. We will account for a 5% loss to follow-up and, therefore, the final sample size will be 830 participants. **Table 1** shows various sample sizes for pairwise comparisons of alternative surveillance frequencies / imaging modalities given varying control event rates and absolute increases in survival.

The definitive sample size calculation may be adjusted as we prepare for the transition from the feasibility to the definitive phase as a result of data collected during the pilot study.

Table 1. Sample Size Per Group for 80% power, α=0.05. Event rate = death

		Event Rate in More Intensive Surveillance Group			
		25%	30%	35%	40%
Event Rate in Less Intensive Surveillance Group	35%	696	2832	-	-
	40%	332	752	3020	-
	45%	196	352	792	3148
	50%	132	204	368	816
	55%	96	136	212	372

Analysis plan overview

The analysis and reporting of the trial will follow the CONSORT criteria. The primary analysis will compare the treatment groups on the overall 5-year survival. Two independent comparisons between treatment groups will be made using Cox regression models with time to the definitive primary endpoint. Results will be expressed as effect (ORs for binary outcomes, HRs for time-dependent outcomes and mean difference for continuous outcomes), corresponding 2-sided 95% CIs and associated p-values.

Analysis of feasibility outcomes

A full description of the measures, variables, and methods of analysis are shown in **Table 2**. We will record the total number of participants enrolled on a monthly basis. Each participating site will keep a Screening Log of included and excluded patients. We will also keep a record of participants who miss visits, and those who are withdrawn or lost to follow-up. These will be reported using descriptive statistics – reported as counts (percent) for categorical variables and mean (standard deviation) for continuous variables with 95% confidence intervals. We will report the proportion of complete CRFs as descriptive data.

Table 2. Summary of Feasibility Outcomes Analysis Plan

Objective	Outcome	Criteria for success of feasibility	Method of analysis
To determine the feasibility of conducting the multi-centre SAFETY international RCT	Recruitment Measure	Enrollment of pilot sample within two years	Descriptive statistics – reported as counts (percent) for categorical variables and means (standard deviation) for continuous variables with 95% CI
	Protocol Adherence Measure	Protocol adherence of 85% or greater	
	Participant Retention Measure	Loss-to-participant follow-up of 15% or less	
	Maintenance of Data Quality Measure	Data completeness of 95% or greater for the definitive primary outcome Data completeness of 85% or greater for the secondary outcomes	

Ethical considerations

This study is to be conducted according to international standards of Good Clinical Practice, applicable government regulations, and institutional research policies and procedures. All study

intervention phase (surveillance) arms fall within the spectrum of current standard practice, as do the standardized post-intervention phase follow-up visits. This trial has received *Pro Tempore* ethics approval from the McMaster / Hamilton Health Sciences Research Ethics Board on August 23rd, 2018. The study protocol will be submitted to a properly constituted independent ethics committee, in agreement with local legal prescriptions, for formal approval of the study conduct at each participating clinical site. A copy of this approval will be provided to the Methods Centre by each participating clinical site prior to the local commencement of the study.

Study Timeline

We expect that the pilot study will take just over three years to complete. We estimate that recruitment will take approximately one year to complete per site. The initiation of screening and enrollment will likely be staggered across the participating clinical sites due to the variability in the time required to obtain ethics approval and negotiate institutional contracts. We expect a further two years for all pilot participants to complete the intervention phase of the trial. Although we will not have complete post-intervention phase data for any pilot participants, we anticipate being able to determine feasibility at the end of the intervention phase based on our feasibility objectives. We plan *a priori* to transition directly from the pilot phase to the definitive phase if feasibility is established.

Data Safety Monitoring Board

As per the principles established by the *Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group* charter, a DSMB will oversee the safety of the trial participants and the overall conduct of the trial. The Committee members will be independent of the trial, free of

conflicts with any of the investigative team, and will consist of two orthopaedic oncologists, a medical oncologist, a radiologist, and a biostatistician. The DSMB will frequently review enrollment and demographic summaries, listings of protocol deviations, and summaries and listings of serious adverse events. They will advise the Principal Investigator and SAFETY study team on any concerns related to participant safety and trial conduct and will make recommendations for: A) study continuation as designed; B) study termination; C) study continuation with major or minor modifications; or D) temporary study suspension of enrollment until some uncertainty is resolved.

Potential impact of the study

The benefit of this pilot study would be to determine the feasibility of the SAFETY trial. This is essential prior to undertaking a large multi-centre RCT. Experience gained during the pilot phase will provide insight into methods to increase enrollment, strategies to maintain protocol adherence and the adjustment of recruitment expectations. In addition, the ultimate success of the pilot phase will support funding requests for the definitive phase of the multi-centre SAFETY trial.

Once the feasibility endpoints are reached, we will transition directly into and begin recruiting for the definitive SAFETY trial. The ultimate goal of the SAFETY trial is to provide high-quality evidence for surveillance strategies following the treatment of STS, which will allow for the development of evidence-based clinical practice guidelines for sarcoma patients worldwide.

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Figure legend

Figure 1. Study flow diagram

Data statement

All data from this work will be maintained in security and confidentiality at the Methods Centre at McMaster University. Access to additional unpublished data will be reviewed on a case-by-case basis and will accord with the guidelines of our local institutional research ethics board.

Authors' contributions

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: All
- Drafting the work: MG, TS, and KM
- Revising it critically for important intellectual content: All
- Final approval of the version to be published: All
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All

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Competing interests statement

Dr. Bhandari, Dr. Ghert, Dr. Randall, and Dr. Hayden report personal fees from consultancy and/or royalties outside the submitted work.

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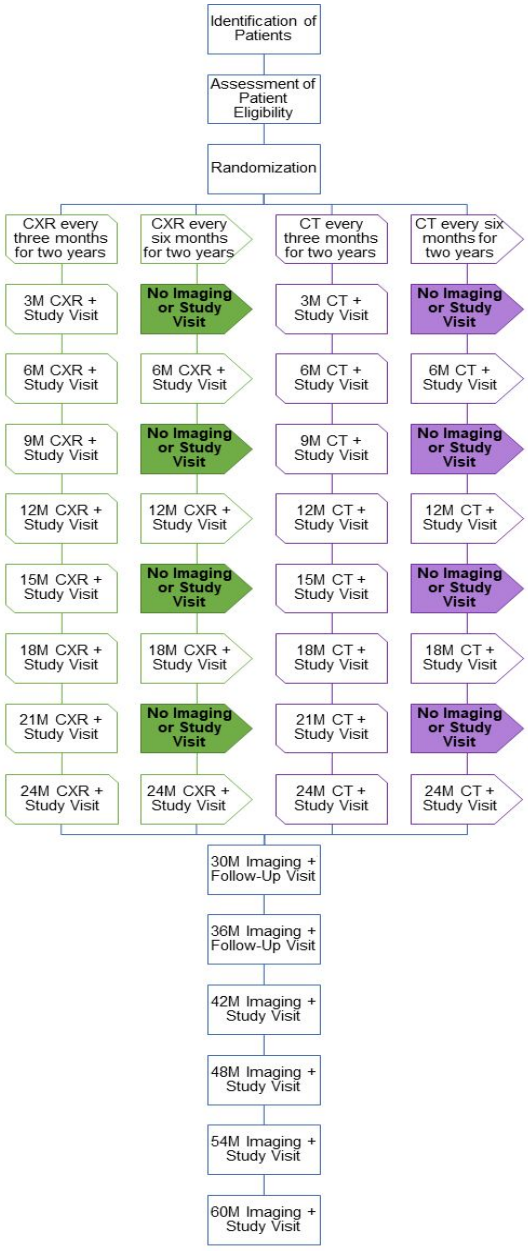

Figure 1.

M = month; CXR = chest X-ray; CT = computed tomography

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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		Reporting Item	Page Number
Title	# 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	N/A
Trial registration: dataset	#2b	All items from the World Health Organization Trial Registration Data Set	N/A

Protocol version	# 3	Date and version identifier	1
Funding	# 4	Sources and types of financial, material, and other support	HAHSO

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2,3,28

Roles and responsibilities: sponsor contact inf	5b	Name and contact information for the trial sponsor	N/A

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Role and responsibilities: sponsor and funder	# 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

Roles and responsibilities: committees	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)	18, 24, 25

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	6, 7, 8

Background and rationale: choice of comparat	6b	Explanation for choice of comparators	6

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Objectives	# 7	Specific objectives or hypotheses	9, 10, 11
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, non-inferiority, exploratory)	9
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	11

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)	12
Interventions: description	# 11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14

Interventions: modifications	# 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

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19, 20

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12, 13
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	See note 1

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)	24
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	20, 21
Recruitment	# 15	Strategies for achieving adequate participant enrolment to reach target sample size	13, 14

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	14

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	14

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19

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Blinding (masking): emergency unblinding	# 17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Data collection plan	# 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	N/A

Data collection plan: retention	# 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	19

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	24, 25
Statistics: outcomes	#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	22

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

Statistics: analysis population and missing data	#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)	N/A

Data monitoring committee	# 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		24, 25

Data monitoring: interim analysis	# 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	N/A
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	24, 25
Auditi	# 23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24, 25

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Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23, 24

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)	N/A
Consent or assent	# 26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, 14

Consent or assent: ancillary studies	#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	13, 14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	28

Data access	# 29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
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: trial results	# 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	N/A	

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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

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Author notes

1. 15, 16, 17, 18

BMJ Open

The Surveillance AFter Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot study to determine the feasibility of a multi-centre randomized controlled trial

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Original article

The Surveillance AFter Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot study to determine the feasibility of a multi-centre randomized controlled trial

The SAFETY Investigators

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Abstract

Introduction Following the treatment of patients with soft tissue sarcomas (STS) that are not metastatic at presentation, the high risk for local and systemic disease recurrence necessitates post-treatment surveillance. Systemic recurrence is most often detected in the lungs. The most appropriate surveillance frequency and modality remain unknown and, as such, clinical practice is highly varied. We plan to assess the feasibility of conducting a multi-centre randomised controlled trial (RCT) that will evaluate the effect on overall five-year survival of two different surveillance frequencies and imaging modalities in patients with STS who undergo surgical excision with curative intent.

Methods and analysis The SAFETY trial will be a multi-centre 2X2 factorial randomized controlled trial. Patients with non-metastatic primary Grade II or III STS treated with excision will be allocated to one of four treatment arms: (1) chest radiograph (CXR) every three months for two years; (2) CXR every six months for two years; (3) chest computed tomography (CT) every three months for two years; or (4) chest CT every six months for two years. The primary outcome of the pilot study is the feasibility of a definitive RCT based on a combination of feasibility endpoints. Secondary outcomes for the pilot study include the primary outcome of the definitive trial (overall survival), patient-reported outcomes on anxiety, satisfaction and quality of life, local recurrence-free survival, metastasis-free survival, treatment-related complications, and net healthcare costs related to surveillance.

Ethics and dissemination This trial received *Pro Tempore* ethics approval from the McMaster / Hamilton Health Sciences Research Ethics Board. Final ethics approval will be obtained prior to commencing patient recruitment. Once feasibility has been established and the definitive protocol is finalized, the study will transition to the definitive study.

Article summary

Article focus

Surveillance AFter Extremity Tumour surgerY (SAFETY) is a pragmatic 2x2 factorial international multi-centre randomised controlled trial that aims to understand the impact of surveillance frequency and imaging modality on overall 5-year survival in patients with soft tissue sarcomas who underwent surgical resection. A pilot study assessing the feasibility of the definitive study will be undertaken first.

Strengths and limitations of this study

- The SAFETY trial will be an international multi-centre 2X2 factorial randomized controlled trial
- The trial will answer a high priority question for sarcoma surgeons
- The SAFETY trial will build on the international collaboration and experience of the PARITY trial
- The feasibility pilot study is essential before undertaking this large multi-centre trial
- The success of the pilot study is dependent on the ability of clinical sites to recruit patients, comply with the protocol, and complete high quality follow-up data

Keywords: surveillance; soft tissue sarcoma; study protocol; randomized controlled trial; pilot study

Background

Magnitude of the problem

Sarcomas are malignancies of connective tissue that most commonly occur in the extremities. Sarcomas can arise within bone (bone sarcoma) or soft-tissue (soft-tissue sarcoma [STS]). Chemotherapy is not curative for the vast majority of patients with STS(1); therefore, surgery is the standard treatment for STS, with radiation considered important for local disease control.

Following treatment for a STS that is not metastatic at presentation, the risk for local and systemic disease recurrence necessitates careful post-operative surveillance. Between 40% and 50% of all sarcoma patients will develop a local or distant recurrence; however, the risk of recurrence is greatest in the first few years, with 68% occurring by two years and 90% by five years(2-4). Metastasis to the lung is the most frequent single location of disease recurrence in sarcoma patients, occurring in the majority of patients with metastases(4-7). Therefore, routine follow-up after completing sarcoma treatment is standard practice in the first five years after surgery. These visits typically include a clinical history, physical examination, and imaging of the lungs (chest radiograph [CXR], or computed tomography [CT] scan of the lungs).

Surveillance strategies for long-term follow-up of sarcoma patients have not been well researched and current guidelines are based on expert opinion, not on high quality evidence(8, 9). As such, current clinical practice is highly varied, with survey data of musculoskeletal oncologists showing that the number of clinic visits ranges from two to 12, the number of CXRs obtained ranges from zero to 13, and the number of CT scans ranges from one to eight in the first year of surveillance(10-12). The current National Comprehensive Cancer Network guidelines suggest that stage II or III tumors should be followed with chest imaging (CT or CXR) every two to six months for the first two to three years and then annually thereafter, while stage I tumors could be followed less frequently during the first two to three years (13).

Best evidence for surveillance strategies

Post-treatment soft-tissue sarcoma surveillance is an integral element of patient care. Although earlier detection of metastatic disease may improve long-term survival, no study has yet provided definitive evidence to support this assumption. In order to assess the available evidence, we completed a systematic review of the available randomized controlled trial (RCT) evidence for surveillance in sarcoma management(14). A single study (published separately with early and longer-term follow-up) was identified(15, 16). The authors of this single-centre study found that three-year overall and disease-free survival was not worse in sarcoma patients who had less intensive surveillance (CXRs) than those with more intensive surveillance (CT scans)(15). Due to the sample size, this trial could not conclusively demonstrate non-inferiority in overall or disease-free survival for a six-monthly interval of follow-up visits against three-monthly interval (both were 64% and 69%, respectively)(15).

A follow-up study on the same patient cohort with five-year survival outcomes confirmed that more frequent follow-up did not improve survival and that, although CT scans detected pulmonary metastasis earlier, they did not lead to better survival compared with CXRs(16). However, this was a single-centre study with relatively small numbers and, therefore, confidence in the results and generalizability of the data to other centres is limited. In addition, a relatively small proportion of screened patients (42%) that were eligible for the trial were included due to the exclusion of patients unlikely to follow-up, thus possibly introducing selection bias(15). Furthermore, low-grade sarcomas were eligible and included in this study, even though they have little metastatic potential and tumour-related mortality; their inclusion may have diminished the magnitude of the effects of the interventions(15). Finally, the majority of the included patients were bone sarcoma patients, thereby limiting the interpretation to STS patients(15).

Risks and benefits of intensive surveillance

Regular, intensive surveillance is more likely to identify recurrent disease earlier than would less intensive surveillance. This type of surveillance may provide reassurance to patients and clinicians; however, the adverse effects of intensive surveillance practices are also noteworthy. The costs that healthcare systems incur as a result of sarcoma surveillance are substantial and could be in excess of USD $20,000 for high-grade sarcomas(17). Furthermore, intensive surveillance can threaten the financial security of patients, due in part to the direct (including travel, accommodation, personal care, and homemaking) and indirect costs (including lost wages for patients and their caregivers) incurred as a result of follow-up appointments(18). As a result, patients' health and quality of life can be dramatically impacted(18-20).

Secondary investigations and earlier knowledge of disease recurrence can also induce anxiety and impact the psychosocial wellbeing for those whose mortality risk cannot be significantly reduced by further medical interventions(21). Overcrowded clinics and long wait times may constitute other important factors that affect patients' psychosocial wellbeing(22). Finally, the use of CT has raised concerns over unnecessary radiation exposure compared to radiographs, although lower dose CT scans may mitigate some of these concerns(23).

Surveillance research as a priority in orthopedic oncology

We recently published a modified Delphi study in which we aimed to identify a clinically relevant consensus-based research agenda in the sarcoma field(24). From this Delphi process that included 80 orthopaedic oncologists and patient representation (with participation from 18 countries), we identified critical research priorities in the field of orthopaedic oncology and determined the top

four feasible and important research questions that will directly inform patient care and enhance clinical practice. This study identified the evaluation of post-operative surveillance strategies as the highest-ranking research priority in the sarcoma field(24).

Study design

We plan to assess the feasibility of conducting the pragmatic, international, multi-centre, 2X2 factorial Surveillance AFter Extremity Tumour surgerY (SAFETY) RCT that answers the following questions: In extremity STS patients who undergo surgical resection with curative intent,)(1) what is the impact of surveillance frequency (every three vs. every six months) on overall survival at five years, and (2) what is the impact of surveillance imaging modality (CXR vs. CT scan) on overall survival at five years? To assess feasibility, we will conduct a pilot study. Study participants will be randomized to one of four possible treatment arms (see Study Interventions below). Randomization will occur at the end of active treatment (surgery ± systemic treatment ± local radiation). Following the two-year intervention phase, study participants will continue to be assessed at regular intervals for an additional three years. As such, all pilot study patients will be transitioned into the definitive study and be included in it. Details of the flow of each study arm are outlined in Figure 1. We anticipate the duration of the pilot study to be three years in order to collect intervention phase data on all participants. The primary outcome of the pilot study is the feasibility of a definitive RCT based on a combination of feasibility endpoints.

The 2x2 factorial study design is ideal and the most efficient method to study two treatment interventions in a single RCT, particularly when there is no interaction between the two interventions. This is unlike a scenario in which the two interventions are medications that may have a synergistic or negative effect when combined. A Bayesian design would be useful do avoid

the question of whether or not an interaction exists, however for the purposes of the present trial it is clear that no interaction exists between the frequency and intensity of surveillance. As Freidlin and Korn discuss in their commentary, the 2x2 factorial design is an efficient design to evaluate two interventions in a cancer clinical trial when there are no interactions between treatments(25).

Objectives

Pilot study primary research objectives

The primary objective of the pilot study will be to determine whether it is feasible to conduct a large multi-centre RCT that will evaluate the impact of surveillance strategies on patient survival following extremity STS surgery. To do so, we will assess our ability to:

A) Recruit patients across multiple participating clinical sites;

B) Ensure compliance with the study protocol, including the application of eligibility criteria, timing of intervention phase and post-intervention phase visits and imaging modality;

C) Maintain completeness of follow-up data;

D) Maintain completeness of cost analysis data; and

E) Maintain data quality.

Pilot study secondary research objectives

The secondary objectives of the pilot study will include assessing the impact of either surveillance frequency (every three vs. every six months) or imaging modality (CXR vs. CT scan) on:

A) Overall survival;

B) Patient anxiety, satisfaction and quality of life;

C) Local recurrence-free survival and metastasis-free survival;

D) Treatment-related complications; and

E) Net direct healthcare costs and net costs of treatment and treatment-related complications once metastases are detected.

Hypothesis

Pilot study

We hypothesize that the SAFETY trial will be feasible due to: A) its pragmatic design; B) our established international collaborative research network; C) our qualified, multi-disciplinary study team; D) our existing trial infrastructure; and E) the priority of the study question.

Definitive study

There are two hypotheses:

1- More frequent post-operative surveillance (compared to less frequent post-operative surveillance) in the first two years following the surgical excision of a STS will improve survival over five years;

2 - The use of post-operative CT scans (compared to CXR) in the first two years following the surgical excision of a STS will improve survival over five years.

Study setting

This study will be coordinated by the Methods Centre within the Centre for Evidence-Based Orthopaedics (CEO) at McMaster University (Hamilton, ON, Canada). For the pilot study, we expect that patients will be enrolled from ten clinical sites across four continents. Clinical sites will be carefully screened prior to participation in the study. The clinical site inclusion criteria are: I) adequate research personnel and infrastructure to manage the study; II) sufficiently high

extremity STS volume to complete enrollment within the study timeline (defined as greater than or equal to (≥) 20 patients per year); III) commitment from all or most orthopaedic oncologists to participate in the trial; and IV) access to the two imaging modalities. The exclusion criteria are: I) a lack of interest in the trial; II) anticipated challenges with protocol compliance; III) conflicting studies, in the judgment of the Principal Investigator, that would inhibit patient participation; and IV) financial or contract constraints.

Patient eligibility criteria

Inclusion criteria

Patients who meet all of the following criteria will be included:

1) Age of 18 years or older;
2) Diagnosed with a primary extremity grade II or III STS;
3) Undergone surgical resection of the tumour with curative intent and grossly negative margins (R0 or R1 resection margins);
4) Completed neoadjuvant or adjuvant radiation and / or chemotherapy, if applicable;
5) The tumour size is greater than or equal to (≥) five centimeters according to the pathology report or pre-treatment MRI if neoadjuvant radiation and / or chemotherapy are given; and
6) Provision of informed consent.

Exclusion criteria

Patients who meet any of the following criteria will be excluded:

1) Metastatic disease at initial presentation based on thoracic imaging (a second CT scan may be required to confirm that indeterminate nodules are false positives before the patient can be enrolled provided that the second CT scan shows no evidence of metastatic disease);
2) Undergone surgical excision of a local recurrence;
3) Diagnosis of one of the special sub-types: myxoid / round cell liposarcoma or extra-skeletal Ewing's sarcoma (These sarcomas have different metastatic patterns, which necessitate different surveillance protocols);
4) Previous diagnosis of a genetic syndrome with an elevated risk of malignancy, such as Li-Fraumeni Syndrome (such individuals appear to be at an elevated risk for radiation-induced cancers, so the use of CT scans should be limited);
5) Previous diagnosis with a co-morbid condition that has a life expectancy of less than one year;
6) The site-specific surveillance protocol for the patient's disease is not compatible with the study protocol (i.e., regular planned whole-body imaging with positron emission tomography [PET] scans);
7) Diagnosed with another malignancy within the past five years;
8) Likely problems, in the judgment of the investigator, with maintaining follow-up; and
9) Currently enrolled in a study that does not permit co-enrollment;
10) The patient has already been enrolled in the SAFETY trial.

Recruitment and screening

Each participating clinical site will have a locally responsible investigator who will oversee the local administration of the trial, screen STS patients for eligibility, and develop a site-specific patient enrollment plan. A Screening Form will be completed for all STS patients aged 18 years

or older, irrespective of whether they are eligible to participate in the study or not. Patients will become eligible, will be screened and consented during the first clinic visit at which all treatment is complete, the surgical wound has healed, and the plan for post-treatment surveillance is discussed with the patient. The process of obtaining and documenting informed consent will be completed in accordance with local Good Clinical Practice recommendations. Consent procedures will comply with the appropriate ethics committee and the Health Insurance Portability and Accountability Act (where applicable).

Randomisation and allocation of patients to study groups

A centralised and automated internet-based randomisation system using random variable block sizes will assign participants to the study groups. Study personnel at each participating site will complete this task. Randomisation will occur only after eligibility is confirmed and consent to participate has been obtained. Participants will be stratified based on clinical site and peri-operative chemotherapy.

Study interventions

Participants will be randomised to one of four treatment groups:

1) CXR every three months for two years;
2) CXR every six months for two years;
3) Chest CT every three months for two years; or
4) Chest CT every six months for two years.

Following completion of the intervention phase, participants will continue to be followed in the study for an additional three years. During this three-year post-intervention phase,

participants will be followed at least every six months as per National Comprehensive Cancer Network (NCCN) guidelines(13). If possible, thoracic imaging will continue at each scheduled post-intervention phase visit according to the participants' original allocations.

Relapse

Local imaging and clinical assessment of the primary tumour site will be carried out as per the standard protocol at each participating clinical site. Further diagnostic tests will be performed in the presence of clinical symptoms or radiologic findings suggestive of disease relapse. Recurrence will be radiologically or histologically confirmed and classified as local or systemic (metastasis) recurrence. The first modality suggesting disease relapse in participants with confirmed local or systemic recurrence will be recorded as responsible for its detection.

Outcome measures

Pilot study primary outcome

To evaluate feasibility, we will assess the number of patients screened and recruited at each participating clinical site, participant retention, and maintenance of data quality. In addition, we will evaluate the utilization of an internet-based centralized randomisation system focusing on the accuracy of data entry, appropriate stratification of participants and the minimization of randomisation errors. Finally, we will evaluate investigator and participant compliance with the study protocol, including the application of eligibility criteria, compliance with the surveillance imaging and frequency regimens, frequency of crossover and timing of post-intervention phase visits. The a priori criteria for the success of the pilot study are listed below:

A) *Recruitment Measure:* We will consider our recruitment strategy feasible if we are able to enroll the pilot sample of 195 patients (approximately 20 patients from each clinical site participating in the pilot study) within two years. See sample size determination below. As such, we will aim to recruit 100 patients during the first year. If we are unable to achieve at least 90% of this goal (90 patients) then we will plan to increase the number of participating sites as a study rescue measure.

B) *Protocol Adherence Measure:* During the pilot study of the PARITY trial, we were able to maintain an overall protocol adherence rate in excess of 90%(26). Recent reports prepared for the PARITY Data and Safety Monitoring Board (DSMB) indicate a similar protocol adherence rate. However, given the greater complexity and longer duration of the SAFETY trial interventions, we will consider our protocol adherence strategies feasible if there is adherence of 85% or greater to the visit windows and imaging modality prescribed by the protocol.

C) *Participant Retention Measure:* While 20% loss-to-follow-up has traditionally been considered acceptable in clinical research, evidence from other orthopaedic trials suggests that bias begins to affect study results at even lower rates of loss-to-follow-up(27). Therefore, we will consider our participant retention strategies feasible if no more than 15% of participants are lost-to-follow-up.

D) *Maintenance of Data Quality Measure:* We obtained a data completeness rate of approximately 90% in the PARITY trial pilot study (26). Therefore, we will consider our data quality strategies feasible if we are able to maintain 95% or greater completeness of participant follow-up data for the definitive primary outcome. We will also consider our data quality strategies feasible if we are able to maintain 85% or greater completeness of participant follow-up data for the secondary outcomes.

Pilot study secondary outcomes

The main secondary outcome for the pilot study will be death from any cause. Data on secondary outcomes for the definitive trial, which are listed below, will also be collected. These include:

A) *Patient-reported outcome measures:* The validated Patient-Reported Outcomes Measurement Information System (PROMIS)® Cancer-Anxiety questionnaire, PROMIS® Satisfaction with Social Roles and Activities questionnaire, and the EuroQol-5 Dimension (EQ-5D) will be used to assess patient anxiety, satisfaction and quality of life, respectively. These questionnaires will be administered at the baseline visit, as well as the 6-month, 12-month, 18-month and 24-month intervention phase, as well as 36-month, 48-month and 60-month post-intervention phase visits.

B) *Local recurrence-free survival (LRFS) outcome measure:* LRFS will be defined as the length of time from randomization that the participant survives with no detection of recurrent disease at the initial tumor site or operative field.

C) *Metastasis-free survival* (*MFS) outcome measure:* MFS will be defined as the length of time from randomization that the participant survives with no detection of systemic disease recurrence at any anatomic location.

D) *Treatment-related complications outcome measures:* Treatment-related complications will include both chemotherapy-related complications, such as febrile neutropenia, fungal infections or sepsis, and thoracotomy-related complications, such as pneumothorax, or surgical site infections.

E) *Net healthcare costs outcome measures*: We will perform an incremental cost analysis of net costs of surveillance and costs incurred from metastasis treatment and metastasis treatment related complications. Unit costs for all resources used by trial participants will be obtained from regional statistics and from centers participating in the trial. These unit costs will be combined with the resource volumes to obtain a net cost per participant over their time in the trial.

Protecting against sources of bias

Adjudication of outcomes

An independent Central Adjudication Committee (CAC) will review all situations where eligibility is in doubt, as well as all reported instances of disease relapse, treatment-related complications, and death to determine whether a study event has occurred. The SAFETY CAC will be comprised of two orthopaedic oncologists, one medical oncologist, and one radiologist. All participating clinical sites will submit digital imaging and relevant hospital records to the Methods Centre via a web-based platform for events that require adjudication.

Blinding

The local clinical team, site study personnel and participants cannot be blinded to the treatment allocation. The CAC will be blinded to surveillance frequency. The data analysts will, however, remain blinded during the trial's analysis.

Maximization of follow-up

We anticipate only minimal losses to follow-up in our musculoskeletal oncology population. Nonetheless, the following procedures will be implemented to minimize losses:

- Individuals likely to present problems with compliance to the study protocol or maintaining follow-up will be excluded;
- At the time of randomization, participants will be asked to provide their contact information, as well as the contact information of their family physician and three alternate contacts;

- Participants who refuse to return for a study assessment will be asked if they are willing to provide follow-up data (to determine survival and to complete study questionnaires) via telephone;
- If a participant cannot be reached, their status regarding the primary study outcome will be assessed by reviewing their medical records;
- Study personnel will remind participants of upcoming clinic visits;
- To assuage possible concerns related to less frequent follow-up, participants will be encouraged to schedule an ad hoc visit anytime they are concerned, even if it breaks the surveillance protocol to which they were assigned;
- Participants will be provided with access to educational content, such as a video that demonstrates how to self-examine for a local recurrence of their STS; and
- Parking and travel vouchers will be provided to participants, where possible, to alleviate the costs associated with the study.

Minimization of crossovers of surveillance interventions

Crossovers are unlikely for either surveillance intervention as investigators will be requesting the imaging modality during surveillance visits. Any deviation with regards to frequency or imaging modality will be documented. In the event of disease recurrence or progression, the following standardized management protocols will be adopted:

- Local Recurrence: the participant will have a lung CT scan to confirm no progression of their systemic disease before continuing with the study protocol.

- Metastases: the participant will no longer be followed as per the study protocol, but per the appropriate follow-up for the interventions required for the treatment of metastases; however, the participant will continue to be followed in the trial.

For both events, the specific imaging modality used to detect either the local recurrence or the metastases will be documented.

Patients that have incidental or off-protocol imaging will not crossover, however this will be documented as a protocol deviation. In the case of a CXR that warrants further investigation with a CT scan, this will be documented. If the patient is found to have disease recurrence, we will document how the disease recurrence was (A) first identified; and (B) confirmed. If after a CT scan the patient is found to not have disease recurrence, the patient will resume surveillance as per the arm to which they were randomised.

Sample size determination

Pilot study sample size

The confidence interval approach was used to calculate the required sample size for the pilot study(28). We determined *a priori* that the definitive trial would only be feasible if our protocol adherence rate was at least 85%. Using a 95% confidence level and a 5% margin of error, we calculated a required sample size of 195 patients.

Definitive study sample size

Our best estimate of the control group overall five-year survival for both the surveillance frequency and imaging modality is 55%(16). Given that intensive surveillance will detect metastatic disease at an earlier stage, we will use a superiority design to compare survival between more versus less

intensive surveillance. A 10% absolute increase in overall five-year survival associated with both more frequent surveillance and the use of CT scans represents a clinically important difference, as outlined by the American Society of Clinical Oncology's statement on clinically meaningful outcomes in cancer trials(29). Therefore, the definitive trial will be powered to detect an absolute difference of 10% in overall five-year survival.

With a desired power of 0.80, we calculated a sample size of 396 participants per study arm. We will account for a 5% loss to follow-up and, therefore, the final sample size will be 830 participants. **Table 1** shows various sample sizes for pairwise comparisons of alternative surveillance frequencies / imaging modalities given varying control event rates and absolute increases in survival. Statistical Package for the Social Sciences (SPSS) (IBM Corporation) software was used for sample size calculation.

The definitive sample size calculation may be adjusted as we prepare for the transition from the pilot to the definitive study as a result of data collected during the pilot study. One factor we may consider will be the percent lost to follow-up by the end of the pilot study. Other factors such as the estimated control group overall five-year survival, the clinically meaningful outcome, and power cannot be amended.

Table 1. Sample Size Per Group for 80% power, α=0.05. Event rate = death

		Event Rate in More Intensive Surveillance Group			
		25%	30%	35%	40%
Event Rate in Less Intensive Surveillance Group	35%	696	2832	-	-
	40%	332	752	3020	-
	45%	196	352	792	3148

	50%	132	204	368	816
	55%	96	136	212	372

Analysis of feasibility outcomes

A full description of the measures, variables, and methods of analysis are shown in **Table 2**. We will record the total number of participants enrolled on a monthly basis. Each participating site will keep a Screening Log of included and excluded patients. We will also keep a record of participants who miss visits, and those who are withdrawn or lost to follow-up. These will be reported using descriptive statistics – reported as counts (percent) for categorical variables and mean (standard deviation) for continuous variables with 95% confidence intervals. We will report the proportion of complete CRFs as descriptive data.

Analysis of definitive study primary outcome

The analysis and reporting of the trial will follow the CONSORT criteria. The primary analysis will compare the treatment groups on the overall 5-year survival. Two independent comparisons between treatment groups will be made using Cox regression models with time to the definitive primary endpoint. Results will be expressed as effect (ORs for binary outcomes, HRs for time-dependent outcomes and mean difference for continuous outcomes), corresponding 2-sided 95% CIs and associated p-values.

Table 2. Summary of Feasibility Outcomes Analysis Plan

Objective	Outcome	Criteria for success of feasibility	Method of analysis
To determine the feasibility of conducting the multi-centre SAFETY international RCT	Recruitment Measure	Enrollment of pilot sample within two years	Descriptive statistics reported as counts (perce for categorical variables a means (standard deviatio for continuous variables w 95% CI
	Protocol Adherence Measure	Protocol adherence of 85% or greater	
	Participant Retention Measure	Loss-to-participant follow-up of 15% or less	
	Maintenance of Data Quality Measure	Data completeness of 95% or greater for the definitive primary outcome Data completeness of 85% or greater for the secondary outcomes	

Ethical considerations

This study is to be conducted according to international standards of Good Clinical Practice, applicable government regulations, and institutional research policies and procedures. All study intervention phase (surveillance) arms fall within the spectrum of current standard practice, as do the standardized post-intervention phase follow-up visits. This trial has received *Pro Tempore* ethics approval from the McMaster / Hamilton Health Sciences Research Ethics Board on August 23rd, 2018. The study protocol will be submitted to a properly constituted independent ethics

committee, in agreement with local legal prescriptions, for formal approval of the study conduct at each participating clinical site. A copy of this approval will be provided to the Methods Centre by each participating clinical site prior to the local commencement of the study.

Study Timeline

We expect that the pilot study will take just over three years to complete. We estimate that recruitment will take approximately one year to complete per site. The initiation of screening and enrollment will likely be staggered across the participating clinical sites due to the variability in the time required to obtain ethics approval and negotiate institutional contracts. Therefore the pilot study recruitment timeline will be up to two years. We expect a further one year for all pilot participants to complete the intervention phase of the trial. Although we will not have complete post-intervention phase data for any pilot participants, we anticipate being able to determine feasibility at the end of the intervention phase based on our feasibility objectives. We plan *a priori* to transition directly from the pilot to the definitive study if feasibility is established.

Data Safety Monitoring Board

As per the principles established by the *Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group* charter, a DSMB will oversee the safety of the trial participants and the overall conduct of the trial. The Committee members will be independent of the trial, free of conflicts with any of the investigative team, and will consist of two orthopaedic oncologists, a medical oncologist, a radiologist, and a biostatistician. The DSMB will frequently review enrollment and demographic summaries, listings of protocol deviations, and summaries and listings of serious adverse events. They will advise the Principal Investigator and SAFETY study

team on any concerns related to participant safety and trial conduct and will make recommendations for: A) study continuation as designed; B) study termination; C) study continuation with major or minor modifications; or D) temporary study suspension of enrollment until some uncertainty is resolved.

Potential impact of the study

The benefit of this pilot study would be to determine the feasibility of the SAFETY trial. This is essential prior to undertaking a large multi-centre RCT. Experience gained during the pilot study will provide insight into methods to increase enrollment, strategies to maintain protocol adherence and the adjustment of recruitment expectations. In addition, the ultimate success of the pilot study will support funding requests for the definitive study of the multi-centre SAFETY trial.

Once the feasibility endpoints are reached, we will transition directly into and begin recruiting for the definitive SAFETY trial. The ultimate goal of the SAFETY trial is to provide high-quality evidence for surveillance strategies following the treatment of STS, which will allow for the development of evidence-based clinical practice guidelines for sarcoma patients worldwide.

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Figure legend

Figure 1. Study flow diagram

Data statement

All data from this work will be maintained in security and confidentiality at the Methods Centre at McMaster University. Access to additional unpublished data will be reviewed on a case-by-case basis and will accord with the guidelines of our local institutional research ethics board.

Authors' contributions

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- Drafting the work: Michelle Ghert, Patricia Schneider, and Karim Masrouha
- Revising it critically for important intellectual content: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- Final approval of the version to be published: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt

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Competing interests statement

Dr. Bhandari, Dr. Ghert, Dr. Randall, and Dr. Hayden report personal fees from consultancy and/or royalties outside the submitted work.

Word count

4,785

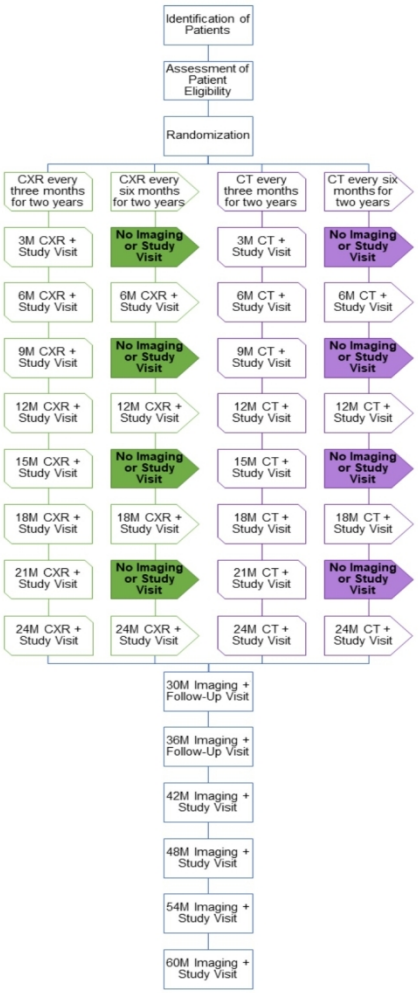

Figure 1.

M = month; CXR = chest X-ray; CT = computed tomography

Study flow diagram

146x146mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	# 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	N/A
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A

Protocol version	# 3	Date and version identifier	1
Funding	# 4	Sources and types of financial, material, and other support	HAHSO

Roles and responsibilities: contributorship	5a	Names, affiliations, and roles of protocol contributors	2,3,28

Roles and responsibilities: sponsor contact inf	5b	Name and contact information for the trial sponsor	N/A

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Role and responsibilities: sponsor and funder	# 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	

Roles and responsibilities: committees	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)	18, 24, 25

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	6, 7, 8

Background and rationale: choice of comparat	6b	Explanation for choice of comparators	6

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Objectives	# 7	Specific objectives or hypotheses	9, 10, 11
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, non-inferiority, exploratory)	9
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	11

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)	12
Interventions: description	# 11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14

Interventions: modifications	# 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

Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19, 20

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12, 13
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	See note 1

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)	24
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	20, 21
Recruitment	# 15	Strategies for achieving adequate participant enrolment to reach target sample size	13, 14

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	14

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	14

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19

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Blinding (masking): emergency unblinding	# 17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Data collection plan	# 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	N/A

Data collection plan: retention	# 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	19

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	24, 25
Statistics: outcomes	#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	22

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

Statistics: analysis population and missing data	#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)	N/A

Data monitoring committee	# 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		24, 25

Data monitoring: interim analysis	# 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	N/A
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	24, 25
Auditi	# 23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24, 25

n g			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23, 24

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)	N/A
Consent or assent	# 26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, 14

Consent to ancillary studies	#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	13, 14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	28

Data access	# 29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
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: trial results	# 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	N/A

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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

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Author notes

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BMJ Open

The Surveillance AFter Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot study to determine the feasibility of a multi-centre randomized controlled trial

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The Surveillance AFter Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot study to determine the feasibility of a multi-centre randomized controlled trial

The SAFETY Investigators

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Abstract

Introduction Following the treatment of patients with soft tissue sarcomas (STS) that are not metastatic at presentation, the high risk for local and systemic disease recurrence necessitates post-treatment surveillance. Systemic recurrence is most often detected in the lungs. The most appropriate surveillance frequency and modality remain unknown and, as such, clinical practice is highly varied. We plan to assess the feasibility of conducting a multi-centre randomised controlled trial (RCT) that will evaluate the effect on overall five-year survival of two different surveillance frequencies and imaging modalities in patients with STS who undergo surgical excision with curative intent.

Methods and analysis The SAFETY trial will be a multi-centre 2x2 factorial randomized controlled trial. Patients with non-metastatic primary Grade II or III STS treated with excision will be allocated to one of four treatment arms: (1) chest radiograph (CXR) every three months for two years; (2) CXR every six months for two years; (3) chest computed tomography (CT) every three months for two years; or (4) chest CT every six months for two years. The primary outcome of the pilot study is the feasibility of a definitive RCT based on a combination of feasibility endpoints. Secondary outcomes for the pilot study include the primary outcome of the definitive trial (overall survival), patient-reported outcomes on anxiety, satisfaction and quality of life, local recurrence-free survival, metastasis-free survival, treatment-related complications, and net healthcare costs related to surveillance.

Ethics and dissemination This trial received *Pro Tempore* ethics approval from the McMaster / Hamilton Health Sciences Research Ethics Board. Final ethics approval will be obtained prior to commencing patient recruitment. Once feasibility has been established and the definitive protocol is finalized, the study will transition to the definitive study.

Article summary

Strengths and limitations of this study

- The SAFETY trial will be an international multi-centre 2x2 factorial randomized controlled trial
- The trial will answer a high priority question for sarcoma surgeons
- The SAFETY trial will build on the international collaboration and experience of the PARITY trial
- The feasibility pilot study is essential before undertaking this large multi-centre trial
- The success of the pilot study is dependent on the ability of clinical sites to recruit patients, comply with the protocol, and complete high quality follow-up data

Keywords: surveillance; soft tissue sarcoma; study protocol; randomized controlled trial; pilot study

Background

Magnitude of the problem

Sarcomas are malignancies of connective tissue that most commonly occur in the extremities. Sarcomas can arise within bone (bone sarcoma) or soft-tissue (soft-tissue sarcoma [STS]). Chemotherapy is not curative for the vast majority of patients with STS(1); therefore, surgery is the standard treatment for STS, with radiation considered important for local disease control.

Following treatment for a STS that is not metastatic at presentation, the risk for local and systemic disease recurrence necessitates careful post-operative surveillance. Between 40% and 50% of all sarcoma patients will develop a local or distant recurrence; however, the risk of recurrence is greatest in the first few years, with 68% occurring by two years and 90% by five years(2-4). Metastasis to the lung is the most frequent single location of disease recurrence in sarcoma patients, occurring in the majority of patients with metastases(4-7). Therefore, routine follow-up after completing sarcoma treatment is standard practice in the first five years after surgery. These visits typically include a clinical history, physical examination, and imaging of the lungs (chest radiograph [CXR], or computed tomography [CT] scan of the lungs).

Surveillance strategies for long-term follow-up of sarcoma patients have not been well researched and current guidelines are based on expert opinion, not on high quality evidence(8, 9). As such, current clinical practice is highly varied, with survey data of musculoskeletal oncologists showing that the number of clinic visits ranges from two to 12, the number of CXRs obtained ranges from zero to 13, and the number of CT scans ranges from one to eight in the first year of surveillance(10-12). The current National Comprehensive Cancer Network guidelines suggest that stage II or III tumors should be followed with chest imaging (CT or CXR) every two to six months

for the first two to three years and then annually thereafter, while stage I tumors could be followed less frequently during the first two to three years (13).

Best evidence for surveillance strategies

Post-treatment soft-tissue sarcoma surveillance is an integral element of patient care. Although earlier detection of metastatic disease may improve long-term survival, no study has yet provided definitive evidence to support this assumption. In order to assess the available evidence, we completed a systematic review of the available randomized controlled trial (RCT) evidence for surveillance in sarcoma management(14). A single study (published separately with early and longer-term follow-up) was identified(15, 16). The authors of this single-centre study found that three-year overall and disease-free survival was not worse in sarcoma patients who had less intensive surveillance (CXRs) than those with more intensive surveillance (CT scans)(15). Due to the sample size, this trial could not conclusively demonstrate non-inferiority in overall or disease-free survival for a six-monthly interval of follow-up visits against three-monthly interval (both were 64% and 69%, respectively)(15).

A follow-up study on the same patient cohort with five-year survival outcomes confirmed that more frequent follow-up did not improve survival and that, although CT scans detected pulmonary metastasis earlier, they did not lead to better survival compared with CXRs(16). However, this was a single-centre study with relatively small numbers and, therefore, confidence in the results and generalizability of the data to other centres is limited. In addition, a relatively small proportion of screened patients (42%) that were eligible for the trial were included due to the exclusion of patients unlikely to follow-up, thus possibly introducing selection bias(15). Furthermore, low-grade sarcomas were eligible and included in this study, even though they have

little metastatic potential and tumour-related mortality; their inclusion may have diminished the magnitude of the effects of the interventions(15). Finally, the majority of the included patients were bone sarcoma patients, thereby limiting the interpretation to STS patients(15).

Risks and benefits of intensive surveillance

Regular, intensive surveillance is more likely to identify recurrent disease earlier than would less intensive surveillance. This type of surveillance may provide reassurance to patients and clinicians; however, the adverse effects of intensive surveillance practices are also noteworthy. The costs that healthcare systems incur as a result of sarcoma surveillance are substantial and could be in excess of USD $20,000 for high-grade sarcomas(17). Furthermore, intensive surveillance can threaten the financial security of patients, due in part to the direct (including travel, accommodation, personal care, and homemaking) and indirect costs (including lost wages for patients and their caregivers) incurred as a result of follow-up appointments(18). As a result, patients' health and quality of life can be dramatically impacted(18-20).

Secondary investigations and earlier knowledge of disease recurrence can also induce anxiety and impact the psychosocial wellbeing for those whose mortality risk cannot be significantly reduced by further medical interventions(21). Overcrowded clinics and long wait times may constitute other important factors that affect patients' psychosocial wellbeing(22). Finally, the use of CT has raised concerns over unnecessary radiation exposure compared to radiographs, although lower dose CT scans may mitigate some of these concerns(23).

Surveillance research as a priority in orthopedic oncology

We recently published a modified Delphi study in which we aimed to identify a clinically relevant consensus-based research agenda in the sarcoma field(24). From this Delphi process that included 80 orthopaedic oncologists and patient representation (with participation from 18 countries), we identified critical research priorities in the field of orthopaedic oncology and determined the top four feasible and important research questions that will directly inform patient care and enhance clinical practice. This study identified the evaluation of post-operative surveillance strategies as the highest-ranking research priority in the sarcoma field(24).

Patient and public involvement

To ensure that we maintain a patient-centered approach to the design and development of this study, we required the opportunity for open dialogue between the multidisciplinary and international SAFETY study team, along with patient / caregiver representatives and other key stakeholders. To facilitate their interaction and collaboration, we held an in-person Protocol Development Meeting in Toronto, ON, Canada in May 2018. At this meeting, we made critical decisions with respect to the study protocol, including: A) study design; B) primary and secondary outcomes; C) patient eligibility; D) follow-up timeframe; E) methods to protect against bias; F) randomization stratification; and G) further patient engagement. We also had the opportunity to discuss several issues that may compromise the study's success and strategize ways to manage these challenges, such as: I) acceptable surveillance schedules that account for differences in international standards of clinical practice; II) possible ethical concerns; III) patient compliance; IV) local implementation and procedural variation; V) competing studies; and VI) funding opportunities.

We are also conducting a patient survey to assess international patient willingness to participate in a study that randomizes patients to a post-operative surveillance regimen in the management of a primary extremity sarcoma. Since there is no available validated tool to assess patient opinions and preferences, we developed a unique patient questionnaire for the purposes of this study. All new patients who present to a participating sarcoma clinic are screened for study participation. The preliminary survey questionnaire responses suggest that most sarcoma patients believe that they have a good understanding of clinical research. Furthermore, over half of respondents feel comfortable with being randomized to receive a treatment. Ultimately, almost 80% of respondents have indicated that they would agree to participate in the SAFETY trial if eligible.

Study design

We plan to assess the feasibility of conducting the pragmatic, international, multi-centre, 2x2 factorial Surveillance AFter Extremity Tumour surgerY (SAFETY) RCT that answers the following questions: In extremity STS patients who undergo surgical resection with curative intent,)(1) what is the impact of surveillance frequency (every three vs. every six months) on overall survival at five years, and (2) what is the impact of surveillance imaging modality (CXR vs. CT scan) on overall survival at five years? To assess feasibility, we will conduct a pilot study. Study participants will be randomized to one of four possible treatment arms (see Study Interventions below). Randomization will occur at the end of active treatment (surgery ± systemic treatment ± local radiation). Following the two-year intervention phase, study participants will continue to be assessed at regular intervals for an additional three years. As such, all pilot study patients will be transitioned into the definitive study and be included in it. Details of the flow of each study arm

are outlined in Figure 1. We anticipate the duration of the pilot study to be three years in order to collect intervention phase data on all participants. The primary outcome of the pilot study is the feasibility of a definitive RCT based on a combination of feasibility endpoints.

The 2x2 factorial study design is ideal and the most efficient method to study two treatment interventions in a single RCT, particularly when there is no interaction between the two interventions. This is unlike a scenario in which the two interventions are medications that may have a synergistic or negative effect when combined. A Bayesian design would be useful do avoid the question of whether or not an interaction exists, however for the purposes of the present trial it is clear that no interaction exists between the frequency and intensity of surveillance. As Freidlin and Korn discuss in their commentary, the 2x2 factorial design is an efficient design to evaluate two interventions in a cancer clinical trial when there are no interactions between treatments(25).

Objectives

Pilot study primary research objectives

The primary objective of the pilot study will be to determine whether it is feasible to conduct a large multi-centre RCT that will evaluate the impact of surveillance strategies on patient survival following extremity STS surgery. To do so, we will assess our ability to:

A) Recruit patients across multiple participating clinical sites;

B) Ensure compliance with the study protocol, including the application of eligibility criteria, timing of intervention phase and post-intervention phase visits and imaging modality;

C) Maintain completeness of follow-up data;

D) Maintain completeness of cost analysis data; and

E) Maintain data quality.

Pilot study secondary research objectives

The secondary objectives of the pilot study will include assessing the impact of either surveillance frequency (every three vs. every six months) or imaging modality (CXR vs. CT scan) on:

A) Overall survival;

B) Patient anxiety, satisfaction and quality of life;

C) Local recurrence-free survival and metastasis-free survival;

D) Treatment-related complications; and

E) Net direct healthcare costs and net costs of treatment and treatment-related complications once metastases are detected.

Hypothesis

Pilot study

We hypothesize that the SAFETY trial will be feasible due to: A) its pragmatic design; B) our established international collaborative research network; C) our qualified, multi-disciplinary study team; D) our existing trial infrastructure; and E) the priority of the study question.

Definitive study

There are two hypotheses:

1- More frequent post-operative surveillance (compared to less frequent post-operative surveillance) in the first two years following the surgical excision of a STS will improve survival over five years;

2 - The use of post-operative CT scans (compared to CXR) in the first two years following the surgical excision of a STS will improve survival over five years.

Study setting

This study will be coordinated by the Methods Centre within the Centre for Evidence-Based Orthopaedics (CEO) at McMaster University (Hamilton, ON, Canada). For the pilot study, we expect that patients will be enrolled from ten clinical sites across four continents. Clinical sites will be carefully screened prior to participation in the study. The clinical site inclusion criteria are: I) adequate research personnel and infrastructure to manage the study; II) sufficiently high extremity STS volume to complete enrollment within the study timeline (defined as greater than or equal to (≥) 20 patients per year); III) commitment from all or most orthopaedic oncologists to participate in the trial; and IV) access to the two imaging modalities. The exclusion criteria are: I) a lack of interest in the trial; II) anticipated challenges with protocol compliance; III) conflicting studies, in the judgment of the Principal Investigator, that would inhibit patient participation; and IV) financial or contract constraints.

Patient eligibility criteria

Inclusion criteria

Patients who meet all of the following criteria will be included:

1) Age of 18 years or older;
2) Diagnosed with a primary extremity grade II or III STS;
3) Undergone surgical resection of the tumour with curative intent and grossly negative margins (R0 or R1 resection margins);
4) Completed neoadjuvant or adjuvant radiation and / or chemotherapy, if applicable;

5) The tumour size is greater than or equal to (≥) five centimeters according to the pathology report or pre-treatment MRI if neoadjuvant radiation and / or chemotherapy are given; and
6) Provision of informed consent.

Exclusion criteria

Patients who meet any of the following criteria will be excluded:

1) Metastatic disease at initial presentation based on thoracic imaging (a second CT scan may be required to confirm that indeterminate nodules are false positives before the patient can be enrolled provided that the second CT scan shows no evidence of metastatic disease);
2) Undergone surgical excision of a local recurrence;
3) Diagnosis of one of the special sub-types: myxoid / round cell liposarcoma or extra-skeletal Ewing's sarcoma (These sarcomas have different metastatic patterns, which necessitate different surveillance protocols);
4) Previous diagnosis of a genetic syndrome with an elevated risk of malignancy, such as Li-Fraumeni Syndrome (such individuals appear to be at an elevated risk for radiation-induced cancers, so the use of CT scans should be limited);
5) Previous diagnosis with a co-morbid condition that has a life expectancy of less than one year;
6) The site-specific surveillance protocol for the patient's disease is not compatible with the study protocol (i.e., regular planned whole-body imaging with positron emission tomography [PET] scans);
7) Diagnosed with another malignancy within the past five years;
8) Likely problems, in the judgment of the investigator, with maintaining follow-up; and
9) Currently enrolled in a study that does not permit co-enrollment;

10) The patient has already been enrolled in the SAFETY trial.

Recruitment and screening

Each participating clinical site will have a locally responsible investigator who will oversee the local administration of the trial, screen STS patients for eligibility, and develop a site-specific patient enrollment plan. A Screening Form will be completed for all STS patients aged 18 years or older, irrespective of whether they are eligible to participate in the study or not. Patients will become eligible, will be screened and consented during the first clinic visit at which all treatment is complete, the surgical wound has healed, and the plan for post-treatment surveillance is discussed with the patient. The process of obtaining and documenting informed consent will be completed in accordance with local Good Clinical Practice recommendations. Consent procedures will comply with the appropriate ethics committee and the Health Insurance Portability and Accountability Act (where applicable).

Randomisation and allocation of patients to study groups

A centralised and automated internet-based randomisation system using random variable block sizes will assign participants to the study groups. Study personnel at each participating site will complete this task. Randomisation will occur only after eligibility is confirmed and consent to participate has been obtained. Participants will be stratified based on clinical site and peri-operative chemotherapy.

Study interventions

Participants will be randomised to one of four treatment groups:

1) CXR every three months for two years;
2) CXR every six months for two years;
3) Chest CT every three months for two years; or
4) Chest CT every six months for two years.

Following completion of the intervention phase, participants will continue to be followed in the study for an additional three years. During this three-year post-intervention phase, participants will be followed at least every six months as per National Comprehensive Cancer Network (NCCN) guidelines(13). If possible, thoracic imaging will continue at each scheduled post-intervention phase visit according to the participants' original allocations.

Relapse

Local imaging and clinical assessment of the primary tumour site will be carried out as per the standard protocol at each participating clinical site. Further diagnostic tests will be performed in the presence of clinical symptoms or radiologic findings suggestive of disease relapse. Recurrence will be radiologically or histologically confirmed and classified as local or systemic (metastasis) recurrence. The first modality suggesting disease relapse in participants with confirmed local or systemic recurrence will be recorded as responsible for its detection.

Outcome measures

Pilot study primary outcome

To evaluate feasibility, we will assess the number of patients screened and recruited at each participating clinical site, participant retention, and maintenance of data quality. In addition, we will evaluate the utilization of an internet-based centralized randomisation system focusing on the

accuracy of data entry, appropriate stratification of participants and the minimization of randomisation errors. Finally, we will evaluate investigator and participant compliance with the study protocol, including the application of eligibility criteria, compliance with the surveillance imaging and frequency regimens, frequency of crossover and timing of post-intervention phase visits. As discussed by Moore *et al.,* the pilot study will investigate the process of the proposed definitive trial rather than its outcomes (26). The *a priori* criteria for the success of the pilot study are listed below:

A) *Recruitment Measure:* We will consider our recruitment strategy feasible if we are able to enroll the pilot sample of 195 patients (approximately 20 patients from each clinical site participating in the pilot study) within two years. See sample size determination below. As such, we will aim to recruit 100 patients during the first year. If we are unable to achieve at least 90% of this goal (90 patients) then we will plan to increase the number of participating sites as a study rescue measure.

B) *Protocol Adherence Measure:* During the pilot study of the PARITY trial, we were able to maintain an overall protocol adherence rate in excess of 90%(27). Recent reports prepared for the PARITY Data and Safety Monitoring Board (DSMB) indicate a similar protocol adherence rate. However, given the greater complexity and longer duration of the SAFETY trial interventions, we will consider our protocol adherence strategies feasible if there is adherence of 85% or greater to the visit windows and imaging modality prescribed by the protocol.

C) *Participant Retention Measure:* While 20% loss-to-follow-up has traditionally been considered acceptable in clinical research, evidence from other orthopaedic trials suggests that bias begins to affect study results at even lower rates of loss-to-follow-up(28). Therefore, we will consider our participant retention strategies feasible if no more than 15% of participants are lost-to-follow-up.

D) *Maintenance of Data Quality Measure:* We obtained a data completeness rate of approximately 90% in the PARITY trial pilot study (27). Therefore, we will consider our data quality strategies feasible if we are able to maintain 95% or greater completeness of participant follow-up data for the definitive primary outcome. We will also consider our data quality strategies feasible if we are able to maintain 85% or greater completeness of participant follow-up data for the secondary outcomes.

Pilot study secondary outcomes

Death from any cause will be recorded during the pilot study. Data on secondary outcomes for the definitive trial, which are listed below, will also be collected. These include:

A) *Patient-reported outcome measures:* The validated Patient-Reported Outcomes Measurement Information System (PROMIS)® Cancer-Anxiety questionnaire, PROMIS® Satisfaction with Social Roles and Activities questionnaire, and the EuroQol-5 Dimension (EQ-5D) will be used to assess patient anxiety, satisfaction and quality of life, respectively. These questionnaires will be administered at the baseline visit, as well as the 6-month, 12-month, 18-month and 24-month intervention phase, as well as 36-month, 48-month and 60-month post-intervention phase visits.

B) *Local recurrence-free survival (LRFS) outcome measure:* LRFS will be defined as the length of time from randomization that the participant survives with no detection of recurrent disease at the initial tumor site or operative field.

C) *Metastasis-free survival* (*MFS) outcome measure:* MFS will be defined as the length of time from randomization that the participant survives with no detection of systemic disease recurrence at any anatomic location.

D) *Treatment-related complications outcome measures:* Treatment-related complications will include both chemotherapy-related complications, such as febrile neutropenia, fungal infections or sepsis, and thoracotomy-related complications, such as pneumothorax, or surgical site infections.

E) *Net healthcare costs outcome measures*: We will perform an incremental cost analysis of net costs of surveillance and costs incurred from metastasis treatment and metastasis treatment related complications. Unit costs for all resources used by trial participants will be obtained from regional statistics and from centers participating in the trial. These unit costs will be combined with the resource volumes to obtain a net cost per participant over their time in the trial.

Protecting against sources of bias

Adjudication of outcomes

An independent Central Adjudication Committee (CAC) will review all situations where eligibility is in doubt, as well as all reported instances of disease relapse, treatment-related complications, and death to determine whether a study event has occurred. The SAFETY CAC will be comprised of two orthopaedic oncologists, one medical oncologist, and one radiologist. All participating clinical sites will submit digital imaging and relevant hospital records to the Methods Centre via a web-based platform for events that require adjudication.

Blinding

The local clinical team, site study personnel and participants cannot be blinded to the treatment allocation. The CAC will be blinded to surveillance frequency. The data analysts will, however, remain blinded during the trial's analysis.

Maximization of follow-up

We anticipate only minimal losses to follow-up in our musculoskeletal oncology population. Nonetheless, the following procedures will be implemented to minimize losses:

- Individuals likely to present problems with compliance to the study protocol or maintaining follow-up will be excluded;
- At the time of randomization, participants will be asked to provide their contact information, as well as the contact information of their family physician and three alternate contacts;
- Participants who refuse to return for a study assessment will be asked if they are willing to provide follow-up data (to determine survival and to complete study questionnaires) via telephone;
- If a participant cannot be reached, their status regarding the primary study outcome will be assessed by reviewing their medical records;
- Study personnel will remind participants of upcoming clinic visits;
- To assuage possible concerns related to less frequent follow-up, participants will be encouraged to schedule an ad hoc visit anytime they are concerned, even if it breaks the surveillance protocol to which they were assigned;
- Participants will be provided with access to educational content, such as a video that demonstrates how to self-examine for a local recurrence of their STS; and
- Parking and travel vouchers will be provided to participants, where possible, to alleviate the costs associated with the study.

Minimization of crossovers of surveillance interventions

Crossovers are unlikely for either surveillance intervention as investigators will be requesting the imaging modality during surveillance visits. Any deviation with regards to frequency or imaging modality will be documented. In the event of disease recurrence or progression, the following standardized management protocols will be adopted:

- Local Recurrence: the participant will have a lung CT scan to confirm no progression of their systemic disease before continuing with the study protocol.
- Metastases: the participant will no longer be followed as per the study protocol, but per the appropriate follow-up for the interventions required for the treatment of metastases; however, the participant will continue to be followed in the trial.

For both events, the specific imaging modality used to detect either the local recurrence or the metastases will be documented.

Patients that have incidental or off-protocol imaging will not crossover, however this will be documented as a protocol deviation. In the case of a CXR that warrants further investigation with a CT scan, this will be documented. If the patient is found to have disease recurrence, we will document how the disease recurrence was (A) first identified; and (B) confirmed. If after a CT scan the patient is found to not have disease recurrence, the patient will resume surveillance as per the arm to which they were randomised.

Sample size determination

Pilot study sample size

The confidence interval approach was used to calculate the required sample size for the pilot study(29). We determined *a priori* that the definitive trial would only be feasible if our protocol

adherence rate was at least 85%. Using a 95% confidence level and a 5% margin of error, we calculated a required sample size of 195 patients.

Definitive study sample size

Our best estimate of the control group overall five-year survival for both the surveillance frequency and imaging modality is 55%(16). Given that intensive surveillance will detect metastatic disease at an earlier stage, we will use a superiority design to compare survival between more versus less intensive surveillance. A 10% absolute increase in overall five-year survival associated with both more frequent surveillance and the use of CT scans represents a clinically important difference, as outlined by the American Society of Clinical Oncology's statement on clinically meaningful outcomes in cancer trials(30). Therefore, the definitive trial will be powered to detect an absolute difference of 10% in overall five-year survival.

With a desired power of 0.80, we calculated a sample size of 396 participants per study arm. We will account for a 5% loss to follow-up and, therefore, the final sample size will be 830 participants. **Table 1** shows various sample sizes for pairwise comparisons of alternative surveillance frequencies / imaging modalities given varying control event rates and absolute increases in survival. Statistical Package for the Social Sciences (SPSS) (IBM Corporation) software was used for sample size calculation.

The definitive sample size calculation may be adjusted as we prepare for the transition from the pilot to the definitive study as a result of data collected during the pilot study. One factor we may consider will be the percent lost to follow-up by the end of the pilot study. Other factors such as the estimated control group overall five-year survival, the clinically meaningful outcome, and power cannot be amended. The rationale for transition of subject data from the pilot study to the

definitive study has previously been discussed (31). It is acceptable to pool the data if the study methods are not adjusted following the pilot study, and the research tools are standardized.

Table 1. Sample Size Per Group for 80% power, α=0.05. Event rate = death

		Event Rate in More Intensive Surveillance Group			
		25%	30%	35%	40%
Event Rate in Less Intensive Surveillance Group	35%	696	2832	-	-
	40%	332	752	3020	-
	45%	196	352	792	3148
	50%	132	204	368	816
	55%	96	136	212	372

Analysis of feasibility outcomes

A full description of the measures, variables, and methods of analysis are shown in **Table 2**. We will record the total number of participants enrolled on a monthly basis. Each participating site will keep a Screening Log of included and excluded patients. We will also keep a record of participants who miss visits, and those who are withdrawn or lost to follow-up. These will be reported using descriptive statistics – reported as counts (percent) for categorical variables and

mean (standard deviation) for continuous variables with 95% confidence intervals. We will report the proportion of complete CRFs as descriptive data.

Analysis of definitive study primary outcome

The analysis and reporting of the trial will follow the CONSORT criteria(32). The primary analysis will compare the treatment groups on the overall 5-year survival. Two independent comparisons between treatment groups will be made using Cox regression models with time to the definitive primary endpoint(33). Results will be expressed as effect (ORs for binary outcomes, HRs for time-dependent outcomes and mean difference for continuous outcomes), corresponding 2-sided 95% CIs and associated p-values.

Table 2. Summary of Feasibility Outcomes Analysis Plan

Objective	Outcome	Criteria for success of feasibility	Method of analysis
To determine the feasibility of conducting the multi-centre SAFETY international RCT	Recruitment Measure	Enrollment of pilot sample within two years	Descriptive statistics – reported as counts (percent) for categorical variables and means (standard deviation) for continuous variables with 95% CI
	Protocol Adherence Measure	Protocol adherence of 85% or greater	
	Participant Retention Measure	Loss-to-participant follow-up of 15% or less	

	Maintenance of Data Quality Measure	Data completeness of 95% or greater for the definitive primary outcome Data completeness of 85% or greater for the secondary outcomes	

Ethical considerations

This study is to be conducted according to international standards of Good Clinical Practice, applicable government regulations, and institutional research policies and procedures. All study intervention phase (surveillance) arms fall within the spectrum of current standard practice, as do the standardized post-intervention phase follow-up visits. This trial has received *Pro Tempore* ethics approval from the McMaster / Hamilton Health Sciences Research Ethics Board on August 23rd, 2018. The study protocol will be submitted to a properly constituted independent ethics committee, in agreement with local legal prescriptions, for formal approval of the study conduct at each participating clinical site. A copy of this approval will be provided to the Methods Centre by each participating clinical site prior to the local commencement of the study.

Study Timeline

We expect that the pilot study will take just over three years to complete. We estimate that recruitment will take approximately one year to complete per site. The initiation of screening and enrollment will likely be staggered across the participating clinical sites due to the variability in the time required to obtain ethics approval and negotiate institutional contracts. Therefore the pilot study recruitment timeline will be up to two years. We expect a further one year for all pilot participants to complete the intervention phase of the trial. Although we will not have complete post-intervention phase data for any pilot participants, we anticipate being able to determine feasibility at the end of the intervention phase based on our feasibility objectives. We plan *a priori* to transition directly from the pilot to the definitive study if feasibility is established.

Data Safety Monitoring Board

As per the principles established by the *Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group* charter, a DSMB will oversee the safety of the trial participants and the overall conduct of the trial. The Committee members will be independent of the trial, free of conflicts with any of the investigative team, and will consist of two orthopaedic oncologists, a medical oncologist, a radiologist, and a biostatistician. The DSMB will frequently review enrollment and demographic summaries, listings of protocol deviations, and summaries and listings of serious adverse events. They will advise the Principal Investigator and SAFETY study team on any concerns related to participant safety and trial conduct and will make recommendations for: A) study continuation as designed; B) study termination; C) study continuation with major or minor modifications; or D) temporary study suspension of enrollment until some uncertainty is resolved.

Knowledge Dissemination

The results of the study will be submitted for publication regardless of whether there are significant findings, as well as posted on ClinicalTrials.gov. In addition to scientific manuscripts and presentations, we plan to prepare study reports and press releases for patients and other stakeholders that are transparent, and that the language is understandable to the general public.

Potential impact of the study

The benefit of this pilot study would be to determine the feasibility of the SAFETY trial. This is essential prior to undertaking a large multi-centre RCT. Experience gained during the pilot study will provide insight into methods to increase enrollment, strategies to maintain protocol adherence and the adjustment of recruitment expectations. In addition, the ultimate success of the pilot study will support funding requests for the definitive study of the multi-centre SAFETY trial.

Once the feasibility endpoints are reached, we will transition directly into and begin recruiting for the definitive SAFETY trial. The ultimate goal of the SAFETY trial is to provide high-quality evidence for surveillance strategies following the treatment of STS, which will allow for the development of evidence-based clinical practice guidelines for sarcoma patients worldwide.

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Figure legend

Figure 1. Study flow diagram

Data statement

All data from this work will be maintained in security and confidentiality at the Methods Centre at McMaster University. Access to additional unpublished data will be reviewed on a case-by-case basis and will accord with the guidelines of our local institutional research ethics board.

Authors' contributions

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- Drafting the work: Michelle Ghert, Patricia Schneider, and Karim Masrouha
- Revising it critically for important intellectual content: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- Final approval of the version to be published: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt

- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt

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Competing interests statement

Dr. Bhandari, Dr. Ghert, Dr. Randall, and Dr. Hayden report personal fees from consultancy and/or royalties outside the submitted work.

Word count

5,205

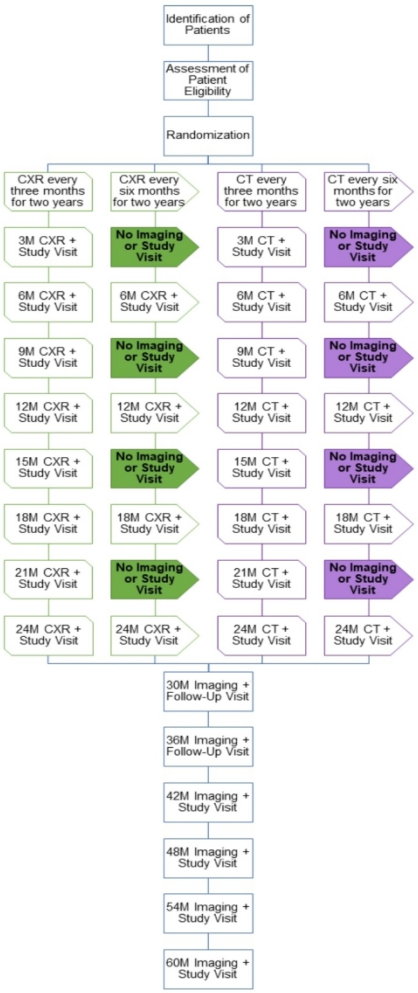

Figure 1.

M = month; CXR = chest X-ray; CT = computed tomography

Study flow diagram

146x146mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	# 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	N/A
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A

Protocol version	# 3	Date and version identifier	1
Funding	# 4	Sources and types of financial, material, and other support	HAHSO

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2,3,28

Roles and responsibilities: sponsor contact inf	# 5b	Name and contact information for the trial sponsor	N/A

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Role and responsibilities: sponsor and funder	# 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	

Roles and responsibilities: committees	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)	18, 24, 25

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	6, 7, 8

Background and rationale: choice of comparat	6b	Explanation for choice of comparators	6

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Objectives	# 7	Specific objectives or hypotheses	9, 10, 11
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, non-inferiority, exploratory)	9
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	11

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)	12
Interventions: description	# 11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14

Interventions: modifications	# 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

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19, 20

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12, 13
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	See note 1

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)	24
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	20, 21
Recruitment	# 15	Strategies for achieving adequate participant enrolment to reach target sample size	13, 14

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	14

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	14

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19

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Blinding (masking): emergency unblinding	# 17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Data collection plan	# 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	N/A

Data collection plan: retention	#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	19

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	24, 25
Statistics: outcomes	#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	22

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

Statistics: analysis population and missing data	# 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)	N/A	

Data monitoring committee	# 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		24, 25

Data monitoring: interim analysis	# 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	N/A
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	24, 25
Auditi	# 23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24, 25

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Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23, 24

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)	N/A
Consent or assent	# 26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, 14

Consent to ancillary studies	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	13, 14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	28

Data access	# 29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
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: trial results	# 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	N/A	

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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

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Author notes

1. 15, 16, 17, 18

BMJ Open

The Surveillance AFter Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot study to determine the feasibility of a multi-centre randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029054.R3
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Secondary Subject Heading:	Surgery
Keywords:	surveillance, soft tissue sarcoma, study protocol, randomised controlled trial, pilot study

Original article

The Surveillance AFter Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot study to determine the feasibility of a multi-centre randomized controlled trial

The SAFETY Investigators

Protocol version 1; December 3, 2018

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Abstract

Introduction Following the treatment of patients with soft tissue sarcomas (STS) that are not metastatic at presentation, the high risk for local and systemic disease recurrence necessitates post-treatment surveillance. Systemic recurrence is most often detected in the lungs. The most appropriate surveillance frequency and modality remain unknown and, as such, clinical practice is highly varied. We plan to assess the feasibility of conducting a multi-centre randomised controlled trial (RCT) that will evaluate the effect on overall five-year survival of two different surveillance frequencies and imaging modalities in patients with STS who undergo surgical excision with curative intent.

Methods and analysis The SAFETY trial will be a multi-centre 2x2 factorial randomized controlled trial. Patients with non-metastatic primary Grade II or III STS treated with excision will be allocated to one of four treatment arms: (1) chest radiograph (CXR) every three months for two years; (2) CXR every six months for two years; (3) chest computed tomography (CT) every three months for two years; or (4) chest CT every six months for two years. The primary outcome of the pilot study is the feasibility of a definitive RCT based on a combination of feasibility endpoints. Secondary outcomes for the pilot study include the primary outcome of the definitive trial (overall survival), patient-reported outcomes on anxiety, satisfaction and quality of life, local recurrence-free survival, metastasis-free survival, treatment-related complications, and net healthcare costs related to surveillance.

Ethics and dissemination This trial received provisional ethics approval from the McMaster / Hamilton Health Sciences Research Ethics Board on August 7, 2019 (Project number 7562). Final ethics approval will be obtained prior to commencing patient recruitment. Once feasibility has

been established and the definitive protocol is finalized, the study will transition to the definitive study.

Article summary

Strengths and limitations of this study

- The SAFETY trial will be an international multi-centre 2x2 factorial randomized controlled trial
- The trial will answer a high priority question for sarcoma surgeons
- The SAFETY trial will build on the international collaboration and experience of the PARITY trial
- The feasibility pilot study is essential before undertaking this large multi-centre trial
- The success of the pilot study is dependent on the ability of clinical sites to recruit patients, comply with the protocol, and complete high quality follow-up data

Keywords: surveillance; soft tissue sarcoma; study protocol; randomized controlled trial; pilot study

Background

Magnitude of the problem

Sarcomas are malignancies of connective tissue that most commonly occur in the extremities. Sarcomas can arise within bone (bone sarcoma) or soft-tissue (soft-tissue sarcoma [STS]). Chemotherapy is not curative for the vast majority of patients with STS(1); therefore, surgery is the standard treatment for STS, with radiation considered important for local disease control.

Following treatment for a STS that is not metastatic at presentation, the risk for local and systemic disease recurrence necessitates careful post-operative surveillance. Between 40% and 50% of all sarcoma patients will develop a local or distant recurrence; however, the risk of recurrence is greatest in the first few years, with 68% occurring by two years and 90% by five years(2-4). Metastasis to the lung is the most frequent single location of disease recurrence in sarcoma patients, occurring in the majority of patients with metastases(4-7). Therefore, routine follow-up after completing sarcoma treatment is standard practice in the first five years after surgery. These visits typically include a clinical history, physical examination, and imaging of the lungs (chest radiograph [CXR], or computed tomography [CT] scan of the lungs).

Surveillance strategies for long-term follow-up of sarcoma patients have not been well researched and current guidelines are based on expert opinion, not on high quality evidence(8, 9). As such, current clinical practice is highly varied, with survey data of musculoskeletal oncologists showing that the number of clinic visits ranges from two to 12, the number of CXRs obtained ranges from zero to 13, and the number of CT scans ranges from one to eight in the first year of surveillance(10-12). The current National Comprehensive Cancer Network guidelines suggest that stage II or III tumors should be followed with chest imaging (CT or CXR) every two to six months

for the first two to three years and then annually thereafter, while stage I tumors could be followed less frequently during the first two to three years (13).

Best evidence for surveillance strategies

Post-treatment soft-tissue sarcoma surveillance is an integral element of patient care. Although earlier detection of metastatic disease may improve long-term survival, no study has yet provided definitive evidence to support this assumption. In order to assess the available evidence, we completed a systematic review of the available randomized controlled trial (RCT) evidence for surveillance in sarcoma management(14). A single study (published separately with early and longer-term follow-up) was identified(15, 16). The authors of this single-centre study found that three-year overall and disease-free survival was not worse in sarcoma patients who had less intensive surveillance (CXRs) than those with more intensive surveillance (CT scans)(15). Due to the sample size, this trial could not conclusively demonstrate non-inferiority in overall or disease-free survival for a six-monthly interval of follow-up visits against three-monthly interval (both were 64% and 69%, respectively)(15).

A follow-up study on the same patient cohort with five-year survival outcomes confirmed that more frequent follow-up did not improve survival and that, although CT scans detected pulmonary metastasis earlier, they did not lead to better survival compared with CXRs(16). However, this was a single-centre study with relatively small numbers and, therefore, confidence in the results and generalizability of the data to other centres is limited. In addition, a relatively small proportion of screened patients (42%) that were eligible for the trial were included due to the exclusion of patients unlikely to follow-up, thus possibly introducing selection bias(15). Furthermore, low-grade sarcomas were eligible and included in this study, even though they have

little metastatic potential and tumour-related mortality; their inclusion may have diminished the magnitude of the effects of the interventions(15). Finally, the majority of the included patients were bone sarcoma patients, thereby limiting the interpretation to STS patients(15).

Risks and benefits of intensive surveillance

Regular, intensive surveillance is more likely to identify recurrent disease earlier than would less intensive surveillance. This type of surveillance may provide reassurance to patients and clinicians; however, the adverse effects of intensive surveillance practices are also noteworthy. The costs that healthcare systems incur as a result of sarcoma surveillance are substantial and could be in excess of USD $20,000 for high-grade sarcomas(17). Furthermore, intensive surveillance can threaten the financial security of patients, due in part to the direct (including travel, accommodation, personal care, and homemaking) and indirect costs (including lost wages for patients and their caregivers) incurred as a result of follow-up appointments(18). As a result, patients' health and quality of life can be dramatically impacted(18-20).

Secondary investigations and earlier knowledge of disease recurrence can also induce anxiety and impact the psychosocial wellbeing for those whose mortality risk cannot be significantly reduced by further medical interventions(21). Overcrowded clinics and long wait times may constitute other important factors that affect patients' psychosocial wellbeing(22). Finally, the use of CT has raised concerns over unnecessary radiation exposure compared to radiographs, although lower dose CT scans may mitigate some of these concerns(23).

Surveillance research as a priority in orthopedic oncology

We recently published a modified Delphi study in which we aimed to identify a clinically relevant consensus-based research agenda in the sarcoma field(24). From this Delphi process that included 80 orthopaedic oncologists and patient representation (with participation from 18 countries), we identified critical research priorities in the field of orthopaedic oncology and determined the top four feasible and important research questions that will directly inform patient care and enhance clinical practice. This study identified the evaluation of post-operative surveillance strategies as the highest-ranking research priority in the sarcoma field(24).

Patient and public involvement

To ensure that we maintain a patient-centered approach to the design and development of this study, we required the opportunity for open dialogue between the multidisciplinary and international SAFETY study team, along with patient / caregiver representatives and other key stakeholders. To facilitate their interaction and collaboration, we held an in-person Protocol Development Meeting in Toronto, ON, Canada in May 2018. At this meeting, we made critical decisions with respect to the study protocol, including: A) study design; B) primary and secondary outcomes; C) patient eligibility; D) follow-up timeframe; E) methods to protect against bias; F) randomization stratification; and G) further patient engagement. We also had the opportunity to discuss several issues that may compromise the study's success and strategize ways to manage these challenges, such as: I) acceptable surveillance schedules that account for differences in international standards of clinical practice; II) possible ethical concerns; III) patient compliance; IV) local implementation and procedural variation; V) competing studies; and VI) funding opportunities.

We are also conducting a patient survey to assess international patient willingness to participate in a study that randomizes patients to a post-operative surveillance regimen in the management of a primary extremity sarcoma. Since there is no available validated tool to assess patient opinions and preferences, we developed a unique patient questionnaire for the purposes of this study. All new patients who present to a participating sarcoma clinic are screened for study participation. The preliminary survey questionnaire responses suggest that most sarcoma patients believe that they have a good understanding of clinical research. Furthermore, over half of respondents feel comfortable with being randomized to receive a treatment. Ultimately, almost 80% of respondents have indicated that they would agree to participate in the SAFETY trial if eligible.

Study design

We plan to assess the feasibility of conducting the pragmatic, international, multi-centre, 2x2 factorial Surveillance AFter Extremity Tumour surgerY (SAFETY) RCT that answers the following questions: In extremity STS patients who undergo surgical resection with curative intent,)(1) what is the impact of surveillance frequency (every three vs. every six months) on overall survival at five years, and (2) what is the impact of surveillance imaging modality (CXR vs. CT scan) on overall survival at five years? To assess feasibility, we will conduct a pilot study. Study participants will be randomized to one of four possible treatment arms (see Study Interventions below). Randomization will occur at the end of active treatment (surgery ± systemic treatment ± local radiation). Following the two-year intervention phase, study participants will continue to be assessed at regular intervals for an additional three years. As such, all pilot study patients will be transitioned into the definitive study and be included in it. Details of the flow of each study arm

are outlined in Figure 1. We anticipate the duration of the pilot study to be three years in order to collect intervention phase data on all participants. The primary outcome of the pilot study is the feasibility of a definitive RCT based on a combination of feasibility endpoints.

The 2x2 factorial study design is ideal and the most efficient method to study two treatment interventions in a single RCT, particularly when there is no interaction between the two interventions. This is unlike a scenario in which the two interventions are medications that may have a synergistic or negative effect when combined. A Bayesian design would be useful do avoid the question of whether or not an interaction exists, however for the purposes of the present trial it is clear that no interaction exists between the frequency and intensity of surveillance. As Freidlin and Korn discuss in their commentary, the 2x2 factorial design is an efficient design to evaluate two interventions in a cancer clinical trial when there are no interactions between treatments(25).

Objectives

Pilot study primary research objectives

The primary objective of the pilot study will be to determine whether it is feasible to conduct a large multi-centre RCT that will evaluate the impact of surveillance strategies on patient survival following extremity STS surgery. To do so, we will assess our ability to:

A) Recruit patients across multiple participating clinical sites;

B) Ensure compliance with the study protocol, including the application of eligibility criteria, timing of intervention phase and post-intervention phase visits and imaging modality;

C) Maintain completeness of follow-up data;

D) Maintain completeness of cost analysis data; and

E) Maintain data quality.

Pilot study secondary research objectives

The secondary objectives of the pilot study will include assessing the impact of either surveillance frequency (every three vs. every six months) or imaging modality (CXR vs. CT scan) on:

A) Overall survival;

B) Patient anxiety, satisfaction and quality of life;

C) Local recurrence-free survival and metastasis-free survival;

D) Treatment-related complications; and

E) Net direct healthcare costs and net costs of treatment and treatment-related complications once metastases are detected.

Hypothesis

Pilot study

We hypothesize that the SAFETY trial will be feasible due to: A) its pragmatic design; B) our established international collaborative research network; C) our qualified, multi-disciplinary study team; D) our existing trial infrastructure; and E) the priority of the study question.

Definitive study

There are two hypotheses:

1- More frequent post-operative surveillance (compared to less frequent post-operative surveillance) in the first two years following the surgical excision of a STS will improve survival over five years;

2 - The use of post-operative CT scans (compared to CXR) in the first two years following the surgical excision of a STS will improve survival over five years.

Study setting

This study will be coordinated by the Methods Centre within the Centre for Evidence-Based Orthopaedics (CEO) at McMaster University (Hamilton, ON, Canada). For the pilot study, we expect that patients will be enrolled from ten clinical sites across four continents. Clinical sites will be carefully screened prior to participation in the study. The clinical site inclusion criteria are: I) adequate research personnel and infrastructure to manage the study; II) sufficiently high extremity STS volume to complete enrollment within the study timeline (defined as greater than or equal to (≥) 20 patients per year); III) commitment from all or most orthopaedic oncologists to participate in the trial; and IV) access to the two imaging modalities. The exclusion criteria are: I) a lack of interest in the trial; II) anticipated challenges with protocol compliance; III) conflicting studies, in the judgment of the Principal Investigator, that would inhibit patient participation; and IV) financial or contract constraints.

Patient eligibility criteria

Inclusion criteria

Patients who meet all of the following criteria will be included:

1) Age of 18 years or older;
2) Diagnosed with a primary extremity grade II or III STS;
3) Undergone surgical resection of the tumour with curative intent and grossly negative margins (R0 or R1 resection margins);
4) Completed neoadjuvant or adjuvant radiation and / or chemotherapy, if applicable;

5) The tumour size is greater than or equal to (≥) five centimeters according to the pathology report or pre-treatment MRI if neoadjuvant radiation and / or chemotherapy are given; and
6) Provision of informed consent.

Exclusion criteria

Patients who meet any of the following criteria will be excluded:

1) Metastatic disease at initial presentation based on thoracic imaging (a second CT scan may be required to confirm that indeterminate nodules are false positives before the patient can be enrolled provided that the second CT scan shows no evidence of metastatic disease);
2) Undergone surgical excision of a local recurrence;
3) Diagnosis of one of the special sub-types: myxoid / round cell liposarcoma or extra-skeletal Ewing's sarcoma (These sarcomas have different metastatic patterns, which necessitate different surveillance protocols);
4) Previous diagnosis of a genetic syndrome with an elevated risk of malignancy, such as Li-Fraumeni Syndrome (such individuals appear to be at an elevated risk for radiation-induced cancers, so the use of CT scans should be limited);
5) Previous diagnosis with a co-morbid condition that has a life expectancy of less than one year;
6) The site-specific surveillance protocol for the patient's disease is not compatible with the study protocol (i.e., regular planned whole-body imaging with positron emission tomography [PET] scans);
7) Diagnosed with another malignancy within the past five years;
8) Likely problems, in the judgment of the investigator, with maintaining follow-up; and
9) Currently enrolled in a study that does not permit co-enrollment;

10) The patient has already been enrolled in the SAFETY trial.

Recruitment and screening

Each participating clinical site will have a locally responsible investigator who will oversee the local administration of the trial, screen STS patients for eligibility, and develop a site-specific patient enrollment plan. A Screening Form will be completed for all STS patients aged 18 years or older, irrespective of whether they are eligible to participate in the study or not. Patients will become eligible, will be screened and consented during the first clinic visit at which all treatment is complete, the surgical wound has healed, and the plan for post-treatment surveillance is discussed with the patient. The process of obtaining and documenting informed consent will be completed in accordance with local Good Clinical Practice recommendations. Consent procedures will comply with the appropriate ethics committee and the Health Insurance Portability and Accountability Act (where applicable).

Randomisation and allocation of patients to study groups

A centralised and automated internet-based randomisation system using random variable block sizes will assign participants to the study groups. Study personnel at each participating site will complete this task. Randomisation will occur only after eligibility is confirmed and consent to participate has been obtained. Participants will be stratified based on clinical site and peri-operative chemotherapy.

Study interventions

Participants will be randomised to one of four treatment groups:

1) CXR every three months for two years;

2) CXR every six months for two years;

3) Chest CT every three months for two years; or

4) Chest CT every six months for two years.

Following completion of the intervention phase, participants will continue to be followed in the study for an additional three years. During this three-year post-intervention phase, participants will be followed at least every six months as per National Comprehensive Cancer Network (NCCN) guidelines(13). If possible, thoracic imaging will continue at each scheduled post-intervention phase visit according to the participants' original allocations.

Relapse

Local imaging and clinical assessment of the primary tumour site will be carried out as per the standard protocol at each participating clinical site. Further diagnostic tests will be performed in the presence of clinical symptoms or radiologic findings suggestive of disease relapse. Recurrence will be radiologically or histologically confirmed and classified as local or systemic (metastasis) recurrence. The first modality suggesting disease relapse in participants with confirmed local or systemic recurrence will be recorded as responsible for its detection.

Outcome measures

Pilot study primary outcome

To evaluate feasibility, we will assess the number of patients screened and recruited at each participating clinical site, participant retention, and maintenance of data quality. In addition, we will evaluate the utilization of an internet-based centralized randomisation system focusing on the

accuracy of data entry, appropriate stratification of participants and the minimization of randomisation errors. Finally, we will evaluate investigator and participant compliance with the study protocol, including the application of eligibility criteria, compliance with the surveillance imaging and frequency regimens, frequency of crossover and timing of post-intervention phase visits. As discussed by Moore *et al.,* the pilot study will investigate the process of the proposed definitive trial rather than its outcomes (26). The *a priori* criteria for the success of the pilot study are listed below:

A) *Recruitment Measure:* We will consider our recruitment strategy feasible if we are able to enroll the pilot sample of 195 patients (approximately 20 patients from each clinical site participating in the pilot study) within two years. See sample size determination below. As such, we will aim to recruit 100 patients during the first year. If we are unable to achieve at least 90% of this goal (90 patients) then we will plan to increase the number of participating sites as a study rescue measure.

B) *Protocol Adherence Measure:* During the pilot study of the PARITY trial, we were able to maintain an overall protocol adherence rate in excess of 90%(27). Recent reports prepared for the PARITY Data and Safety Monitoring Board (DSMB) indicate a similar protocol adherence rate. However, given the greater complexity and longer duration of the SAFETY trial interventions, we will consider our protocol adherence strategies feasible if there is adherence of 85% or greater to the visit windows and imaging modality prescribed by the protocol.

C) *Participant Retention Measure:* While 20% loss-to-follow-up has traditionally been considered acceptable in clinical research, evidence from other orthopaedic trials suggests that bias begins to affect study results at even lower rates of loss-to-follow-up(28). Therefore, we will consider our participant retention strategies feasible if no more than 15% of participants are lost-to-follow-up.

D) *Maintenance of Data Quality Measure:* We obtained a data completeness rate of approximately 90% in the PARITY trial pilot study (27). Therefore, we will consider our data quality strategies feasible if we are able to maintain 95% or greater completeness of participant follow-up data for the definitive primary outcome. We will also consider our data quality strategies feasible if we are able to maintain 85% or greater completeness of participant follow-up data for the secondary outcomes.

Pilot study secondary outcomes

Death from any cause will be recorded during the pilot study. Data on secondary outcomes for the definitive trial, which are listed below, will also be collected. These include:

A) *Patient-reported outcome measures:* The validated Patient-Reported Outcomes Measurement Information System (PROMIS)® Cancer-Anxiety questionnaire, PROMIS® Satisfaction with Social Roles and Activities questionnaire, and the EuroQol-5 Dimension (EQ-5D) will be used to assess patient anxiety, satisfaction and quality of life, respectively. These questionnaires will be administered at the baseline visit, as well as the 6-month, 12-month, 18-month and 24-month intervention phase, as well as 36-month, 48-month and 60-month post-intervention phase visits.

B) *Local recurrence-free survival (LRFS) outcome measure:* LRFS will be defined as the length of time from randomization that the participant survives with no detection of recurrent disease at the initial tumor site or operative field.

C) *Metastasis-free survival* (*MFS) outcome measure:* MFS will be defined as the length of time from randomization that the participant survives with no detection of systemic disease recurrence at any anatomic location.

D) *Treatment-related complications outcome measures:* Treatment-related complications will include both chemotherapy-related complications, such as febrile neutropenia, fungal infections or sepsis, and thoracotomy-related complications, such as pneumothorax, or surgical site infections.

E) *Net healthcare costs outcome measures*: We will perform an incremental cost analysis of net costs of surveillance and costs incurred from metastasis treatment and metastasis treatment related complications. Unit costs for all resources used by trial participants will be obtained from regional statistics and from centers participating in the trial. These unit costs will be combined with the resource volumes to obtain a net cost per participant over their time in the trial.

Protecting against sources of bias

Adjudication of outcomes

An independent Central Adjudication Committee (CAC) will review all situations where eligibility is in doubt, as well as all reported instances of disease relapse, treatment-related complications, and death to determine whether a study event has occurred. The SAFETY CAC will be comprised of two orthopaedic oncologists, one medical oncologist, and one radiologist. All participating clinical sites will submit digital imaging and relevant hospital records to the Methods Centre via a web-based platform for events that require adjudication.

Blinding

The local clinical team, site study personnel and participants cannot be blinded to the treatment allocation. The CAC will be blinded to surveillance frequency. The data analysts will, however, remain blinded during the trial's analysis.

Maximization of follow-up

We anticipate only minimal losses to follow-up in our musculoskeletal oncology population. Nonetheless, the following procedures will be implemented to minimize losses:

- Individuals likely to present problems with compliance to the study protocol or maintaining follow-up will be excluded;
- At the time of randomization, participants will be asked to provide their contact information, as well as the contact information of their family physician and three alternate contacts;
- Participants who refuse to return for a study assessment will be asked if they are willing to provide follow-up data (to determine survival and to complete study questionnaires) via telephone;
- If a participant cannot be reached, their status regarding the primary study outcome will be assessed by reviewing their medical records;
- Study personnel will remind participants of upcoming clinic visits;
- To assuage possible concerns related to less frequent follow-up, participants will be encouraged to schedule an ad hoc visit anytime they are concerned, even if it breaks the surveillance protocol to which they were assigned;
- Participants will be provided with access to educational content, such as a video that demonstrates how to self-examine for a local recurrence of their STS; and
- Parking and travel vouchers will be provided to participants, where possible, to alleviate the costs associated with the study.

Minimization of crossovers of surveillance interventions

Crossovers are unlikely for either surveillance intervention as investigators will be requesting the imaging modality during surveillance visits. Any deviation with regards to frequency or imaging modality will be documented. In the event of disease recurrence or progression, the following standardized management protocols will be adopted:

- Local Recurrence: the participant will have a lung CT scan to confirm no progression of their systemic disease before continuing with the study protocol.
- Metastases: the participant will no longer be followed as per the study protocol, but per the appropriate follow-up for the interventions required for the treatment of metastases; however, the participant will continue to be followed in the trial.

For both events, the specific imaging modality used to detect either the local recurrence or the metastases will be documented.

Patients that have incidental or off-protocol imaging will not crossover, however this will be documented as a protocol deviation. In the case of a CXR that warrants further investigation with a CT scan, this will be documented. If the patient is found to have disease recurrence, we will document how the disease recurrence was (A) first identified; and (B) confirmed. If after a CT scan the patient is found to not have disease recurrence, the patient will resume surveillance as per the arm to which they were randomised.

Sample size determination

Pilot study sample size

The confidence interval approach was used to calculate the required sample size for the pilot study(29). We determined *a priori* that the definitive trial would only be feasible if our protocol

adherence rate was at least 85%. Using a 95% confidence level and a 5% margin of error, we calculated a required sample size of 195 patients.

Definitive study sample size

Our best estimate of the control group overall five-year survival for both the surveillance frequency and imaging modality is 55%(16). Given that intensive surveillance will detect metastatic disease at an earlier stage, we will use a superiority design to compare survival between more versus less intensive surveillance. A 10% absolute increase in overall five-year survival associated with both more frequent surveillance and the use of CT scans represents a clinically important difference, as outlined by the American Society of Clinical Oncology's statement on clinically meaningful outcomes in cancer trials(30). Therefore, the definitive trial will be powered to detect an absolute difference of 10% in overall five-year survival.

With a desired power of 0.80, we calculated a sample size of 396 participants per study arm. We will account for a 5% loss to follow-up and, therefore, the final sample size will be 830 participants. **Table 1** shows various sample sizes for pairwise comparisons of alternative surveillance frequencies / imaging modalities given varying control event rates and absolute increases in survival. Statistical Package for the Social Sciences (SPSS) (IBM Corporation) software was used for sample size calculation.

The definitive sample size calculation may be adjusted as we prepare for the transition from the pilot to the definitive study as a result of data collected during the pilot study. One factor we may consider will be the percent lost to follow-up by the end of the pilot study. Other factors such as the estimated control group overall five-year survival, the clinically meaningful outcome, and power cannot be amended. The rationale for transition of subject data from the pilot study to the

definitive study has previously been discussed (31). It is acceptable to pool the data if the study methods are not adjusted following the pilot study, and the research tools are standardized.

Table 1. Sample Size Per Group for 80% power, α=0.05. Event rate = death

		Event Rate in More Intensive Surveillance Group			
		25%	30%	35%	40%
Event Rate in Less Intensive Surveillance Group	35%	696	2832	-	-
	40%	332	752	3020	-
	45%	196	352	792	3148
	50%	132	204	368	816
	55%	96	136	212	372

Analysis of feasibility outcomes

A full description of the measures, variables, and methods of analysis are shown in **Table 2**. We will record the total number of participants enrolled on a monthly basis. Each participating site will keep a Screening Log of included and excluded patients. We will also keep a record of participants who miss visits, and those who are withdrawn or lost to follow-up. These will be

reported using descriptive statistics – reported as counts (percent) for categorical variables and mean (standard deviation) for continuous variables with 95% confidence intervals. We will report the proportion of complete CRFs as descriptive data.

Analysis of definitive study primary outcome

The analysis and reporting of the trial will follow the CONSORT criteria(32). The primary analysis will compare the treatment groups on the overall 5-year survival. Two independent comparisons between treatment groups will be made using Cox regression models with time to the definitive primary endpoint(33). Results will be expressed as effect (ORs for binary outcomes, HRs for time-dependent outcomes and mean difference for continuous outcomes), corresponding 2-sided 95% CIs and associated p-values.

Table 2. Summary of Feasibility Outcomes Analysis Plan

Objective	Outcome	Criteria for success of feasibility	Method of analysis
To determine the feasibility of conducting the multi-centre SAFETY international RCT	Recruitment Measure	Enrollment of pilot sample within two years	Descriptive statistics – reported as counts (percent) for categorical variables and means (standard deviation) for continuous variables with 95% CI
	Protocol Adherence Measure	Protocol adherence of 85% or greater	
	Participant Retention Measure	Loss-to-participant follow-up of 15% or less	

	Maintenance of Data Quality Measure	Data completeness of 95% or greater for the definitive primary outcome Data completeness of 85% or greater for the secondary outcomes	

Ethical considerations

This study is to be conducted according to international standards of Good Clinical Practice, applicable government regulations, and institutional research policies and procedures. All study intervention phase (surveillance) arms fall within the spectrum of current standard practice, as do the standardized post-intervention phase follow-up visits. This trial has received provisional ethics approval from the McMaster / Hamilton Health Sciences Research Ethics Board on August 7, 2019 (Project number 7562). The study protocol will be submitted to a properly constituted independent ethics committee, in agreement with local legal prescriptions, for formal approval of the study

conduct at each participating clinical site. A copy of this approval will be provided to the Methods Centre by each participating clinical site prior to the local commencement of the study.

Study Timeline

We expect that the pilot study will take just over three years to complete. We estimate that recruitment will take approximately one year to complete per site. The initiation of screening and enrollment will likely be staggered across the participating clinical sites due to the variability in the time required to obtain ethics approval and negotiate institutional contracts. Therefore the pilot study recruitment timeline will be up to two years. We expect a further one year for all pilot participants to complete the intervention phase of the trial. Although we will not have complete post-intervention phase data for any pilot participants, we anticipate being able to determine feasibility at the end of the intervention phase based on our feasibility objectives. We plan *a priori* to transition directly from the pilot to the definitive study if feasibility is established.

Data Safety Monitoring Board

As per the principles established by the *Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group* charter, a DSMB will oversee the safety of the trial participants and the overall conduct of the trial. The Committee members will be independent of the trial, free of conflicts with any of the investigative team, and will consist of two orthopaedic oncologists, a medical oncologist, a radiologist, and a biostatistician. The DSMB will frequently review enrollment and demographic summaries, listings of protocol deviations, and summaries and listings of serious adverse events. They will advise the Principal Investigator and SAFETY study team on any concerns related to participant safety and trial conduct and will make

recommendations for: A) study continuation as designed; B) study termination; C) study continuation with major or minor modifications; or D) temporary study suspension of enrollment until some uncertainty is resolved.

Knowledge Dissemination

The results of the study will be submitted for publication regardless of whether there are significant findings, as well as posted on ClinicalTrials.gov. The trial has been registered on clinicaltrials.gov. The registration number is NCT03944798. In addition to scientific manuscripts and presentations, we plan to prepare study reports and press releases for patients and other stakeholders that are transparent, and that the language is understandable to the general public.

Potential impact of the study

The benefit of this pilot study would be to determine the feasibility of the SAFETY trial. This is essential prior to undertaking a large multi-centre RCT. Experience gained during the pilot study will provide insight into methods to increase enrollment, strategies to maintain protocol adherence and the adjustment of recruitment expectations. In addition, the ultimate success of the pilot study will support funding requests for the definitive study of the multi-centre SAFETY trial.

Once the feasibility endpoints are reached, we will transition directly into and begin recruiting for the definitive SAFETY trial. The ultimate goal of the SAFETY trial is to provide high-quality evidence for surveillance strategies following the treatment of STS, which will allow for the development of evidence-based clinical practice guidelines for sarcoma patients worldwide.

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Figure legend

Figure 1. Study flow diagram

Data statement

All data from this work will be maintained in security and confidentiality at the Methods Centre at McMaster University. Access to additional unpublished data will be reviewed on a case-by-case basis and will accord with the guidelines of our local institutional research ethics board.

Authors' contributions

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay

Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt

- Drafting the work: Michelle Ghert, Patricia Schneider, and Karim Masrouha
- Revising it critically for important intellectual content: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- Final approval of the version to be published: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt

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Competing interests statement

Dr. Bhandari, Dr. Ghert, Dr. Randall, and Dr. Hayden report personal fees from consultancy and/or royalties outside the submitted work.

Word count

5,223

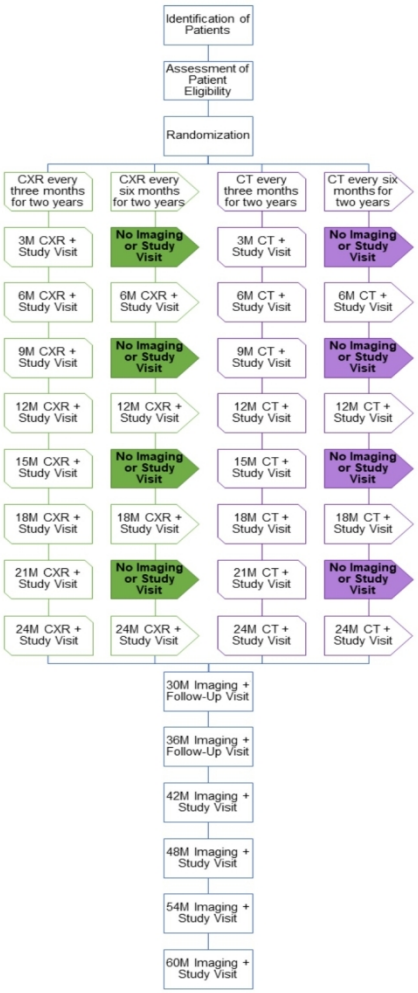

Figure 1.

M = month; CXR = chest X-ray; CT = computed tomography

Study flow diagram

146x146mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	# 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	N/A
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A

Protocol version	# 3	Date and version identifier	1
Funding	# 4	Sources and types of financial, material, and other support	HAHSO

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2,3,28

Roles and responsibilities: sponsor contact inf	5b	Name and contact information for the trial sponsor	N/A

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Role and responsibilities: sponsor and funder	# 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

Roles and responsibilities: committees	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)	18, 24, 25

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	6, 7, 8

Background and rationale: choice of comparat	6b	Explanation for choice of comparators	6

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Objectives	# 7	Specific objectives or hypotheses	9, 10, 11
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, non-inferiority, exploratory)	9
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	11

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)	12
Interventions: description	# 11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14

Interventions: modifications	# 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

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19, 20

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12, 13
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	See note 1

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)	24
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	20, 21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13, 14

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	14

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	14

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19

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Blinding (masking): emergency unblinding	# 17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Data collection plan	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	N/A

Data collection plan: retention	#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	19

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	24, 25
Statistics: outcomes	#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	22

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

Statistics: analysis population and missing data	#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)	N/A

Data monitoring committee	# 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	24, 25

Data monitoring: interim analysis	# 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	N/A
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	24, 25
Auditi	# 23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24, 25

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Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23, 24

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)	N/A
Consent or assent	# 26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, 14

Consent or assent: ancillary studies	#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	13, 14
Declaration of interests	# 28	Financial and other competing interests for principal investigators for the overall trial and each study site	28

Data access	# 29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
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: trial results	# 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	N/A	

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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

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Author notes

1. 15, 16, 17, 18