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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029054
Article Type:	Protocol
Date Submitted by the Author:	12-Jan-2019
Complete List of Authors:	Ghert, Michelle; McMaster University, Department of Surgery; Hamilton Health Sciences, Juravinski Cancer Centre
Keywords:	surveillance, soft tissue sarcoma, study protocol, randomised controlled trial, pilot study

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Manuscripts

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3 *Original article*
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5 **The Surveillance AftEr Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot**
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7 **study to determine the feasibility of a multi-centre randomized controlled trial**
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10 The SAFETY Investigators
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14 **Protocol version 1; December 3, 2018**
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26 **Correspondence and reprints**
27

28 Michelle Ghert, MD, FRCSC
29

30 Professor of Surgery
31

32 Division of Orthopaedic Surgery
33

34 Department of Surgery
35

36 McMaster University
37

38 711 Concession Street
39

40 Hamilton, ON
41

42 Canada
43

44 Tel: 905-387-9495 ext 64089
45

46 Fax: 905-381-7071
47

48 Email: mghert@hhsc.ca
49
50

51 **Contributor list with affiliations**
52
53
54
55
56
57
58
59
60

1
2
3 Michelle Ghert, MD, FRCSC (Steering Committee Chair)
4 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
5
6

7 Mohit Bhandari, MD, PhD, FRCSC
8 Department of Surgery & Department of Health Research Methods, Evidence and Impact,
9 McMaster University (Hamilton, Ontario, Canada)
10
11

12 Anthony Bozzo, MD
13 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
14
15

16 P.D. Sander Dijkstra, MD, PhD
17 Department of Orthopaedics, Leiden University Medical Center (Leiden, the Netherlands)
18
19

20 Anthony Griffin, MSc
21 Musculoskeletal Oncology Unit, Mount Sinai Hospital (Toronto, Ontario, Canada)
22
23

24 Robert Grimer, MB BS, DSc, FRCS, FRCS Ed(Orth)
25 Department of Surgery, University of Birmingham (Birmingham, United Kingdom)
26
27

28 James Hayden, MD, PhD, FACS
29 Department of Orthopaedics & Rehabilitation, Oregon Health & Science University (Portland,
30 Oregon, USA)
31
32

33 Arlene Manherz
34 (Community)
35
36

37 Karim Masrouha, MD
38 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
39
40

41 Paula McKay, BSc
42 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
43
44

45 Benjamin Miller, MD, MS, FACS
46 Department of Orthopaedics & Rehabilitation, University of Iowa (Iowa City, Iowa, USA)
47
48

49 Naveen Parasu, MD, MRCP (UK), MRCR (UK), FRCPC
50 Department of Radiology, McMaster University (Hamilton, Ontario, Canada)
51
52

53 Ajay Puri, MS (Ortho)
54 Department of Surgical Oncology, Tata Memorial Centre (Mumbai, India)
55
56

57 R. Lor Randall, MD, FACS
58
59
60

1
2
3 Department of Orthopaedic Surgery, University of California, Davis (Sacramento, California,
4 USA)
5

6
7 Patricia Schneider, BSc
8 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
9

10
11 Sheila Sprague, PhD
12 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
13

14
15 Nina Szpakowski, MSc, DVM
16 (Community)
17

18
19 Lehana Thabane, PhD
20 Department of Health Research Methods, Evidence and Impact, McMaster University
21 (Hamilton, Ontario, Canada)
22

23
24 Robert Turcotte, MD, FRCSC
25 Department of Surgery, McGill University (Montreal, Quebec, Canada)
26

27
28 Roberto Vélez, MD, PhD
29 Department of Orthopaedic Surgery, Hospital Vall d'Hebron (Barcelona, Catalunya, Spain)
30

31
32 David Wilson, MD, MSc
33 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
34

35
36 Kevin Zbuk, MD, FRCPC
37 Department of Oncology, McMaster University (Hamilton, Ontario, Canada)
38

39
40 Gordon Guyatt, MD, FRCPC
41 Department of Medicine & Department of Health Research Methods, Evidence and Impact,
42 McMaster University (Hamilton, Ontario, Canada)
43
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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

1
2
3 Sarcomas are malignancies of connective tissue that most commonly occur in the extremities.
4
5 Sarcomas can arise within bone (bone sarcoma) or soft-tissue (soft-tissue sarcoma [STS]).
6
7
8 Chemotherapy is not curative for the vast majority of patients with STS(1); therefore, surgery is
9
10 the standard treatment for STS, with radiation considered important for local disease control.
11

12 Following treatment for a STS that is not metastatic at presentation, the risk for local and
13
14 systemic disease recurrence necessitates careful post-operative surveillance. Between 40% and
15
16 50% of all sarcoma patients will develop a local or distant recurrence; however, the risk of
17
18 recurrence is greatest in the first few years, with 68% occurring by two years and 90% by five
19
20 years(2-4). Metastasis to the lung is the most frequent single location of disease recurrence in
21
22 sarcoma patients, occurring in the majority of patients with metastases(4-7). Therefore, routine
23
24 follow-up after completing sarcoma treatment is standard practice in the first five years after
25
26 surgery. These visits typically include a clinical history, physical examination, and imaging of the
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28 lungs (chest radiograph [CXR], or computed tomography [CT] scan of the lungs).
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33 Surveillance strategies for long-term follow-up of sarcoma patients have not been well
34
35 researched and current guidelines are based on expert opinion, not on high quality evidence(8, 9).
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37 As such, current clinical practice is highly varied, with survey data of musculoskeletal oncologists
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39 showing that the number of clinic visits ranges from two to 12, the number of CXRs obtained
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41 ranges from zero to 13, and the number of CT scans ranges from one to eight in the first year of
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43 surveillance(10-12).
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49 *Best evidence for surveillance strategies*

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51 In order to assess the available evidence, we completed a systematic review of the available
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53 randomized controlled trial (RCT) evidence for surveillance in sarcoma management(13). A single
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3 study (published separately with early and longer-term follow-up) was identified(14, 15). The
4 authors of this single-centre study found that three-year overall and disease-free survival was not
5 worse in sarcoma patients who had less intensive surveillance (CXR) than those with more
6 intensive surveillance (CT scans)(14). Due to the sample size, this trial could not conclusively
7 demonstrate non-inferiority in overall or disease-free survival for a six-monthly interval of follow-
8 up visits against three-monthly interval (both were 64% and 69%, respectively)(14).
9

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11
12 A follow-up study on the same patient cohort with five-year survival outcomes confirmed
13 that more frequent follow-up did not improve survival and that, although CT scans detected
14 pulmonary metastasis earlier, they did not lead to better survival compared with CXRs(15).
15 However, this was a single-centre study with relatively small numbers and, therefore, confidence
16 in the results and generalizability of the data to other centres is limited. In addition, a relatively
17 small proportion of screened patients (42%) that were eligible for the trial were included due to
18 the exclusion of patients unlikely to follow-up, thus possibly introducing selection bias(14).
19 Furthermore, low-grade sarcomas were eligible and included in this study, even though they have
20 little metastatic potential and tumour-related mortality; their inclusion may have diminished the
21 magnitude of the effects of the interventions(14). Finally, the majority of the included patients
22 were bone sarcoma patients, thereby limiting the interpretation to STS patients(14).
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44 *Risks and benefits of intensive surveillance*

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46 Regular, intensive surveillance is more likely to identify recurrent disease earlier than would less
47 intensive surveillance. This type of surveillance may provide reassurance to patients and clinicians;
48 however, the adverse effects of intensive surveillance practices are also noteworthy. The costs that
49 healthcare systems incur as a result of sarcoma surveillance are substantial and could be in excess
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3 of USD \$20,000 for high-grade sarcomas(16). Furthermore, intensive surveillance can threaten the
4 financial security of patients, due in part to the direct (including travel, accommodation, personal
5 care, and homemaking) and indirect costs (including lost wages for patients and their caregivers)
6 incurred as a result of follow-up appointments(17). As a result, patients' health and quality of life
7 can be dramatically impacted(17-19).

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

21 22 23 24 25 26 27 28 29 30 31 *Surveillance research as a priority in orthopaedic oncology*

32
33 We recently published a modified Delphi study in which we aimed to identify a clinically relevant
34 consensus-based research agenda in the sarcoma field(23). From this Delphi process that included
35 80 orthopaedic oncologists and patient representation (with participation from 18 countries), we
36 identified critical research priorities in the field of orthopaedic oncology and determined the top
37 four feasible and important research questions that will directly inform patient care and enhance
38 clinical practice. This study identified the evaluation of post-operative surveillance strategies as
39 the highest-ranking research priority in the sarcoma field(23).

40 41 42 43 44 45 46 47 48 49 50 51 **Study design**

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

35 *Primary Feasibility Research Objectives*

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37 The primary objective of the pilot study will be to determine whether it is feasible to conduct a
38 large multi-centre RCT that will evaluate the impact of surveillance strategies on patient survival
39 following extremity STS surgery. To do so, we will assess our ability to:
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- 45 A) Recruit patients across multiple participating clinical sites;
- 46 B) Ensure compliance with the study protocol, including the application of eligibility criteria,
47 timing of intervention phase and post-intervention phase visits and imaging modality;
- 48 C) Maintain completeness of follow-up data;
- 49 D) Maintain completeness of cost analysis data; and
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3 E) Maintain data quality.
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8 *Secondary Feasibility Research Objectives*

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10 The secondary objectives of the pilot study will include assessing the impact of either surveillance
11 frequency (every three vs. every six months) or imaging modality (CXR vs. CT scan) on:
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14 A) Overall five-year survival;
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16 B) Patient anxiety, satisfaction and quality of life;
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18 C) Local recurrence-free survival and metastasis-free survival;
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20 D) Treatment-related complications; and
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22 E) Net direct healthcare costs and net costs of treatment and treatment-related complications once
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metastases are detected.

31 **Hypothesis**

32 *Pilot Study*

33 We hypothesize that the SAFETY trial will be feasible due to: A) its pragmatic design; B) our
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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.

44 *Definitive Study*

45 We hypothesize that more frequent post-operative surveillance (compared to less frequent post-
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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 (\geq) 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 (\geq) 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.

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6 *Exclusion criteria*

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

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10 1) Metastatic disease at initial presentation based on thoracic imaging (a second CT scan may be
11 required to confirm that indeterminate nodules are false positives before the patient can be
12 enrolled provided that the second CT scan shows no evidence of metastatic disease);
13
14 2) Undergone surgical excision of a local recurrence;
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16 3) Diagnosis of one of the special sub-types: myxoid / round cell liposarcoma or extra-skeletal
17 Ewing's sarcoma (These sarcomas have different metastatic patterns, which necessitate
18 different surveillance protocols);
19
20 4) Previous diagnosis of a genetic syndrome with an elevated risk of malignancy, such as Li-
21 Fraumeni Syndrome (such individuals appear to be at an elevated risk for radiation-induced
22 cancers, so the use of CT scans should be limited);
23
24 5) Previous diagnosis with a co-morbid condition that has a life expectancy of less than one year;
25
26 6) The site-specific surveillance protocol for the patient's disease is not compatible with the study
27 protocol (i.e., regular planned whole-body imaging with positron emission tomography [PET]
28 scans);
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30 7) Diagnosed with another malignancy within the past five years;
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32 8) Likely problems, in the judgment of the investigator, with maintaining follow-up; and
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34 9) Currently enrolled in a study that does not permit co-enrollment.
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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;

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3 3) Chest CT every three months for two years; or
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5 4) Chest CT every six months for two years.
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8 Following completion of the intervention phase, participants will continue to be followed
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10 in the study for an additional three years. During this three-year post-intervention phase,
11
12 participants will be followed at least every six months as per National Comprehensive Cancer
13
14 Network (NCCN) guidelines(24). If possible, thoracic imaging will continue at each scheduled
15
16 post-intervention phase visit according to the participants' original allocations.
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21 **Relapse**

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24 Local imaging and clinical assessment of the primary tumour site will be carried out as per the
25
26 standard protocol at each participating clinical site. Further diagnostic tests will be performed in
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28 the presence of clinical symptoms or radiologic findings suggestive of disease relapse. Recurrence
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30 will be radiologically or histologically confirmed and classified as local or systemic (metastasis)
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32 recurrence. The first modality suggesting disease relapse in participants with confirmed local or
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34 systemic recurrence will be recorded as responsible for its detection.
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40 **Outcome measures**

41 *Primary outcome*

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44 To evaluate feasibility, we will assess the number of patients screened and recruited at each
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46 participating clinical site, participant retention, and maintenance of data quality. In addition, we
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48 will evaluate the utilization of an internet-based centralized randomisation system focusing on the
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50 accuracy of data entry, appropriate stratification of participants and the minimization of
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52 randomisation errors. Finally, we will evaluate investigator and participant compliance with the
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3 study protocol, including the application of eligibility criteria, compliance with the surveillance
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5 imaging and frequency regimens, frequency of crossover and timing of post-intervention phase
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7 visits. The a priori criteria for the success of the pilot phase are listed below.
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12 *Recruitment Measure:* We will consider our recruitment strategy feasible if we are able to enroll
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14 the pilot sample of 195 patients (approximately 20 patients from each clinical site participating in
15
16 the pilot phase) within two years. See sample size determination below.
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21 *Protocol Adherence Measure:* During the pilot phase of the PARITY trial, we were able to
22
23 maintain an overall protocol adherence rate in excess of 90%(25). Recent reports prepared for the
24
25 PARITY Data and Safety Monitoring Board (DSMB) indicate a similar protocol adherence rate.
26
27 However, given the greater complexity and longer duration of the SAFETY trial interventions, we
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29 will consider our protocol adherence strategies feasible if there is adherence of 85% or greater to
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31 the visit windows and imaging modality prescribed by the protocol.
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37 *Participant Retention Measure:* While 20% loss-to-follow-up has traditionally been considered
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39 acceptable in clinical research, evidence from other orthopaedic trials suggests that bias begins to
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41 affect study results at even lower rates of loss-to-follow-up(26). Therefore, we will consider our
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43 participant retention strategies feasible if no more than 15% of participants are lost-to-follow-up.
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49 *Maintenance of Data Quality Measure:* We obtained a data completeness rate of approximately
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51 90% in the PARITY trial pilot phase(25). Therefore, we will consider our data quality strategies
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53 feasible if we are able to maintain 95% or greater completeness of participant follow-up data for
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3 the definitive primary outcome. We will also consider our data quality strategies feasible if we are
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5 able to maintain 85% or greater completeness of participant follow-up data for the secondary
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7 outcomes.
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10 11 12 *Secondary outcomes*

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14 The main secondary outcome for the feasibility study will be the primary outcome of the definitive
15
16 trial, which is overall five-year survival. The outcome measure will be death from any cause. Data
17
18 on secondary outcomes for the definitive trial, which are listed below, will also be collected.
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24 *Patient-reported outcome measures:* The validated Patient-Reported Outcomes Measurement
25
26 Information System (PROMIS)[®] Cancer-Anxiety questionnaire, PROMIS[®] Satisfaction with
27
28 Social Roles and Activities questionnaire, and the EuroQol-5 Dimension (EQ-5D) will be used to
29
30 assess patient anxiety, satisfaction and quality of life, respectively. These questionnaires will be
31
32 administered at the baseline visit, as well as the 6-month, 12-month, 18-month and 24-month
33
34 intervention phase, as well as 36-month, 48-month and 60-month post-intervention phase visits.
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41 *Local recurrence-free survival (LRFS) outcome measure:* LRFS will be defined as the length of
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43 time from randomization that the participant survives with no detection of recurrent disease at the
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45 initial tumor site or operative field.
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50 *Metastasis-free survival (MFS) outcome measure:* MFS will be defined as the length of time from
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52 randomization that the participant survives with no detection of systemic disease recurrence at any
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54 anatomic location.
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6 *Treatment-related complications outcome measures:* Treatment-related complications will include
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8 both chemotherapy-related complications, such as febrile neutropenia, fungal infections or sepsis,
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10 and thoracotomy-related complications, such as pneumothorax, or surgical site infections.
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15 *Net healthcare costs outcome measures:* We will perform an incremental cost analysis of net costs
16
17 of surveillance and costs incurred from metastasis treatment and metastasis treatment related
18
19 complications. Unit costs for all resources used by trial participants will be obtained from regional
20
21 statistics and from centers participating in the trial. These unit costs will be combined with the
22
23 resource volumes to obtain a net cost per participant over their time in the trial.
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28 **Protecting against sources of bias**

29 *Adjudication of outcomes*

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33 An independent Central Adjudication Committee (CAC) will review all situations where eligibility
34
35 is in doubt, as well as all reported instances of disease relapse, treatment-related complications,
36
37 and death to determine whether a study event has occurred. The SAFETY CAC will be comprised
38
39 of two orthopaedic oncologists, one medical oncologist, and one radiologist. All participating
40
41 clinical sites will submit digital imaging and relevant hospital records to the Methods Centre via a
42
43 web-based platform for events that require adjudication.
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49 *Blinding*

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3 The local clinical team, site study personnel and participants cannot be blinded to the treatment
4 allocation. The CAC will be blinded to surveillance frequency. The data analysts will, however,
5 remain blinded during the trial's analysis.
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10 11 12 *Maximization of follow-up* 13

14 We anticipate only minimal losses to follow-up in our musculoskeletal oncology population.
15
16 Nonetheless, the following procedures will be implemented to minimize losses:
17

- 18
19 ▪ Individuals likely to present problems with compliance to the study protocol or maintaining
20 follow-up will be excluded;
21
22
- 23 ▪ At the time of randomization, participants will be asked to provide their contact information,
24 as well as the contact information of their family physician and three alternate contacts;
25
26
- 27 ▪ Participants who refuse to return for a study assessment will be asked if they are willing to
28 provide follow-up data via telephone;
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30
- 31 ▪ If a participant cannot be reached, their status regarding the primary study outcome will be
32 assessed by reviewing their medical records;
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- 35 ▪ Study personnel will remind participants of upcoming clinic visits;
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- 38 ▪ To assuage possible concerns related to less frequent follow-up, participants will be encouraged
39 to schedule an ad hoc visit anytime they are concerned, even if it breaks the surveillance
40 protocol to which they were assigned;
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- 43 ▪ Participants will be provided with access to educational content, such as a video that
44 demonstrates how to self-examine for a local recurrence of their STS; and
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- 47 ▪ Parking and travel vouchers will be provided to participants, where possible, to alleviate the
48 costs associated with the study.
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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, $\alpha=0.05$. 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

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2
3 intervention phase (surveillance) arms fall within the spectrum of current standard practice, as do
4
5 the standardized post-intervention phase follow-up visits. This trial has received *Pro Tempore*
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7 ethics approval from the McMaster / Hamilton Health Sciences Research Ethics Board on August
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9 23rd, 2018. The study protocol will be submitted to a properly constituted independent ethics
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11 committee, in agreement with local legal prescriptions, for formal approval of the study conduct
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13 at each participating clinical site. A copy of this approval will be provided to the Methods Centre
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15 by each participating clinical site prior to the local commencement of the study.
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22 **Study Timeline**

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24 We expect that the pilot study will take just over three years to complete. We estimate that
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26 recruitment will take approximately one year to complete per site. The initiation of screening and
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28 enrollment will likely be staggered across the participating clinical sites due to the variability in
29
30 the time required to obtain ethics approval and negotiate institutional contracts. We expect a further
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32 two years for all pilot participants to complete the intervention phase of the trial. Although we will
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34 not have complete post-intervention phase data for any pilot participants, we anticipate being able
35
36 to determine feasibility at the end of the intervention phase based on our feasibility objectives. We
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38 plan *a priori* to transition directly from the pilot phase to the definitive phase if feasibility is
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40 established.
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47 **Data Safety Monitoring Board**

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

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26 The benefit of this pilot study would be to determine the feasibility of the SAFETY trial. This is
27 essential prior to undertaking a large multi-centre RCT. Experience gained during the pilot phase
28 will provide insight into methods to increase enrollment, strategies to maintain protocol adherence
29 and the adjustment of recruitment expectations. In addition, the ultimate success of the pilot phase
30 will support funding requests for the definitive phase of the multi-centre SAFETY trial.
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38 Once the feasibility endpoints are reached, we will transition directly into and begin
39 recruiting for the definitive SAFETY trial. The ultimate goal of the SAFETY trial is to provide
40 high-quality evidence for surveillance strategies following the treatment of STS, which will allow
41 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

Funding

This research is supported by funding through the Hamilton Academic Health Science Organization (HAHSO) Innovation Grant.

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

4,265

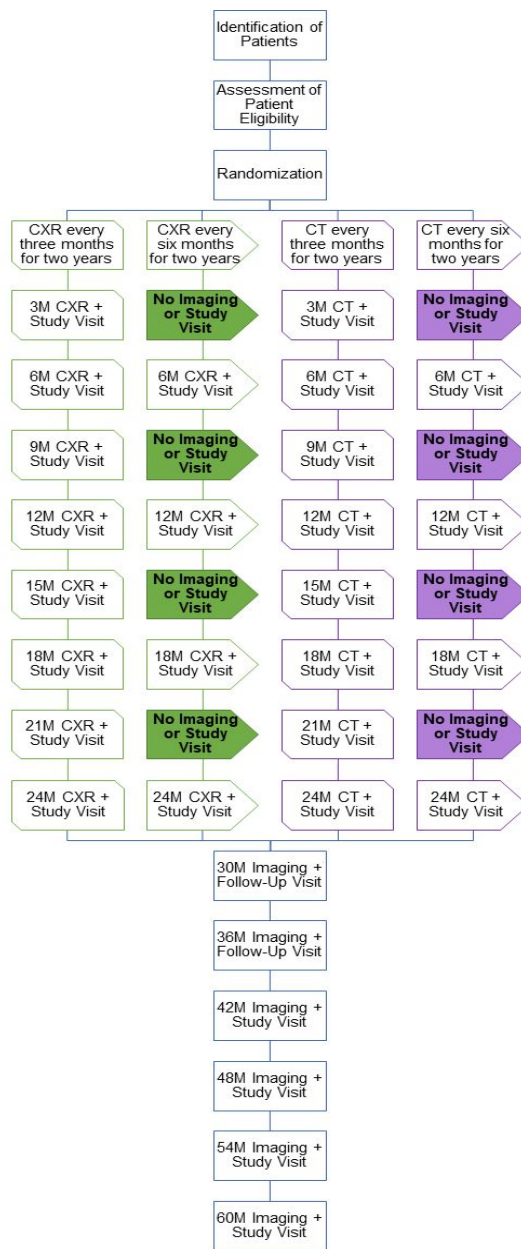


Figure 1.

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.

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

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Page

Number

Reporting Item

T #	Descriptive title identifying the study design, population,	1
it 1	interventions, and, if applicable, trial acronym	
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1 T # Trial identifier and registry name. If not yet registered, N/A
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22 T # All items from the World Health Organization Trial N/A
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23 F # Sources and types of financial, material, and other support HAHSO
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1 R # Names, affiliations, and roles of protocol contributors 2,3,28
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1	R #	Name and contact information for the trial sponsor	N/A
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1 R # Role of study sponsor and funders, if any, in study design; N/A
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3 o 5 collection, management, analysis, and interpretation of
4 l c data; writing of the report; and the decision to submit the
5 e report for publication, including whether they will have
6 s ultimate authority over any of these activities
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1 R # Composition, roles, and responsibilities of the coordinating 18, 24, 25
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3 o 5 centre, steering committee, endpoint adjudication
4 l d committee, data management team, and other individuals or
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6 e groups overseeing the trial, if applicable (see Item 21a for
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8 s data monitoring committee)
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1 B # Description of research question and justification for 6, 7, 8
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3 a 6 undertaking the trial, including summary of relevant studies
4 c a (published and unpublished) examining benefits and harms
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1 B # Explanation for choice of comparators

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1	O #	Specific objectives or hypotheses	9, 10, 11
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16	T #	Description of trial design including type of trial (eg,	9
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20		inferiority, exploratory)	
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31	S #	Description of study settings (eg, community clinic,	11
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34	u	collected. Reference to where list of study sites can be	
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1 E # Inclusion and exclusion criteria for participants. If
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6 i surgeons, psychotherapists)

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24 I # Interventions for each group with sufficient detail to allow
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1 I # Criteria for discontinuing or modifying allocated N/A
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3 n 1 interventions for a given trial participant (eg, drug dose
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1 I # Relevant concomitant care and interventions that are 12, 13
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41 O # Primary, secondary, and other outcomes, including the See note 1
 42 u 1 specific measurement variable (eg, systolic blood pressure),
 43 t 2 analysis metric (eg, change from baseline, final value, time
 44 c to event), method of aggregation (eg, median, proportion),
 45 o and time point for each outcome. Explanation of the clinical
 46 m relevance of chosen efficacy and harm outcomes is strongly
 47 e recommended
 48 s

1	P	#	Time schedule of enrolment, interventions (including any	24
2				
3	a	1	run-ins and washouts), assessments, and visits for	
4	rt	3	participants. A schematic diagram is highly recommended	
5			(see Figure)	
6	i			
7	c			
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9	i			
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11	P			
12	a			
13	n			
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15	t			
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18	m			
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20	li			
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22	n			
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24	e			
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27	S	#	Estimated number of participants needed to achieve study	20, 21
28	a	1	objectives and how it was determined, including clinical	
29				
30	m	4	and statistical assumptions supporting any sample size	
31	p		calculations	
32				
33	l			
34	e			
35				
36	si			
37	z			
38				
39	e			
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41				
42	R	#	Strategies for achieving adequate participant enrolment to	13, 14
43	e	1	reach target sample size	
44				
45	c	5		
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1 A # Method of generating the allocation sequence (eg,
2 ll 1 computer-generated random numbers), and list of any
3 o 6 factors for stratification. To reduce predictability of a
4 c a random sequence, details of any planned restriction (eg,
5 a blocking) should be provided in a separate document that is
6 ti unavailable to those who enrol participants or assign
7 o interventions
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1 A # Mechanism of implementing the allocation sequence (eg,
2 ll 1 central telephone; sequentially numbered, opaque, sealed
3 o 6 envelopes), describing any steps to conceal the sequence
4 c b until interventions are assigned
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6 a
7 ti
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9 n
10 c
11 o
12 n
13 c
14 o
15 n
16 c
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19 l
20 m
21 e
22 n
23 t
24 m
25 e
26 c
27 h
28 a
29 n
30 is
31 m

1 A # Who will generate the allocation sequence, who will enrol 14
2 ll 1 participants, and who will assign participants to
3 o 6 interventions

4 c c
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12 m
13 p
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15 e
16 m
17 e
18 n
19 t
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21 ti
22 o
23 n

35 B # Who will be blinded after assignment to interventions (eg, 19
36 li 1 trial participants, care providers, outcome assessors, data
37 n 7 analysts), and how

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45 m
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1 B # If blinded, circumstances under which unblinding is N/A
2
3 li 1 permissible, and procedure for revealing a participant's
4 n 7 allocated intervention during the trial
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6 d b
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12 m
13 a
14 s
15 k
16 i
17 n
18 g
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24 g
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27 c
28 y
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N/A

1 D # Plans for assessment and collection of outcome, baseline,
2
3 a 1 and other trial data, including any related processes to
4 t 8 promote data quality (eg, duplicate measurements, training
5 a a of assessors) and a description of study instruments (eg,
6 c questionnaires, laboratory tests) along with their reliability
7 o and validity, if known. Reference to where data collection
8 ll forms can be found, if not in the protocol
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1 D # Plans to promote participant retention and complete follow- 19
2 a 1 up, including list of any outcome data to be collected for
3 t 8 participants who discontinue or deviate from intervention
4 a b protocols
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6 c
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1 D # Plans for data entry, coding, security, and storage, including 24, 25
2
3 a 1 any related processes to promote data quality (eg, double
4 t 9 data entry; range checks for data values). Reference to
5
6 a where details of data management procedures can be found,
7 m if not in the protocol
8
9 a
10 n
11 a
12 g
13 e
14 m
15 e
16 n
17 t

23 S # Statistical methods for analysing primary and secondary 22
24 t 2 outcomes. Reference to where other details of the statistical
25 a 0 analysis plan can be found, if not in the protocol
26
27 ti a
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29 st
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31 i
32 c
33 s:
34 o
35 u
36 t
37 c
38 o
39 m
40 e
41 s

1	S	#	Methods for any additional analyses (eg, subgroup and	N/A
2				
3	t	2	adjusted analyses)	
4	a	0		
5				
6	t	i	b	
7				
8	s			
9	i			
10				
11	c			
12	s:			
13	a			
14	d			
15				
16	d			
17				
18	i			
19				
20	o			
21				
22	n			
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24	a			
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26	l			
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28	a			
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1	S	#	Definition of analysis population relating to protocol non-	N/A
2				
3	t	2	adherence (eg, as randomised analysis), and any statistical	
4	a	0	methods to handle missing data (eg, multiple imputation)	
5				
6	t	i	c	
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8	s	t		
9	i			
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11	c			
12	s:			
13	a			
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15	n			
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53	is			
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55	si			
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57	n			
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24, 25

1 D # Composition of data monitoring committee (DMC);
2
3 a 2 summary of its role and reporting structure; statement of
4 t 1 whether it is independent from the sponsor and competing
5 a a interests; and reference to where further details about its
6 m charter can be found, if not in the protocol. Alternatively,
7 o an explanation of why a DMC is not needed
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1	D #	Description of any interim analyses and stopping	N/A
2			
3	a 2	guidelines, including who will have access to these interim	
4	t 1	results and make the final decision to terminate the trial	
5			
6	a b		
7	m		
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9	o		
10	n		
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15	n		
16	g		
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18	i		
19	n		
20	t		
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41	H #	Plans for collecting, assessing, reporting, and managing	24, 25
42	a 2	solicited and spontaneously reported adverse events and	
43	r 2	other unintended effects of trial interventions or trial	
44	m	conduct	
45			
46	s		
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49			
50	A #	Frequency and procedures for auditing trial conduct, if any,	24, 25
51	u 2	and whether the process will be independent from	
52	d 3	investigators and the sponsor	
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54	it		
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R # Plans for seeking research ethics committee / institutional
e 2 review board (REC / IRB) approval
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1	P	#	Plans for communicating important protocol modifications	N/A
2				
3	r	2	(eg, changes to eligibility criteria, outcomes, analyses) to	
4				
5	o	5	relevant parties (eg, investigators, REC / IRBs, trial	
6	t		participants, trial registries, journals, regulators)	
7				
8	o			
9	c			
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11	o			
12	l			
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14	a			
15	m			
16	e			
17	n			
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19	d			
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21	m			
22	e			
23				
24	n			
25	ts			
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27				
28	C	#	Who will obtain informed consent or assent from potential	13, 14
29				
30	o	2	trial participants or authorised surrogates, and how (see	
31				
32	n	6	Item 32)	
33	s	a		
34	e			
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36	n			
37	t			
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39	o			
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41	r			
42	a			
43	s			
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1 C # Additional consent provisions for collection and use of N/A
2
3 o 2 participant data and biological specimens in ancillary
4 n 6 studies, if applicable
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6 s b
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12 t
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1 C # How personal information about potential and enrolled 13, 14
2
3 o 2 participants will be collected, shared, and maintained in
4 n 7 order to protect confidentiality before, during, and after the
5 fi trial
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21 D # Financial and other competing interests for principal 28
22 e 2 investigators for the overall trial and each study site
23 c 8

24 l
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26 r
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37 r
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1 D # Statement of who will have access to the final trial dataset, N/A
2
3 a 2 and disclosure of contractual agreements that limit such
4 t 9 access for investigators
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6 a
7 a
8 c
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10 c
11 e
12 s
13 s
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17 A # Provisions, if any, for ancillary and post-trial care, and for N/A
18 n 3 compensation to those who suffer harm from trial
19 c 0 participation
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21 il
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N/A

D # Plans for investigators and sponsor to communicate trial
is 3 results to participants, healthcare professionals, the public,
s 1 and other relevant groups (eg, via publication, reporting in
e a results databases, or other data sharing arrangements),
m including any publication restrictions
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1 D # Authorship eligibility guidelines and any intended use of N/A
2
3 is 3 professional writers
4 s 1
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1 D # Plans, if any, for granting public access to the full protocol, N/A
2 is 3 participant-level dataset, and statistical code
3 s 1
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12 p
13 o
14 li
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17 :
18 r
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24 u
25 c
26 i
27 b
28 l
29 e
30 r
31 e
32 s
33 e
34 a
35 r
36 c
37 h

1	I	#	Model consent form and other related documentation given	N/A
2				
3	n	3	to participants and authorised surrogates	
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21	n			
22	t			
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24	m			
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26	a			
27	t			
28				
29	e			
30	ri			
31				
32	a			
33	ls			
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35				
36	B	#	Plans for collection, laboratory evaluation, and storage of	N/A
37	i	3	biological specimens for genetic or molecular analysis in	
38				
39	o	3	the current trial and for future use in ancillary studies, if	
40				
41	l		applicable	
42				
43	o			
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45	g			
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49	c			
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Author notes

1. 15, 16, 17, 18

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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**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029054.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Jul-2019
Complete List of Authors:	Ghert, Michelle; McMaster University, Department of Surgery; Hamilton Health Sciences, Juravinski Cancer Centre
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Surgery
Keywords:	surveillance, soft tissue sarcoma, study protocol, randomised controlled trial, pilot study

SCHOLARONE™
Manuscripts

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2
3 *Original article*
4

5 **The Surveillance AftEr Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot**
6
7 **study to determine the feasibility of a multi-centre randomized controlled trial**
8

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10 The SAFETY Investigators
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15 **Protocol version 1; December 3, 2018**
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25

26 **Correspondence and reprints**
27

28 Michelle Ghert, MD, FRCSC
29

30 Professor of Surgery
31

32 Division of Orthopaedic Surgery
33

34 Department of Surgery
35

36 McMaster University
37

38 711 Concession Street
39

40 Hamilton, ON
41

42 Canada
43

44 Tel: 905-387-9495 ext 64089
45

46 Fax: 905-381-7071
47

48 Email: mgbert@hhsc.ca
49

50
51
52
53 **Contributor list with affiliations**
54
55
56
57
58
59
60

1
2
3 Michelle Ghert, MD, FRCSC (Steering Committee Chair)
4 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
5
6

7 Mohit Bhandari, MD, PhD, FRCSC
8 Department of Surgery & Department of Health Research Methods, Evidence and Impact,
9 McMaster University (Hamilton, Ontario, Canada)
10
11

12 Anthony Bozzo, MD
13 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
14
15

16 P.D. Sander Dijkstra, MD, PhD
17 Department of Orthopaedics, Leiden University Medical Center (Leiden, the Netherlands)
18
19

20 Anthony Griffin, MSc
21 Musculoskeletal Oncology Unit, Mount Sinai Hospital (Toronto, Ontario, Canada)
22
23

24 Robert Grimer, MB BS, DSc, FRCS, FRCS Ed(Orth)
25 Department of Surgery, University of Birmingham (Birmingham, United Kingdom)
26
27

28 James Hayden, MD, PhD, FACS
29 Department of Orthopaedics & Rehabilitation, Oregon Health & Science University (Portland,
30 Oregon, USA)
31
32

33 Arlene Manherz
34 (Community)
35
36

37 Karim Masrouha, MD
38 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
39
40

41 Paula McKay, BSc
42 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
43
44

45 Benjamin Miller, MD, MS, FACS
46 Department of Orthopaedics & Rehabilitation, University of Iowa (Iowa City, Iowa, USA)
47
48

49 Naveen Parasu, MD, MRCP (UK), MRCR (UK), FRCPC
50 Department of Radiology, McMaster University (Hamilton, Ontario, Canada)
51
52

53 Ajay Puri, MS (Ortho)
54 Department of Surgical Oncology, Tata Memorial Centre (Mumbai, India)
55
56

57 R. Lor Randall, MD, FACS
58
59
60

1
2
3 Department of Orthopaedic Surgery, University of California, Davis (Sacramento, California,
4 USA)
5

6
7 Patricia Schneider, BSc
8 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
9

10
11 Sheila Sprague, PhD
12 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
13

14
15 Nina Szpakowski, MSc, DVM
16 (Community)
17

18
19 Lehana Thabane, PhD
20 Department of Health Research Methods, Evidence and Impact, McMaster University
21 (Hamilton, Ontario, Canada)
22

23
24 Robert Turcotte, MD, FRCSC
25 Department of Surgery, McGill University (Montreal, Quebec, Canada)
26

27
28 Roberto Vélez, MD, PhD
29 Department of Orthopaedic Surgery, Hospital Vall d'Hebron (Barcelona, Catalunya, Spain)
30

31
32 David Wilson, MD, MSc
33 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
34

35
36 Kevin Zbuk, MD, FRCPC
37 Department of Oncology, McMaster University (Hamilton, Ontario, Canada)
38

39
40 Gordon Guyatt, MD, FRCPC
41 Department of Medicine & Department of Health Research Methods, Evidence and Impact,
42 McMaster University (Hamilton, Ontario, Canada)
43
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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

1
2
3 Sarcomas are malignancies of connective tissue that most commonly occur in the extremities.
4
5 Sarcomas can arise within bone (bone sarcoma) or soft-tissue (soft-tissue sarcoma [STS]).
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8 Chemotherapy is not curative for the vast majority of patients with STS(1); therefore, surgery is
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10 the standard treatment for STS, with radiation considered important for local disease control.
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12 Following treatment for a STS that is not metastatic at presentation, the risk for local and
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14 systemic disease recurrence necessitates careful post-operative surveillance. Between 40% and
15
16 50% of all sarcoma patients will develop a local or distant recurrence; however, the risk of
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18 recurrence is greatest in the first few years, with 68% occurring by two years and 90% by five
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20 years(2-4). Metastasis to the lung is the most frequent single location of disease recurrence in
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22 sarcoma patients, occurring in the majority of patients with metastases(4-7). Therefore, routine
23
24 follow-up after completing sarcoma treatment is standard practice in the first five years after
25
26 surgery. These visits typically include a clinical history, physical examination, and imaging of the
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28 lungs (chest radiograph [CXR], or computed tomography [CT] scan of the lungs).
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33 Surveillance strategies for long-term follow-up of sarcoma patients have not been well
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35 researched and current guidelines are based on expert opinion, not on high quality evidence(8, 9).
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37 As such, current clinical practice is highly varied, with survey data of musculoskeletal oncologists
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39 showing that the number of clinic visits ranges from two to 12, the number of CXRs obtained
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41 ranges from zero to 13, and the number of CT scans ranges from one to eight in the first year of
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43 surveillance(10-12). The current National Comprehensive Cancer Network guidelines suggest that
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45 stage II or III tumors should be followed with chest imaging (CT or CXR) every two to six months
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47 for the first two to three years and then annually thereafter, while stage I tumors could be followed
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49 less frequently during the first two to three years (13).
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3 *Best evidence for surveillance strategies*
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5 Post-treatment soft-tissue sarcoma surveillance is an integral element of patient care. Although
6 earlier detection of metastatic disease may improve long-term survival, no study has yet provided
7 definitive evidence to support this assumption. In order to assess the available evidence, we
8 completed a systematic review of the available randomized controlled trial (RCT) evidence for
9 surveillance in sarcoma management(14). A single study (published separately with early and
10 longer-term follow-up) was identified(15, 16). The authors of this single-centre study found that
11 three-year overall and disease-free survival was not worse in sarcoma patients who had less
12 intensive surveillance (CXR) than those with more intensive surveillance (CT scans)(15). Due to
13 the sample size, this trial could not conclusively demonstrate non-inferiority in overall or disease-
14 free survival for a six-monthly interval of follow-up visits against three-monthly interval (both
15 were 64% and 69%, respectively)(15).
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31 A follow-up study on the same patient cohort with five-year survival outcomes confirmed
32 that more frequent follow-up did not improve survival and that, although CT scans detected
33 pulmonary metastasis earlier, they did not lead to better survival compared with CXRs(16).
34 However, this was a single-centre study with relatively small numbers and, therefore, confidence
35 in the results and generalizability of the data to other centres is limited. In addition, a relatively
36 small proportion of screened patients (42%) that were eligible for the trial were included due to
37 the exclusion of patients unlikely to follow-up, thus possibly introducing selection bias(15).
38 Furthermore, low-grade sarcomas were eligible and included in this study, even though they have
39 little metastatic potential and tumour-related mortality; their inclusion may have diminished the
40 magnitude of the effects of the interventions(15). Finally, the majority of the included patients
41 were bone sarcoma patients, thereby limiting the interpretation to STS patients(15).
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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

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

12 We plan to assess the feasibility of conducting the pragmatic, international, multi-centre, 2X2
13 factorial Surveillance After Extremity Tumour surgery (SAFETY) RCT that answers the
14 following questions: In extremity STS patients who undergo surgical resection with curative intent,
15 (1) what is the impact of surveillance frequency (every three vs. every six months) on overall
16 survival at five years, and (2) what is the impact of surveillance imaging modality (CXR vs. CT
17 scan) on overall survival at five years? To assess feasibility, we will conduct a pilot study. Study
18 participants will be randomized to one of four possible treatment arms (see Study Interventions
19 below). Randomization will occur at the end of active treatment (surgery ± systemic treatment ±
20 local radiation). Following the two-year intervention phase, study participants will continue to be
21 assessed at regular intervals for an additional three years. As such, all pilot study patients will be
22 transitioned into the definitive study and be included in it. Details of the flow of each study arm
23 are outlined in Figure 1. We anticipate the duration of the pilot study to be three years in order to
24 collect intervention phase data on all participants. The primary outcome of the pilot study is the
25 feasibility of a definitive RCT based on a combination of feasibility endpoints.
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47 The 2x2 factorial study design is ideal and the most efficient method to study two treatment
48 interventions in a single RCT, particularly when there is no interaction between the two
49 interventions. This is unlike a scenario in which the two interventions are medications that may
50 have a synergistic or negative effect when combined. A Bayesian design would be useful do avoid
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3 the question of whether or not an interaction exists, however for the purposes of the present trial it
4 is clear that no interaction exists between the frequency and intensity of surveillance. As Freidlin
5 and Korn discuss in their commentary, the 2x2 factorial design is an efficient design to evaluate
6 two interventions in a cancer clinical trial when there are no interactions between treatments(25).
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13 **Objectives**

14 *Pilot study primary research objectives*

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16 The primary objective of the pilot study will be to determine whether it is feasible to conduct a
17 large multi-centre RCT that will evaluate the impact of surveillance strategies on patient survival
18 following extremity STS surgery. To do so, we will assess our ability to:
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- 23 A) Recruit patients across multiple participating clinical sites;
 - 24 B) Ensure compliance with the study protocol, including the application of eligibility criteria,
25 timing of intervention phase and post-intervention phase visits and imaging modality;
 - 26 C) Maintain completeness of follow-up data;
 - 27 D) Maintain completeness of cost analysis data; and
 - 28 E) Maintain data quality.
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41 *Pilot study secondary research objectives*

42 The secondary objectives of the pilot study will include assessing the impact of either surveillance
43 frequency (every three vs. every six months) or imaging modality (CXR vs. CT scan) on:
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- 48 A) Overall survival;
 - 49 B) Patient anxiety, satisfaction and quality of life;
 - 50 C) Local recurrence-free survival and metastasis-free survival;
 - 51 D) Treatment-related complications; and
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3 E) Net direct healthcare costs and net costs of treatment and treatment-related complications once
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5 metastases are detected.
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10 **Hypothesis**

11 *Pilot study*

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

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26 There are two hypotheses:

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28 1- More frequent post-operative surveillance (compared to less frequent post-operative
29 surveillance) in the first two years following the surgical excision of a STS will improve survival
30 over five years;
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35 2 - The use of post-operative CT scans (compared to CXR) in the first two years following the
36 surgical excision of a STS will improve survival over five years.
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43 **Study setting**

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

20 *Inclusion criteria*

21 Patients who meet all of the following criteria will be included:
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- 24 1) Age of 18 years or older;
- 25 2) Diagnosed with a primary extremity grade II or III STS;
- 26 3) Undergone surgical resection of the tumour with curative intent and grossly negative margins
27 (R0 or R1 resection margins);
- 28 4) Completed neoadjuvant or adjuvant radiation and / or chemotherapy, if applicable;
- 29 5) The tumour size is greater than or equal to (\geq) five centimeters according to the pathology
30 report or pre-treatment MRI if neoadjuvant radiation and / or chemotherapy are given; and
31 6) Provision of informed consent.
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47 *Exclusion criteria*

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

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

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3 participants will be followed at least every six months as per National Comprehensive Cancer
4 Network (NCCN) guidelines(13). If possible, thoracic imaging will continue at each scheduled
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6 post-intervention phase visit according to the participants' original allocations.
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10 11 12 **Relapse**

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14 Local imaging and clinical assessment of the primary tumour site will be carried out as per the
15 standard protocol at each participating clinical site. Further diagnostic tests will be performed in
16
17 the presence of clinical symptoms or radiologic findings suggestive of disease relapse. Recurrence
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19 will be radiologically or histologically confirmed and classified as local or systemic (metastasis)
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21 recurrence. The first modality suggesting disease relapse in participants with confirmed local or
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23 systemic recurrence will be recorded as responsible for its detection.
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31 **Outcome measures**

32 *Pilot study primary outcome*

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34 To evaluate feasibility, we will assess the number of patients screened and recruited at each
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36 participating clinical site, participant retention, and maintenance of data quality. In addition, we
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38 will evaluate the utilization of an internet-based centralized randomisation system focusing on the
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40 accuracy of data entry, appropriate stratification of participants and the minimization of
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42 randomisation errors. Finally, we will evaluate investigator and participant compliance with the
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44 study protocol, including the application of eligibility criteria, compliance with the surveillance
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46 imaging and frequency regimens, frequency of crossover and timing of post-intervention phase
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48 visits. The a priori criteria for the success of the pilot study are listed below:
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3 A) *Recruitment Measure*: We will consider our recruitment strategy feasible if we are able to enroll
4 the pilot sample of 195 patients (approximately 20 patients from each clinical site participating in
5 the pilot study) within two years. See sample size determination below. As such, we will aim to
6 recruit 100 patients during the first year. If we are unable to achieve at least 90% of this goal (90
7 patients) then we will plan to increase the number of participating sites as a study rescue measure.

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

16
17 C) *Participant Retention Measure*: While 20% loss-to-follow-up has traditionally been considered
18 acceptable in clinical research, evidence from other orthopaedic trials suggests that bias begins to
19 affect study results at even lower rates of loss-to-follow-up(27). Therefore, we will consider our
20 participant retention strategies feasible if no more than 15% of participants are lost-to-follow-up.

21
22 D) *Maintenance of Data Quality Measure*: We obtained a data completeness rate of approximately
23 90% in the PARITY trial pilot study (26). Therefore, we will consider our data quality strategies
24 feasible if we are able to maintain 95% or greater completeness of participant follow-up data for
25 the definitive primary outcome. We will also consider our data quality strategies feasible if we are
26 able to maintain 85% or greater completeness of participant follow-up data for the secondary
27 outcomes.

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54 *Pilot study secondary outcomes*
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3 The main secondary outcome for the pilot study will be death from any cause. Data on secondary
4 outcomes for the definitive trial, which are listed below, will also be collected. These include:
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7 A) *Patient-reported outcome measures*: The validated Patient-Reported Outcomes Measurement
8 Information System (PROMIS)[®] Cancer-Anxiety questionnaire, PROMIS[®] Satisfaction with
9 Social Roles and Activities questionnaire, and the EuroQol-5 Dimension (EQ-5D) will be used to
10 assess patient anxiety, satisfaction and quality of life, respectively. These questionnaires will be
11 administered at the baseline visit, as well as the 6-month, 12-month, 18-month and 24-month
12 intervention phase, as well as 36-month, 48-month and 60-month post-intervention phase visits.
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16 B) *Local recurrence-free survival (LRFS) outcome measure*: LRFS will be defined as the length
17 of time from randomization that the participant survives with no detection of recurrent disease at
18 the initial tumor site or operative field.
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21 C) *Metastasis-free survival (MFS) outcome measure*: MFS will be defined as the length of time
22 from randomization that the participant survives with no detection of systemic disease recurrence
23 at any anatomic location.
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27 D) *Treatment-related complications outcome measures*: Treatment-related complications will
28 include both chemotherapy-related complications, such as febrile neutropenia, fungal infections or
29 sepsis, and thoracotomy-related complications, such as pneumothorax, or surgical site infections.
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33 E) *Net healthcare costs outcome measures*: We will perform an incremental cost analysis of net
34 costs of surveillance and costs incurred from metastasis treatment and metastasis treatment related
35 complications. Unit costs for all resources used by trial participants will be obtained from regional
36 statistics and from centers participating in the trial. These unit costs will be combined with the
37 resource volumes to obtain a net cost per participant over their time in the trial.
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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;

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- 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.

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- 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.

10 For both events, the specific imaging modality used to detect either the local recurrence or the
11 metastases will be documented.
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14 Patients that have incidental or off-protocol imaging will not crossover, however this will
15 be documented as a protocol deviation. In the case of a CXR that warrants further investigation
16 with a CT scan, this will be documented. If the patient is found to have disease recurrence, we will
17 document how the disease recurrence was (A) first identified; and (B) confirmed. If after a CT
18 scan the patient is found to not have disease recurrence, the patient will resume surveillance as per
19 the arm to which they were randomised.
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31 **Sample size determination**

32 *Pilot study sample size*

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

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49 Our best estimate of the control group overall five-year survival for both the surveillance frequency
50 and imaging modality is 55%(16). Given that intensive surveillance will detect metastatic disease
51 at an earlier stage, we will use a superiority design to compare survival between more versus less
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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, $\alpha=0.05$. 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 (percentage) 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

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3 committee, in agreement with local legal prescriptions, for formal approval of the study conduct
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5 at each participating clinical site. A copy of this approval will be provided to the Methods Centre
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7 by each participating clinical site prior to the local commencement of the study.
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10 11 12 **Study Timeline**

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14 We expect that the pilot study will take just over three years to complete. We estimate that
15
16 recruitment will take approximately one year to complete per site. The initiation of screening and
17
18 enrollment will likely be staggered across the participating clinical sites due to the variability in
19
20 the time required to obtain ethics approval and negotiate institutional contracts. Therefore the pilot
21
22 study recruitment timeline will be up to two years. We expect a further one year for all pilot
23
24 participants to complete the intervention phase of the trial. Although we will not have complete
25
26 post-intervention phase data for any pilot participants, we anticipate being able to determine
27
28 feasibility at the end of the intervention phase based on our feasibility objectives. We plan *a priori*
29
30 to transition directly from the pilot to the definitive study if feasibility is established.
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38 **Data Safety Monitoring Board**

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40 As per the principles established by the *Data Monitoring Committees: Lessons, Ethics, Statistics*
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42 (*DAMOCLES*) *Study Group* charter, a DSMB will oversee the safety of the trial participants and
43
44 the overall conduct of the trial. The Committee members will be independent of the trial, free of
45
46 conflicts with any of the investigative team, and will consist of two orthopaedic oncologists, a
47
48 medical oncologist, a radiologist, and a biostatistician. The DSMB will frequently review
49
50 enrollment and demographic summaries, listings of protocol deviations, and summaries and
51
52 listings of serious adverse events. They will advise the Principal Investigator and SAFETY study
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3 team on any concerns related to participant safety and trial conduct and will make
4 recommendations for: A) study continuation as designed; B) study termination; C) study
5 continuation with major or minor modifications; or D) temporary study suspension of enrollment
6 until some uncertainty is resolved.
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15 **Potential impact of the study**

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17 The benefit of this pilot study would be to determine the feasibility of the SAFETY trial. This is
18 essential prior to undertaking a large multi-centre RCT. Experience gained during the pilot study
19 will provide insight into methods to increase enrollment, strategies to maintain protocol adherence
20 and the adjustment of recruitment expectations. In addition, the ultimate success of the pilot study
21 will support funding requests for the definitive study of the multi-centre SAFETY trial.
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28 Once the feasibility endpoints are reached, we will transition directly into and begin
29 recruiting for the definitive SAFETY trial. The ultimate goal of the SAFETY trial is to provide
30 high-quality evidence for surveillance strategies following the treatment of STS, which will allow
31 for the development of evidence-based clinical practice guidelines for sarcoma patients worldwide.
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40 **References**

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Figure legend

Figure 1. Study flow diagram

Data statement

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3 All data from this work will be maintained in security and confidentiality at the Methods Centre
4
5 at McMaster University. Access to additional unpublished data will be reviewed on a case-by-
6
7 case basis and will accord with the guidelines of our local institutional research ethics board.
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9

10 11 12 **Authors' contributions**

- 13
14 • Substantial contributions to the conception or design of the work; or the acquisition,
15 analysis, or interpretation of data for the work: Michelle Ghert; Mohit Bhandari;
16 Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden;
17 Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay
18 Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana
19 Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- 20 • Drafting the work: Michelle Ghert, Patricia Schneider, and Karim Masrouha
- 21 • Revising it critically for important intellectual content: Michelle Ghert; Mohit Bhandari;
22 Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden;
23 Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay
24 Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana
25 Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- 26 • Final approval of the version to be published: Michelle Ghert; Mohit Bhandari; Anthony
27 Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene
28 Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri;
29 R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane;
30 Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
- 31 • Agreement to be accountable for all aspects of the work in ensuring that questions related
32 to the accuracy or integrity of any part of the work are appropriately investigated and
33 resolved: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra;
34 Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha;
35 Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia
36 Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto
37 Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt

38 39 40 41 42 43 44 45 46 **Funding**

47
48 This research is supported by funding through the Hamilton Academic Health Science
49
50 Organization (HAHSO) Innovation Grant.
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52

53 54 55 56 **Competing interests statement**

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

Word count

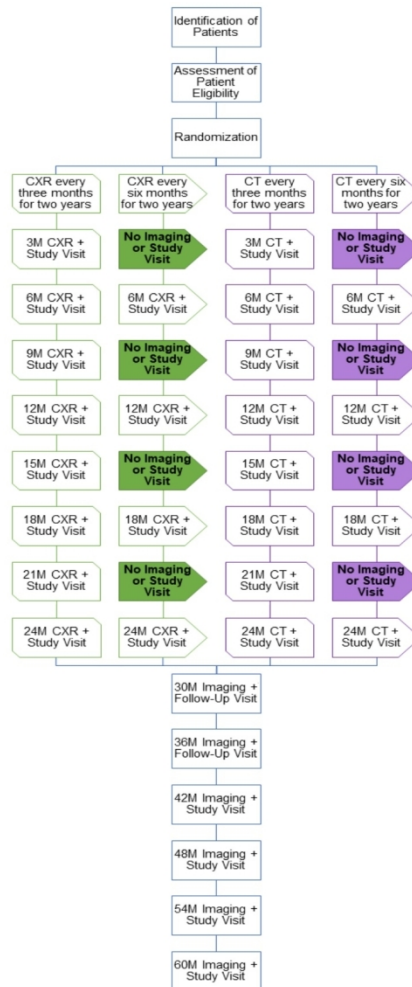
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For peer review only

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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

Page

Number

Reporting Item

T #	Descriptive title identifying the study design, population,	1
it 1	interventions, and, if applicable, trial acronym	
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1 T # Trial identifier and registry name. If not yet registered, N/A
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3 ri 2 name of intended registry
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22 T # All items from the World Health Organization Trial N/A
23 ri 2 Registration Data Set
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1 P # Date and version identifier 1
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23 F # Sources and types of financial, material, and other support HAHSO
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1 R # Names, affiliations, and roles of protocol contributors 2,3,28
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1	R #	Name and contact information for the trial sponsor	N/A
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1 R # Role of study sponsor and funders, if any, in study design; N/A
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3 o 5 collection, management, analysis, and interpretation of
4 l c data; writing of the report; and the decision to submit the
5 e report for publication, including whether they will have
6 s ultimate authority over any of these activities
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1 R # Composition, roles, and responsibilities of the coordinating 18, 24, 25
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3 o 5 centre, steering committee, endpoint adjudication
4 l d committee, data management team, and other individuals or
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6 e groups overseeing the trial, if applicable (see Item 21a for
7
8 s data monitoring committee)
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B # Description of research question and justification for
a 6 undertaking the trial, including summary of relevant studies
c a (published and unpublished) examining benefits and harms
k for each intervention

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1 B # Explanation for choice of comparators

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1	O #	Specific objectives or hypotheses	9, 10, 11
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16	T #	Description of trial design including type of trial (eg,	9
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18	ri	8 parallel group, crossover, factorial, single group), allocation	
19	a	ratio, and framework (eg, superiority, equivalence, non-	
20		inferiority, exploratory)	
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31	S #	Description of study settings (eg, community clinic,	11
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33	t	9 academic hospital) and list of countries where data will be	
34	u	collected. Reference to where list of study sites can be	
35		obtained	
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1 E # Inclusion and exclusion criteria for participants. If 12
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3 li 1 applicable, eligibility criteria for study centres and
4 g 0 individuals who will perform the interventions (eg,
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6 i surgeons, psychotherapists)

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24 I # Interventions for each group with sufficient detail to allow 14
25 n 1 replication, including how and when they will be
26 t 1 administered

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1 I # Criteria for discontinuing or modifying allocated N/A
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3 n 1 interventions for a given trial participant (eg, drug dose
4 t 1 change in response to harms, participant request, or
5 e b improving / worsening disease)
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1 I # Strategies to improve adherence to intervention protocols, 19, 20
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3 n 1 and any procedures for monitoring adherence (eg, drug
4 t 1 tablet return; laboratory tests)
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1 I # Relevant concomitant care and interventions that are
 2 n 1 permitted or prohibited during the trial
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41 O # Primary, secondary, and other outcomes, including the See note 1
 42 u 1 specific measurement variable (eg, systolic blood pressure),
 43 t 2 analysis metric (eg, change from baseline, final value, time
 44 c to event), method of aggregation (eg, median, proportion),
 45 o and time point for each outcome. Explanation of the clinical
 46 m relevance of chosen efficacy and harm outcomes is strongly
 47 e recommended
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1	P	#	Time schedule of enrolment, interventions (including any	24
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3	a	1	run-ins and washouts), assessments, and visits for	
4	rt	3	participants. A schematic diagram is highly recommended	
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27	S	#	Estimated number of participants needed to achieve study	20, 21
28	a	1	objectives and how it was determined, including clinical	
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30	m	4	and statistical assumptions supporting any sample size	
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34	e			
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36	si			
37	z			
38				
39	e			
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42	R	#	Strategies for achieving adequate participant enrolment to	13, 14
43	e	1	reach target sample size	
44				
45	c	5		
46	r			
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48	u			
49	it			
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51	m			
52	e			
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1 A # Method of generating the allocation sequence (eg,
2 ll 1 computer-generated random numbers), and list of any
3 o 6 factors for stratification. To reduce predictability of a
4 c a random sequence, details of any planned restriction (eg,
5 a blocking) should be provided in a separate document that is
6 ti unavailable to those who enrol participants or assign
7 o interventions
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1 A # Mechanism of implementing the allocation sequence (eg,
2 ll 1 central telephone; sequentially numbered, opaque, sealed
3 o 6 envelopes), describing any steps to conceal the sequence
4 c b until interventions are assigned
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6 a
7 ti
8 o
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10 c
11 o
12 n
13 c
14 o
15 n
16 c
17 e
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19 l
20 m
21 e
22 n
23 t
24 m
25 e
26 c
27 h
28 a
29 n
30 is
31 m

1 A # Who will generate the allocation sequence, who will enrol 14
2 ll 1 participants, and who will assign participants to
3 o 6 interventions

4 c c
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6 a
7 ti
8 o
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11 i
12 m
13 p
14 l
15 e
16 m
17 e
18 n
19 t
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21 ti
22 o
23 n

35 B # Who will be blinded after assignment to interventions (eg, 19
36 li 1 trial participants, care providers, outcome assessors, data
37 n 7 analysts), and how

40 d a
41 i
42 n
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45 m
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47 s
48 k
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1 B # If blinded, circumstances under which unblinding is N/A
2
3 li 1 permissible, and procedure for revealing a participant's
4 n 7 allocated intervention during the trial
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6 d b
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9 n
10 g
11 (
12 m
13 a
14 s
15 k
16 i
17 n
18 g
19):
20 e
21 m
22 e
23 r
24 g
25 e
26 n
27 c
28 y
29 u
30 n
31 b
32 li
33 n
34 d
35 i
36 n
37 g

N/A

1 D # Plans for assessment and collection of outcome, baseline,
2
3 a 1 and other trial data, including any related processes to
4 t 8 promote data quality (eg, duplicate measurements, training
5 a a of assessors) and a description of study instruments (eg,
6 c questionnaires, laboratory tests) along with their reliability
7 o and validity, if known. Reference to where data collection
8 ll forms can be found, if not in the protocol
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11 e
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13 c
14 ti
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1 D # Plans to promote participant retention and complete follow- 19
2 a 1 up, including list of any outcome data to be collected for
3 t 8 participants who discontinue or deviate from intervention
4 a b protocols
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6 c
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8 o
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10 ll
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12 e
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14 c
15 ti
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1 D # Plans for data entry, coding, security, and storage, including 24, 25
2
3 a 1 any related processes to promote data quality (eg, double
4 t 9 data entry; range checks for data values). Reference to
5
6 a where details of data management procedures can be found,
7 m if not in the protocol
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9 a
10 n
11 a
12 g
13 e
14 m
15 e
16 n
17 t

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24 S # Statistical methods for analysing primary and secondary 22
25 t 2 outcomes. Reference to where other details of the statistical
26 a 0 analysis plan can be found, if not in the protocol
27
28 ti a
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30 st
31 i
32 c
33 s:
34 o
35 u
36 t
37 c
38 o
39 m
40 e
41 s

1	S	#	Methods for any additional analyses (eg, subgroup and	N/A
2				
3	t	2	adjusted analyses)	
4	a	0		
5				
6	t	i	b	
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8	s	t		
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10	i			
11				
12	c			
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14	s:			
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16	a			
17				
18	d			
19				
20	d			
21				
22	i			
23				
24	o			
25				
26	n			
27				
28	a			
29				
30	l			
31				
32	a			
33				
34	n			
35				
36	a			
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38	l			
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40	y			
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42	s			
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44	e			
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1 S # Definition of analysis population relating to protocol non- N/A
2 t 2 adherence (eg, as randomised analysis), and any statistical
3 a 0 methods to handle missing data (eg, multiple imputation)
4 ti c
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6 st
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8 i
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10 c
11 s:
12 a
13 n
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15 l
16 y
17 si
18 s
19 p
20 o
21 p
22 u
23 l
24 a
25 ti
26 o
27 n
28 a
29 n
30 d
31 m
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33 si
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1 D # Composition of data monitoring committee (DMC);
2
3 a 2 summary of its role and reporting structure; statement of
4 t 1 whether it is independent from the sponsor and competing
5 a a interests; and reference to where further details about its
6 m charter can be found, if not in the protocol. Alternatively,
7 o an explanation of why a DMC is not needed
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1	D #	Description of any interim analyses and stopping	N/A
2			
3	a 2	guidelines, including who will have access to these interim	
4	t 1	results and make the final decision to terminate the trial	
5			
6	a b		
7	m		
8			
9	o		
10	n		
11	it		
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13	o		
14	ri		
15	n		
16	g		
17	:		
18	i		
19	n		
20	t		
21	e		
22	ri		
23	m		
24	a		
25	n		
26	a		
27	l		
28	y		
29	si		
30	s		
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41	H #	Plans for collecting, assessing, reporting, and managing	24, 25
42	a 2	solicited and spontaneously reported adverse events and	
43	r 2	other unintended effects of trial interventions or trial	
44	m	conduct	
45			
46	s		
47			
48			
49			
50	A #	Frequency and procedures for auditing trial conduct, if any,	24, 25
51	u 2	and whether the process will be independent from	
52	d 3	investigators and the sponsor	
53			
54	it		
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11 R # Plans for seeking research ethics committee / institutional 23, 24
12 e 2 review board (REC / IRB) approval
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14 s 4
15 e
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17 r
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20 e
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22 h
23 i
24 c
25 s
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27 p
28 p
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1	P	#	Plans for communicating important protocol modifications	N/A
2				
3	r	2	(eg, changes to eligibility criteria, outcomes, analyses) to	
4				
5	o	5	relevant parties (eg, investigators, REC / IRBs, trial	
6	t		participants, trial registries, journals, regulators)	
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8	o			
9	c			
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11	o			
12	l			
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14	a			
15	m			
16	e			
17	n			
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19	d			
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21	m			
22	e			
23				
24	n			
25	ts			
26				
27				
28	C	#	Who will obtain informed consent or assent from potential	13, 14
29				
30	o	2	trial participants or authorised surrogates, and how (see	
31				
32	n	6	Item 32)	
33	s	a		
34	e			
35				
36	n			
37	t			
38				
39	o			
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41	r			
42	a			
43	s			
44				
45	s			
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1 C # Additional consent provisions for collection and use of N/A
2
3 o 2 participant data and biological specimens in ancillary
4 n 6 studies, if applicable
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6 s b
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12 t
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14 o
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16 r
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20 s
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22 s
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24 e
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26 n
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28 t:
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32 n
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1 C # How personal information about potential and enrolled 13, 14
2
3 o 2 participants will be collected, shared, and maintained in
4 n 7 order to protect confidentiality before, during, and after the
5 fi trial
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7 d
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9 e

10 n
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14 t
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21 D # Financial and other competing interests for principal 28
22 e 2 investigators for the overall trial and each study site
23 c 8

24 l
25 a
26 r
27 a
28 ti
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30 n
31 o
32 f
33 i
34 n
35 t
36 e
37 r
38 e
39 st
40 s
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1 D # Statement of who will have access to the final trial dataset, N/A
2
3 a 2 and disclosure of contractual agreements that limit such
4 t 9 access for investigators
5

6 a
7 a
8 c
9 c
10 c
11 e
12 s
13 s
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17 A # Provisions, if any, for ancillary and post-trial care, and for N/A
18 n 3 compensation to those who suffer harm from trial
19 c 0 participation
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21 il
22 l
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24 r
25 y
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27 n
28 d
29 p
30 o
31 st
32 tr
33 i
34 a
35 l
36 c
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N/A

D # Plans for investigators and sponsor to communicate trial
is 3 results to participants, healthcare professionals, the public,
s 1 and other relevant groups (eg, via publication, reporting in
e a results databases, or other data sharing arrangements),
m including any publication restrictions
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1 D # Authorship eligibility guidelines and any intended use of N/A
2
3 is 3 professional writers
4 s 1
5 e b
6 m
7 i
8 n
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10 ti
11 o
12 n
13 p
14 o
15 li
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25 s
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1 D # Plans, if any, for granting public access to the full protocol, N/A
2 is 3 participant-level dataset, and statistical code
3 s 1
4 e c
5 m
6 i
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8 a
9 ti
10 o
11 n
12 p
13 o
14 li
15 c
16 y
17 :
18 r
19 e
20 p
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22 o
23 d
24 u
25 c
26 i
27 b
28 l
29 e
30 r
31 e
32 s
33 e
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35 r
36 c
37 h

1	I	#	Model consent form and other related documentation given	N/A
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3	n	3	to participants and authorised surrogates	
4	f	2		
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11	e			
12	d			
13				
14	c			
15	o			
16	n			
17				
18	s			
19				
20	e			
21	n			
22	t			
23				
24	m			
25				
26	a			
27	t			
28				
29	e			
30	ri			
31				
32	a			
33	ls			
34				
35				
36	B	#	Plans for collection, laboratory evaluation, and storage of	N/A
37	i	3	biological specimens for genetic or molecular analysis in	
38				
39	o	3	the current trial and for future use in ancillary studies, if	
40				
41	l		applicable	
42				
43	o			
44				
45	g			
46				
47	i			
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49	c			
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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029054.R2
Article Type:	Protocol
Date Submitted by the Author:	09-Aug-2019
Complete List of Authors:	Ghert, Michelle; McMaster University, Department of Surgery; Hamilton Health Sciences, Juravinski Cancer Centre
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Surgery
Keywords:	surveillance, soft tissue sarcoma, study protocol, randomised controlled trial, pilot study

SCHOLARONE™
Manuscripts

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2
3 *Original article*
4

5 **The Surveillance AftEr Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot**
6
7 **study to determine the feasibility of a multi-centre randomized controlled trial**
8
9

10 The SAFETY Investigators
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14 **Protocol version 1; December 3, 2018**
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26 **Correspondence and reprints**
27

28 Michelle Ghert, MD, FRCSC
29

30 Professor of Surgery
31

32 Division of Orthopaedic Surgery
33

34 Department of Surgery
35

36 McMaster University
37

38 711 Concession Street
39

40 Hamilton, ON
41

42 Canada
43

44 Tel: 905-387-9495 ext 64089
45

46 Fax: 905-381-7071
47

48 Email: mghert@hhsc.ca
49
50

51 **Contributor list with affiliations**
52
53
54
55
56
57
58
59
60

1
2
3 Michelle Ghert, MD, FRCSC (Steering Committee Chair)
4 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
5
6

7 Mohit Bhandari, MD, PhD, FRCSC
8 Department of Surgery & Department of Health Research Methods, Evidence and Impact,
9 McMaster University (Hamilton, Ontario, Canada)
10

11 Anthony Bozzo, MD
12 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
13
14

15 P.D. Sander Dijkstra, MD, PhD
16 Department of Orthopaedics, Leiden University Medical Center (Leiden, the Netherlands)
17
18

19 Anthony Griffin, MSc
20 Musculoskeletal Oncology Unit, Mount Sinai Hospital (Toronto, Ontario, Canada)
21
22

23 Robert Grimer, MB BS, DSc, FRCS, FRCS Ed(Orth)
24 Department of Surgery, University of Birmingham (Birmingham, United Kingdom)
25
26

27 James Hayden, MD, PhD, FACS
28 Department of Orthopaedics & Rehabilitation, Oregon Health & Science University (Portland,
29 Oregon, USA)
30

31 Arlene Manherz
32 (Community)
33
34

35 Karim Masrouha, MD
36 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
37
38

39 Paula McKay, BSc
40 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
41
42

43 Benjamin Miller, MD, MS, FACS
44 Department of Orthopaedics & Rehabilitation, University of Iowa (Iowa City, Iowa, USA)
45
46

47 Naveen Parasu, MD, MRCP (UK), MRCR (UK), FRCPC
48 Department of Radiology, McMaster University (Hamilton, Ontario, Canada)
49
50

51 Ajay Puri, MS (Ortho)
52 Department of Surgical Oncology, Tata Memorial Centre (Mumbai, India)
53
54

55 R. Lor Randall, MD, FACS
56
57
58
59
60

1
2
3 Department of Orthopaedic Surgery, University of California, Davis (Sacramento, California,
4 USA)
5

6
7 Patricia Schneider, BSc
8 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
9

10
11 Sheila Sprague, PhD
12 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
13

14
15 Nina Szpakowski, MSc, DVM
16 (Community)
17

18
19 Lehana Thabane, PhD
20 Department of Health Research Methods, Evidence and Impact, McMaster University
21 (Hamilton, Ontario, Canada)
22

23
24 Robert Turcotte, MD, FRCSC
25 Department of Surgery, McGill University (Montreal, Quebec, Canada)
26

27
28 Roberto Vélez, MD, PhD
29 Department of Orthopaedic Surgery, Hospital Vall d'Hebron (Barcelona, Catalunya, Spain)
30

31
32 David Wilson, MD, MSc
33 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
34

35
36 Kevin Zbuk, MD, FRCPC
37 Department of Oncology, McMaster University (Hamilton, Ontario, Canada)
38

39
40 Gordon Guyatt, MD, FRCPC
41 Department of Medicine & Department of Health Research Methods, Evidence and Impact,
42 McMaster University (Hamilton, Ontario, Canada)
43
44
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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

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2
3 for the first two to three years and then annually thereafter, while stage I tumors could be followed
4
5 less frequently during the first two to three years (13).
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10 *Best evidence for surveillance strategies*

11
12 Post-treatment soft-tissue sarcoma surveillance is an integral element of patient care. Although
13
14 earlier detection of metastatic disease may improve long-term survival, no study has yet provided
15
16 definitive evidence to support this assumption. In order to assess the available evidence, we
17
18 completed a systematic review of the available randomized controlled trial (RCT) evidence for
19
20 surveillance in sarcoma management(14). A single study (published separately with early and
21
22 longer-term follow-up) was identified(15, 16). The authors of this single-centre study found that
23
24 three-year overall and disease-free survival was not worse in sarcoma patients who had less
25
26 intensive surveillance (CXR) than those with more intensive surveillance (CT scans)(15). Due to
27
28 the sample size, this trial could not conclusively demonstrate non-inferiority in overall or disease-
29
30 free survival for a six-monthly interval of follow-up visits against three-monthly interval (both
31
32 were 64% and 69%, respectively)(15).
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38 A follow-up study on the same patient cohort with five-year survival outcomes confirmed
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40 that more frequent follow-up did not improve survival and that, although CT scans detected
41
42 pulmonary metastasis earlier, they did not lead to better survival compared with CXRs(16).
43
44 However, this was a single-centre study with relatively small numbers and, therefore, confidence
45
46 in the results and generalizability of the data to other centres is limited. In addition, a relatively
47
48 small proportion of screened patients (42%) that were eligible for the trial were included due to
49
50 the exclusion of patients unlikely to follow-up, thus possibly introducing selection bias(15).
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53 Furthermore, low-grade sarcomas were eligible and included in this study, even though they have
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3 little metastatic potential and tumour-related mortality; their inclusion may have diminished the
4 magnitude of the effects of the interventions(15). Finally, the majority of the included patients
5 were bone sarcoma patients, thereby limiting the interpretation to STS patients(15).
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10 11 12 *Risks and benefits of intensive surveillance* 13

14 Regular, intensive surveillance is more likely to identify recurrent disease earlier than would less
15 intensive surveillance. This type of surveillance may provide reassurance to patients and clinicians;
16 however, the adverse effects of intensive surveillance practices are also noteworthy. The costs that
17 healthcare systems incur as a result of sarcoma surveillance are substantial and could be in excess
18 of USD \$20,000 for high-grade sarcomas(17). Furthermore, intensive surveillance can threaten the
19 financial security of patients, due in part to the direct (including travel, accommodation, personal
20 care, and homemaking) and indirect costs (including lost wages for patients and their caregivers)
21 incurred as a result of follow-up appointments(18). As a result, patients' health and quality of life
22 can be dramatically impacted(18-20).
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35 Secondary investigations and earlier knowledge of disease recurrence can also induce
36 anxiety and impact the psychosocial wellbeing for those whose mortality risk cannot be
37 significantly reduced by further medical interventions(21). Overcrowded clinics and long wait
38 times may constitute other important factors that affect patients' psychosocial wellbeing(22).
39 Finally, the use of CT has raised concerns over unnecessary radiation exposure compared to
40 radiographs, although lower dose CT scans may mitigate some of these concerns(23).
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51 *Surveillance research as a priority in orthopedic oncology* 52 53 54 55 56 57 58 59 60

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3 We recently published a modified Delphi study in which we aimed to identify a clinically relevant
4 consensus-based research agenda in the sarcoma field(24). From this Delphi process that included
5
6 80 orthopaedic oncologists and patient representation (with participation from 18 countries), we
7
8 identified critical research priorities in the field of orthopaedic oncology and determined the top
9
10 four feasible and important research questions that will directly inform patient care and enhance
11
12 clinical practice. This study identified the evaluation of post-operative surveillance strategies as
13
14 the highest-ranking research priority in the sarcoma field(24).
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22 **Patient and public involvement**

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24 To ensure that we maintain a patient-centered approach to the design and development of this
25
26 study, we required the opportunity for open dialogue between the multidisciplinary and
27
28 international SAFETY study team, along with patient / caregiver representatives and other key
29
30 stakeholders. To facilitate their interaction and collaboration, we held an in-person Protocol
31
32 Development Meeting in Toronto, ON, Canada in May 2018. At this meeting, we made critical
33
34 decisions with respect to the study protocol, including: A) study design; B) primary and secondary
35
36 outcomes; C) patient eligibility; D) follow-up timeframe; E) methods to protect against bias; F)
37
38 randomization stratification; and G) further patient engagement. We also had the opportunity to
39
40 discuss several issues that may compromise the study's success and strategize ways to manage
41
42 these challenges, such as: I) acceptable surveillance schedules that account for differences in
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44 international standards of clinical practice; II) possible ethical concerns; III) patient compliance;
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46 IV) local implementation and procedural variation; V) competing studies; and VI) funding
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48 opportunities.
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3 We are also conducting a patient survey to assess international patient willingness to
4 participate in a study that randomizes patients to a post-operative surveillance regimen in the
5 management of a primary extremity sarcoma. Since there is no available validated tool to assess
6 patient opinions and preferences, we developed a unique patient questionnaire for the purposes
7 of this study. All new patients who present to a participating sarcoma clinic are screened for study
8 participation. The preliminary survey questionnaire responses suggest that most sarcoma
9 patients believe that they have a good understanding of clinical research. Furthermore, over half
10 of respondents feel comfortable with being randomized to receive a treatment. Ultimately,
11 almost 80% of respondents have indicated that they would agree to participate in the SAFETY
12 trial if eligible.
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30 **Study design**

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32 We plan to assess the feasibility of conducting the pragmatic, international, multi-centre, 2x2
33 factorial Surveillance AftEr Extremity Tumour surgery (SAFETY) RCT that answers the
34 following questions: In extremity STS patients who undergo surgical resection with curative intent,
35 (1) what is the impact of surveillance frequency (every three vs. every six months) on overall
36 survival at five years, and (2) what is the impact of surveillance imaging modality (CXR vs. CT
37 scan) on overall survival at five years? To assess feasibility, we will conduct a pilot study. Study
38 participants will be randomized to one of four possible treatment arms (see Study Interventions
39 below). Randomization will occur at the end of active treatment (surgery \pm systemic treatment \pm
40 local radiation). Following the two-year intervention phase, study participants will continue to be
41 assessed at regular intervals for an additional three years. As such, all pilot study patients will be
42 transitioned into the definitive study and be included in it. Details of the flow of each study arm
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3 are outlined in Figure 1. We anticipate the duration of the pilot study to be three years in order to
4 collect intervention phase data on all participants. The primary outcome of the pilot study is the
5 feasibility of a definitive RCT based on a combination of feasibility endpoints.
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10 The 2x2 factorial study design is ideal and the most efficient method to study two treatment
11 interventions in a single RCT, particularly when there is no interaction between the two
12 interventions. This is unlike a scenario in which the two interventions are medications that may
13 have a synergistic or negative effect when combined. A Bayesian design would be useful to avoid
14 the question of whether or not an interaction exists, however for the purposes of the present trial it
15 is clear that no interaction exists between the frequency and intensity of surveillance. As Freidlin
16 and Korn discuss in their commentary, the 2x2 factorial design is an efficient design to evaluate
17 two interventions in a cancer clinical trial when there are no interactions between treatments(25).
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29 **Objectives**

30 *Pilot study primary research objectives*

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32 The primary objective of the pilot study will be to determine whether it is feasible to conduct a
33 large multi-centre RCT that will evaluate the impact of surveillance strategies on patient survival
34 following extremity STS surgery. To do so, we will assess our ability to:
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41 A) Recruit patients across multiple participating clinical sites;
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43 B) Ensure compliance with the study protocol, including the application of eligibility criteria,
44 timing of intervention phase and post-intervention phase visits and imaging modality;
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47 C) Maintain completeness of follow-up data;
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49 D) Maintain completeness of cost analysis data; and
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51 E) Maintain data quality.
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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 (\geq) 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 (\geq) 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;

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3 10) The patient has already been enrolled in the SAFETY trial.
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8 **Recruitment and screening**

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

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

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53 Participants will be randomised to one of four treatment groups:
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- 3 1) CXR every three months for two years;
- 4
- 5 2) CXR every six months for two years;
- 6
- 7 3) Chest CT every three months for two years; or
- 8
- 9 4) Chest CT every six months for two years.
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12 Following completion of the intervention phase, participants will continue to be followed
13 in the study for an additional three years. During this three-year post-intervention phase,
14 participants will be followed at least every six months as per National Comprehensive Cancer
15 Network (NCCN) guidelines(13). If possible, thoracic imaging will continue at each scheduled
16 post-intervention phase visit according to the participants' original allocations.
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26 **Relapse**

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

45 *Pilot study primary outcome*

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47 To evaluate feasibility, we will assess the number of patients screened and recruited at each
48 participating clinical site, participant retention, and maintenance of data quality. In addition, we
49 will evaluate the utilization of an internet-based centralized randomisation system focusing on the
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3 accuracy of data entry, appropriate stratification of participants and the minimization of
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5 randomisation errors. Finally, we will evaluate investigator and participant compliance with the
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7 study protocol, including the application of eligibility criteria, compliance with the surveillance
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9 imaging and frequency regimens, frequency of crossover and timing of post-intervention phase
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11 visits. As discussed by Moore *et al.*, the pilot study will investigate the process of the proposed
12
13 definitive trial rather than its outcomes (26). The *a priori* criteria for the success of the pilot study
14
15 are listed below:
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19 A) *Recruitment Measure*: We will consider our recruitment strategy feasible if we are able to enroll
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21 the pilot sample of 195 patients (approximately 20 patients from each clinical site participating in
22
23 the pilot study) within two years. See sample size determination below. As such, we will aim to
24
25 recruit 100 patients during the first year. If we are unable to achieve at least 90% of this goal (90
26
27 patients) then we will plan to increase the number of participating sites as a study rescue measure.
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29

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31 B) *Protocol Adherence Measure*: During the pilot study of the PARITY trial, we were able to
32
33 maintain an overall protocol adherence rate in excess of 90%(27). Recent reports prepared for the
34
35 PARITY Data and Safety Monitoring Board (DSMB) indicate a similar protocol adherence rate.
36
37 However, given the greater complexity and longer duration of the SAFETY trial interventions, we
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39 will consider our protocol adherence strategies feasible if there is adherence of 85% or greater to
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41 the visit windows and imaging modality prescribed by the protocol.
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45 C) *Participant Retention Measure*: While 20% loss-to-follow-up has traditionally been considered
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47 acceptable in clinical research, evidence from other orthopaedic trials suggests that bias begins to
48
49 affect study results at even lower rates of loss-to-follow-up(28). Therefore, we will consider our
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51 participant retention strategies feasible if no more than 15% of participants are lost-to-follow-up.
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3 D) *Maintenance of Data Quality Measure*: We obtained a data completeness rate of approximately
4
5 90% in the PARITY trial pilot study (27). Therefore, we will consider our data quality strategies
6
7 feasible if we are able to maintain 95% or greater completeness of participant follow-up data for
8
9 the definitive primary outcome. We will also consider our data quality strategies feasible if we are
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11 able to maintain 85% or greater completeness of participant follow-up data for the secondary
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13 outcomes.
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19 *Pilot study secondary outcomes*
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21 Death from any cause will be recorded during the pilot study. Data on secondary outcomes for the
22
23 definitive trial, which are listed below, will also be collected. These include:
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26 A) *Patient-reported outcome measures*: The validated Patient-Reported Outcomes Measurement
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28 Information System (PROMIS)[®] Cancer-Anxiety questionnaire, PROMIS[®] Satisfaction with
29
30 Social Roles and Activities questionnaire, and the EuroQol-5 Dimension (EQ-5D) will be used to
31
32 assess patient anxiety, satisfaction and quality of life, respectively. These questionnaires will be
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34 administered at the baseline visit, as well as the 6-month, 12-month, 18-month and 24-month
35
36 intervention phase, as well as 36-month, 48-month and 60-month post-intervention phase visits.
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39 B) *Local recurrence-free survival (LRFS) outcome measure*: LRFS will be defined as the length
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41 of time from randomization that the participant survives with no detection of recurrent disease at
42
43 the initial tumor site or operative field.
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46 C) *Metastasis-free survival (MFS) outcome measure*: MFS will be defined as the length of time
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48 from randomization that the participant survives with no detection of systemic disease recurrence
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50 at any anatomic location.
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3 D) *Treatment-related complications outcome measures*: Treatment-related complications will
4 include both chemotherapy-related complications, such as febrile neutropenia, fungal infections or
5
6 include both chemotherapy-related complications, such as febrile neutropenia, fungal infections or
7
8 sepsis, and thoracotomy-related complications, such as pneumothorax, or surgical site infections.
9

10 E) *Net healthcare costs outcome measures*: We will perform an incremental cost analysis of net
11
12 costs of surveillance and costs incurred from metastasis treatment and metastasis treatment related
13
14 complications. Unit costs for all resources used by trial participants will be obtained from regional
15
16 statistics and from centers participating in the trial. These unit costs will be combined with the
17
18 resource volumes to obtain a net cost per participant over their time in the trial.
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24 **Protecting against sources of bias**

25 *Adjudication of outcomes*

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27 An independent Central Adjudication Committee (CAC) will review all situations where eligibility
28
29 is in doubt, as well as all reported instances of disease relapse, treatment-related complications,
30
31 and death to determine whether a study event has occurred. The SAFETY CAC will be comprised
32
33 of two orthopaedic oncologists, one medical oncologist, and one radiologist. All participating
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35 clinical sites will submit digital imaging and relevant hospital records to the Methods Centre via a
36
37 web-based platform for events that require adjudication.
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44 *Blinding*

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

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

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12 ▪ Local Recurrence: the participant will have a lung CT scan to confirm no progression of their
13 systemic disease before continuing with the study protocol.
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15 ▪ Metastases: the participant will no longer be followed as per the study protocol, but per the
16 appropriate follow-up for the interventions required for the treatment of metastases; however,
17 the participant will continue to be followed in the trial.
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24 For both events, the specific imaging modality used to detect either the local recurrence or the
25 metastases will be documented.
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28 Patients that have incidental or off-protocol imaging will not crossover, however this will
29 be documented as a protocol deviation. In the case of a CXR that warrants further investigation
30 with a CT scan, this will be documented. If the patient is found to have disease recurrence, we will
31 document how the disease recurrence was (A) first identified; and (B) confirmed. If after a CT
32 scan the patient is found to not have disease recurrence, the patient will resume surveillance as per
33 the arm to which they were randomised.
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44 **Sample size determination**

45 *Pilot study sample size*

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47 The confidence interval approach was used to calculate the required sample size for the pilot
48 study(29). We determined *a priori* that the definitive trial would only be feasible if our protocol
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3 adherence rate was at least 85%. Using a 95% confidence level and a 5% margin of error, we
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5 calculated a required sample size of 195 patients.
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10 *Definitive study sample size*

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12 Our best estimate of the control group overall five-year survival for both the surveillance frequency
13
14 and imaging modality is 55%(16). Given that intensive surveillance will detect metastatic disease
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16 at an earlier stage, we will use a superiority design to compare survival between more versus less
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18 intensive surveillance. A 10% absolute increase in overall five-year survival associated with both
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20 more frequent surveillance and the use of CT scans represents a clinically important difference, as
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22 outlined by the American Society of Clinical Oncology's statement on clinically meaningful
23
24 outcomes in cancer trials(30). Therefore, the definitive trial will be powered to detect an absolute
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26 difference of 10% in overall five-year survival.
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31 With a desired power of 0.80, we calculated a sample size of 396 participants per study
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33 arm. We will account for a 5% loss to follow-up and, therefore, the final sample size will be 830
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35 participants. **Table 1** shows various sample sizes for pairwise comparisons of alternative
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37 surveillance frequencies / imaging modalities given varying control event rates and absolute
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39 increases in survival. Statistical Package for the Social Sciences (SPSS) (IBM Corporation)
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41 software was used for sample size calculation.
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45 The definitive sample size calculation may be adjusted as we prepare for the transition from
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47 the pilot to the definitive study as a result of data collected during the pilot study. One factor we
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49 may consider will be the percent lost to follow-up by the end of the pilot study. Other factors such
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51 as the estimated control group overall five-year survival, the clinically meaningful outcome, and
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53 power cannot be amended. The rationale for transition of subject data from the pilot study to the
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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, $\alpha=0.05$. 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	
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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](https://www.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

Acknowledgement

We would like to thank our patient advisers, Nina Szpakowski and Arlene Manherz, for their contributions.

Funding

This research is supported by funding through the Hamilton Academic Health Science Organization (HAHSO) and the Canadian Cancer Society Research Institute (CCSRI) Innovation Grants.

Competing interests statement

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

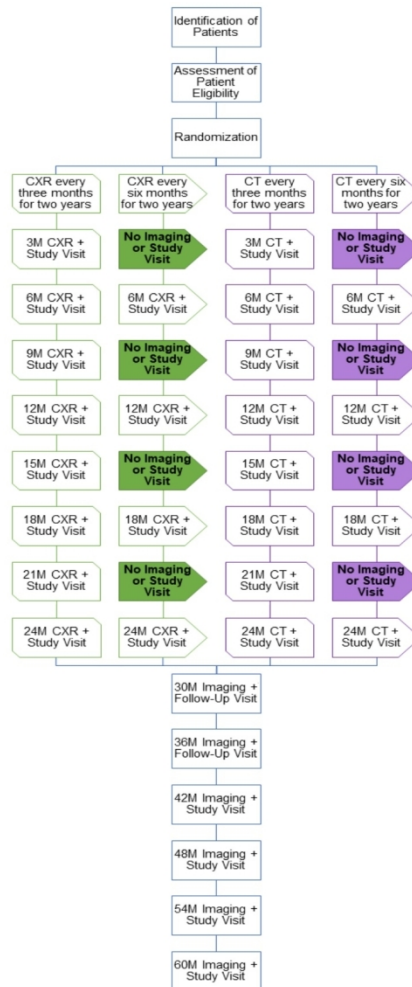
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Figure 1.

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



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

Page

Number

Reporting Item

T #	Descriptive title identifying the study design, population,	1
it 1	interventions, and, if applicable, trial acronym	
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e		

1 T # Trial identifier and registry name. If not yet registered, N/A
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3 ri 2 name of intended registry
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22 T # All items from the World Health Organization Trial N/A
23 ri 2 Registration Data Set
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23 F # Sources and types of financial, material, and other support HAHSO
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1 R # Names, affiliations, and roles of protocol contributors 2,3,28
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1	R #	Name and contact information for the trial sponsor	N/A
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1	R #	Role of study sponsor and funders, if any, in study design;	N/A
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3	o 5	collection, management, analysis, and interpretation of	
4	l c	data; writing of the report; and the decision to submit the	
5		report for publication, including whether they will have	
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1 R # Composition, roles, and responsibilities of the coordinating 18, 24, 25
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3 o 5 centre, steering committee, endpoint adjudication
4 l d committee, data management team, and other individuals or
5 e groups overseeing the trial, if applicable (see Item 21a for
6 s data monitoring committee)
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B # Description of research question and justification for

a 6 undertaking the trial, including summary of relevant studies

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1 B # Explanation for choice of comparators

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1	O #	Specific objectives or hypotheses	9, 10, 11
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16	T #	Description of trial design including type of trial (eg,	9
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18	ri	8 parallel group, crossover, factorial, single group), allocation	
19	a	ratio, and framework (eg, superiority, equivalence, non-	
20		inferiority, exploratory)	
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31	S #	Description of study settings (eg, community clinic,	11
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33	t	9 academic hospital) and list of countries where data will be	
34	u	collected. Reference to where list of study sites can be	
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1	E #	Inclusion and exclusion criteria for participants. If	12
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3	li 1	applicable, eligibility criteria for study centres and	
4	g 0	individuals who will perform the interventions (eg,	
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24	I #	Interventions for each group with sufficient detail to allow	14
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1 I # Criteria for discontinuing or modifying allocated N/A
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3 n 1 interventions for a given trial participant (eg, drug dose
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5 e b improving / worsening disease)
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1 I # Strategies to improve adherence to intervention protocols, 19, 20
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3 n 1 and any procedures for monitoring adherence (eg, drug
4 t 1 tablet return; laboratory tests)
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1	I #	Relevant concomitant care and interventions that are	12, 13
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41	O #	Primary, secondary, and other outcomes, including the	See note 1
42	u 1	specific measurement variable (eg, systolic blood pressure),	
43	t 2	analysis metric (eg, change from baseline, final value, time	
44	c	to event), method of aggregation (eg, median, proportion),	
45	o	and time point for each outcome. Explanation of the clinical	
46	m	relevance of chosen efficacy and harm outcomes is strongly	
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1	P	#	Time schedule of enrolment, interventions (including any	24
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3	a	1	run-ins and washouts), assessments, and visits for	
4	rt	3	participants. A schematic diagram is highly recommended	
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27	S	#	Estimated number of participants needed to achieve study	20, 21
28	a	1	objectives and how it was determined, including clinical	
29				
30	m	4	and statistical assumptions supporting any sample size	
31	p		calculations	
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33	l			
34	e			
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36	si			
37	z			
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39	e			
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42	R	#	Strategies for achieving adequate participant enrolment to	13, 14
43	e	1	reach target sample size	
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45	c	5		
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1 A # Method of generating the allocation sequence (eg,
2 ll 1 computer-generated random numbers), and list of any
3 o 6 factors for stratification. To reduce predictability of a
4 c a random sequence, details of any planned restriction (eg,
5 a blocking) should be provided in a separate document that is
6 ti unavailable to those who enrol participants or assign
7 o interventions
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1 A # Mechanism of implementing the allocation sequence (eg,
2 ll 1 central telephone; sequentially numbered, opaque, sealed
3 o 6 envelopes), describing any steps to conceal the sequence
4 c b until interventions are assigned
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12 n
13 c
14 o
15 n
16 c
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19 l
20 m
21 e
22 n
23 t
24 m
25 e
26 c
27 h
28 a
29 n
30 is
31 m

1 A # Who will generate the allocation sequence, who will enrol 14
2 ll 1 participants, and who will assign participants to
3 o 6 interventions

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12 m
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16 m
17 e
18 n
19 t
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21 ti
22 o
23 n

35 B # Who will be blinded after assignment to interventions (eg, 19
36 li 1 trial participants, care providers, outcome assessors, data
37 n 7 analysts), and how

40 d a
41 i
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1 B # If blinded, circumstances under which unblinding is N/A
2
3 li 1 permissible, and procedure for revealing a participant's
4 n 7 allocated intervention during the trial
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6 d b
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10 g
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13 a
14 s
15 k
16 i
17 n
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19):
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21 m
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24 g
25 e
26 n
27 c
28 y
29 u
30 n
31 b
32 li
33 n
34 d
35 i
36 n
37 g

N/A

1 D # Plans for assessment and collection of outcome, baseline,
2
3 a 1 and other trial data, including any related processes to
4 t 8 promote data quality (eg, duplicate measurements, training
5 a a of assessors) and a description of study instruments (eg,
6 c questionnaires, laboratory tests) along with their reliability
7 o and validity, if known. Reference to where data collection
8 ll forms can be found, if not in the protocol
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1 D # Plans to promote participant retention and complete follow- 19
2 a 1 up, including list of any outcome data to be collected for
3 t 8 participants who discontinue or deviate from intervention
4 a b protocols
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6 c
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1 D # Plans for data entry, coding, security, and storage, including 24, 25
2
3 a 1 any related processes to promote data quality (eg, double
4 t 9 data entry; range checks for data values). Reference to
5
6 a where details of data management procedures can be found,
7 m if not in the protocol
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9 a
10 n
11 a
12 g
13 e
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15 e
16 n
17 t

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24 S # Statistical methods for analysing primary and secondary 22
25 t 2 outcomes. Reference to where other details of the statistical
26 a 0 analysis plan can be found, if not in the protocol
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28 ti a
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30 st
31 i
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33 s:
34 o
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37 c
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41 s

1	S	#	Methods for any additional analyses (eg, subgroup and	N/A
2				
3	t	2	adjusted analyses)	
4	a	0		
5				
6	t	i	b	
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8	s	t		
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10	i			
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12	c			
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14	s:			
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16	a			
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18	d			
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20	d			
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22	i			
23				
24	o			
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26	n			
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28	a			
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30	l			
31				
32	a			
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34	n			
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36	a			
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1	S	#	Definition of analysis population relating to protocol non-	N/A
2				
3	t	2	adherence (eg, as randomised analysis), and any statistical	
4	a	0	methods to handle missing data (eg, multiple imputation)	
5				
6	t	i	c	
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8	s	t		
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10	i			
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52	d			
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56	is			
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60	n			

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1 D # Composition of data monitoring committee (DMC);
2
3 a 2 summary of its role and reporting structure; statement of
4 t 1 whether it is independent from the sponsor and competing
5 a a interests; and reference to where further details about its
6 m charter can be found, if not in the protocol. Alternatively,
7 o an explanation of why a DMC is not needed
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1	D #	Description of any interim analyses and stopping	N/A
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3	a 2	guidelines, including who will have access to these interim	
4	t 1	results and make the final decision to terminate the trial	
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6	a b		
7	m		
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18	i		
19	n		
20	t		
21	e		
22	ri		
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41	H #	Plans for collecting, assessing, reporting, and managing	24, 25
42	a 2	solicited and spontaneously reported adverse events and	
43	r 2	other unintended effects of trial interventions or trial	
44	m	conduct	
45			
46	s		
47			
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49			
50	A #	Frequency and procedures for auditing trial conduct, if any,	24, 25
51	u 2	and whether the process will be independent from	
52	d 3	investigators and the sponsor	
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R # Plans for seeking research ethics committee / institutional
e 2 review board (REC / IRB) approval
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1	P	#	Plans for communicating important protocol modifications	N/A
2				
3	r	2	(eg, changes to eligibility criteria, outcomes, analyses) to	
4				
5	o	5	relevant parties (eg, investigators, REC / IRBs, trial	
6	t		participants, trial registries, journals, regulators)	
7				
8	o			
9	c			
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14	a			
15	m			
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17	n			
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21	m			
22	e			
23				
24	n			
25	ts			
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27				
28	C	#	Who will obtain informed consent or assent from potential	13, 14
29				
30	o	2	trial participants or authorised surrogates, and how (see	
31				
32	n	6	Item 32)	
33	s	a		
34	e			
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36	n			
37	t			
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41	r			
42	a			
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1 C # Additional consent provisions for collection and use of N/A
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3 o 2 participant data and biological specimens in ancillary
4 n 6 studies, if applicable
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6 s b
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12 t
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22 s
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1 C # How personal information about potential and enrolled 13, 14
2
3 o 2 participants will be collected, shared, and maintained in
4 n 7 order to protect confidentiality before, during, and after the
5 fi trial
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20 D # Financial and other competing interests for principal 28
21 e 2 investigators for the overall trial and each study site
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1 D # Statement of who will have access to the final trial dataset, N/A
2
3 a 2 and disclosure of contractual agreements that limit such
4 t 9 access for investigators
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6 a
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10 c
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17 A # Provisions, if any, for ancillary and post-trial care, and for N/A
18 n 3 compensation to those who suffer harm from trial
19 c 0 participation
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21 il
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N/A

D # Plans for investigators and sponsor to communicate trial
is 3 results to participants, healthcare professionals, the public,
s 1 and other relevant groups (eg, via publication, reporting in
e a results databases, or other data sharing arrangements),
m including any publication restrictions
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1 D # Authorship eligibility guidelines and any intended use of N/A
2
3 is 3 professional writers
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1 D # Plans, if any, for granting public access to the full protocol, N/A
2 is 3 participant-level dataset, and statistical code
3 s 1
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11 n
12 p
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14 li
15 c
16 y
17 :
18 r
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24 u
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31 e
32 s
33 e
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35 r
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37 h

1	I	#	Model consent form and other related documentation given	N/A
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3	n	3	to participants and authorised surrogates	
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26	a			
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29	e			
30	ri			
31				
32	a			
33	ls			
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35				
36	B	#	Plans for collection, laboratory evaluation, and storage of	N/A
37	i	3	biological specimens for genetic or molecular analysis in	
38				
39	o	3	the current trial and for future use in ancillary studies, if	
40				
41	l		applicable	
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43	o			
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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**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029054.R3
Article Type:	Protocol
Date Submitted by the Author:	22-Aug-2019
Complete List of Authors:	Ghert, Michelle; McMaster University, Department of Surgery; Hamilton Health Sciences, Juravinski Cancer Centre
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Surgery
Keywords:	surveillance, soft tissue sarcoma, study protocol, randomised controlled trial, pilot study

SCHOLARONE™
Manuscripts

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2
3 *Original article*
4

5 **The Surveillance AftEr Extremity Tumour surgerY (SAFETY) Trial: Protocol for a pilot**
6
7 **study to determine the feasibility of a multi-centre randomized controlled trial**
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10 The SAFETY Investigators
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15 **Protocol version 1; December 3, 2018**
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26 **Correspondence and reprints**
27

28 Michelle Ghert, MD, FRCSC
29

30 Professor of Surgery
31

32 Division of Orthopaedic Surgery
33

34 Department of Surgery
35

36 McMaster University
37

38 711 Concession Street
39

40 Hamilton, ON
41

42 Canada
43

44 Tel: 905-387-9495 ext 64089
45

46 Fax: 905-381-7071
47

48 Email: mghert@hhsc.ca
49

50
51
52
53 **Contributor list with affiliations**
54
55
56
57
58
59
60

1
2
3 Michelle Ghert, MD, FRCSC (Steering Committee Chair)
4 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
5
6

7 Mohit Bhandari, MD, PhD, FRCSC
8 Department of Surgery & Department of Health Research Methods, Evidence and Impact,
9 McMaster University (Hamilton, Ontario, Canada)
10
11

12 Anthony Bozzo, MD
13 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
14
15

16 P.D. Sander Dijkstra, MD, PhD
17 Department of Orthopaedics, Leiden University Medical Center (Leiden, the Netherlands)
18
19

20 Anthony Griffin, MSc
21 Musculoskeletal Oncology Unit, Mount Sinai Hospital (Toronto, Ontario, Canada)
22
23

24 Robert Grimer, MB BS, DSc, FRCS, FRCS Ed(Orth)
25 Department of Surgery, University of Birmingham (Birmingham, United Kingdom)
26
27

28 James Hayden, MD, PhD, FACS
29 Department of Orthopaedics & Rehabilitation, Oregon Health & Science University (Portland,
30 Oregon, USA)
31
32

33 Arlene Manherz
34 (Community)
35
36

37 Karim Masrouha, MD
38 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
39
40

41 Paula McKay, BSc
42 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
43
44

45 Benjamin Miller, MD, MS, FACS
46 Department of Orthopaedics & Rehabilitation, University of Iowa (Iowa City, Iowa, USA)
47
48

49 Naveen Parasu, MD, MRCP (UK), MRCR (UK), FRCPC
50 Department of Radiology, McMaster University (Hamilton, Ontario, Canada)
51
52

53 Ajay Puri, MS (Ortho)
54 Department of Surgical Oncology, Tata Memorial Centre (Mumbai, India)
55
56

57 R. Lor Randall, MD, FACS
58
59
60

1
2
3 Department of Orthopaedic Surgery, University of California, Davis (Sacramento, California,
4 USA)
5

6
7 Patricia Schneider, BSc
8 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
9

10
11 Sheila Sprague, PhD
12 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
13

14
15 Nina Szpakowski, MSc, DVM
16 (Community)
17

18
19 Lehana Thabane, PhD
20 Department of Health Research Methods, Evidence and Impact, McMaster University
21 (Hamilton, Ontario, Canada)
22

23
24 Robert Turcotte, MD, FRCSC
25 Department of Surgery, McGill University (Montreal, Quebec, Canada)
26

27
28 Roberto Vélez, MD, PhD
29 Department of Orthopaedic Surgery, Hospital Vall d'Hebron (Barcelona, Catalunya, Spain)
30

31
32 David Wilson, MD, MSc
33 Department of Surgery, McMaster University (Hamilton, Ontario, Canada)
34

35
36 Kevin Zbuk, MD, FRCPC
37 Department of Oncology, McMaster University (Hamilton, Ontario, Canada)
38

39
40 Gordon Guyatt, MD, FRCPC
41 Department of Medicine & Department of Health Research Methods, Evidence and Impact,
42 McMaster University (Hamilton, Ontario, Canada)
43
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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

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2
3 been established and the definitive protocol is finalized, the study will transition to the definitive
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5 study.
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10 **Article summary**

11 12 13 14 **Strengths and limitations of this study**

- 15
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17 • The SAFETY trial will be an international multi-centre 2x2 factorial randomized controlled
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19 trial
- 20
21 • The trial will answer a high priority question for sarcoma surgeons
- 22
23 • The SAFETY trial will build on the international collaboration and experience of the PARITY
24
25 trial
- 26
27 • The feasibility pilot study is essential before undertaking this large multi-centre trial
- 28
29 • The success of the pilot study is dependent on the ability of clinical sites to recruit patients,
30
31 comply with the protocol, and complete high quality follow-up data
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39 **Keywords:** surveillance; soft tissue sarcoma; study protocol; randomized controlled trial; pilot
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41 study
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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

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3 for the first two to three years and then annually thereafter, while stage I tumors could be followed
4
5 less frequently during the first two to three years (13).
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10 *Best evidence for surveillance strategies*

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12 Post-treatment soft-tissue sarcoma surveillance is an integral element of patient care. Although
13
14 earlier detection of metastatic disease may improve long-term survival, no study has yet provided
15
16 definitive evidence to support this assumption. In order to assess the available evidence, we
17
18 completed a systematic review of the available randomized controlled trial (RCT) evidence for
19
20 surveillance in sarcoma management(14). A single study (published separately with early and
21
22 longer-term follow-up) was identified(15, 16). The authors of this single-centre study found that
23
24 three-year overall and disease-free survival was not worse in sarcoma patients who had less
25
26 intensive surveillance (CXR) than those with more intensive surveillance (CT scans)(15). Due to
27
28 the sample size, this trial could not conclusively demonstrate non-inferiority in overall or disease-
29
30 free survival for a six-monthly interval of follow-up visits against three-monthly interval (both
31
32 were 64% and 69%, respectively)(15).
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38 A follow-up study on the same patient cohort with five-year survival outcomes confirmed
39
40 that more frequent follow-up did not improve survival and that, although CT scans detected
41
42 pulmonary metastasis earlier, they did not lead to better survival compared with CXRs(16).
43
44 However, this was a single-centre study with relatively small numbers and, therefore, confidence
45
46 in the results and generalizability of the data to other centres is limited. In addition, a relatively
47
48 small proportion of screened patients (42%) that were eligible for the trial were included due to
49
50 the exclusion of patients unlikely to follow-up, thus possibly introducing selection bias(15).
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53 Furthermore, low-grade sarcomas were eligible and included in this study, even though they have
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3 little metastatic potential and tumour-related mortality; their inclusion may have diminished the
4 magnitude of the effects of the interventions(15). Finally, the majority of the included patients
5 were bone sarcoma patients, thereby limiting the interpretation to STS patients(15).
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10 11 12 *Risks and benefits of intensive surveillance* 13

14 Regular, intensive surveillance is more likely to identify recurrent disease earlier than would less
15 intensive surveillance. This type of surveillance may provide reassurance to patients and clinicians;
16 however, the adverse effects of intensive surveillance practices are also noteworthy. The costs that
17 healthcare systems incur as a result of sarcoma surveillance are substantial and could be in excess
18 of USD \$20,000 for high-grade sarcomas(17). Furthermore, intensive surveillance can threaten the
19 financial security of patients, due in part to the direct (including travel, accommodation, personal
20 care, and homemaking) and indirect costs (including lost wages for patients and their caregivers)
21 incurred as a result of follow-up appointments(18). As a result, patients' health and quality of life
22 can be dramatically impacted(18-20).
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35 Secondary investigations and earlier knowledge of disease recurrence can also induce
36 anxiety and impact the psychosocial wellbeing for those whose mortality risk cannot be
37 significantly reduced by further medical interventions(21). Overcrowded clinics and long wait
38 times may constitute other important factors that affect patients' psychosocial wellbeing(22).
39 Finally, the use of CT has raised concerns over unnecessary radiation exposure compared to
40 radiographs, although lower dose CT scans may mitigate some of these concerns(23).
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51 *Surveillance research as a priority in orthopedic oncology* 52 53 54 55 56 57 58 59 60

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3 We recently published a modified Delphi study in which we aimed to identify a clinically relevant
4 consensus-based research agenda in the sarcoma field(24). From this Delphi process that included
5
6 80 orthopaedic oncologists and patient representation (with participation from 18 countries), we
7
8 identified critical research priorities in the field of orthopaedic oncology and determined the top
9
10 four feasible and important research questions that will directly inform patient care and enhance
11
12 clinical practice. This study identified the evaluation of post-operative surveillance strategies as
13
14 the highest-ranking research priority in the sarcoma field(24).
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21 **Patient and public involvement**

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23 To ensure that we maintain a patient-centered approach to the design and development of this
24
25 study, we required the opportunity for open dialogue between the multidisciplinary and
26
27 international SAFETY study team, along with patient / caregiver representatives and other key
28
29 stakeholders. To facilitate their interaction and collaboration, we held an in-person Protocol
30
31 Development Meeting in Toronto, ON, Canada in May 2018. At this meeting, we made critical
32
33 decisions with respect to the study protocol, including: A) study design; B) primary and secondary
34
35 outcomes; C) patient eligibility; D) follow-up timeframe; E) methods to protect against bias; F)
36
37 randomization stratification; and G) further patient engagement. We also had the opportunity to
38
39 discuss several issues that may compromise the study's success and strategize ways to manage
40
41 these challenges, such as: I) acceptable surveillance schedules that account for differences in
42
43 international standards of clinical practice; II) possible ethical concerns; III) patient compliance;
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45 IV) local implementation and procedural variation; V) competing studies; and VI) funding
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47 opportunities.
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3 We are also conducting a patient survey to assess international patient willingness to
4 participate in a study that randomizes patients to a post-operative surveillance regimen in the
5 management of a primary extremity sarcoma. Since there is no available validated tool to assess
6 patient opinions and preferences, we developed a unique patient questionnaire for the purposes
7 of this study. All new patients who present to a participating sarcoma clinic are screened for study
8 participation. The preliminary survey questionnaire responses suggest that most sarcoma
9 patients believe that they have a good understanding of clinical research. Furthermore, over half
10 of respondents feel comfortable with being randomized to receive a treatment. Ultimately,
11 almost 80% of respondents have indicated that they would agree to participate in the SAFETY
12 trial if eligible.
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30 **Study design**

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32 We plan to assess the feasibility of conducting the pragmatic, international, multi-centre, 2x2
33 factorial Surveillance AftEr Extremity Tumour surgery (SAFETY) RCT that answers the
34 following questions: In extremity STS patients who undergo surgical resection with curative intent,
35 (1) what is the impact of surveillance frequency (every three vs. every six months) on overall
36 survival at five years, and (2) what is the impact of surveillance imaging modality (CXR vs. CT
37 scan) on overall survival at five years? To assess feasibility, we will conduct a pilot study. Study
38 participants will be randomized to one of four possible treatment arms (see Study Interventions
39 below). Randomization will occur at the end of active treatment (surgery \pm systemic treatment \pm
40 local radiation). Following the two-year intervention phase, study participants will continue to be
41 assessed at regular intervals for an additional three years. As such, all pilot study patients will be
42 transitioned into the definitive study and be included in it. Details of the flow of each study arm
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3 are outlined in Figure 1. We anticipate the duration of the pilot study to be three years in order to
4 collect intervention phase data on all participants. The primary outcome of the pilot study is the
5 feasibility of a definitive RCT based on a combination of feasibility endpoints.
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10 The 2x2 factorial study design is ideal and the most efficient method to study two treatment
11 interventions in a single RCT, particularly when there is no interaction between the two
12 interventions. This is unlike a scenario in which the two interventions are medications that may
13 have a synergistic or negative effect when combined. A Bayesian design would be useful to avoid
14 the question of whether or not an interaction exists, however for the purposes of the present trial it
15 is clear that no interaction exists between the frequency and intensity of surveillance. As Freidlin
16 and Korn discuss in their commentary, the 2x2 factorial design is an efficient design to evaluate
17 two interventions in a cancer clinical trial when there are no interactions between treatments(25).
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30 **Objectives**

31 *Pilot study primary research objectives*

32 The primary objective of the pilot study will be to determine whether it is feasible to conduct a
33 large multi-centre RCT that will evaluate the impact of surveillance strategies on patient survival
34 following extremity STS surgery. To do so, we will assess our ability to:
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41 A) Recruit patients across multiple participating clinical sites;
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43 B) Ensure compliance with the study protocol, including the application of eligibility criteria,
44 timing of intervention phase and post-intervention phase visits and imaging modality;
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47 C) Maintain completeness of follow-up data;
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49 D) Maintain completeness of cost analysis data; and
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51 E) Maintain data quality.
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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 (\geq) 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;

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- 2
- 3 5) The tumour size is greater than or equal to (\geq) five centimeters according to the pathology
- 4 report or pre-treatment MRI if neoadjuvant radiation and / or chemotherapy are given; and
- 5
- 6
- 7
- 8 6) Provision of informed consent.
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11

12 *Exclusion criteria*

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

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- 16
- 17 1) Metastatic disease at initial presentation based on thoracic imaging (a second CT scan may be
- 18 required to confirm that indeterminate nodules are false positives before the patient can be
- 19 enrolled provided that the second CT scan shows no evidence of metastatic disease);
- 20
- 21
- 22
- 23
- 24 2) Undergone surgical excision of a local recurrence;
- 25
- 26 3) Diagnosis of one of the special sub-types: myxoid / round cell liposarcoma or extra-skeletal
- 27 Ewing's sarcoma (These sarcomas have different metastatic patterns, which necessitate
- 28 different surveillance protocols);
- 29
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- 32
- 33 4) Previous diagnosis of a genetic syndrome with an elevated risk of malignancy, such as Li-
- 34 Fraumeni Syndrome (such individuals appear to be at an elevated risk for radiation-induced
- 35 cancers, so the use of CT scans should be limited);
- 36
- 37
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- 39
- 40 5) Previous diagnosis with a co-morbid condition that has a life expectancy of less than one year;
- 41
- 42
- 43 6) The site-specific surveillance protocol for the patient's disease is not compatible with the study
- 44 protocol (i.e., regular planned whole-body imaging with positron emission tomography [PET]
- 45 scans);
- 46
- 47
- 48
- 49 7) Diagnosed with another malignancy within the past five years;
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- 51 8) Likely problems, in the judgment of the investigator, with maintaining follow-up; and
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- 53
- 54 9) Currently enrolled in a study that does not permit co-enrollment;
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3 10) The patient has already been enrolled in the SAFETY trial.
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8 **Recruitment and screening**

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

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

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53 Participants will be randomised to one of four treatment groups:
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- 3 1) CXR every three months for two years;
- 4
- 5 2) CXR every six months for two years;
- 6
- 7 3) Chest CT every three months for two years; or
- 8
- 9 4) Chest CT every six months for two years.
- 10
- 11

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

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

46 *Pilot study primary outcome*

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48 To evaluate feasibility, we will assess the number of patients screened and recruited at each
49 participating clinical site, participant retention, and maintenance of data quality. In addition, we
50 will evaluate the utilization of an internet-based centralized randomisation system focusing on the
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3 accuracy of data entry, appropriate stratification of participants and the minimization of
4
5 randomisation errors. Finally, we will evaluate investigator and participant compliance with the
6
7 study protocol, including the application of eligibility criteria, compliance with the surveillance
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9 imaging and frequency regimens, frequency of crossover and timing of post-intervention phase
10
11 visits. As discussed by Moore *et al.*, the pilot study will investigate the process of the proposed
12
13 definitive trial rather than its outcomes (26). The *a priori* criteria for the success of the pilot study
14
15 are listed below:
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17

18
19 A) *Recruitment Measure*: We will consider our recruitment strategy feasible if we are able to enroll
20
21 the pilot sample of 195 patients (approximately 20 patients from each clinical site participating in
22
23 the pilot study) within two years. See sample size determination below. As such, we will aim to
24
25 recruit 100 patients during the first year. If we are unable to achieve at least 90% of this goal (90
26
27 patients) then we will plan to increase the number of participating sites as a study rescue measure.
28
29

30
31 B) *Protocol Adherence Measure*: During the pilot study of the PARITY trial, we were able to
32
33 maintain an overall protocol adherence rate in excess of 90%(27). Recent reports prepared for the
34
35 PARITY Data and Safety Monitoring Board (DSMB) indicate a similar protocol adherence rate.
36
37 However, given the greater complexity and longer duration of the SAFETY trial interventions, we
38
39 will consider our protocol adherence strategies feasible if there is adherence of 85% or greater to
40
41 the visit windows and imaging modality prescribed by the protocol.
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44
45 C) *Participant Retention Measure*: While 20% loss-to-follow-up has traditionally been considered
46
47 acceptable in clinical research, evidence from other orthopaedic trials suggests that bias begins to
48
49 affect study results at even lower rates of loss-to-follow-up(28). Therefore, we will consider our
50
51 participant retention strategies feasible if no more than 15% of participants are lost-to-follow-up.
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3 D) *Maintenance of Data Quality Measure*: We obtained a data completeness rate of approximately
4 90% in the PARITY trial pilot study (27). Therefore, we will consider our data quality strategies
5 feasible if we are able to maintain 95% or greater completeness of participant follow-up data for
6 the definitive primary outcome. We will also consider our data quality strategies feasible if we are
7 able to maintain 85% or greater completeness of participant follow-up data for the secondary
8 outcomes.
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19 *Pilot study secondary outcomes*

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21 Death from any cause will be recorded during the pilot study. Data on secondary outcomes for the
22 definitive trial, which are listed below, will also be collected. These include:
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25 A) *Patient-reported outcome measures*: The validated Patient-Reported Outcomes Measurement
26 Information System (PROMIS)[®] Cancer-Anxiety questionnaire, PROMIS[®] Satisfaction with
27 Social Roles and Activities questionnaire, and the EuroQol-5 Dimension (EQ-5D) will be used to
28 assess patient anxiety, satisfaction and quality of life, respectively. These questionnaires will be
29 administered at the baseline visit, as well as the 6-month, 12-month, 18-month and 24-month
30 intervention phase, as well as 36-month, 48-month and 60-month post-intervention phase visits.
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33 B) *Local recurrence-free survival (LRFS) outcome measure*: LRFS will be defined as the length
34 of time from randomization that the participant survives with no detection of recurrent disease at
35 the initial tumor site or operative field.
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38 C) *Metastasis-free survival (MFS) outcome measure*: MFS will be defined as the length of time
39 from randomization that the participant survives with no detection of systemic disease recurrence
40 at any anatomic location.
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3 D) *Treatment-related complications outcome measures*: Treatment-related complications will
4 include both chemotherapy-related complications, such as febrile neutropenia, fungal infections or
5
6 include both chemotherapy-related complications, such as febrile neutropenia, fungal infections or
7
8 sepsis, and thoracotomy-related complications, such as pneumothorax, or surgical site infections.
9

10 E) *Net healthcare costs outcome measures*: We will perform an incremental cost analysis of net
11
12 costs of surveillance and costs incurred from metastasis treatment and metastasis treatment related
13
14 complications. Unit costs for all resources used by trial participants will be obtained from regional
15
16 statistics and from centers participating in the trial. These unit costs will be combined with the
17
18 resource volumes to obtain a net cost per participant over their time in the trial.
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24 **Protecting against sources of bias**

25 26 *Adjudication of outcomes*

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28 An independent Central Adjudication Committee (CAC) will review all situations where eligibility
29
30 is in doubt, as well as all reported instances of disease relapse, treatment-related complications,
31
32 and death to determine whether a study event has occurred. The SAFETY CAC will be comprised
33
34 of two orthopaedic oncologists, one medical oncologist, and one radiologist. All participating
35
36 clinical sites will submit digital imaging and relevant hospital records to the Methods Centre via a
37
38 web-based platform for events that require adjudication.
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44 45 *Blinding*

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

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

- 11
12 ▪ Local Recurrence: the participant will have a lung CT scan to confirm no progression of their
13 systemic disease before continuing with the study protocol.
- 14
15 ▪ Metastases: the participant will no longer be followed as per the study protocol, but per the
16 appropriate follow-up for the interventions required for the treatment of metastases; however,
17 the participant will continue to be followed in the trial.
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24 For both events, the specific imaging modality used to detect either the local recurrence or the
25 metastases will be documented.
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28 Patients that have incidental or off-protocol imaging will not crossover, however this will
29 be documented as a protocol deviation. In the case of a CXR that warrants further investigation
30 with a CT scan, this will be documented. If the patient is found to have disease recurrence, we will
31 document how the disease recurrence was (A) first identified; and (B) confirmed. If after a CT
32 scan the patient is found to not have disease recurrence, the patient will resume surveillance as per
33 the arm to which they were randomised.
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45 **Sample size determination**

46 *Pilot study sample size*

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48 The confidence interval approach was used to calculate the required sample size for the pilot
49 study(29). We determined *a priori* that the definitive trial would only be feasible if our protocol
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3 adherence rate was at least 85%. Using a 95% confidence level and a 5% margin of error, we
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5 calculated a required sample size of 195 patients.
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10 *Definitive study sample size*

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12 Our best estimate of the control group overall five-year survival for both the surveillance frequency
13
14 and imaging modality is 55%(16). Given that intensive surveillance will detect metastatic disease
15
16 at an earlier stage, we will use a superiority design to compare survival between more versus less
17
18 intensive surveillance. A 10% absolute increase in overall five-year survival associated with both
19
20 more frequent surveillance and the use of CT scans represents a clinically important difference, as
21
22 outlined by the American Society of Clinical Oncology's statement on clinically meaningful
23
24 outcomes in cancer trials(30). Therefore, the definitive trial will be powered to detect an absolute
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26 difference of 10% in overall five-year survival.
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31 With a desired power of 0.80, we calculated a sample size of 396 participants per study
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33 arm. We will account for a 5% loss to follow-up and, therefore, the final sample size will be 830
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35 participants. **Table 1** shows various sample sizes for pairwise comparisons of alternative
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37 surveillance frequencies / imaging modalities given varying control event rates and absolute
38
39 increases in survival. Statistical Package for the Social Sciences (SPSS) (IBM Corporation)
40
41 software was used for sample size calculation.
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45 The definitive sample size calculation may be adjusted as we prepare for the transition from
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47 the pilot to the definitive study as a result of data collected during the pilot study. One factor we
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49 may consider will be the percent lost to follow-up by the end of the pilot study. Other factors such
50
51 as the estimated control group overall five-year survival, the clinically meaningful outcome, and
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53 power cannot be amended. The rationale for transition of subject data from the pilot study to the
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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, $\alpha=0.05$. 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	
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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

1
2
3 conduct at each participating clinical site. A copy of this approval will be provided to the Methods
4
5 Centre by each participating clinical site prior to the local commencement of the study.
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10 **Study Timeline**

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12 We expect that the pilot study will take just over three years to complete. We estimate that
13
14 recruitment will take approximately one year to complete per site. The initiation of screening and
15
16 enrollment will likely be staggered across the participating clinical sites due to the variability in
17
18 the time required to obtain ethics approval and negotiate institutional contracts. Therefore the pilot
19
20 study recruitment timeline will be up to two years. We expect a further one year for all pilot
21
22 participants to complete the intervention phase of the trial. Although we will not have complete
23
24 post-intervention phase data for any pilot participants, we anticipate being able to determine
25
26 feasibility at the end of the intervention phase based on our feasibility objectives. We plan *a priori*
27
28 to transition directly from the pilot to the definitive study if feasibility is established.
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35 **Data Safety Monitoring Board**

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39 As per the principles established by the *Data Monitoring Committees: Lessons, Ethics, Statistics*
40
41 (*DAMOCLES*) *Study Group* charter, a DSMB will oversee the safety of the trial participants and
42
43 the overall conduct of the trial. The Committee members will be independent of the trial, free of
44
45 conflicts with any of the investigative team, and will consist of two orthopaedic oncologists, a
46
47 medical oncologist, a radiologist, and a biostatistician. The DSMB will frequently review
48
49 enrollment and demographic summaries, listings of protocol deviations, and summaries and
50
51 listings of serious adverse events. They will advise the Principal Investigator and SAFETY study
52
53 team on any concerns related to participant safety and trial conduct and will make
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4 recommendations for: A) study continuation as designed; B) study termination; C) study
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6 continuation with major or minor modifications; or D) temporary study suspension of enrollment
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8 until some uncertainty is resolved.
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11 12 13 **Knowledge Dissemination**

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16 The results of the study will be submitted for publication regardless of whether there are significant
17
18 findings, as well as posted on ClinicalTrials.gov. The trial has been registered on clinicaltrials.gov.
19
20 The registration number is NCT03944798. In addition to scientific manuscripts and presentations,
21
22 we plan to prepare study reports and press releases for patients and other stakeholders that are
23
24 transparent, and that the language is understandable to the general public.
25
26
27

28 29 **Potential impact of the study**

30
31 The benefit of this pilot study would be to determine the feasibility of the SAFETY trial. This is
32
33 essential prior to undertaking a large multi-centre RCT. Experience gained during the pilot study
34
35 will provide insight into methods to increase enrollment, strategies to maintain protocol adherence
36
37 and the adjustment of recruitment expectations. In addition, the ultimate success of the pilot study
38
39 will support funding requests for the definitive study of the multi-centre SAFETY trial.
40
41
42

43 Once the feasibility endpoints are reached, we will transition directly into and begin
44
45 recruiting for the definitive SAFETY trial. The ultimate goal of the SAFETY trial is to provide
46
47 high-quality evidence for surveillance strategies following the treatment of STS, which will allow
48
49 for the development of evidence-based clinical practice guidelines for sarcoma patients worldwide.
50
51
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29 **Figure legend**

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32 Figure 1. Study flow diagram
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36 **Data statement**

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

- 49
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- 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

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2
3 Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana
4 Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
5
6 • Drafting the work: Michelle Ghert, Patricia Schneider, and Karim Masrouha
7
8 • Revising it critically for important intellectual content: Michelle Ghert; Mohit Bhandari;
9 Anthony Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden;
10 Arlene Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay
11 Puri; R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana
12 Thabane; Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
13
14 • Final approval of the version to be published: Michelle Ghert; Mohit Bhandari; Anthony
15 Bozzo; P.D. Sander Dijkstra; Anthony Griffin; Robert Grimer; James Hayden; Arlene
16 Manherz; Karim Masrouha; Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri;
17 R. Lor Randall; Patricia Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane;
18 Robert Turcotte; Roberto Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
19
20 • Agreement to be accountable for all aspects of the work in ensuring that questions related
21 to the accuracy or integrity of any part of the work are appropriately investigated and
22 resolved: Michelle Ghert; Mohit Bhandari; Anthony Bozzo; P.D. Sander Dijkstra;
23 Anthony Griffin; Robert Grimer; James Hayden; Arlene Manherz; Karim Masrouha;
24 Paula McKay; Benjamin Miller; Naveen Parasu; Ajay Puri; R. Lor Randall; Patricia
25 Schneider; Sheila Sprague; Nina Szpakowski; Lehana Thabane; Robert Turcotte; Roberto
26 Vélez; David Wilson; Kevin Zbuk; Gordon Guyatt
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29

30 **Acknowledgement**

31
32 We would like to thank our patient advisers, Nina Szpakowski and Arlene Manherz, for their
33
34 contributions.
35
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38

39 **Funding**

40
41 This research is supported by funding through the Hamilton Academic Health Science
42
43 Organization (HAHSO) and the Canadian Cancer Society Research Institute (CCSRI) Innovation
44
45 Grants.
46
47
48
49
50

51 **Competing interests statement**

52
53 Dr. Bhandari, Dr. Ghert, Dr. Randall, and Dr. Hayden report personal fees from consultancy
54
55 and/or royalties outside the submitted work.
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5 **Word count**
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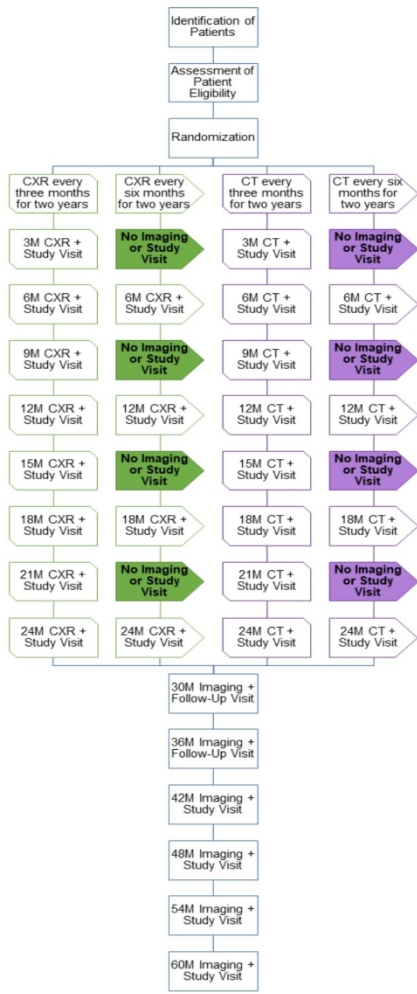
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For peer review only

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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

Page

Number

Reporting Item

T #	Descriptive title identifying the study design, population,	1
it 1	interventions, and, if applicable, trial acronym	
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1 T # Trial identifier and registry name. If not yet registered, N/A
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 3 ri 2 name of intended registry
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22 T # All items from the World Health Organization Trial N/A
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1 P # Date and version identifier 1
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23 F # Sources and types of financial, material, and other support HAHSO
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1 R # Names, affiliations, and roles of protocol contributors 2,3,28
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1	R #	Name and contact information for the trial sponsor	N/A
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1 R # Role of study sponsor and funders, if any, in study design; N/A
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3 o 5 collection, management, analysis, and interpretation of
4 l c data; writing of the report; and the decision to submit the
5 e report for publication, including whether they will have
6 s ultimate authority over any of these activities
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1 R # Composition, roles, and responsibilities of the coordinating 18, 24, 25
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3 o 5 centre, steering committee, endpoint adjudication
4 l d committee, data management team, and other individuals or
5 e groups overseeing the trial, if applicable (see Item 21a for
6 s data monitoring committee)
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1 B # Description of research question and justification for 6, 7, 8
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3 a 6 undertaking the trial, including summary of relevant studies
4 c a (published and unpublished) examining benefits and harms
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1 B # Explanation for choice of comparators
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1	O #	Specific objectives or hypotheses	9, 10, 11
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16	T #	Description of trial design including type of trial (eg,	9
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19	a	ratio, and framework (eg, superiority, equivalence, non-	
20		inferiority, exploratory)	
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31	S #	Description of study settings (eg, community clinic,	11
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33	t	9 academic hospital) and list of countries where data will be	
34	u	collected. Reference to where list of study sites can be	
35		obtained	
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1 E # Inclusion and exclusion criteria for participants. If 12
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3 li 1 applicable, eligibility criteria for study centres and
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5 i surgeons, psychotherapists)
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24 I # Interventions for each group with sufficient detail to allow 14
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1 I # Criteria for discontinuing or modifying allocated N/A
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3 n 1 interventions for a given trial participant (eg, drug dose
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5 e b improving / worsening disease)
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1 I # Strategies to improve adherence to intervention protocols, 19, 20
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4 t 1 tablet return; laboratory tests)
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1	I #	Relevant concomitant care and interventions that are	12, 13
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3	n 1	permitted or prohibited during the trial	
4	t 1		
5	e d		
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7	r		
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9	v		
10	e		
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12	n		
13	ti		
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15	o		
16			
17	n		
18	s:		
19	c		
20			
21	o		
22			
23	n		
24	c		
25			
26	o		
27	m		
28	it		
29			
30	a		
31			
32	n		
33	t		
34			
35	c		
36			
37	a		
38			
39	r		
40			
41	e		
42	O #	Primary, secondary, and other outcomes, including the	See note 1
43	u 1	specific measurement variable (eg, systolic blood pressure),	
44			
45	t 2	analysis metric (eg, change from baseline, final value, time	
46			
47	c	to event), method of aggregation (eg, median, proportion),	
48			
49	o	and time point for each outcome. Explanation of the clinical	
50			
51	m	relevance of chosen efficacy and harm outcomes is strongly	
52			
53	e	recommended	
54			
55	s		
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1	P	#	Time schedule of enrolment, interventions (including any	24
2				
3	a	1	run-ins and washouts), assessments, and visits for	
4	rt	3	participants. A schematic diagram is highly recommended	
5			(see Figure)	
6	i			
7	c			
8				
9	i			
10	P			
11	a			
12	n			
13	t			
14	ti			
15	m			
16	e			
17	li			
18	n			
19	e			
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22				
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26	S	#	Estimated number of participants needed to achieve study	20, 21
27	a	1	objectives and how it was determined, including clinical	
28	m	4	and statistical assumptions supporting any sample size	
29	p		calculations	
30	l			
31	e			
32	si			
33	z			
34	e			
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37				
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41	R	#	Strategies for achieving adequate participant enrolment to	13, 14
42	e	1	reach target sample size	
43	c	5		
44	r			
45	u			
46	it			
47	m			
48	e			
49	n			
50	t			
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1 A # Method of generating the allocation sequence (eg,
2 ll 1 computer-generated random numbers), and list of any
3 o 6 factors for stratification. To reduce predictability of a
4 c a random sequence, details of any planned restriction (eg,
5 a blocking) should be provided in a separate document that is
6 ti unavailable to those who enrol participants or assign
7 o interventions
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1 A # Mechanism of implementing the allocation sequence (eg,
2 ll 1 central telephone; sequentially numbered, opaque, sealed
3 o 6 envelopes), describing any steps to conceal the sequence
4 c b until interventions are assigned

7 a
8 ti
9 o
10 n
11 c
12 o
13 n
14 c
15 e
16 a
17 l
18 m
19 e
20 n
21 t
22 m
23 e
24 c
25 h
26 a
27 n
28 is
29 m

1	A #	Who will generate the allocation sequence, who will enrol	14
2			
3	ll 1	participants, and who will assign participants to	
4	o 6	interventions	
5			
6	c c		
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8	a		
9	ti		
10	o		
11	n		
12	n		
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15	i		
16	m		
17	p		
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19	e		
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21	e		
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23	t		
24	a		
25	ti		
26	o		
27	n		
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35	B #	Who will be blinded after assignment to interventions (eg,	19
36	li 1	trial participants, care providers, outcome assessors, data	
37	n 7	analysts), and how	
38			
39	d a		
40			
41	i		
42	n		
43	g		
44	(
45	m		
46	a		
47	s		
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49	i		
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N/A

1 B # If blinded, circumstances under which unblinding is
2
3 li 1 permissible, and procedure for revealing a participant's
4 n 7 allocated intervention during the trial
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6 d b
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8 i
9 n
10 g
11 (
12 m
13 a
14 s
15 k
16 i
17 n
18 g
19):
20 e
21 m
22 e
23 r
24 g
25 e
26 n
27 c
28 y
29 u
30 n
31 b
32 li
33 n
34 d
35 i
36 n
37 g

1 D # Plans for assessment and collection of outcome, baseline, N/A
2
3 a 1 and other trial data, including any related processes to
4 t 8 promote data quality (eg, duplicate measurements, training
5 a a of assessors) and a description of study instruments (eg,
6 c questionnaires, laboratory tests) along with their reliability
7 o and validity, if known. Reference to where data collection
8 ll forms can be found, if not in the protocol
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10 e
11 c
12 ti
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16 l
17 a
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1 D # Plans to promote participant retention and complete follow- 19
2
3 a 1 up, including list of any outcome data to be collected for
4 t 8 participants who discontinue or deviate from intervention
5
6 a b protocols
7
8 c
9 o
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11 e
12 c
13 ti
14 o
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1 D # Plans for data entry, coding, security, and storage, including 24, 25
2
3 a 1 any related processes to promote data quality (eg, double
4 t 9 data entry; range checks for data values). Reference to
5
6 a where details of data management procedures can be found,
7 m if not in the protocol
8
9 a
10 n
11 a
12 g
13 e
14 m
15 e
16 n
17 t

23 S # Statistical methods for analysing primary and secondary 22
24 t 2 outcomes. Reference to where other details of the statistical
25 a 0 analysis plan can be found, if not in the protocol
26
27 ti a
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29 st
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31 i
32 c
33 s:
34 o
35 u
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1	S	#	Methods for any additional analyses (eg, subgroup and	N/A
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3	t	2	adjusted analyses)	
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6	t	i	b	
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8	s	t		
9				
10	i			
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12	c			
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14	s:			
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16	a			
17				
18	d			
19				
20	d			
21				
22	i			
23				
24	o			
25				
26	n			
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28	a			
29				
30	l			
31				
32	a			
33				
34	n			
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1 S # Definition of analysis population relating to protocol non- N/A
2 t 2 adherence (eg, as randomised analysis), and any statistical
3 a 0 methods to handle missing data (eg, multiple imputation)
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8 i
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11 s:
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13 n
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16 y
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18 s
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24 a
25 ti
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D # Composition of data monitoring committee (DMC);
a 2 summary of its role and reporting structure; statement of
t 1 whether it is independent from the sponsor and competing
a a interests; and reference to where further details about its
m charter can be found, if not in the protocol. Alternatively,
o an explanation of why a DMC is not needed
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1	D #	Description of any interim analyses and stopping	N/A
2			
3	a 2	guidelines, including who will have access to these interim	
4	t 1	results and make the final decision to terminate the trial	
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6	a b		
7	m		
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9	o		
10	n		
11	it		
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13	o		
14	ri		
15	n		
16	g		
17	:		
18	i		
19	n		
20	t		
21	e		
22	ri		
23	m		
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25	n		
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41	H #	Plans for collecting, assessing, reporting, and managing	24, 25
42	a 2	solicited and spontaneously reported adverse events and	
43	r 2	other unintended effects of trial interventions or trial	
44	m	conduct	
45			
46	s		
47			
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50	A #	Frequency and procedures for auditing trial conduct, if any,	24, 25
51	u 2	and whether the process will be independent from	
52	d 3	investigators and the sponsor	
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Plans for seeking research ethics committee / institutional review board (REC / IRB) approval 23, 24

1 P # Plans for communicating important protocol modifications N/A
2
3 r 2 (eg, changes to eligibility criteria, outcomes, analyses) to
4 o 5 relevant parties (eg, investigators, REC / IRBs, trial
5 t participants, trial registries, journals, regulators)
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14 m
15 m
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21 n
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28 C # Who will obtain informed consent or assent from potential 13, 14
29 o 2 trial participants or authorised surrogates, and how (see
30 n 6 Item 32)
31 s a
32 e
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34 t
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38 s
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1	C #	Additional consent provisions for collection and use of	N/A
2			
3	o 2	participant data and biological specimens in ancillary	
4	n 6	studies, if applicable	
5			
6	s b		
7	e		
8			
9	n		
10			
11	t		
12	o		
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14	r		
15	a		
16	s		
17	s		
18	e		
19	n		
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21	n		
22	t:		
23	a		
24			
25	n		
26	c		
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30	l		
31	a		
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1 C # How personal information about potential and enrolled 13, 14
2
3 o 2 participants will be collected, shared, and maintained in
4 n 7 order to protect confidentiality before, during, and after the
5 fi trial
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7 d
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11 n
12 ti
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14 li
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17 y

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21 D # Financial and other competing interests for principal 28
22 e 2 investigators for the overall trial and each study site
23 c 8
24
25 l
26
27 a
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29 r
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31 a
32 ti
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34 n
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36 o
37 f
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39 i
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41 n
42 t
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49 s

1 D # Statement of who will have access to the final trial dataset, N/A
2
3 a 2 and disclosure of contractual agreements that limit such
4 t 9 access for investigators
5

6 a
7 a
8 c
9 c
10 c
11 e
12 s
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17 A # Provisions, if any, for ancillary and post-trial care, and for N/A
18 n 3 compensation to those who suffer harm from trial
19 c 0 participation
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1 D # Plans for investigators and sponsor to communicate trial N/A
2
3 is 3 results to participants, healthcare professionals, the public,
4 s 1 and other relevant groups (eg, via publication, reporting in
5 e a results databases, or other data sharing arrangements),
6 m including any publication restrictions
7
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1	D #	Authorship eligibility guidelines and any intended use of	N/A
2			
3	is 3	professional writers	
4	s 1		
5	e b		
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7	m		
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9	i		
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1 D # Plans, if any, for granting public access to the full protocol, N/A
2 is 3 participant-level dataset, and statistical code
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4 e c
5 m
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9 ti
10 o
11 n
12 p
13 o
14 li
15 c
16 y
17 :
18 r
19 e
20 p
21 r
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23 d
24 u
25 c
26 i
27 b
28 l
29 e
30 r
31 e
32 s
33 e
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35 r
36 c
37 h

1	I	#	Model consent form and other related documentation given	N/A
2				
3	n	3	to participants and authorised surrogates	
4	f	2		
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21	n			
22	t			
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24	m			
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26	a			
27	t			
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29	e			
30	ri			
31				
32	a			
33	ls			
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35				
36	B	#	Plans for collection, laboratory evaluation, and storage of	N/A
37	i	3	biological specimens for genetic or molecular analysis in	
38				
39	o	3	the current trial and for future use in ancillary studies, if	
40				
41	l		applicable	
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43	o			
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45	g			
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47	i			
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Author notes

1. 15, 16, 17, 18

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