STUDY PROTOCOL

Title: Patient-Reported Outcomes and Smartphone-Derived Mobility After Bone and Soft Tissue Sarcoma Surgery: A Multicentre Prospective Cohort Study

Brief Title: ACTIVATION: MSK Oncology

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1. Study Objectives

1.1 Purpose

The purpose of this study is to investigate the Patient-Reported Outcome Measure Information System (PROMIS) and mobility metrics in patients undergoing treatment for bone and soft tissue sarcoma using a novel smartphone application entitled Activation Health.

1.2 Specific Aims

1. Compare the responsiveness of five PROMIS short forms to the Toronto Extremity Salvage Score (TESS) for assessing recovery after sarcoma surgery
2. Determine the minimal clinically important difference (MCID) for five PROMIS short forms in the sarcoma population
3. Assess the feasibility and usability of a Activation Health for remote PROM survey administration and mobility data collection in the sarcoma population
4. Correlate PROM scores with mobility metrics to define recovery trajectories after sarcoma surgery
5. Identify demographic and socioeconomic factors that influence survey responses app engagement with the Activation Health app in the sarcoma population

1.3 Expected Outcomes

1. Validation of PROMIS as an outcome measure in the sarcoma population
2. Determine the MCID for PROMIS in the sarcoma population
3. Validation of the Activation Health app in the sarcoma population
4. Establish longitudinal recovery trends in PROMs and mobility metrics following sarcoma treatment
5. Understand barriers to survey responses and app engagement in the sarcoma population

2. Background

2.1 MSK Oncology

Bone and soft tissue sarcomas are rare mesenchymal-derived neoplasms, making up about 1% of all adult cancers.[1] Management typically involves radiation therapy, chemotherapy, and surgical resection, with or without limb reconstruction.[2–4] The diagnosis, intensive treatment regimen, and surgery-induced deficits significantly impact patient quality of life and function. Evaluating outcomes in sarcoma is challenging due to disease heterogeneity, complexity, and variation in surgical strategy.

Patient-reported outcomes measures (PROMs) are crucial for evaluating treatment outcomes and facilitating patient-centered care.[5,6] Traditional validated PROMs, like the TESS, have important limitations including participant burden, ceiling effects, and limited assessment of overall health. The Patient Reported Outcomes Measurement Information System (PROMIS) uses multiple short surveys to measure patient-reported symptoms across multiple health domains.[7] It has been validated and utilized across orthopaedic and non-orthopaedic populations.[8] However, its utility, sensitivity, and clinical significance in bone and soft tissue sarcoma patients has not been defined.[9]

While PROMs provide valuable insights into patient symptoms, objective measures of recovery are not routinely collected to complement these findings. Mobility is an understudied aspect of postoperative recovery that may provide additional insight into patient function. Advances in smartphone technology offer an opportunity to remotely collect objective mobility data in a continuous, real-world setting. To this end, our group has developed Activation Health (Calgary, AB, Canada), a novel research smartphone application (app) designed to remotely collect PROMs and mobility data.

2.2 Study Rationale

The purpose of this study is to investigate the PROMIS and mobility metrics in patients undergoing treatment for MSK tumors using the Activation Health. Evaluating longitudinal changes in PROMIS scores and mobility metrics may provide significant insight into recovery following treatment. Remote data collection for PROMIS and mobility data enhances accessibility and convenience for oncology patients already burdened with multiple appointments. The development of a remote capture system to record longitudinal changes in PROMs and patient mobility has substantial potential to enhance musculoskeletal oncology research and ultimately improve patient-centered cancer care.

2.3 Hypotheses

1. The PROMIS physical function (PF), upper extremity (UE), pain interference (PI), global health (GH), and self-efficacy (SE) short forms will demonstrate greater responsiveness to changes in patient health and function following sarcoma surgery compared to the TESS.

2. Clinically meaningful changes in PROMIS scores can be identified to establish MCIDs specific to the sarcoma population.
3. The Activation Health app will successfully capture PROMs at predefined intervals and continuously collect mobility metrics, demonstrating high patient compliance, data completeness, and satisfaction.
4. Longitudinal changes in PROM scores are expected to correlate with smartphone-derived mobility metrics, providing complementary measures of recovery trajectories following sarcoma surgery.
5. Demographic and socioeconomic factors will influence survey completion rates and engagement with the Activation Health app.

3. Study Design

3.1 Summary of Design
This is a prospective, multicentre longitudinal cohort study involving the University of Calgary, University of Toronto, Mayo Clinic Rochester, and Mayo Clinic Arizona.

3.2 Study Duration
Participant recruitment for the study will last for four years and patients will be followed for two years after enrollment, or until the end of active disease treatment. The total study duration will be 5 years.

3.3 Inclusion Criteria
All eligible patients will be seen by a musculoskeletal oncology surgeons at one of the participating sites. All adult patients (≥18 years) diagnosed with bone sarcoma, soft tissue sarcoma, or giant cell tumor of bone undergoing operative tumor resection are eligible. Tumors can be primary or recurrent, and can be located in the pelvis, lower extremities, or upper extremities. Participants must be English-speaking to be included in the study.

3.4 Exclusion Criteria
Patients with metastatic bone tumors, atypical lipomatous tumors, and dermatofibrosarcoma protuberans will be excluded. Pregnant patients and patients unwilling or unable to attend all follow-up evaluations will be excluded. Lastly, patients with significant cognitive impairment or communication barriers that prevent informed consent and independent completion of study questionnaires will be excluded.

3.5 Data Collection
Clinical data will be collected by an approved member of the research team using the local electronic medical record and a standardized case repot form. Participants will download the Activation Health app on their smartphone. A demographics survey, TESS, and PROMIS PF, UE, PI, GH, and SE surveys will be administered remotely through the Activation Health app and Qualtrics. Completion of these surveys will be prompted via push notifications pre-treatment and at regularly scheduled intervals within the two-year post-treatment period, or until the end of active disease treatment. At the end of study participation, an additional survey will be administered assess participant phone use habits and app function.

Mobility metrics will be passively collected by the Activation Health app throughout study involvement. The mobility metrics of interest include but are not limited to step count, distance travelled, move time, flights of stairs climbed, walking steadiness, walking asymmetry, double support time, walking speed, and step length. Additionally, physiological parameters such as heart rate variability will be collected from participants with a compatible smartwatch.

Below is a list of the data that is planned to be collected:

Demographics

- Date of birth
- Sex
- Gender
- Hand dominance
- Height
- Weight
- Body mass index
- Ethnicity
- Education level
- Employment status
- Annual household income
- Living situation
- Primary language
- Tobacco use
- Alcohol use
- Cannabis use
- Other substance use

Clinical information:

- Biopsy status
- Biopsy date
- Biopsy hospital
- Diagnosis date
- Tumor type
- Bone or soft tissue location
- Bening or malignant tumor
- Presenting status
- Laterality
- Anatomical site
- Depth
- Size
- Maximum diameter
- Grade
- Margins
- Percent necrosis
- Treatment strategy
- Prior surgery
- Date of surgery
- Surgical procedure
- Closure
- Associated vascular procedure
- Radiation status
- Radiation dose

- Chemotherapy status
- Chemotherapy start date
- Other therapies
- Complication status
- Complication type
- Complication description
- Surgery to manage complication
- Date of complication surgery
- Relapse status
- Relapse date
- Surgery for relapse
- Date of relapse surgery
- Relapse radiation
- Relapse chemotherapy
- Other therapy for relapse
- Status at final follow-up

Intervention variables:

- PROMIS PF
- PROMIS UE
- PROMIS PI
- PROMIS GH
- PROMIS SE
- TESS Lower Extremity
- TESS Upper Extremity
- App survey
- Step count
- Distance travelled
- Move time
- Flights of stairs climbed
- Walking steadiness
- Walking asymmetry
- Double support time
- Walking speed
- Step length
- Heart rate variability*

*Measures that will be obtained only in patients with a compatible smart watch

3.6 Data Storage

The Activation Health app complies with institutional data usage regulations as well as Apple and Android guidelines. All mobility data is encrypted by the participant's smartphone when it is transferred to the Activation Health app, and all data will remain

encrypted during transport to our database on a secure, ethics-approved, university-compliant server. All mobility data will only be connected to the participant's study ID in the database. Likewise, PROM data will be collected using the university-approved Qualtrics platform and linked to the participant's study ID manually or automatically through the Activation Health app.

All identifying data will be stored in a password protected file on a secure university-approved server. Any physical documentation pertaining to the study will be stored in a locked filing cabinet within the orthopaedic oncology research offices at each participating site. These documents will only be accessible to the immediate study team. Exported files for data analysis and publication of results will not include any identifying information.

3.7 Potential Benefits

There is no direct benefit to the participant from engaging in the study. However, by recording and evaluating longitudinal changes in PROM scores and mobility metrics, the study will provide valuable insights into the trajectory of post-treatment recovery and identify critical periods for intervention aimed at enhancing patient-centered cancer care. To increase accessibility and convenience for patients, all necessary study participation can be completed remotely through the Activation Health app, alleviating any monetary, travel, and emotional burdens associated with in-person visits to our site.

3.8 Potential Risks

This study introduces limited risk to the participant. This study will utilize limited identifiable data and follow university-compliant storage procedures for identifying information. All survey and activity data will be linked to the participant's study ID immediately after collection, and the master list linking identifying information to study IDs will be stored in a password protected file in on a secure university-approved server. Only necessary study personnel will have access to identifying information. Any published results from this study will be in aggregate and will not be linked to identifiable patient information. In addition, the Activation Health app does not have access to any other data or identifiable information on the participant's smartphone, including GPS data.

We will also consult with University of Calgary IT Services as needed prior to the implementation of the Activation Health app for any study participants. Participant contact will be limited to initial patient recruitment, distribution of important study updates affecting participation, and distributing Qualtrics survey links and downloading activity data for participants not using the Activation Health app.

We have already addressed partnership risks with our app developer through university mediations, including intellectual property stipulations.

3.9 Clinical Consent

Participants must provide informed consent to join the study. The nature and scope of this study involves minimal risk to patients' welfare, as the study does not involve

interventions that will interfere with their routine clinical care. It would be inappropriate to seek consent from authorized third parties acting on behalf of these individuals as the study requires patients to be free of any cognitive impairments. Only information necessary for study objectives will be collected. Patient privacy and confidentiality will be strictly followed as per local institutional policies. The study team consists of active clinical staff involved in the care of the patient population of interest or those with research expertise for the design or analysis of the study. A small number of researchers will have access to participant identifying information, which will be treated with respect and in a confidential manner.

4. Statistical Analysis

4.1 Sample Size

We will include all eligible subjects identified by musculoskeletal oncology surgeons at each site. We hope to enroll as many patients as possible into our study, however, anticipate enrolling approximately 800 sarcoma patients during the study period. This estimate is based on current surgical volumes and patient capture rates for collecting quality of life and functional data.

4.2 Data Analysis

The statistical analysis plan has been reviewed by a statistician through the University of Calgary Department of Surgery. All statistical analysis will be conducted using Python software. Summary statistics will describe population demographic and clinical characteristics. Continuous data will be represented as means with standard deviation or medians with interquartile range, and categorical data as proportions. Individual-level socioeconomic status will be calculated using household income, education level, and occupation. These three indicators will be standardized and converted into z scores, then summed to determine socioeconomic status. The statistical analysis plan for each project aim is described below:

1. The responsiveness of the PROMIS PF and UE short forms will be independently compared to the TESS using effect size and standardized response means. These measures will allow for comparison of whether the T-scores scores changed by a small or large amount over time. Additionally, the aggregate score of all the PROMIS short forms will be compared to TESS. Aggregate scores will be calculated by averaging the five domain-specific T-scores.
2. MCIDs will be calculated using anchor-based methods. Seven-point patient global impression of change questions have been created for each PROMIS short form.
3. Survey response rates, mobility data collection rates, and loss to follow-up will be measured.
4. Mobility data will undergo principal component analysis to derive a composite index capturing the key features of interest. Ordinal logistic regression will be used to determine if mobility metrics collected form a smartphone are associated with patient-reported activity level, as assessed by a seven-point PGIC anchor question. Linear mixed-effects regression models will assess whether mobility changes are associated with changes in PROM scores.
5. The proportion of PROM surveys that are completed will be calculated. Logistic regression will be used to identify demographic factors that predict survey completion, with survey completion represented as a binary variable (yes or no).

5. Study Management

5.1 Day to Day Management
Coordination of the study will be the responsibility of the principal investigator (J. Kendal) and the orthopedic oncology research team.

5.2 Funding
The study is supported by grant funding from multiple sources: American Academy of Orthopaedic Surgeons, Musculoskeletal Tumor Society, and Sarcoma Strong ($110,000), Orthopaedic Research Portfolio Catalyst Grant Competition ($25,000), Calgary Surgical Research Development Fund ($4000), Calgary Orthopaedic Resident Education Fund ($6000), and SPARC Ignite Grant ($20,000). The research team will continue to pursue other grant and external funding opportunities throughout the study period.

5.3 Data Sharing
Identifiable data will not be shared between study sites. The University of Calgary is the lead site and a Clinical Trial Agreement (ClinicalTrials.gov ID: NCT07227961) is in effect.

5.4 Regulatory Binder
The regulatory binder for the study will be kept in the orthopedic oncology research offices at each participating site and contain all pertinent study information.

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