Study Protocol and Statistical Analysis Plan

Title: Evaluating the Implementation, Utility, and Clinical Importance of the Patient-Reported Outcome Measure Information System (PROMIS) in Sarcoma Patients: A Multi-Centered Prospective Cohort Study

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Primary Investigator: Dr. Joe Kendal

Co-Investigators:
Dr. Michael Monument
Dr. Shannon Puloski
Dr. Jay Wunder
Dr. Aaron Gazendam
Dr. Kim Tsoi
Dr. Peter Ferguson
Dr. Matthew Houdek
Dr. Krista Goulding

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1 Study Objectives

1.1 Problem to be investigated

The purpose of this study is to investigate the Patient-Reported Outcome Measure Information System (PROMIS) and mobility in patients with sarcoma treated surgically using a novel smartphone application, ACTIVATION (Activity Capture To Investigate Voluntary AcTivity In Orthopaedic populatioNs).

1.2 Specific Aims

1. Compare PROMIS to the current gold standard, the Toronto Extremity Salvage Score (TESS), in sarcoma
2. Determine the minimal clinically important difference (MCID) for PROMIS in sarcoma
3. Assess the feasibility and usability of a novel app for remote questionnaire administration and mobility data collection
4. Correlate PROMIS and TESS scores with mobility metrics to define recovery trajectories
5. Identify demographic and socioeconomic factors that influence app engagement

1.3 Expected Outcomes

1. Validation of PROMIS as an outcome measure for sarcoma patients and comparison to the TESS
2. Determine the MCID for PROMIS in sarcoma
3. Validation of the ACTIVATION app
4. Establish longitudinal recovery trends in PROMIS, TESS, and mobility metrics following surgical management
5. Understand barriers to app engagement

2 Background

2.1 Overview of Sarcoma

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 significant floor and ceiling effects. PROMIS assesses physical, mental, and social well-being, using item response theory in a standardized manner for precise and sensitive measures.[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]

2.2 Study Rationale

A critical but under investigated parameter in musculoskeletal oncology is patient mobility. Mobility metrics are inadequately measured due to the lack of appropriate standardized methodologies for capturing granular longitudinal changes. Evaluating longitudinal changes in PROMIS scores and mobility parameters may provide significant insight into post-operative recovery for sarcoma patients.[10-12]

Remote data collection for PROMIS and functional data enhances accessibility and convenience for patients already burdened with multiple appointments.[26] Remote data capture has proven effective in other orthopaedic populations, such as hip and knee arthroplasty, improving PROM compliance.[13] The development of a remote capture system to record longitudinal changes in PROMS and patient mobility has the potential to enhance musculoskeletal oncology research and ultimately improve patient-centered cancer care.

2.3 Hypotheses

We hypothesize that the ACTIVATION app will successfully capture PROMIS scores at timed intervals and continuous mobility metrics, demonstrating high compliance, accuracy, and patient satisfaction due to its user-friendly design. Longitudinal changes in PROMIS global health (GH), pain interference (PI), self-efficacy (SE), upper extremity function (UEF), and physical function (PF) scores are expected to correlate significantly with post-operative recovery trajectories in sarcoma patients.

3 Study Design

3.1 Summary of Design

This is a prospective, multicentre longitudinal cohort study involving the University of Calgary, Mount Sinai Hospital in Toronto, Mayo Clinic Minnesota and Mayo Clinic Arizona.

3.2 Study Duration

Participant recruitment will last for four years and patients will be followed for one year after enrolment, resulting in a total study duration of 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. Patient must speak English and have an iPhone or Android 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

Study participants will be asked to complete a demographic intake form and clinical data will be obtained through the local electronic medical record. Participants will be asked to download the ACTIVATION app on their phone. The TESS and PROMIS GH, PI, SE, UEF, and PF questionnaires will be administered through the ACTIVATION app. Completion of these forms will be prompted via push notifications preoperatively and at six-weeks, three-months, six-months, and 1-year post-operative. Mobility metrics will be passively collected by the app throughout study involvement. The mobility metrics of interest include step count, distance travelled, flights climbed, gait asymmetry, distinct activity periods (>10 minutes), and total time spent in activity. Additionally, physiologic parameters will be collected from participants with a compatible smartwatch including maximum oxygen consumption (VO_2 max), heart rate, and heart rate variability. At the end of study participation, two additional surveys will be administered. The first survey will assess phone carrying habits in the participant. The second survey will gather feedback on the app's interface, navigation, and overall user experience. These measurements are considered to be above standard practice. Below is a list of the data that is planned to be collected:

Demographic information:

- Date of birth
- Sex
- Body mass index
- Ethnicity
- Education level
- Employment status
- Medical history
- Substance use

Clinical information:

- Diagnosis date
- Tumor type
- Tumor location
- Biopsy date
- Biopsy type
- Surgery date
- Surgical procedure
- Associated plastics surgical procedures (e.g. skin graft or flap)
- Application of negative pressure dressing
- Other local or systematic treatment (chemotherapy, radiation therapy)
- Surgical complications

Intervention variables:

- Step count
- Distance travelled
- Flights climbed
- Gait asymmetry
- Distinct activity periods (>10 minutes)
- Total time spent in activity
- VO_2 max*
- Heart rate*
- Heart rate variability*
- PROMIS scores
- TESS scores

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

3.6 Data Storage

The ACTIVATION app complies with University of Calgary data usage regulations and Apple's HealthKit guidelines. All health and activity data is encrypted by default on iPhones and is available only to the user. Study data will always be encrypted, when the ACTIVATION app transmits the data to our servers it will occur via an encrypted tunnel through a Cloudflare relay (Cloudflare's zero trust network access), to a secure, ethics-approved research server hosted by University of Calgary research services. The research server is protected from any outside access via the Cloudflare tunnel and has no externally addressable IP address. The server runs a Postgres database which will further encrypt and store all data and is continuously scanned for vulnerabilities by the University of Calgary research services. The data stored on the Postgres database will be associated to participants unique device code and will contain no information about the participant directly and will be replicated within the server cluster for redundancy. Following all the best practices outline by University of Calgary research services. All potential documents that can link a subject to their encrypted ID will be stored in separate location on a OneDrive level 4 server that is associated with the study. Aggregated research data compiled by querying the database will also be stored on university of Calgary OneDrive servers in an encrypted folder separate from other study documents. Identifiable medical information will be stored in our MSK oncology database using the web-based Research Electronic Data Capture (REDCap) server as previously approved in HREBA.CC-20-0335. Identifying data that will be stored in this database includes patient ULI or PHN and date of birth. This will be included for the purpose of coordinated data collection and data audits. Access to both cloud and REDCap servers is limited to personnel directly involved with the study and is further restricted, based on their responsibilities within the study. Any physical documentation pertaining to the study will be stored in a secured lockbox within the orthopaedic oncology research office at the Arthur Child Comprehensive Cancer Centre and be only accessible to the immediate study team. This is a secured location, accessible only with clearance approved by the University of Calgary and AHS, and is under the supervision of the Orthopedic Oncology research team. Any output from the database including exported files for analysis and publication of the results will not include any identifying information. Security concerns and the management of these concerns is outlined in the Potential Risks 3.8.

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 PROMIS scores and mobility profiles, the study will provide valuable insights into the trajectory of post-operative functional 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 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 standard storage procedures for confidential health information. To manage the potential risk of data being exposed to anyone outside the study team, our app does not have access to any other data or

identifiable information on the participant's iPhone. All data will have been encrypted with the operating system already, and all data extracted using the ACTIVATION app will be further encrypted for transport to our encrypted database on a secure server as explained in Data Storage 3.6. All activity data will only be connected to the participant's study ID in the database, and the key to identify participants' activity will also be encrypted, stored separately from the database, and will be restricted such that only necessary study personnel will have access to it. Absolutely no GPS type data will be collected, and the iPhone app will not have access to any other data stored on the participant's phone. We will also consult with University of Calgary IT Services as needed prior to the implementation of our app for any study participants. Patient contact can be limited to the initial patient recruitment into the study but does not need to be limited to this study milestone. Any published results from this study will be in aggregate and will not be linked to identifiable patient information. We have already addressed partnership risks with our app developer through university mediations, including intellectual property stipulations.

3.9 Clinical Consent

Participant consent is requested. 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 cancer 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 provincial or state policy. 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 patient information, which will be treated with respect and in a confidential manner. The identifiable patient information will include a PHN or ULI and date of birth.

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

Descriptive statistics will be employed to summarize the demographic and clinical characteristics of the study population. Longitudinal changes in PROMIS scores over time will be analyzed using linear mixed-effects models, adjusting for potential confounders. Comparison with traditional outcome measures, such as the TESS will be conducted using correlation coefficients, Bland-Altman plots, and linear regression models. Given the considerable heterogeneity within the sarcoma population, subgroups based on location and tumor type (soft tissue vs. bone) will be created and analyzed.

The study aims to establish minimal clinically important differences (MCIDs) for PROMIS scores through distribution-based and anchor-based methods. In the current study, the distribution-based MCIDs will be calculated utilizing the one-half SD of baseline scores and the one-half SD of change scores within the groups from baseline to 12-month follow-up. In anchor-based methods, the MCID is established by relating a difference in outcome scores to a patient-important improvement or deterioration that is captured by an independent measure (the anchor) that is itself interpretable. For our anchor, we will utilize a questionnaire, “compared to your initial evaluation, how would you describe you function (pain/overall health) now?” Responses will range from “Much improved, improved, slightly improved, no change, slight worse, worse, much worse”. This outcome is patient centered, easily understandable and relevant to patients. Patients who reported changes from one adjacent score to the next (e.g. no difference to slightly improved) represented a small but meaningful change equivalent to the MCID.

For the anchor-based approach, the relationship between changes in the external anchor and changes in PROMIS will be examined using receiver operating characteristic (ROC) curve analysis. The ROC method plots the sensitivity against 1-specificity for the range of PROMIS scores in relation to the probability of detecting improvement as judged by a change score of one point on the external anchor. The ROC analysis will be performed to differentiate between patients with PROMIS scores who reported a change score of 0 on the external anchor and those who had change score of +1 on the external anchor. The MCID cut-offs were estimated by calculating the Youden Index which balances the sensitivity and specificity of the PROMIS change thresholds based on the external anchor. Youden’s Index provides an overall indicator of test performance and is recommended when establishing MCIDs based on the ROC analysis.

A survey will be administered at the end of each patient's study participation to assess the app function and user-friendliness. We will also explore phone use habits, including where patients keep their phone while walking and how often they have it with them. These methods will help us gather detailed feedback regarding the user experience of the app including ease of navigation, clarity of instructions and overall satisfaction. In assessing feasibility, we will record the proportion of patients who utilize the app. This will involve tracing download and registration rates as well as active usage statistics. We will compare PROM completion rates between patients who use the app and those who complete the PROMs exclusively in the clinic. Logistic regression analysis will explore factors influencing PROM completion rates through the app, including patient demographics and socioeconomic status.

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 concept was initiated using the principal investigator's operational grant, but a grant has recently been obtained from the American Academy of Orthopaedic Surgeons and Musculoskeletal Tumor Society (US $110,000) for this multicenter trial. We also have received the following smaller grants to support this study: Orthopaedic Research Portfolio Catalyst Grant Competition ($25,000) and Calgary Surgical Research Development Fund ($4000). The research team will continue to pursue other grant and external funding opportunities.

5.3 Management of Confidential Health Data

We will take all appropriate measures to protect the privacy of included patients. A small number of researchers will have access to patient information, which will be treated with respect and in a confidential manner. All patient data will be stored on a secure, cloud- and web-based REDCap databases developed in accordance with institutional regulations; thus, no patient data is stored on the local hard drives of data entry computers. This software is commonly used by researchers at the University of Calgary. The HIPAA privacy rules and HIPAA security rules mandate that covered entities have in place appropriate policies and procedures to protect the confidentiality and security of protected health information. REDCap meets these requirements. REDCap is a 21 CFR part II compliant research software application that limits user access to the appropriate study, site, and role. Online database control software will be utilized to safely maintain confidentiality, comply with record retention, and provide us with the capability to enter information from multiple sites.

Personal information such as name, address, telephone number, and insurance numbers will never be entered in spreadsheets for analysis. A limited amount of identifying information will be collected purely for the purpose of coordinated data entry and data audits. This information will not be included in analysis or any data outputs. Following the completion of the study, research data will be kept securely in accordance with the policy for long-term storage from the University of Calgary and the HREBA. When the mandated period expires, all research data will be destroyed. The published results from this study will be in aggregate and will not be linked to identifiable patient information.

5.4 Data Sharing

Anonymized data will not be shared beyond the immediate research team. The University of Calgary is the lead site and Clinical Trial Agreements (CTA) will be put in place between sites.

5.5 Regulatory Binder

The regulatory binder for the study will be kept in the orthopedic oncology research office and contain all pertinent study information.

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