Machine Learning Prediction of Local Recurrence in Extremity Soft Tissue Sarcoma: Evaluating Detailed Surgical Margin Status Using the Australian ACCORD Database

Background and Significance

Primary bone and soft tissue sarcomas represent a rare and heterogeneous group of malignancies [1,2]. Surgical resection, aiming for a wide excision with negative margins, stands as the cornerstone of curative treatment for localized primary bone and soft tissue sarcomas [1,2]. The fundamental aim of sarcoma surgery is undoubtedly to achieve an R0 resection [1,7]. Indeed, positive or uncertain surgical margins are recognized as the most reliable predictor of local recurrence [2], with insufficient margins potentially leading to alarmingly high local recurrence rates, ranging from 80% to 90% [2]. However, beyond the basic distinction of negative vs. positive margins, there is **significant controversy** regarding the optimal **width** of surgical margins needed to minimize recurrence and maximize survival [1,2]. Multiple systematic reviews and meta-analyses have confirmed that positive margins portend worse local control and survival [1,2], yet a **precise, universally accepted safe margin distance** remains elusive [1,2,7,16]. Some studies have suggested specific cutoff points, such as greater than 5 mm, greater than 10 mm, or even greater than 2 cm, as potentially "adequate" margins [1,32, 23,30,3,13,55,56,10,11]. Conversely, other studies have reported no significant difference in local recurrence rates between very narrow negative margins (less than 1 mm) and slightly wider negative margins in certain contexts [24,25,32]. For instance, one cohort study found that a margin greater than 10 mm did not significantly improve local recurrence-free survival or overall survival compared to a margin greater than 5 mm [25]. This challenges the notion that “wider is always better” and raises concerns about potentially increasing surgical morbidity, such as more extensive tissue loss, without additional oncological benefit [1,7,16,24]. On the other hand, some evidence indicates that resection margins greater than 5 mm should be attained when feasible to minimize the risk of local recurrence, although margins less than 5 mm might be acceptable when combined with adjuvant radiotherapy to preserve critical structures [21,31]. This ongoing lack of consensus on an optimal margin width creates uncertainty in surgical planning and follow-up strategies [1,7,16].

Several factors contribute to this controversy. Sarcomas comprise over 100 subtypes with diverse biological behaviors, so a margin width sufficient for one histological subtype or tumor location might be inadequate for another [1,2]. Moreover, increasing the margin often involves a **trade-off between oncological control and function**: more extensive resection may reduce recurrence risk but can impair limb function or quality of life [2,7]. Surgeons must frequently balance the goal of wider excision against the desire to spare critical neurovascular structures or avoid amputation [2,7]. This delicate balance underscores the need for better risk stratification tools – to identify which patients truly benefit from wider margins and which can safely undergo more conservative resection with adjuvant therapy, maintaining function without compromising outcomes [2,18,19].

In the Australian context, current national guidelines from organizations like ANZSA, Cancer Australia, and the Royal Australasian College of Surgeons emphasize the importance of achieving negative surgical margins and managing sarcoma patients in specialized multidisciplinary centers [1,2,5,13,18,30,33,34,50]. However, these guidelines generally do not provide specific, metric-based recommendations for optimal surgical margin width [5,13,18,30,32,33]. The prevailing recommendation is "wide local excision" where possible [3,13,18,30,33,55,56], acknowledging that what constitutes an adequate margin may depend on anatomical and patient factors [13,18,32]. The absence of specific metric-based margin guidelines reflects the ongoing controversy and lack of universal consensus in the literature, as well as the heterogeneous nature of sarcoma cases [1,7,16]. This gap in guidance is particularly relevant in Australia and New Zealand, where care is centralized to expert sarcoma units yet clinicians face uncertainty regarding the necessary margin width in various clinical scenarios [1,13,32]. Addressing this knowledge gap is critical for improving patient outcomes in our region [2].

Why this research is significant: Resolving (or at least clarifying) the margin-width controversy would directly impact clinical practice and patient care. Some key points of significance include:

- **Improving Local Control and Survival:** Reducing local recurrence translates to better overall survival and less need for morbid re-operations. By investigating margins in detail, we aim to refine surgical guidelines so that patients receive operations tailored to minimize recurrence risk [1,2]. If we can identify a more precise margin threshold (or a risk profile that predicts recurrence), surgeons can plan resections that achieve optimal oncologic clearance, thereby improving local recurrence-free survival (LRFS) [1,2,7,16,23,24,30].
- **Optimizing Functional Preservation:** In sarcoma surgery, **bigger margins** often mean sacrificing more tissue (sometimes including major muscles, nerves, or bone) [7]. If our analysis finds that beyond a certain margin width there is no added benefit, surgeons could avoid unnecessarily radical resections in some cases [23,24,25,30]. Conversely, if very narrow margins are shown to carry substantially higher risk in certain patients, it would justify more aggressive surgery in those instances [1,21,22,31,33]. Our study will help delineate when a small margin might be safely accepted (especially with adjuvant radiotherapy) versus when a wider margin is crucial [21,31]. This nuanced understanding will aid surgeons in balancing oncologic and functional outcomes on a per-patient basis [2,7].
- **Leveraging Australian Data:** We will utilize the Australian Comprehensive Cancer Outcomes and Research Database (**ACCORD**) [v,vi], sarcoma registry as our data source. ACCORD is a national clinical registry that aggregates detailed information on sarcoma patients across specialist centers in Australia. By analyzing **real-world Australian data**, our findings will be directly applicable to the local healthcare context. Notably, our recent literature review **recommended leveraging the ACCORD database for research** to address questions like margin prognostication in an Australian population. Using this rich dataset, which includes patients treated at high-volume sarcoma centers, ensures that the results will be relevant to ANZ practice and can potentially inform local clinical guidelines [5,50].
- **Applying Machine Learning for Deeper Insights:** Traditional statistical analyses (e.g. single-variable comparisons of margin groups) may not fully capture the complex interactions between margin width and other prognostic factors [i]. We propose applying state-of-the-art **machine learning (ML)** techniques, specifically

survival analysis models, to discover patterns and predictors of recurrence that might be missed by conventional methods [i,iv]. ML algorithms can simultaneously consider multiple variables (tumor size, grade, margin, adjuvant therapy, etc.) and their non-linear interactions, potentially revealing subtleties such as certain subgroups of patients for whom a small margin suffices versus those who need more clearance [ii, xiv,i, iv]. This innovative approach aligns with identified research gaps: a recent report on orthopedic oncology in ANZ highlighted the need to apply machine learning to large clinical datasets like ACCORD to improve predictions of outcomes such as recurrence [25,34]. Our project directly addresses this gap by bringing advanced ML predictive modeling into the study of sarcoma surgery[i].

- **Alignment with ANZSA Priorities:** The Australia and New Zealand Sarcoma Association (ANZSA) prioritizes research that improves patient outcomes and translates into better care in specialist centers [vii,5,6,50]. By focusing on a key clinical controversy (surgical margins)[1,2] and aiming to produce a practical decision-support tool, our proposal is well aligned with ANZSA's mission to support **translational research** in sarcoma. It leverages a national collaborative resource (ACCORD) available to ANZSA members, encourages multidisciplinary collaboration between data scientists and sarcoma clinicians [5,50,13,18], and addresses a question of immediate relevance to surgeons and patients. In summary, this study will generate evidence to guide surgical practice, exemplifying the kind of high-impact research ANZSA seeks to fund [xv]

Given the importance of surgical margins [2] and the current lack of consensus [1], our investigation is both timely and highly significant. It will fill a crucial knowledge gap using contemporary analytical methods, ultimately aiming to **improve clinical decision-making and patient outcomes** in sarcoma care within Australia, New Zealand, and beyond.

Aims and Objectives

Primary Aim: To determine whether a *detailed quantification of surgical margin width* can better predict local recurrence outcomes in high-grade extremity soft tissue sarcoma than the conventional binary classification (negative vs. positive margin). Specifically, using the Australian ACCORD sarcoma registry data, we will evaluate if incorporating **granular margin status** (exact millimetric width or categorized ranges of negative margins) into machine learning survival models provides a superior prediction of 5-year local recurrence-free survival (LRFS) compared to models using the simple R-classification (R0 vs R1/R2). We hypothesize that a more nuanced margin variable will significantly improve predictive accuracy. The success of this aim will be measured by model performance metrics, chiefly the concordance index (C-index) for 5-year LRFS prediction. Our target is a C-index > 0.70 on an independent test dataset [iii, i], indicating a good discriminative ability. Achieving this would suggest that detailed margin information adds prognostic value beyond the basic margin status alone [i, iii].

Secondary Aim: To develop and internally validate a **clinical risk stratification tool** [i](e.g. a risk score or nomogram) for personalized prediction of local recurrence, based on the best-performing machine learning model [ii] from Aim 1. This tool will integrate detailed margin status with other key patient and tumor factors to estimate an individual patient's probability of 5-year LRFS. The objective is to create a prototype tool capable of stratifying patients into risk groups (e.g. low, intermediate, high risk of recurrence) to guide clinical decision-making [i]. We aim to show that this tool can meaningfully distinguish patient risk

groups, for example by producing distinct Kaplan-Meier survival curves for each risk tier with statistically significant separation. The tool's predictions will be checked for calibration and clinical plausibility [i]. By the end of the project, we intend to have a usable risk prediction model that can be presented as a simple nomogram or web-based calculator for potential use in multidisciplinary team discussions.

These aims are designed to be **SMART** (Specific, Measurable, Achievable, Relevant, Time-bound):

- *Specific:* The study focuses on **high-grade extremity soft tissue sarcoma** patients [1,2] in the ACCORD registry (population), examines **surgical margin width** as the key prognostic factor (predictor)[1,2, 13,18,22,24,30,32,33], uses **machine learning-based survival analysis** (approach) to compare against standard margin classification (comparison), and evaluates **5-year local recurrence-free survival** (outcome). The risk tool will explicitly target individualized LRFS risk estimation and patient stratification.
- *Measurable:* We will use quantifiable performance metrics [i,iv] (C-index, sensitivity/specificity for recurrence risk groups, calibration plots, log-rank test p-values, etc.) to evaluate success [i]. For example, the primary model's improvement will be measured by a higher C-index [iv] relative to a baseline model [i], and the secondary tool by its ability to separate Kaplan-Meier curves of risk groups [iv].
- *Achievable:* The project is feasible in scope – ACCORD data access is available to ANZSA members [v,vi], and our team has the required expertise in both sarcoma clinical management and machine learning. We will utilize existing computing resources and well-established ML algorithms (described below) within a one-year timeframe. Contingency plans (such as focusing on pre-existing data or simplifying models) are in place should data access or other challenges arise, ensuring the aims remain attainable.
- *Relevant:* This research directly addresses a pressing clinical question in sarcoma care (optimal margin needed)[1,25,34] and aligns with ANZSA's goal of improving sarcoma outcomes through research [vii]. A successful result will have clear implications for surgical practice and patient management, underlining the project's relevance to the sarcoma community.
- *Time-bound:* Both aims are structured to be completed within a 12-month project period. Interim milestones are defined (see Timeline) to ensure steady progress, with final deliverables – the comparative analysis results and the risk tool prototype – scheduled by project end (anticipated June 30, 2026, assuming a mid-2025 start).

In summary, our objectives are to **use machine learning to clarify the prognostic role of margin width** in sarcoma and to **translate these findings into a practical tool** that can guide surgeons and oncologists in treatment planning. By achieving these aims, the project will provide evidence to inform an optimal margin strategy and improve personalized care for sarcoma patients.

Methods

Study Design and Data Source: This is a retrospective cohort study using data from the Australian Comprehensive Cancer Outcomes and Research Database (**ACCORD**) sarcoma registry. ACCORD is a multi-center registry that prospectively collects clinical data on sarcoma patients across Australia, managed in collaboration with BioGrid Australia [v,vi].

Access to the ACCORD database will be obtained via ANZSA; we have identified the data custodian (Ms. Susie Bae at Peter MacCallum Cancer Centre) and will formally request the relevant dataset [viii]. Using ACCORD ensures a robust sample size and diversity of cases from specialist sarcoma centers nation-wide, providing high external validity for our findings in the Australasian context. The cohort will be restricted to patients meeting specific criteria (detailed below) to address our research question.

Cohort Inclusion/Exclusion Criteria: We will include **adult patients with primary high-grade (FNCLCC Grade 2 or 3) extremity soft tissue sarcomas** who underwent definitive surgical resection with curative intent and have recorded surgical margin information in ACCORD. Focusing on high-grade limb sarcomas ensures a relatively homogeneous cohort where local control is critical and margin status is particularly impactful on outcomes [2,7]. Low-grade tumors and non-extremity locations will be excluded, as their biology (and margin considerations) differ. Key criteria are as follows:

- **Inclusion:** Histologically confirmed high-grade soft tissue sarcoma of an extremity (upper or lower limb) [1,2]; surgery at a specialist sarcoma center with intent to cure (limb-sparing or amputation) [1,2,6,32]; documented surgical margin status (including at least the R0/R1 classification, and preferably measured margin distance) [26,27,46]; available data on important covariates (patient demographics, tumor size, depth, histological subtype, use of radiotherapy/chemotherapy) [7]; and a minimum follow-up duration sufficient to ascertain local recurrence or at least 5-year status (patients lost to follow-up before 5 years without recurrence will be censored) [7,22].
- **Exclusion:** Patients with metastatic disease at presentation (since margin decisions are less relevant when disease is already systemic) [1,2]; cases that had neoadjuvant therapy altering the primary tumor before surgery (to avoid confounding margin assessment)[2] or those with prior surgical attempts; low-grade (Grade 1) sarcomas [2,7]; tumors in axial locations (retroperitoneal, trunk) or bone sarcomas (which have different margin considerations) [7,25,34]; and any patients lacking detailed margin data or other essential outcome data. These criteria yield a focused, high-risk cohort ideally suited to studying how margin width affects local recurrence [iv].

Outcome Definition: The primary outcome is **local recurrence-free survival (LRFS)**, defined as the time from initial surgery to the first occurrence of local tumor recurrence, or to last follow-up if no local recurrence (censored). We will calculate 5-year LRFS for each patient. Local recurrence will be determined as per ACCORD registry definitions (typically radiologically or pathologically confirmed recurrence in the primary site or surgical bed). We will not specifically examine distant metastasis or overall survival in this project's primary aims, though these data are in ACCORD and could be explored secondarily. By focusing on LRFS, we hone in on the direct impact of surgical margins on local tumor control.

Predictor Variables and Key Covariates: The central independent variable of interest is **surgical margin status**, which we will capture in multiple ways for analysis:

- *Conventional Margin Status (R Classification):* We will use the standard **Residual Tumor classification (R0, R1, R2)** as recorded in pathology reports [6,16,32]. R0 indicates microscopically clear margins, R1 indicates microscopic residual tumor (tumor at or very close to inked margin), and R2 indicates gross residual disease. This binary/ternary classification (often simplified to R0 vs R1+) will serve as the baseline predictor.

- *Detailed Margin Width:* Where available, we will extract the **exact numerical margin distance** (in millimeters) recorded for the closest margin. Using this, we will create categorized variables that have been suggested in literature: e.g. **"≤1 mm", "1–5 mm", ">5 mm"** (and possibly ">10 mm" if data permit) [1,23,24,25,30,32,33]. These categories allow us to test thresholds that prior studies have debated. If detailed margin measurements are not uniformly available, we will rely on whatever granularity is present (some centers may record margins as ranges).
- *UICC R+1mm Classification:* We will also consider a hybrid classification sometimes referenced, where **R0 is defined as a margin ≥1 mm** of clear tissue [6,16,32]. In this scheme, a margin <1 mm (even if no tumor is inked) could be treated as "close margin" akin to R1. This nuanced classification will be compared to see if it improves outcome prediction over the traditional R0/R1 dichotomy.

All margin variables will be carefully derived and cross-checked with operative and pathology reports in ACCORD to ensure accuracy.

In addition to margin status, our models will include other important **covariates** known to influence sarcoma outcomes, such as: **patient age**, tumor size (continuous in cm), **tumor depth** (superficial vs deep), **histologic subtype**, **tumor grade** (all included are high-grade but Grade II vs III might be noted), **tumor site** (proximal vs distal limb, etc.), **type of surgery** (limb-sparing vs amputation), use of **adjuvant radiotherapy** and/or chemotherapy, and **year of treatment/center** (to account for any temporal or center effects). These variables ensure that the model can adjust for other prognostic factors while evaluating the independent contribution of margin width to recurrence risk.

Data Extraction and Preprocessing: Upon receiving the dataset from ANZSA, we will perform rigorous data cleaning and preprocessing before analysis:

- We will **extract relevant fields** from ACCORD, including those for outcomes (dates of surgery, recurrence, last follow-up), margin details, and all covariates as listed [v,vi]. If the registry does not directly provide a pre-computed margin distance, we will derive it from pathology text if possible.
- **Data cleaning** will involve checking for missing or inconsistent entries. We anticipate some missing data (e.g. margin distance not recorded for some older cases). We will employ appropriate strategies: if a critical variable like margin is missing, that case may be excluded; for other variables, we may use imputation (e.g. multiple imputation for missing tumor size or follow-up time) if the missingness is moderate [i,ii,iv,ix]. We will ensure that the final analysis dataset has complete information for all included patients on the variables needed. All preprocessing steps, including any data transformations (e.g. converting text descriptors of margins into numeric values), will be documented for reproducibility [iv].
- We will then create our derived **margin variables** as described and finalize the dataset for modeling once we have a clean, annotated table with one record per patient, containing the outcome (time to local recurrence/censoring), an event indicator (recurrence or not by 5 years), and all predictor variables.

Machine Learning Analysis Plan: We will employ modern machine learning approaches tailored for survival outcomes (time-to-event data) to build predictive models of 5-year LRFS:

- **Model Types:** We plan to explore several model types for comparison:
    - *Regularized Cox Proportional Hazards model:* A traditional Cox model with Lasso or Ridge regularization will serve as a baseline ML approach [p1,p3,p4]. The Cox model can incorporate all covariates and give a hazard ratio-based interpretation[iv], while regularization will handle any multicollinearity and prevent overfitting given the number of predictors [p1,p4,p41,p16,iv,].
    - *Ensemble tree-based methods:* We will use **Random Survival Forests (RSF)** and **Gradient-Boosted Survival (e.g. survival XGBoost)** models [p1,p3,p4]. These non-parametric methods can capture non-linear interactions and are well-suited to handling complex relationships without the proportional hazards assumption [p1,p3,p4,p41,iv]. They can inherently model interactions between margin width and other factors.
    - *Other methods:* If time permits or if beneficial, we may try additional techniques such as **survival support vector machines [iv]** or a simple **deep learning model** (e.g. DeepSurv) for comparison [p1,p3,p4,p24]. However, priority will be given to the interpretable models (Cox, RSF, XGBoost) which are more likely to yield clinically explainable results.
- **Training and Validation:** We will split the data into a **training set and a hold-out test set** [i,iii,ix,x] (e.g. 70% train, 30% test), ensuring the split is stratified by event occurrence so that the test set has a representative fraction of recurrences. On the training set, we will perform k-fold **cross-validation** [i, iv, x ,xi, iii, xii, p17] (e.g. 5-fold CV) for model training and hyperparameter tuning [p17, iv, iii, ix, x]. During cross-validation, we will evaluate model performance (C-index primarily) on the validation folds to select the best model configurations [i, iv, iii, ix, p15, p17]. Key hyperparameters might include depth of trees, number of trees for RSF, or regularization strength for Cox, etc [p15, p17, i, iii, ix, xiii]. We will use the cross-validation results to avoid overfitting and decide which type of model (and which margin variable formulation) performs best [i, p15, p17, iii, x,xi,xii, xiii].
- **Handling of Margin Variables:** We will run parallel analyses to compare the predictive value of margin definitions [i]. For instance, we will train one set of models using the simple R0/R1 margin variable, and another set using the detailed margin width categories [xi]. By comparing their performance on identical patients, we can assess whether more detailed margin info improves prediction [i]. This addresses the primary aim directly. We expect that models using the richer margin data (exact width or multi-category) will outperform those using just R0/R1, if indeed margin width carries additional prognostic significance [1,32].
- **Performance Metrics:** The primary metric is the **Harrell's concordance index (C-index)** for survival, which measures how well the model's risk predictions rank patients by outcome [iv]. We will compute the C-index for each model via cross-validation [i, iii] and ultimately on the independent test set [i]. We target a C-index > 0.70 for the best model, which would be a meaningful improvement over chance (0.50) and indicative of good predictive accuracy. We will also consider the **Integrated Brier Score (IBS)** as a secondary metric, which summarizes prediction error over time (lower IBS indicates better accuracy) [iv]. Model calibration will be checked by comparing predicted 5-year recurrence probabilities against observed outcomes (perhaps via calibration plots) [i, iv]. For the risk stratification tool, we will assess how well the model can stratify patients: we'll form risk groups based on predicted risk and then use **Kaplan-Meier survival analysis with log-rank tests** to see if the groups have significantly different outcomes.

- **Feature Importance and Interpretation:** One advantage of ML is revealing which factors contribute most to predictions [ii, ix, p1, p13]. For tree-based models, we will compute variable importance scores (e.g. how much splitting on margin improves the model) [ii, p1, p13]. We may also use SHAP (Shapley Additive Explanations) values to quantify the impact of each feature (including margin width) on the risk prediction for individual cases [p1, p13, ii]. This will tell us, for example, if *margin width emerges as one of the top predictors* of recurrence relative to tumor size, grade, etc., and how different margin lengths shift predicted risk. Such interpretation is crucial for clinical trust: if the ML model is dominated by sensible clinical factors, we gain confidence in its validity [ii, p1, p13, i]. We will specifically examine how the model treats a margin of 1 mm vs 10 mm, etc., to see the estimated risk differences.
- **Risk Tool Development:** For the secondary aim, once we identify the **best-performing model** (e.g. suppose an RSF using margin categories is best, or a Cox model with margin as a continuous variable is best), we will use that to create a user-friendly risk prediction tool. If the final model is a Cox model, a nomogram could be constructed to calculate the 5-year recurrence probability from a patient's covariates. If it's a more complex model, we will devise a points-based score or an online calculator. The tool will output an individual's predicted 5-year LRFS (or risk of recurrence) and categorize them into a risk group. We will validate this tool on the **held-out test set**: for each patient in the test set, we'll compute their risk group from the tool and then observe their actual outcome to ensure the tool's stratifications are prognostically meaningful [i]. We anticipate forming about 3 risk groups (for example: low risk ~90% 5-year LRFS, intermediate ~70-80%, high risk <50% LRFS, if the data support such splits). Demonstrating clear separation in Kaplan-Meier curves between these groups (with a significant log-rank p-value) will indicate the tool's utility. We will also check that the predicted probabilities are well-calibrated to observed outcomes [i, iv], adjusting the model if necessary for better calibration [iv].

Throughout the modeling process, we will adhere to best practices of machine learning in healthcare: data will be split only once (to keep the test set truly unseen), cross-validation will be solely within training data, and all hyperparameter tuning will avoid peeking at test results. We will also perform sensitivity analyses, such as including vs. excluding patients who got adjuvant radiation (which could mitigate margin effects), to see if the model's conclusions hold. If sample size allows, we might do subgroup analyses (e.g. by histological subtype) to ensure no single subtype skews the results.

Ethics and Governance: We will obtain ethical approval via a Human Research Ethics Committee (HREC) given this involves human data (likely a low/negligible risk application because it's de-identified registry data). We will also execute a data use agreement with ANZSA/BioGrid for ACCORD. All data handling and analysis will comply with relevant patient privacy regulations and registry policies. Only de-identified data will be used for analysis, and results will be reported in aggregate.

By employing this rigorous methodology, we aim to fully exploit the ACCORD dataset with cutting-edge analytic techniques while maintaining interpretability and clinical relevance. This approach will allow us to answer the primary question: **does the granularity of margin width meaningfully improve recurrence predictions?** – and if so, to translate that answer into a prototype tool for clinicians. The combination of a rich dataset and advanced analytics positions the project to yield impactful results that can directly inform surgical decision-making.

Expected Outcomes and Impact

Expected Outcomes: At the conclusion of this one-year project, we expect to have:

- **Quantitative Evidence on Margin Width:** A clear analysis comparing models will indicate whether including detailed margin width significantly improves prediction of local recurrence [1,2]. One possible outcome is that **detailed margin data *does* enhance predictive power**, demonstrating, for instance, that patients with margins ≤1 mm have measurably higher recurrence risk than those with >5 mm margins, even after adjusting for other factors [1,32,22,23,24,25,30,31,33]. In this scenario, our study would support the argument that "how wide" a margin is matters, not just whether it's negative or positive [1,25,6,7]. Alternatively, it's possible the detailed models perform similarly to the basic model (no substantial gain in C-index [i]), which would suggest that as long as a margin is negative (R0), additional width may not confer as much extra benefit as thought [23,24,25,30,1,7]– at least within the range of margins typically achieved[1]. **Either result is valuable:** confirming additional benefit of wide margins would urge surgeons to aim for a certain minimum clearance when feasible[25,7,13,32], whereas finding little difference would validate more conservative surgeries in appropriate cases[18,19]. We will quantify these effects (e.g. how much the recurrence hazard increases per mm less of margin, etc.), providing empirical data to inform the debate [1,32].
- **Best Margin Classification for Prognostication:** Our comparison will likely identify which margin classification (simple R0/R1, R+1mm, or multi-tiered widths) correlates most strongly with outcomes. For example, we might find that a three-tier system (e.g. margin >5mm, 1–5mm, <1mm/positive) has the highest prognostic discrimination for LRFS. This could directly inform pathology reporting and surgical practice – suggesting that pathology reports should routinely include exact margin measurements because they meaningfully stratify recurrence risk. If the UICC 1mm definition proves superior (i.e. treating <1mm as "involved"), it could influence how surgeons interpret a "close" margin and whether to recommend re-excision or radiation.
- **Validated ML Prediction Model:** We will have developed and internally validated a machine learning model for 5-year local recurrence risk. We expect this model to achieve strong performance (target C-index >0.70) on the test dataset, indicating it's a reliable predictor for new patients. Importantly, the model will consider multiple factors; we anticipate it will confirm known prognostic factors (e.g. tumor size likely a strong predictor of recurrence) and reveal the *independent contribution of margin width* when all factors are considered. For instance, the model might show that for two patients identical in other respects, one with a 2 mm margin and one with a 15 mm margin, the former has a significantly higher predicted recurrence risk – quantifying that difference could shape clinical risk assessments. Additionally, by examining model interpretability outputs (like SHAP values), we'll understand the ranking of factors: if margin comes out near the top, it reinforces the need to get it right; if it's lower, perhaps other factors dominate and margins beyond negative are less critical than assumed.
- **Prototype Risk Stratification Tool:** A practical outcome is a user-friendly risk stratification tool (or nomogram) that clinicians can use to estimate an individual patient's probability of local recurrence at 5 years. For example, a nomogram might allow input of tumor size, grade, subtype, margin width, etc., and output a recurrence risk percentage. We expect our prototype to stratify patients into, say, **Low Risk** (e.g.

<10% chance of local recurrence), **Intermediate Risk** (~10–30% chance), and **High Risk** (>30% chance) – these numbers are illustrative and will be defined by the model's distribution of risk scores. The tool will be backed by our model's validation: we will report, for instance, that High Risk patients identified by the tool indeed had significantly worse observed LRFS (e.g. 50% at 5 years) compared to Low Risk (>90% LRFS), with a clear separation in Kaplan-Meier curves. Such a tool could immediately be tested in prospective settings or considered for integration into multi-disciplinary team (MDT) decision processes.

Clinical Impact: The potential impact on clinical practice and the health system is substantial:

- For **surgeons and MDTs:** Our findings will provide evidence-based guidance on surgical margin planning. If we demonstrate that, say, achieving >5 mm margin yields markedly better local control than a narrower clear margin, surgeons may attempt more aggressive resections when anatomically possible or ensure adjuvant therapy is used when margins are close. Conversely, if no difference is found beyond a certain width, surgeons could justifiably preserve critical tissues instead of chasing arbitrary large margins, knowing it won't compromise outcomes. This personalization means surgeons can make more **informed trade-offs between tumor clearance and limb function** on a case-by-case basis. The risk tool, in particular, can inform discussions at tumor board meetings: for a given patient, the team could use it to estimate recurrence risk if only a small margin is achievable versus if a wider margin (perhaps requiring a bigger operation) is obtained, and thus weigh the benefits of additional surgery or adjunctive therapy. Ultimately, more nuanced risk stratification should lead to **tailored surgical strategies** – some patients might even avoid unnecessary amputations or complex reconstructions if deemed low-risk with a marginally negative margin plus radiation, while others might be counseled strongly toward en bloc resection of adjacent structures to widen margins if their profile suggests high recurrence risk.
- For **patients:** Improved local control directly improves patient outcomes – local recurrence of sarcoma is a devastating event often requiring mutilating surgery or high-dose radiation, and it increases the risk of mortality. If our project leads to interventions that reduce local recurrence rates (e.g. by identifying patients who need bigger margins or more aggressive adjunct therapy), patients will have better chances of remaining disease-free, translating to improved survival and quality of life. On the other side, patients whose recurrence risk is low even with a limited margin could be spared overtreatment. This means **better functional outcomes** and less morbidity: for instance, preserving a limb or its function because the model indicates a small margin is likely sufficient for that patient. The tool can also empower patients with information – clinicians can explain, "Based on your tumor and surgery, your predicted recurrence risk is X%, which is low, so we are confident the surgery was adequate," or "your risk is higher, so we plan close surveillance or additional therapy." This individualized insight can reduce patient anxiety by clarifying their prognosis and the rationale for adjuvant treatments or follow-up intensity [4]. In a broader sense, the project exemplifies progress toward **personalized medicine** in sarcoma care, moving away from one-size-fits-all rules toward data-driven individualized decisions.
- For the **health system and policy:** If our analysis identifies more optimal margin practices, it can eventually inform **clinical guidelines and protocols** in Australia/NZ.

For example, ANZSA or Cancer Australia guidelines could be updated to incorporate findings (e.g. recommending a margin of at least X mm for certain sarcomas, or using a risk score to guide post-operative radiation decisions). Over time, better local control means fewer costly recurrence treatments (which often involve complex surgery and radiation). Fewer recurrences also mean less burden on tertiary sarcoma centers and can improve overall survival, thereby aligning with health system goals of improving cancer outcomes. Our use of the ACCORD registry data also highlights the value of such registries; a positive impact of this study could encourage continued support for comprehensive data collection, recognizing how it directly leads to care improvements. Additionally, demonstrating a successful application of machine learning to real clinical data in our setting can encourage health services to invest in data analytics for other challenging problems. The translational nature of this project – going from registry data to a potential clinical tool – serves as a model for how research can directly interface with practice.

In summary, the project's outcomes will deliver **new knowledge and practical tools** that can improve decision-making regarding surgical margins in sarcoma. By quantitatively defining the relationship between margin width and outcomes, we will help resolve a long-standing debate. The impact will be better-informed surgeons, more personalized patient care (ensuring those who need wider margins get them, and those who don't aren't unnecessarily harmed), and ultimately, a reduction in local recurrence rates and associated morbidity. The findings could readily be taken up by sarcoma treatment centers in Australia and New Zealand, demonstrating a clear return on investment for ANZSA's support in terms of lives improved and knowledge gained.

Budget Justification

This project will be completed within **1 year** and has been carefully budgeted to cover all necessary direct research expenses, **staying within the ANZSA grant limit of AUD $50,000** (excluding any salary support) (research propsal draft.docx). Per ANZSA guidelines, no investigator salaries or stipends are requested; the budget is focused on data access, computational resources, and dissemination costs, each justified below:

- **ACCORD Data Access Fees:** *Estimated AUD $3,000.* While ANZSA members can request ACCORD data, there may be fees associated with data extraction or administration. Because publicly available information on ACCORD access costs is limited (ANZSA Grant Budget Cost Estimates_.pdf), we allocate this amount to cover any **application fees, data provisioning costs, or BioGrid service charges** for obtaining the specific dataset needed (all high-grade extremity STS cases with required variables). This ensures we can promptly secure the data upon project start. If the data access is granted at no cost (a possibility), these funds will be reallocated to other research expenses or additional analysis (with ANZSA's approval). Engaging with the data custodian early will confirm the actual fee structure (ANZSA Grant Budget Cost Estimates_.pdf). *Justification:* Without the ACCORD data, the project cannot proceed; this cost is essential to obtain the primary data resource underpinning the research.
- **Cloud Computing and Data Storage:** *Estimated AUD $5,000.* We will require significant computing resources for data analysis and machine learning model training. Instead of purchasing hardware, we plan to use **cloud computing services** (such as AWS or Azure) to flexibly access high-performance GPUs/CPUs as needed.

We estimate needing roughly on the order of 100–150 hours of GPU time (for training complex models) and additional CPU time for data processing and cross-validation runs. For example, AWS EC2 GPU instances (e.g., g4dn.xlarge) cost approximately $300 AUD), and we budget extra for peak usage (ANZSA Grant Budget Cost Estimates_.pdf). We also include data storage costs for the dataset and intermediate results: cloud storage rates are low (pennies per GB per month) (ANZSA Grant Budget Cost Estimates_.pdf), so even with large imaging data (which we do not have here, just tabular data), the cost is minimal – on the order of <$100 total. The bulk of this allocation is for compute instances during model development, especially months 6–10 when intensive modeling occurs. *Justification:* ML model training (especially with cross-validation and tuning) can be computationally intensive. Cloud resources will allow us to scale up as needed to run multiple experiments in parallel, ensuring the project stays on schedule. The budgeted amount also provides a buffer to try different platforms or increase computing power if the dataset is larger or models more complex than anticipated. Efficient computing will accelerate research progress and is more cost-effective than buying and maintaining hardware for a short-term project.

- **Software and Tools:** *Estimated AUD $0.* All software needed for this project will be based on open-source tools. We will use programming languages like Python and R, along with free libraries for machine learning (e.g. scikit-learn, PySurvival, lifelines, xgboost) and statistical analysis. The computing budget above covers any server software licensing implicitly (cloud providers include necessary OS/software costs in usage fees). Thus, we do not anticipate any expenditure on software licenses (ANZSA Grant Budget Cost Estimates_.pdf). *Justification:* Utilizing open-source software not only minimizes cost but also ensures reproducibility and transparency (since code can be shared). This approach aligns with best practices in academic research and allows us to direct funds to other needs.
- **Open-Access Publication Fees:** *Estimated AUD $4,000.* We intend to publish the results in a reputable **open-access journal** so that the findings are freely available to the global sarcoma and oncology community. Many high-impact oncology and medical informatics journals charge article processing charges (APCs) for open access. For example, an open-access fee can range from roughly $2,000 to $4,000 USD (≈ $3,000–6,000 AUD) depending on the journal (ANZSA Grant Budget Cost Estimates_.pdf). We budget approximately $4,000 AUD for publication costs, which should cover a mid-to-high tier journal (e.g., *Journal of Clinical Oncology Clinical Informatics* or *BMC Cancer*). We will target journals that are read by both orthopedic oncologists and data scientists to maximize impact. *Justification:* Dissemination of findings is a key goal (see Dissemination Plan). An open-access publication ensures that ANZ surgeons, researchers, and patients can access the results without subscription barriers, which is especially important given ANZSA's broad network. Including the APC in the budget guarantees we can choose the journal based on quality and audience rather than cost. Any unused portion (if we publish in a no-fee journal) will be directed towards conference dissemination or additional analysis.
- **ANZSA Annual Scientific Meeting (ASM) Conference Costs:** *Estimated AUD $3,500.* We plan to present our findings at the ANZSA Annual Scientific Meeting – the premier regional forum for sarcoma research. This cost covers conference registration, travel, and accommodation for one investigator (likely the lead researcher or a junior presenter) to attend and present in 2026:
    - Registration fee: approximately $500 (member early-bird rate) (ANZSA Grant Budget Cost Estimates_.pdf).

    - Travel: since the conference rotates locations, assume it is in Australia (e.g. Brisbane 2026). Round-trip airfare from within Australia/NZ is estimated at ~$1,500–1,800 AUD (ANZSA Grant Budget Cost Estimates_.pdf), based on mid-range booking costs.
    - Accommodation: ~$300 per night for 3 nights ≈ $900 AUD (ANZSA Grant Budget Cost Estimates_.pdf).
    - Per diem (meals/local transport): ~$100 per day for 3 days = $300 AUD (ANZSA Grant Budget Cost Estimates_.pdf). Adding these: ~$500 + $1800 + $900 + $300 = **$3,500 AUD** (we include a small buffer in case of cost fluctuations). *Justification:* Presenting at the ANZSA ASM is expected as part of the grant agreement and is invaluable for rapid dissemination to clinicians (research propsal draft.docx). It provides an opportunity for feedback from experts, fosters collaborations, and raises the profile of the research. Funding the travel ensures we can share results in person with the ANZ sarcoma community, fulfilling the obligation to acknowledge ANZSA's support and spread knowledge (research propsal draft.docx).
- **Ethics and Administrative Costs:** *Estimated AUD $500.* While many ethics applications for minimal-risk projects incur no fees (academia-based), we budget a small amount for any unexpected administrative costs such as HREC application fees or data transfer/secure storage setup. This also provides a slight contingency fund for miscellaneous expenses (e.g., printing posters, minor software plugins, etc.). *Justification:* This ensures that minor but necessary expenditures during the project are covered without needing additional funds.

Total Direct Costs: ~$16,000 AUD, which is comfortably within the $50,000 AUD limit. This budget is deliberately **conservative**; we have padded key areas to account for uncertainty (especially data access and computing). The total is lower than the maximum allowed because we focused on lean spending — if additional funds are available, they could enable extending analyses (e.g., incorporating more data or additional validation studies). However, at minimum, ~$16k is sufficient for the project's success. We will ensure to utilize the grant efficiently, and any surplus can be returned or repurposed for related research with permission. The budgeting aligns with ANZSA's expectation that **salary support is not included** and that funds directly advance the research (research propsal draft.docx).

In conclusion, this budget covers all necessary aspects to complete the project: obtaining data, performing the analyses with adequate computing power, and disseminating the results widely. Each expense directly ties to a project activity or deliverable (data analysis, publication, presentation), ensuring that ANZSA's investment yields tangible outcomes in knowledge and translation. We will provide full accounting in our final report to ANZSA, demonstrating that funds were used solely for the intended research purposes.

Timeline and Milestones

This project is designed to be completed in **12 months**. We propose a start date of July 1, 2025 (contingent on grant funding and data access approval), with completion by June 30, 2026. The timeline is structured with clear milestones to track progress, aligned with our SMART objectives and the sequence of research activities. Below is a month-by-month plan:

- **Months 1–3 (Initiation and Data Acquisition):**
  Milestone 1 (Month 1): Project Kick-off and Ethics Approval Initiation. In the

first month, we will finalize the detailed research protocol and submit the Human Research Ethics Committee (HREC) application (research propsal draft.docx). This includes drafting any required analysis plans and securing institutional approvals. By the end of Month 1, the ethics submission should be lodged, and we will prepare the data request paperwork for ANZSA.

Milestone 2 (Month 2): ACCORD Data Access Request Submitted. We will formally apply to ANZSA/BioGrid for access to the ACCORD sarcoma registry data (research propsal draft.docx). This involves specifying the cohort and variables needed (as per our inclusion criteria) and coordinating with the data manager (e.g., Jasmine Mar or Susie Bae) to ensure our request is complete and clear (research propsal draft.docx). We anticipate iterative communications this month to address any queries about the data extract. Simultaneously, by Month 2 we expect ethics approval to be in review; we will respond promptly to any HREC feedback.

Milestone 3 (By end of Month 3): Data Access Approval and Data Receipt. We aim to have the data access **approved and the dataset in hand by the end of the third month** (research propsal draft.docx). This timing assumes a smooth process; ANZSA's review and data preparation might take several weeks. If approval is delayed, we have contingency plans (such as continuing the literature review, preparing analysis code on synthetic data, etc.) to stay productive (research propsal draft.docx). By the end of Month 3, we should either have the ACCORD data or at least a firm date for its release. *Deliverable:* Confirmation of data access and preliminary ACCORD dataset loaded into our secure analysis environment.

- **Months 4–6 (Data Preparation and Exploratory Analysis):**

Milestone 4 (Month 4): Data Cleaning and Preprocessing Complete. Once data is received, we will spend several weeks cleaning it (research propsal draft.docx). By mid-Month 4, we expect to have dealt with missing values, corrected inconsistencies, and structured the dataset properly. We will document all cleaning steps in a data dictionary/log. If any critical data is missing or unclear, we will consult with the registry team early. By the end of Month 4, we plan to have a "clean" analysis-ready dataset where all variables of interest are present and formatted (research propsal draft.docx).

Milestone 5 (Month 5): Exploratory Data Analysis (EDA) & Margin Variable Definition. During Month 5, we will conduct a thorough EDA. This includes summarizing patient demographics, tumor characteristics, distribution of margin widths, and incidence of local recurrence in the cohort (research propsal draft.docx). We will generate plots/tables to understand the data (e.g., how many patients have margins <1mm, 1–5mm, etc., and what are their recurrence rates). Crucially, this is when we define the categories for margin variables based on the data distribution and literature (confirming that, for example, we have enough patients in each margin subgroup to justify certain cutoffs) (research propsal draft.docx). If needed, we might adjust our margin grouping strategy here. By the end of Month 5, we will have a clear plan for which margin definitions to test and have updated the dataset with those new variables.

Milestone 6 (End of Month 6): Dataset Frozen for Modeling. We aim to lock in the final analytic dataset by the midpoint of the project (research propsal draft.docx). By the end of Month 6, the dataset will be fully annotated and ready for modeling – meaning we won't add new variables or cases beyond this point, to prevent "shifting targets." At this stage, we will also split the data into training and hold-out test sets. *Deliverable:* A finalized dataset (with training/test split) and an EDA report summarizing cohort characteristics and justifying our modeling approach.

- **Months 7–9 (Model Development and Interim Analysis):**
  Milestone 7 (Month 7): Feature Engineering and Initial Model Setup. Kicking off the modeling phase, we will create any additional features if needed (feature engineering) (research propsal draft.docx). For example, we might create an interaction term if we suspect, say, margin importance differs by tumor size (though many ML models handle interactions implicitly). We will then implement the selected ML models (Cox, RSF, XGBoost, etc.) and run some initial training on the data subset to ensure code is working. By end of Month 7, all modeling pipelines (code for cross-validation, hyperparameter tuning) should be ready and tested on a small scale (research propsal draft.docx).
  Milestone 8 (Month 8): Model Training with Cross-Validation. In Month 8, we will execute full model training runs using cross-validation for each model and each margin variable scenario (research propsal draft.docx). This is the heavy computation period where we leverage the cloud resources. We will systematically tune hyperparameters (using grid search or Bayesian optimization) and record performance metrics. We plan to have intermediate results by mid-Month 8 to gauge which models are promising. By end of Month 8, we intend to have one or two top-performing models identified for each approach (e.g., "Cox model with margin as continuous" vs "RSF with categorical margin"), along with their cross-validated performance. We will ensure all training is logged for reproducibility (research propsal draft.docx).
  Milestone 9 (End of Month 9): Interim Analysis and Model Selection for Testing. At the 3/4 mark, we will analyze the cross-validation outcomes in depth (research propsal draft.docx). We'll compare the C-indices of models that used different margin definitions. For instance, if the detailed margin model shows a clear improvement over the R0/R1 model (even if slight), that will be a key finding. We will also consider model complexity and interpretability in selecting finalists. By end of Month 9, we expect to **select the final model(s)** to carry forward for evaluation on the hold-out test set (research propsal draft.docx). We may choose a single best model or two complementary models (e.g., if Cox and RSF both perform well, we might present both for their different insights). *Deliverable:* An interim report (internal) summarizing model performances and the tentative choice of the final modeling approach for each aim.
- **Months 10–12 (Validation, Tool Development, and Dissemination):**
  Milestone 10 (Month 10): Test Set Evaluation of Final Model(s). In Month 10, we will take the chosen model(s) and apply them to the untouched test dataset to obtain an unbiased performance estimate (research propsal draft.docx). We will calculate the C-index on the test set and other metrics like calibration. Meeting our primary success criterion – e.g., C-index > 0.70 – will be checked now (research propsal draft.docx). We will also compare the model's predictions to actual outcomes in the test set to ensure it behaves as expected. If the performance is significantly worse than in cross-validation (indicating potential overfitting), we may need to revisit model complexity or consider an alternative model (hence allowing this in Month 10 still). Assuming performance is acceptable, this marks completion of the primary analysis.
  Milestone 11 (Month 11): Comparative Analysis of Margin Definitions & Feature Importance. With final results in hand, Month 11 will focus on extracting insights and creating outputs for the research questions. We will statistically compare the performance of different margin approaches (for example, using a DeLong test or similar for differences in C-index, if applicable) (research propsal draft.docx). We will also generate **feature importance rankings** or SHAP plots for the final model (research propsal draft.docx). This will allow us to articulate which factors were most

influential (e.g., margin width, tumor size, etc.). We'll also conduct any subgroup or sensitivity analyses now to test the robustness of findings (for instance, how does the model perform on subgroups like tumors >10cm). The goal by end of Month 11 is to fully interpret the model: understand how much improvement the detailed margin gave us and what it means clinically. Concurrently, we will start drafting figures and tables for publication (Kaplan-Meier curves of risk groups, etc.).
Milestone 12 (End of Month 12): Risk Tool Prototype and Dissemination Preparations. The final month is dedicated to translation and dissemination. We will develop the **risk prediction tool prototype** based on the final model (research propsal draft.docx). For example, if it's a nomogram, we will create it and possibly a simple spreadsheet or web app for demonstration. We will validate that the tool's risk grouping performs as intended (reproducing the risk group separation on the test set) (research propsal draft.docx). In parallel, we will finalize the **manuscript** for publication, including all results and an introduction/background (much of which is prepared from our proposal writing and literature review). We will target submission to a journal shortly after project end. We will also prepare an **abstract for the ANZSA Annual Scientific Meeting (ASM)** – typically ANZSA's conference abstracts are due a few months before the conference, and since our project ends mid-2026, it aligns well with submitting for the 2026 ASM. By project end, we plan to have a draft abstract or presentation outline ready (research propsal draft.docx).
Deliverables: (1) A functioning risk calculator prototype (even if rudimentary), (2) a completed draft manuscript, and (3) an abstract submitted to or ready for the ANZSA ASM. We will also ensure all **acknowledgments** to ANZSA are in place, meeting their expectation that we credit the association in publications and presentations (research propsal draft.docx).

Throughout the project, we will hold regular team meetings (at least monthly, possibly biweekly during analysis phase) to monitor progress against this timeline. If any milestone is not met on time, we will immediately implement catch-up strategies (e.g., allocate more computing resources to shorten training time, or streamline analyses). The timeline is **ambitious but feasible**, as each step has some buffer built-in (for instance, we allowed three months for data access recognizing it might be done by 2 months). We also note that the timeline aligns with the one-year funding period of the ANZSA grant and includes the key output (conference presentation) within that period.

This schedule ensures that by the project's end, we have not only completed the research aims but also prepared to **disseminate the knowledge without delay**. The sequential milestones will keep the project on track and the team accountable, while the final month's focus on writing and presentation will maximize the impact of the work.

Dissemination Plan

Disseminating the results of this project to the scientific, clinical, and patient communities is a high priority. We will employ a multi-pronged dissemination strategy to ensure the findings reach all relevant stakeholders and drive changes in practice:

- **Peer-Reviewed Publication:** We will write a full manuscript and submit it to a high-quality **open-access journal** by the end of the project. Possible target journals include those in oncology or biomedical informatics (for example, *Clinical Orthopaedics and Related Research*, *Journal of Surgical Oncology*, or *JCO Clinical Cancer*

Informatics). Publishing in an open-access format will allow **any clinician or researcher worldwide to read and use our results freely**, in line with the principles of broad knowledge sharing. The paper will detail the background margin controversy, our methods (so others can reproduce or build on them), the results (with tables of model performance and perhaps a nomogram figure), and interpretation including how this could inform surgical practice. We will also include supplementary material such as the risk tool formula or even the pseudocode for using it, to encourage adoption. The budget includes funds for any article processing charge, ensuring we can choose the journal based on impact and audience rather than cost. We anticipate submitting the manuscript around August 2026, expecting publication (after peer review and revisions) within late 2026 or early 2027.

- **Conference Presentations:** As specified, we will present at the **ANZSA Annual Scientific Meeting (ASM)** following project completion. The ANZSA ASM (likely in late 2026) is the ideal venue to reach Australian and New Zealand sarcoma specialists, including surgeons, oncologists, and researchers. We plan to submit an abstract highlighting key findings (e.g., "Machine learning model identifies optimal margin thresholds in soft tissue sarcoma") (research propsal draft.docx). Upon acceptance, we will prepare either an oral presentation or poster. The presentation will focus on clinical implications – for example, presenting a case example to illustrate how the risk tool could be used in deciding surgical margins or adjuvant therapy. We will also engage in Q&A to gather feedback and suggestions for next steps from the sarcoma community. In addition to ANZSA's meeting, we will consider presenting at other relevant conferences:
    - **Clinical Oncology Society of Australia (COSA)** Annual Meeting or the **Australian Orthopaedic Association (AOA)** conference, to reach a broader oncology or orthopedic audience.
    - If the work has a strong computational aspect, we might also target a data science in medicine conference (such as IEEE International Conference on Biomedical Informatics) to share the ML methodology. Each of these presentations broadens the exposure of our work and can spark collaborative opportunities or interest in external validation of our model in other datasets.
- **ANZSA Network and Communications:** We will leverage ANZSA's channels to disseminate findings to its members and stakeholders:
    - We will prepare a summary of results for the **ANZSA newsletter or website**. ANZSA often features updates from funded projects; we will write a lay-summary focusing on what the results mean for practice (suitable for a general medical audience) and acknowledge ANZSA's support.
    - We will also offer to conduct a webinar or talk as part of any ANZSA educational series, to go over the findings with clinicians who could not attend the conference. This could be a virtual presentation allowing interactive discussion on how to implement the findings in different hospitals.
    - Collaboration with specialist sarcoma centers: since our data comes from these centers, we will circulate our results to the participating institutions. For instance, if data included patients from Royal Prince Alfred, Peter Mac, etc., we will send our published paper and an executive summary to those centers' sarcoma units. This closes the loop by informing those who contributed data about the outcomes of the research.
- **Patient and Public Outreach:** While the project is technical, the implications matter to patients (it deals with surgical approach and outcomes). We will coordinate with

ANZSA's patient advocacy groups or communications team to share a patient-friendly summary. This might be an article or infographic explaining:
    - The question we investigated (optimal margins in sarcoma surgery).
    - What we found (e.g., "analysis of hundreds of ANZ patients suggests margins above X mm don't further reduce recurrence, which could spare some patients from more extensive surgery" or conversely "confirms bigger margins are better up to Y mm, reinforcing aggressive surgery for high-risk tumors").
    - How it could influence their care. This could be published on ANZSA's patient information portal or social media. By informing patients, we empower them to discuss surgical options knowledgeably with their doctors.
- **Data and Tool Accessibility:** To facilitate further research and external validation, we will **share our methodology and possibly de-identified outputs**. While the raw ACCORD data cannot be made public (it's confidential), we can share derived anonymized data or code:
    - Our analysis code (in R/Python notebooks) will be shared on a platform like GitHub, along with documentation. This enables other researchers to replicate our analysis on their own data or extend it.
    - If permissible, we will release the *trained model* coefficients or even a simple web-based calculator for the risk tool. For example, we could create an online app (using Shiny for R or a simple Flask app for Python) where clinicians can input patient characteristics to get a recurrence risk estimate. This would purely be for demonstration/research use initially, not a clinical-grade tool, but it can accelerate uptake and feedback. Even a spreadsheet calculator or nomogram diagram as supplemental material to the publication would help end-users apply the findings.
    - We will also encourage ANZSA to consider hosting the risk tool on their website if it proves accurate, as a resource for members. This would firmly embed the outcome of the research into practice, accessible alongside other guidelines.
- **Future Collaboration and Translation:** We intend to actively engage with guideline committees or working groups post-publication. For instance, the Cancer Council Australia or ANZSA guidelines working party on sarcoma might be interested in our data for updating recommendations. We will make ourselves available to present our results in those forums. Additionally, we plan to discuss with sarcoma surgeons the possibility of a **prospective validation** study or implementation study (which could be the next grant application). By disseminating now, we lay the groundwork for such multi-center prospective efforts where our risk model could be tested in real-time for decision support.

By deploying these dissemination avenues, we ensure that the knowledge gained does not remain confined to academic journals but is actively communicated to those who can use it – surgeons making margin decisions, oncologists planning therapy, patients understanding their treatment, and policy-makers shaping guidelines. Our commitment to open access and engagement with ANZSA's community aligns with the **expectations of ANZSA-funded research to be widely shared and acknowledged** (research propsal draft.docx). Within a year of project completion, we anticipate that our findings will be well known in the ANZ sarcoma community and beyond, sparking discussions and possibly influencing practice regarding surgical margins.

Alignment with ANZSA Priorities and Translational Relevance

This proposal is closely aligned with the strategic priorities of the Australia and New Zealand Sarcoma Association (ANZSA), particularly in fostering collaboration across specialist centers, generating evidence to inform clinical practice, and ultimately translating research findings into better patient outcomes.

Collaboration with Specialist Sarcoma Centers: ANZSA emphasizes the importance of managing sarcoma patients in specialized, multidisciplinary centers of excellence (Sarcoma Margin Controversy Literature Review_.pdf). Our project inherently builds on data from these centers via the ACCORD registry, which itself is a collaborative effort among sarcoma specialists. By using ACCORD, we are effectively *collaborating with all contributing hospitals* – the dataset reflects patients treated at major sarcoma units in Australia (and New Zealand, if included), such as Peter MacCallum Cancer Centre, Royal Brisbane Hospital, Chris O'Brien Lifehouse, etc. We will maintain communication with these centers through ANZSA channels, ensuring our research questions and interpretations consider the on-the-ground realities of different institutions. Furthermore, the investigative team (as implied in this grant) includes clinicians who work at ANZ sarcoma referral centers, ensuring specialist insight guides the project. This multi-center perspective strengthens the study's relevance and facilitates **broader acceptance** of the results, since clinicians are more likely to trust findings derived from collective regional data than from a single institution's experience.

Translational Research Focus: ANZSA's mission is not only to support research in sarcoma but specifically research that can **translate into improved clinical practice and patient care**. We have designed this project with translation at the forefront. The question of surgical margin width is a *direct clinical dilemma* – surgeons routinely face it, and patients' outcomes hinge on it. By tackling this question and developing a risk stratification tool, we create something immediately usable in the clinic (after validation). This is a prime example of translational research: moving from data to decision support. We plan to implement our findings in forms that practitioners can digest (nomograms, guidelines, etc.). Additionally, because our research will produce tangible outputs (like the prototype risk calculator and evidence for margin guidelines), it will not end as an academic exercise. We will actively work with ANZSA to integrate the knowledge into **education and guidelines** – for example, feeding results into any sarcoma surgical workshops or including in ANZSA's educational materials for surgical fellows. ANZSA's priority on translation is further reflected in our dissemination plan (presenting at ANZSA ASM, publishing open-access) which ensures the findings are accessible to those making decisions, not just researchers.

Addressing Identified Gaps in ANZ Context: In a recent analysis of orthopedic oncology needs in Australia/NZ, key research gaps were identified, including the need to leverage the **ACCORD registry** and develop local predictive models for outcomes like recurrence (Orthopedic Oncology ML Research Gaps_.pdf) (Orthopedic Oncology ML Research Gaps_.pdf). This project directly addresses these gaps. We are *leveraging ACCORD* to study a problem highly pertinent to ANZ clinicians and patients, and we are developing a predictive model tailored to our population. By doing so, we align with the recommendation to utilize regional data and focus on issues relevant to our healthcare context (Orthopedic Oncology ML Research Gaps_.pdf). Our project also consciously considers the **unique aspects of the ANZ healthcare system**: for instance, the centralized care model (which is why specialized

center data is crucial) and the typical resource availability (e.g., access to adjuvant radiotherapy across centers). The outcome will be a model and recommendations that fit into the ANZ system, making implementation feasible. ANZSA values projects that understand and integrate regional characteristics rather than importing solutions from elsewhere uncritically. This project was formulated based on an Australian literature review and will deliver results scoped for ANZ practice, fulfilling that criterion.

Contribution to ANZSA's Vision and Sarcoma Research Capacity: By supporting this project, ANZSA would be nurturing a growing area of research – the intersection of sarcoma care and machine learning. This aligns with the priority of innovation. We bring advanced analytical methods to ANZ sarcoma research, which can have a ripple effect: success here could encourage more data-driven studies (e.g., using ACCORD for other questions), and it demonstrates that ANZSA is at the forefront of supporting modern, high-impact research. It also fosters capacity building; for example, junior doctors or data scientists involved will gain experience in multi-center research and ML, contributing to the next generation of sarcoma researchers in the region. ANZSA-funded work that is novel and collaborative enhances ANZSA's reputation and justifies continued funding initiatives.

Patient-Centered Outcomes and Health System Impact: ANZSA ultimately prioritizes improving survival and quality of life for sarcoma patients. Our project, by aiming to reduce local recurrences and avoid unnecessary morbidity, speaks directly to these outcomes. If successful, the translation might mean **fewer patients suffering local relapse** (improving survival) and/or **more patients keeping limb function** (improving quality of life) due to better-informed surgical strategies. These are concrete health benefits that align with the goal of delivering *real-world improvements*. From a health system perspective, preventing recurrences can save significant costs (each complex recurrence treatment can be very expensive, as well as psychologically difficult for patients and families). Thus, ANZSA's support for this research could lead to cost-effective care – a priority for any health system. Moreover, validating that specialized care (with appropriate margin techniques) yields better outcomes will reinforce the policy of referring sarcoma patients to specialist centers, a stance ANZSA advocates.

Compliance with ANZSA Grant Expectations: We have also aligned with all operational expectations of the ANZSA grant:

- We have not requested salary funding, and our budget falls within the stipulated limit (research propsal draft.docx).
- We plan to **acknowledge ANZSA in all publications and presentations**, meeting the grant's requirements for recognition (research propsal draft.docx).
- We aim to present at the ANZSA ASM and publish open-access, which are part of ANZSA's expectations for dissemination (research propsal draft.docx).
- The project fosters collaboration (as described) and has a clear translational endpoint (risk tool), which are often criteria in ANZSA's grant selection (they favor projects that unite multiple institutions and have line-of-sight to clinical application).

In conclusion, this project is **deeply aligned with ANZSA's priorities**. It capitalizes on a collaborative national resource, addresses a pressing clinical question in sarcoma care, uses innovative methodology to yield applicable results, and commits to translating those results into practice. By funding this work, ANZSA will be supporting a project that not only advances scientific understanding but also has immediate potential to change how sarcoma

surgery is planned in Australia and New Zealand, thereby improving patient outcomes – which is the ultimate shared goal of ANZSA and our research team. The synergy between our project aims and ANZSA's mission ensures that this research, if funded, will strongly reflect the value of ANZSA's investment in meaningful sarcoma research.

This section details the qualifications and relevant experience of the Principal Investigator.

Principal Investigator (PI): Dr. Ehsan Pendar

Dr. Ehsan Pendar, an Orthopedic Surgeon with over 14 years of experience, will serve as the sole Principal Investigator for this project. His expertise includes general orthopedics, trauma, and a dedicated focus on orthopedic oncology, underscored by fellowship training at Vienna General Hospital. Dr. Pendar has extensive clinical experience managing musculoskeletal tumors (>1,000 complex oncology cases) and performing surgeries for bone and soft tissue sarcomas, including limb salvage techniques, providing deep clinical context for investigating surgical margins. He is adept at collaborating within Multidisciplinary Teams (MDTs). Dr. Pendar also has significant research and academic experience from his previous role as Assistant Professor at Tehran University of Medical Sciences, contributing to numerous publications [cite: 31, 45-60].

Crucially for this project, Dr. Pendar brings practical machine learning (ML) experience relevant to the proposed methodology. He recently conceptualized, implemented, analyzed, and led the manuscript preparation for a study comparing state-of-the-art generative models (CTGAN, TVAE, CTAB-GAN+) for synthetic data generation using a large SEER sarcoma dataset (N≈40,000), demonstrating proficiency in handling registry data and complex ML model implementation/validation (manuscript in preparation). This hands-on experience is complemented by formal training ('AI in Healthcare Specialization', Stanford University) and familiarity with clinical data systems (EHR/PACS), directly informing his capability to lead the proposed ML analysis using the ACCORD database.

Dr. Pendar possesses relevant project management and leadership skills, evidenced by prior roles directing Orthopedic Oncology services, managing clinics, leading surgical teams, mentoring trainees, and leading quality improvement initiatives.

As PI, Dr. Pendar will personally oversee and conduct all aspects of the project, including protocol development, HREC submission, ACCORD data liaison and interpretation, data preprocessing, machine learning model development and analysis, interpretation of results, and manuscript preparation/dissemination. His unique combination of deep clinical orthopedic oncology expertise and practical ML experience provides the necessary foundation to lead and execute this study effectively as the sole investigator, with the understanding that specialist consultation may be sought if unforeseen highly complex technical challenges arise.

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