Study Design and Statistical Analysis Plan

Efficacy of Ultrasound-Guided Retrolaminar Block Combined with Standard Multimodal Analgesia for Postoperative Pain Management in Lumbar Spine Surgery: A Randomized Controlled Trial

Study Acronym: REALM (Retrolaminar Analgesia for LuMbar Surgery)

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Document Version: 1.0
Date: November 06, 2025

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1. STUDY OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned statistical methods for the REALM study (Retrolaminar Analgesia for LuMbar Surgery), a prospective, randomized controlled trial evaluating the efficacy of ultrasound-guided retrolaminar nerve block as an adjunct to standard multimodal analgesia for postoperative pain management in patients undergoing lumbar spine surgery. This document should be read in conjunction with the study protocol and will guide all statistical analyses to be performed.

2. STUDY OBJECTIVES

2.1 Primary Objective

To compare the total postoperative opioid consumption (measured as cumulative morphine equivalents via patient-controlled analgesia) during the first 24 hours between patients receiving ultrasound-guided retrolaminar block plus standard multimodal analgesia versus patients receiving standard multimodal analgesia alone.

2.2 Secondary Objectives

a) To evaluate pain intensity (Visual Analog Scale 0-10) at 0, 6, 12, 24, 48, and 72 hours postoperatively between both groups.
b) To compare cumulative postoperative opioid consumption at 48 and 72 hours between groups.
c) To determine time to first rescue analgesia request postoperatively.
d) To assess duration of sensory block (thermal and tactile testing).
e) To evaluate incidence of postoperative nausea and vomiting (PONV).
f) To compare length of hospital stay, time in post-anesthesia care unit, and total hospitalization costs.
g) To assess time to independent ambulation.
h) To evaluate sleep quality using validated scales.
i) To measure overall patient satisfaction (Likert scale).
j) To record specific adverse events (local anesthetic toxicity, neurological injury, infection, hematoma).
k) To determine incidence of chronic pain at 3 and 6 months postoperatively.

3. STUDY DESIGN

Design Type: Prospective, randomized, controlled trial with blinded outcome assessment

Randomization: Computer-generated randomization using variable block sizes (blocks of 4 and 6) in a 1:1 allocation ratio

Blinding: Single-blind design (outcome assessors blinded to group allocation). The anesthesiologist performing the block and patients are aware of treatment allocation, but independent evaluators collecting outcome data remain blinded.

Study Population: Adult patients (≥18 years) with ASA physical status I-III scheduled for elective lumbar spine surgery (with or without instrumentation) involving ≤3 vertebral levels

Study Groups:
• **Intervention Group:** Bilateral ultrasound-guided retrolaminar block with levobupivacaine 0.25% (15 ml per side, total 30 ml = 75 mg) performed preoperatively under general anesthesia + standard multimodal analgesia + morphine PCA (0-1-10 regimen: 0 ml/hr basal, 1 mg bolus, 10-minute lockout)
• **Control Group:** Standard multimodal analgesia + morphine PCA (0-1-10 regimen) without regional anesthesia block

Study Duration: Approximately 12-18 months for recruitment and initial follow-up, with extended follow-up at 3 and 6 months for chronic pain assessment

4. SAMPLE SIZE CALCULATION

4.1 Rationale and Assumptions

The sample size calculation is based on the primary outcome: cumulative morphine consumption via PCA during the first 24 postoperative hours. Based on Singh et al. (2020), the control group is expected to consume 7.2 ± 2.0 mg of morphine. We hypothesize that the retrolaminar block will reduce consumption by 50% to approximately 3.6 mg (absolute reduction of 3.6 mg).

4.2 Statistical Parameters

Parameter	Value	Justification
Type I error (α)	0.05 (two-sided)	Standard significance level
Statistical power (1-β)	80%	Standard power for clinical trials
Expected mean difference (Δ)	3.6 mg	50% reduction from 7.2 mg to 3.6 mg
Assumed standard deviation (σ)	2.5 mg	Conservative estimate accounting for technique novelty
Effect size (Cohen's d)	1.44	Large effect size

4.3 Sample Size Formula

For comparison of means between two independent groups with normal distribution:

$$\mathbf{n = 2 \times [(Z_{\alpha/2} + Z_{\beta})^2 \times \sigma^2] / \Delta^2}$$

Where:
• **n** = sample size per group
• $\mathbf{Z_{\alpha/2}}$ = 1.96 (critical value for α = 0.05, two-sided)
• $\mathbf{Z_{\beta}}$ = 0.84 (critical value for 80% power)
• σ = 2.5 mg (standard deviation)
• Δ = 3.6 mg (minimum clinically important difference)

Calculation:
$n = 2 \times [(1.96 + 0.84)^2 \times (2.5)^2] / (3.6)^2$
$n = 2 \times [7.84 \times 6.25] / 12.96$
$n = 2 \times [49.0] / 12.96$
$n \approx 7.6 \rightarrow$ **8 patients per group (minimum)**

4.4 Final Sample Size Determination

Although the calculation yields a minimum of 8 patients per group, we have increased the sample size to **25 patients per group (50 total)** for the following reasons:

1. Novel Technique: This is the first study evaluating retrolaminar block efficacy in lumbar spine surgery at our center. The technique is less standardized than erector spinae plane block, warranting conservative estimates.

2. Enhanced Statistical Power: With 25 patients per group, statistical power increases to >95% for detecting the expected difference, providing robust evidence.

3. Rare Adverse Event Detection: Larger sample enables detection of adverse events with incidence ≥6%, important for safety profile establishment.

4. Subgroup Analysis: Adequate power for pre-specified subgroup analyses (surgery type, number of levels, ASA classification).

5. Attrition Buffer: 10% additional participants (approximately 5 patients) to account for potential losses to follow-up or protocol violations.

6. Feasibility: With our high surgical volume, recruitment of 50 patients is achievable within 12-18 months.

Conclusion: Final sample size of 50 patients (25 per group) provides excellent statistical power, feasibility, and will generate robust evidence for this novel analgesic technique.

5. STATISTICAL METHODS

5.1 General Principles

All statistical analyses will be performed using R software (RStudio 2025.05.1 Build 513© 2009-2025 Posit Software, PBC). A significance level of $\alpha = 0.05$ (two-sided) will be used for all hypothesis tests. The primary analysis will follow the intention-to-treat (ITT) principle, including all randomized patients in their originally assigned groups regardless of protocol adherence. A per-protocol (PP) analysis will be conducted as sensitivity analysis.

5.2 Descriptive Statistics

Continuous Variables:
• Normal distribution: Mean ± standard deviation (SD)
• Non-normal distribution: Median with interquartile range (IQR, 25th-75th percentile)
• Distribution assessed using Shapiro-Wilk test ($p < 0.05$ indicates non-normality)

Categorical Variables:
• Absolute frequencies (n) and percentages (%)
• 95% confidence intervals calculated for proportions where appropriate

5.3 Baseline Characteristics Comparison

Baseline demographic and clinical characteristics will be compared between groups to assess randomization success:

For continuous variables:
• Normally distributed: Independent samples t-test
• Non-normally distributed: Mann-Whitney U test

For categorical variables:
• Expected frequency ≥5 in all cells: Pearson's chi-square test
• Expected frequency <5 in any cell: Fisher's exact test

Note: p-values for baseline comparisons are descriptive only; significant differences do not invalidate randomization but may be considered as covariates in adjusted analyses.

6. PRIMARY OUTCOME ANALYSIS

6.1 Primary Outcome Definition

Outcome: Total cumulative morphine consumption (in milligrams) delivered via patient-controlled analgesia (PCA) pump during the first 24 hours postoperatively.

Measurement: Automatically recorded by PCA pump. Data extracted at exactly 24 hours (±30 minutes) after end of surgery.

Hypothesis: Patients receiving retrolaminar block will have significantly lower opioid consumption compared to control group.

6.2 Statistical Analysis

Step 1: Distribution Assessment
• Shapiro-Wilk test to assess normality
• Visual inspection using Q-Q plots and histograms

Step 2: Primary Comparison
If normally distributed:
• Independent samples t-test (two-sided)
• Report: mean difference with 95% confidence interval, t-statistic, degrees of freedom, p-value
• Effect size: Cohen's d with 95% CI

If non-normally distributed:
• Mann-Whitney U test (two-sided)
• Report: median difference, U-statistic, p-value
• Effect size: rank-biserial correlation

Step 3: Clinical Significance
• Calculate number needed to treat (NNT) if significant reduction observed
• Assess whether mean/median difference exceeds minimal clinically important difference (MCID = 3.6 mg)

6.3 Graphical Presentation

Primary outcome will be visualized using:
1. Box-and-whisker plots comparing distributions between groups
2. Violin plots showing full distribution shapes
3. Forest plot displaying mean/median difference with 95% CI

7. SECONDARY OUTCOMES ANALYSIS

7.1 Pain Intensity Over Time

Outcome: Visual Analog Scale (VAS) scores (0-10) measured at 0, 6, 12, 24, 48, and 72 hours postoperatively

Analysis Method:
• **Primary approach:** Linear mixed-effects model with repeated measures
• Fixed effects: Group (intervention vs. control), Time (as categorical variable), Group×Time interaction
• Random effects: Patient-specific intercepts to account for within-subject correlation
• Covariance structure: Unstructured or AR(1) based on best fit (AIC/BIC criteria)

Alternative approach (if model assumptions violated):
• Repeated measures ANOVA or Friedman test depending on distribution
• Post-hoc pairwise comparisons with Bonferroni correction

Key Analysis Questions:
• Is there a significant Group×Time interaction? (different pain trajectories)
• Are there significant between-group differences at specific time points?
• What is the area under the curve (AUC) for pain over 72 hours?

Graphical Presentation:
• Line graphs with error bars showing mean VAS ± SE at each time point by group
• Spaghetti plots showing individual patient trajectories

7.2 Opioid Consumption at 48 and 72 Hours

Analysis: Similar methodology to primary outcome (t-test or Mann-Whitney U test depending on distribution) at 48 and 72 hours

Adjustment: Bonferroni correction for multiple comparisons (2 additional time points: adjusted $\alpha = 0.025$)

7.3 Time to First Rescue Analgesia

Outcome: Time in minutes from end of surgery to first PCA bolus request

Analysis:
• Kaplan-Meier survival curves for each group
• Log-rank test to compare survival distributions
• Cox proportional hazards regression to calculate hazard ratio (HR) with 95% CI
• Median time to event with 95% CI for each group
• Assumption checking: Schoenfeld residuals for proportional hazards assumption

Censoring: Patients who do not request rescue analgesia within observation period (24 hours) will be censored

7.4 Binary Secondary Outcomes

The following binary outcomes will be analyzed:
• Incidence of postoperative nausea and vomiting (PONV)
• Incidence of chronic pain at 3 months (VAS >3)
• Incidence of chronic pain at 6 months (VAS >3)

Statistical Tests:
• Pearson's chi-square test or Fisher's exact test (if expected frequency <5)

Effect Measures:
• Risk ratio (RR) with 95% confidence interval
• Risk difference (RD) with 95% confidence interval
• Number needed to treat (NNT) or number needed to harm (NNH) when applicable
• Odds ratio (OR) from logistic regression if covariate adjustment needed

7.5 Continuous Secondary Outcomes

The following continuous outcomes will be compared using t-test or Mann-Whitney U test:
• Duration of sensory block (hours)
• Length of hospital stay (days)
• Time in post-anesthesia care unit (hours)
• Time to independent ambulation (hours)
• Sleep quality score
• Patient satisfaction score (Likert scale)
• Total hospitalization costs (USD)

Conservative estimate due to novel technique

Multiple Testing Adjustment: False discovery rate (FDR) control using Benjamini-Hochberg procedure for secondary endpoints (critical FDR = 0.05)

8. SUBGROUP ANALYSIS

8.1 Pre-specified Subgroups

The following pre-specified subgroup analyses will be performed for the primary outcome:

1. Surgery Type:
• With instrumentation vs. without instrumentation

2. Number of Vertebral Levels:
• Single level (1) vs. multiple levels (2-3)

3. ASA Physical Status:
• ASA I-II vs. ASA III

4. Age Groups:
• <60 years vs. ≥60 years

5. Sex:
• Male vs. Female

6. Body Mass Index (BMI):
• <30 kg/m² vs. ≥30 kg/m²

8.2 Subgroup Analysis Methodology

Interaction Testing:
• Test for treatment×subgroup interaction using regression models
• Linear regression for continuous outcomes: Y = β■ + β■(Group) + β■(Subgroup) + β■(Group×Subgroup)
• Interaction term (β■) tests whether treatment effect differs across subgroup levels
• Significance threshold for interaction: $p < 0.10$ (less stringent given exploratory nature)

Within-Subgroup Comparisons:
• Separate treatment effect estimates within each subgroup level
• Forest plot displaying treatment effects and 95% CIs for all subgroups

Interpretation Caution:
• Subgroup analyses are exploratory and hypothesis-generating
• Results should be interpreted with caution due to reduced statistical power
• No adjustment for multiple comparisons in subgroup analyses (report unadjusted p-values with appropriate caveats)

9. SAFETY ANALYSIS

9.1 Adverse Events

All adverse events (AEs) will be recorded and classified by:
• Type/nature of event
• Severity (mild, moderate, severe)
• Relationship to intervention (unrelated, possibly related, probably related, definitely related)
• Outcome (resolved, ongoing, resulted in discontinuation)

Specific Adverse Events of Interest:
• Local anesthetic systemic toxicity (LAST)
• Neurological injury or deficit
• Infection at injection site
• Hematoma at injection site
• Respiratory depression (respiratory rate <8/min or requiring intervention)
• Severe nausea/vomiting requiring multiple antiemetic doses
• Urinary retention requiring catheterization
• Pruritus

Statistical Analysis:
• Incidence rates with 95% exact confidence intervals (Clopper-Pearson method)
• Between-group comparisons using Fisher's exact test
• Risk ratios with 95% CI for events with sufficient frequency

9.2 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) defined as events that:
• Result in death
• Are life-threatening
• Require hospitalization or prolongation of existing hospitalization
• Result in persistent or significant disability/incapacity
• Are medically significant events

All SAEs will be:
• Reported immediately to the Ethics Committee
• Individually described in the safety analysis
• Assessed for relationship to study intervention
• Summarized by frequency and type

10. MISSING DATA HANDLING

10.1 Missing Data Assessment

Extent of Missing Data:
• Proportion of missing data will be reported for each variable
• Pattern of missingness will be assessed (completely at random, at random, not at random)
• Little's MCAR test will be used to test for missing completely at random (MCAR)

Reasons for Missing Data:
• Withdrawal from study
• Loss to follow-up
• Protocol violations
• Technical/measurement issues
• All reasons will be documented and reported

10.2 Missing Data Handling Strategy

Primary Analysis (ITT):

If missing data ≤5%:
• Complete case analysis (listwise deletion)
• Sensitivity analysis comparing baseline characteristics between complete and incomplete cases

If missing data >5%:
• Multiple imputation (MI) using chained equations (MICE)
• Number of imputations: m = 20 (recommended for proportion of missingness up to 50%)
• Imputation model includes: outcome variable, treatment group, baseline characteristics, and auxiliary variables correlated with missingness
• Pooled estimates using Rubin's rules
• Sensitivity analysis comparing complete case analysis with multiple imputation

Primary Outcome:
• If PCA data missing due to technical issues but patient remained in study: impute based on rescue medication use and pain scores
• If patient withdrew: conduct sensitivity analyses under different assumptions (e.g., worst-case, best-case scenarios)

Missing Follow-up Data (3 and 6 months):
• Attempt to contact patients by phone/email
• If permanently lost: consider as separate category in chronic pain analysis
• Inverse probability weighting to account for differential loss to follow-up

11. INTERIM ANALYSIS

Planned Interim Analysis:
One interim analysis for safety will be conducted after enrollment of 25 patients (50% of total sample) who have completed the 72-hour primary follow-up period.

Purpose:
• Safety monitoring only
• NOT for efficacy assessment (no early stopping for efficacy)

Stopping Rules for Safety:
The study may be stopped early if:
• Incidence of serious adverse events clearly related to retrolaminar block exceeds 10%
• Two or more cases of local anesthetic systemic toxicity occur
• Ethics Committee recommends stopping based on safety concerns

Review Committee:
• Principal Investigator
• Two independent anesthesiologists not involved in patient care
• Ethics Committee representative (if needed)

Statistical Considerations:
• No alpha spending function needed (no efficacy testing at interim)
• Safety analysis will be purely descriptive
• No formal hypothesis testing at interim analysis

12. FINAL ANALYSIS AND REPORTING

12.1 Analysis Populations

Intention-to-Treat (ITT) Population:
• All randomized patients analyzed according to their assigned treatment group
• Includes patients with protocol violations or deviations
• Primary analysis population

Per-Protocol (PP) Population:
• Subset of ITT population who completed the study without major protocol violations
• Exclusions: patients who did not receive assigned intervention, major protocol deviations affecting primary outcome
• Used for sensitivity analysis

Safety Population:
• All patients who received any study intervention
• Analyzed according to treatment actually received (as-treated analysis)
• Used for safety and adverse event analyses

12.2 Sensitivity Analyses

The following sensitivity analyses will be performed:

1. Per-Protocol Analysis:
• Compare results with ITT analysis
• Assess impact of protocol violations

2. Adjustment for Baseline Covariates:
• Multiple linear regression adjusting for: age, sex, BMI, ASA status, surgery type, number of levels, baseline pain score
• Compare adjusted vs. unadjusted treatment effects

3. Missing Data Scenarios:
• Complete case analysis vs. multiple imputation
• Worst-case scenario (missing intervention group = maximum observed value; missing control group = minimum observed value)
• Best-case scenario (opposite of worst-case)

4. Outlier Analysis:
• Identify extreme outliers (>3 SD from mean)
• Analyze with and without outliers
• Robust regression methods if outliers present

12.3 Reporting Standards

The final study report will adhere to:
• CONSORT 2010 Statement for reporting randomized controlled trials
• CONSORT extension for non-pharmacologic treatments
• ICH E9 Statistical Principles for Clinical Trials

Required Elements:
• CONSORT flow diagram showing patient enrollment, randomization, follow-up, and analysis
• Baseline characteristics table (Table 1) comparing groups
• Primary outcome results with point estimates, 95% CI, and p-values
• Secondary outcome summary tables
• Forest plots for treatment effects across subgroups
• Safety and adverse event tables
• Sensitivity analysis results

Statistical Reporting:
• All p-values reported to 3 decimal places (except $p<0.001$)
• 95% confidence intervals for all effect estimates
• Exact p-values preferred over "$p<0.05$" statements
• Effect sizes (Cohen's d, risk ratios, hazard ratios) with interpretations
• Statistical software and package versions documented

12.4 Timeline

Data Lock: Upon completion of 6-month follow-up for all patients
Statistical Analysis: Within 4 weeks of data lock
Draft Report: Within 8 weeks of data lock
Final Report: Within 12 weeks of data lock
Manuscript Submission: Within 6 months of data lock
ClinicalTrials.gov Results: Within 12 months of primary completion date (as required by law)

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APPENDIX A: DEFINITIONS AND ABBREVIATIONS

Term	Definition
AE	Adverse Event
AIC	Akaike Information Criterion
ANOVA	Analysis of Variance
AR(1)	Autoregressive structure of order 1
ASA	American Society of Anesthesiologists
AUC	Area Under the Curve
BIC	Bayesian Information Criterion
BMI	Body Mass Index (kg/m²)
CI	Confidence Interval
FDR	False Discovery Rate
HR	Hazard Ratio
IQR	Interquartile Range
ITT	Intention-to-Treat
LAST	Local Anesthetic Systemic Toxicity
MCAR	Missing Completely At Random
MCID	Minimal Clinically Important Difference
MI	Multiple Imputation
MICE	Multiple Imputation by Chained Equations
NNH	Number Needed to Harm
NNT	Number Needed to Treat
OR	Odds Ratio
PCA	Patient-Controlled Analgesia
PONV	Postoperative Nausea and Vomiting
PP	Per-Protocol
RCT	Randomized Controlled Trial
RD	Risk Difference
RR	Risk Ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
VAS	Visual Analog Scale (0-10)

DOCUMENT APPROVAL

The study design, ethical considerations, and statistical analysis plan were approved by the Ethics Committee.

Dr. Roberto Coloma Díaz	*Principal Investigator*
Dr. Nicolas Valls Jiménez	*Study Director*
Dr. Duniel Ortuño Borroto	*Chair, Ethics Committee*