STATISTICAL ANALYSIS PLAN (SAP)

Title:

MULLIGAN'S TECHNIQUE, TOPICAL NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs) OR BOTH FOR KNEE OSTEOARTHRITIS.

Trial Registration Reference number 48294

1. Overview

This Statistical Analysis Plan (SAP) specifies all procedures, populations, handling of missing data, and statistical tests for the randomized controlled trial evaluating:

• Mulligan Mobilization with Movement (MWM)

• Topical diclofenac 2%

• Combination therapy (MWM + diclofenac)

• Control (structured exercise only)

The SAP adheres to CONSORT reporting principles and was finalized prior to full data analysis.

2. Analysis Populations

2.1 Modified Intention-to-Treat (mITT)

The primary analytic population is mITT, defined as:

"All randomized participants who completed at least one post-baseline outcome assessment."

Given the pragmatic design and the fact that participants with zero follow-up cannot contribute any analyzable outcome, the mITT population is appropriate and justified.

2.2 Per-Protocol (PP)

A secondary PP analysis will include participants who:

• completed ≥75% of the exercise program AND

• completed ≥75% of intervention sessions (MWM or diclofenac, when applicable)

• did not receive prohibited treatments (intra-articular injections, arthroplasty) before the 6-month endpoint

3. Missing Data Handling

Follow-up at the primary endpoint (6 months):

• 139 out of 180 participants completed follow-up → 77.2% completion

Missing data were handled using an available-case approach.

Rationale:

• Loss to follow-up exceeded thresholds where imputation becomes preferable.

• The study design is pragmatic; transparency in reporting actual observed outcomes is prioritized.

• No differential dropout due to treatment-related harms was observed.

Final handling:

“No imputation was performed. Available-case analysis was used for all models. Participants with missing data at specific timepoints were excluded only from those corresponding analyses.”

4. Outcomes

4.1 Primary Outcome

• VAS pain during activity (0–10)

Timepoints:

Baseline, Post-treatment (Day 30±2), 3 months, 6 months (primary endpoint)

MCID threshold: 1.5 points

4.2 Secondary Outcomes

• VAS pain relief

• Knee ROM (flexion, extension)

• Isometric muscle strength (quadriceps, hamstrings)

• Knee Society Score (total)

• EQ-5D index (Greek version)

• MCID responder status (≥1.5 reduction in pain)

Timepoints identical to primary outcome.

5. Descriptive Statistics

• Continuous variables: mean ± SD

• Categorical variables: counts (%)

• Visualization via boxplots

6. Normality Testing

Shapiro–Wilk test performed for all outcomes. All primary and secondary variables violated normality assumptions → nonparametric analysis chosen.

7. Primary Analysis

Primary hypothesis:

The combination therapy produces greater improvement in VAS pain at 6 months compared with exercise alone.

Model:

Given non-normal distributions:

• Kruskal–Wallis test for between-group comparisons at each timepoint

• Effect size: eta-squared (η^2)

Post-hoc:

If KW significant → Mann–Whitney U tests with Bonferroni correction.

Adjusted $\alpha = 0.05 / 6$ pairwise tests = 0.0083.

Reporting:

• median, IQR

• adjusted p-values

• η^2 effect sizes with interpretation

8. Secondary Analyses

8.1 Within-Group Changes

• Friedman test for repeated-measures nonparametric analysis

• Kendall's W for effect size

Post-hoc:

Wilcoxon signed-rank tests with Bonferroni $\alpha = 0.0083$.

8.2 MCID Responder Analysis

Binary outcome:

• Achieved MCID vs. not achieved

Statistics:

• Risk Ratio (RR)

• Absolute Risk Difference (ARD)

• Number Needed to Treat (NNT) with 95% CI

9. Software

All analyses performed in:

• Python 3.x

• Libraries: pandas, numpy, scipy.stats, statsmodels, matplotlib

10. Adjustments for Multiplicity

Primary contrast:

• Unadjusted (pre-specified)

Secondary contrasts:

• Bonferroni correction applied within each family of tests.

11. Sensitivity Analyses

Planned:

• Per-protocol analysis

• Comparison of completers vs. non-completers on baseline characteristics

12. Data Transparency

All analytic decisions, including available-case handling and non-imputation, comply with WHO trial transparency standards.

Summary:

The analysis follows mITT principles, uses robust nonparametric testing due to distributional properties, applies appropriate multiplicity correction, and transparently reports missing-data handling. This SAP ensures reproducibility and methodological integrity.