Statistical Analysis Plan

E-PERC: *Early Percutaneous Cryoablation for Pain Control after Rib Fractures for Elderly Patients*

NCT: NCT04482582

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Revised: September 28, 2023

1 Background and sample size

A recent study by Pieracci et al.[1] published in 2020 examined impact of SSRF vs. nonoperative management on outcomes among patients with >3 ipsilateral bicortical rib fractures. The authors found a reduction in numeric pain score (NPS) from 6.3 to 4.7 ($p<0.01$) and 4.5 to 2.9 ($p<0.01$) at one and two weeks, respectively, in patients who underwent SSRF. Assuming a standard deviation of 3, a total of 110 patients would be required to detect a 20% difference with 80% power and a two-sided alpha= 0.05.

Therefore, 110 patients will be enrolled in this study, with approximately equal allocation to the treatment and SOC arms.

2 Primary outcome

The primary outcome is numeric pain score at discharge, which will be verbalized by the patient on a scale of 0 to 10, with 0 being no pain and 10 being the worst pain. Mean pain scores at discharge between treatment groups will be compared using a two-sided two-sample t-test. Standard deviations for each group and a *p* value will be provided.

3 Secondary outcomes

Secondary outcomes include length of hospital stay as recorded in the patient chart. 30-day mortality from time of hospital discharge, need for ICU admission by 30 days post discharge, 30-day rib-specific readmission, daily narcotic equivalents at discharge, 1, 3, and 12 months patient-reported pain scores, and long-term pain and quality of life as measured by McGill Pain Scores, 12-Item Short Form Health Survey (SF-12) Physical Component Score (PCS) and Mental Component Score (MCS), and Glasgow Outcome Scale-Extended (GOS-E) scores at 1, 3 and 12 months post-discharge.

Length of hospital stay will be compared between groups using the Wilcoxon ranked-sum test.

Daily opioid equivalents at discharge and at 1, 3, and 12 months post-discharge will be compared using a Wilcoxon rank-sum test. Proportions of each group on any opioids (MME > 0) will be compared at each timepoint using the chi-squared test.

Thirty-day mortality, need for ICU admission, and thirty-day rib-specific admission will be compared using the chi-squared test for difference in proportions.

McGill PPI pain scores over time (1, 3, and 12 months post-discharge) will be analyzed using a mixed-effects model that will also include pain scores at admission (baseline) and at discharge. McGill PPI, Affective, Sensory, and Visual Analogue scores will be

compared at each of the three follow-up timepoint using a two-sided two-sample t-test or Wilcoxon rank-sum test, depending on distribution.

GOS-E score distributions at 1, 3, and 12 months post-discharge will be compared using the Freeman-Halton test, an extension of Fisher's Exact Test for more than 2 categories.

SF-12 (PCS and MCS) scores over time (1, 3, and 12 months post-discharge) will be evaluated at each timepoint using the Wilcoxon rank-sum test.

These outcomes will be evaluated and presented in the final analysis report with *p* values. Mean and standard deviation will be presented for numeric variables compared using a *t*-test, while median and IQR will be presented for numeric variables compared using the Wilcoxon rank-sum test. Counts and percentages, presented as N (%), will be reported for all categorical variables overall and by group.

4 Interim analyses

To minimize the risk of a Type I Error due to multiple comparisons, the O'Brien-Fleming alpha spending function will be implemented. This function provides adjusted alpha boundaries for two interim analyses (approximately 30% enrollment and 50% enrollment) and the final analysis after enrollment is complete. The significance level will remain at 0.05, though this will be the cumulative significance level for interim and final analyses. The boundary for statistical significance at approximately 30% enrollment is 0.0003; for the subsequent interim analysis at 50% enrollment the boundary will be 0.005, which leaves 0.045 as the boundary for statistical significance for the final analysis.

5 Final analysis

The final analysis will be performed on the full study sample and include all primary and secondary outcomes. Data will be presented by treatment group.

Statistical Plan Amendment for Intent to Treat Analysis: September 2023
Main analysis will be an intention-to-treat analysis, which includes all enrolled participants, regardless of whether they received the treatment or not. Secondary analysis will be the per-protocol analysis population, which includes only participants who received their assigned treatment. The ITT strategy will be implemented on October 1, 2023, to address high rates of screen failures in the intervention arm.

6 References

1. Pieracci, F. M. *et al.* A multicenter, prospective, controlled clinical trial of surgical stabilization of rib fractures in patients with severe, nonflail fracture patterns (Chest Wall Injury Society NONFLAIL). *J. Trauma Acute Care Surg.* **88**, 249–257 (2020).