Appendix D – Trial sequential analysis for a) cumulative 24-hour oral morphine equivalent consumption and b) cumulative difference in area under the curve (AUC) rest pain over 24-hours. The red line represents the cumulative Z-score. The inward sloping red lines represent the trial sequential monitoring boundaries. The outward sloping red lines represent the futility region. The horizontal blue lines represent the threshold for significance.

Sample Size is a Two-sided graph

![Graph showing cumulative Z-score over number of patients](image-url)
Supplemental material

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b)

Sample Size is a Two-sided graph

Cumulative Z-Score

Favours Isp

Favours Control

Sample Size = 1593

Z-curve

Number of patients (Linear scaled)

1178