**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](image-url)
b) Sample Size is a Two-sided graph

Cumulative Z-Score

Favours ISIP

Number of patients (Linear scaled)

Favours Control

Sample Size = 1593

Z-curve

1178