Understanding the trial sequential analysis graph in meta-analysis

Dear Editor,

Meta-analysis of randomized controlled trials (RCTs) is a powerful tool in evidence-based medicine to synthesize and consolidate research findings. When it comes to grades of evidence with a strong recommendation, a meta-analysis of RCTs has level 1A evidence. However, it is prudent to assess the reliability and robustness of these findings to avoid drawing erroneous conclusions. Trial sequential analysis (TSA) offers a valuable approach to enhance the reliability of meta-analysis by controlling the risk of random errors and assessing the need for further trials.[1] Interpreting a TSA graph is essential for understanding the cumulative evidence and making informed decisions in clinical practice.[2]

The cumulative meta-analysis and sequential monitoring boundaries are presented visually in a TSA graph, giving insight into the level of evidence attained.[3,4] The essential components of a TSA graph are described below.

The cumulative test statistics included in the analysis are shown by the Z-curve. It displays the size and direction of the therapeutic impact. TSA utilizes boundaries to assess if the body of data is sufficient to prove a statistically significant treatment effect. These boundaries take into account the hazards of Type I and Type II errors and comprise a conventional alpha boundary and a TSA-adjusted boundary. The typical test boundaries are the two lines that are parallel to one another on the X-axis, joining 2 and -2, and joining the vertical red line. The criteria for statistical significance at a constant Z value of 1.96, or a *P* value of 0.05, are shown by these lines. The lines that make up the futility boundary define the inner wedge. Depending on where the intervention is taking place, the curved red lines represent monitoring boundaries or trial sequence boundaries (for benefit and harm). As studies are added one after another, the X-axis shows the cumulative information size, which represents the total number of subjects included in the analysis.

After achieving the required information size, if the cumulative Z-curve passes the TSA-adjusted boundary, it indicates the presence of a statistically significant effect and suggests that more trials may not be required.

When the TSA-adjusted border is crossed, there is enough data to rule out the null hypothesis. As more trials are added, the likelihood of false positives (Type I error) decreases.[5] While crossing the conventional alpha boundary without crossing the TSA-adjusted boundary raises the possibility of a treatment effect, it also emphasizes the need for more studies to confirm the results and lower the possibility of a false-positive result.[6] If the cumulative Z-curve is confined to the monitoring boundary and has not crossed either boundary, there is insufficient data to conclude that the treatment had a meaningful impact and that more studies are required to arrive at a definitive conclusion. The evidence is inconclusive but directed toward relevance if the Z-curve approaches the TSA-adjusted boundary without crossing it. To fully understand the treatment effect, more

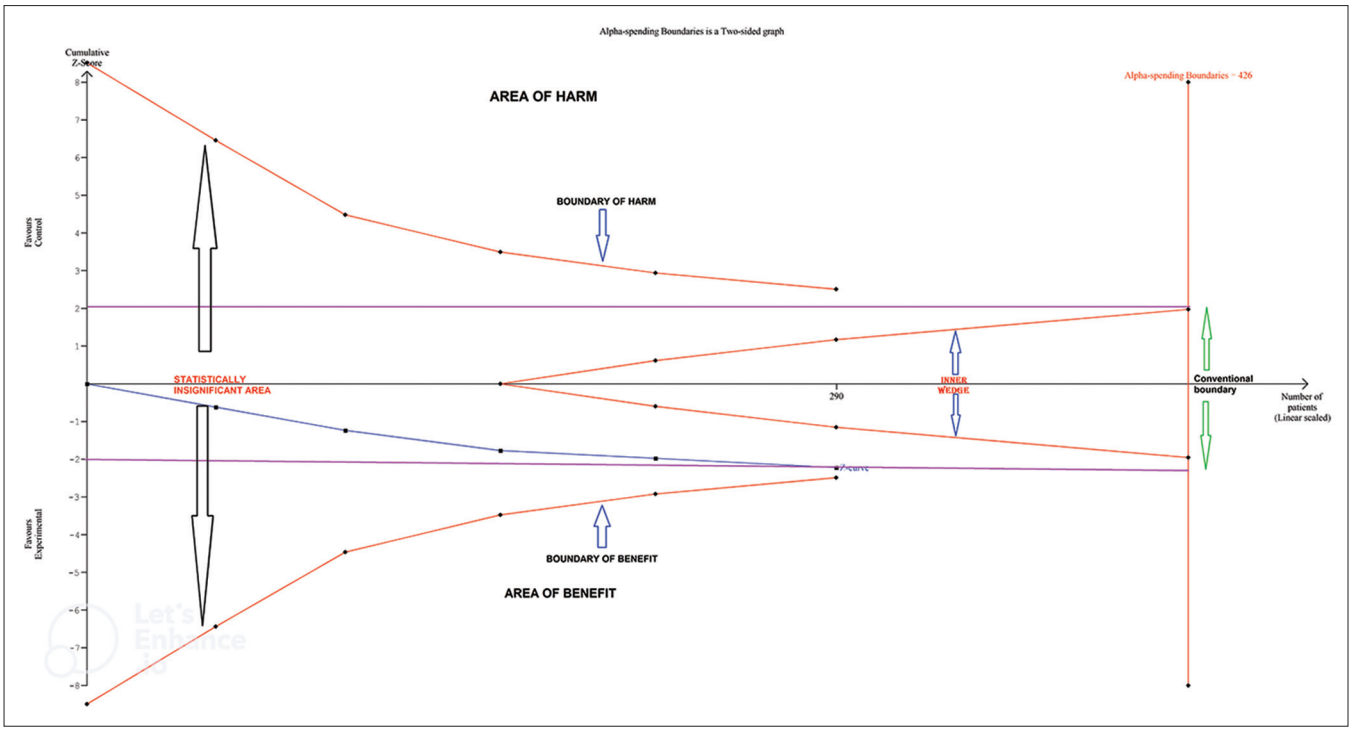

Figure 1: Graph showing a trial sequential analysis plot created using TSA software and fictitious data. The total sample size of the studies included in the meta-analysis was 290. However, the TSA software calculated a required information size of 426. Therefore, the present meta-analysis does not fulfil the number of participants required as calculated by the software. The cumulative Z-curve has crossed the conventional boundary. This means that patients in the experimental group have significantly better analgesia than control

trials are required. If the cumulative Z-curve approaches the inner wedge inside the futility boundary, it signals that no additional investigations are necessary and that it is doubtful that more research would be able to demonstrate statistical significance among the eligible subjects.

Conclusions derived from meta-analyses using conventional methods are more credible when they are interpreted using a TSA graph. In order to decide on the efficacy of a treatment, a TSA graph provides additional information about whether the available data that has been analyzed are sufficient. It enables researchers to avoid drawing incomplete conclusions from inconclusive evidence and directs the prioritization of ongoing investigations. Figure 1 represents a TSA graph with fictitious data to demonstrate various curves and boundaries.

To conclude, it is critical to know how to read a TSA graph when assessing the overall strength of the evidence from a meta-analysis of RCTs. TSA provides a practical method for enhancing the usefulness of findings from meta-analyses and encourages clinical practitioners to apply evidence-based decision-making.

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Conflicts of interest
There are no conflicts of interest.

Abhijit Nair, Nitin K. Borkar[1]
Department of Anaesthesiology, Ibra Hospital, Ministry of Health-Oman, Ibra-414, Sultanate of Oman, [1]Department of Paediatric Surgery, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India

Address for correspondence:
Dr. Abhijit Nair,
Department of Anaesthesiology, Ibra Hospital, Ministry of Health-Oman, P.O. Box 275, Ibra-414, Sultanate of Oman.
E-mail: abhijitnair95@gmail.com

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