Improving Insights on Disease Modification in Alzheimer's Disease by Including Sequential GSTs in the Analysis Hierarchy

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Sequential GSTs provide an objective assessment of the combined evidence for a disease modifying treatment effect from relevant subsets of outcomes.

INTRODUCTION

Measuring disease progression for complex neurodegenerative diseases such as Alzheimer's (AD) is complicated due to the variety of symptoms across cognitive, functional, and global domains. Furthermore, due to the differences in how these outcomes are measured (e.g., patient questionnaire, patient performance, clinician interview, etc.), determining a measurable effect of a disease modifying treatment can be methodologically challenging. If the disease is improved, symptoms across relevant measures are expected to improve, though not necessarily on the same time frame or by the same magnitude. For stakeholders to accurately assess the evidence of an overall treatment effect among combinations of outcomes, multivariate methods that account for relationships among outcomes are needed. A global statistical test (GST) formally quantifies evidence of efficacy of a treatment across multiple endpoints, providing objective interpretation that accounts for aspects of the data that are harder to account for informally, like correlation between endpoints. For post-hoc application of the GST it is important that the components be selected carefully, as simply selecting endpoints with strong results could bias results. Linking the component selection to a prespecified hierarchy ensures that the component selection is scientifically driven and not biased by results. Sequential GSTs (sGSTs) and cumulative p-values can provide objective assessment of the combined evidence for a disease modifying treatment effect from relevant subsets of outcomes in simulated clinical trials.

METHODS

sGSTs are sequences of GSTs in which successive endpoints in a prespecified hierarchy of outcomes are added to the GST in order. At each step of a sGST, a cumulative p-value is calculated associated with results up to that primary or secondary endpoint.

Although primarily used in post-hoc analyses, sGSTs can be integrated into a prespecified analysis plan to add more statistical depth and rigor. In such analyses, family-wise type I error rates are controlled using hierarchical gatekeeping strategies defined by the prespecified order of the outcomes. Using sGSTs and cumulative p-values with various orders of hierarchical gatekeeping improve interpretability without changing target statistical properties or other study design aspects. sGSTs also have the added benefit of being able to account for redundancy and independence between endpoints using correlation.

The process of choosing which endpoints to include in an analysis is inherently subjective as is the relative importance we assign to each analysis. For example, primary endpoints are often clinically more important than secondary ones in addition to having added significance due to their selection as the primary. Incorporating weights into sGSTs allows for quantifying expert judgement on the relative importance of different outcomes objectively. Thus, weighting offers a practical way to bridge the gap between the objective and the subjective interpretations of a trial.

The performance of an sGST can be highlighted in several scenarios of interest. These scenarios include different levels of correlation between endpoints, secondary endpoints with similar magnitude of effects as the primary endpoint, and positive results higher in the order and negative results lower in the order.

We also included a scenario is included that was specifically constructed to illustrate what results would be required from lower-order outcomes to maintain significance exactly at the alpha level.

RESULTS

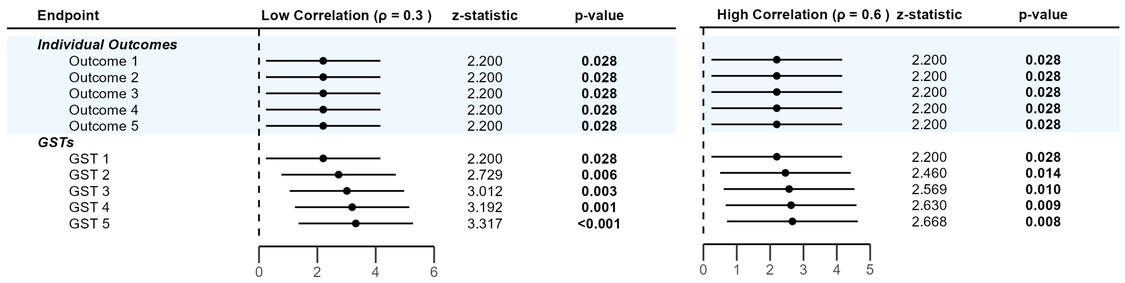

Figure 1: A significant primary endpoint is followed in the sGST hierarchy by four secondary endpoints, all showing a similar magnitude of effect. This shows that consistent results add to the overall body of evidence as expected.

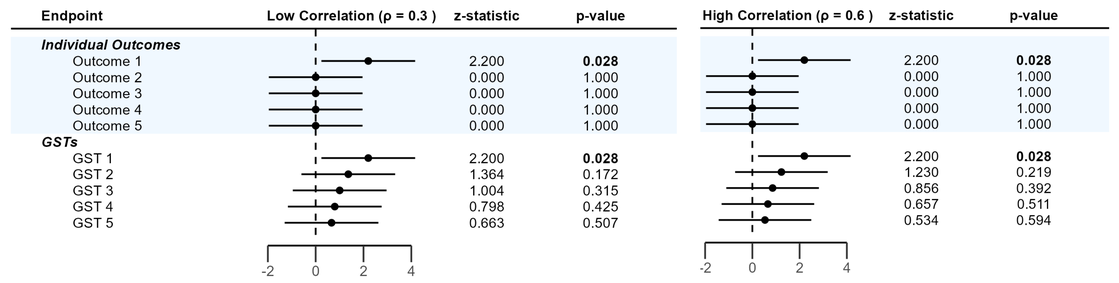

Figure 2: The primary endpoint is significant and the four secondary endpoints in the sGST hierarchy have no effect. This demonstrates that significance immediately vanishes when endpoints do not show any positive trends.

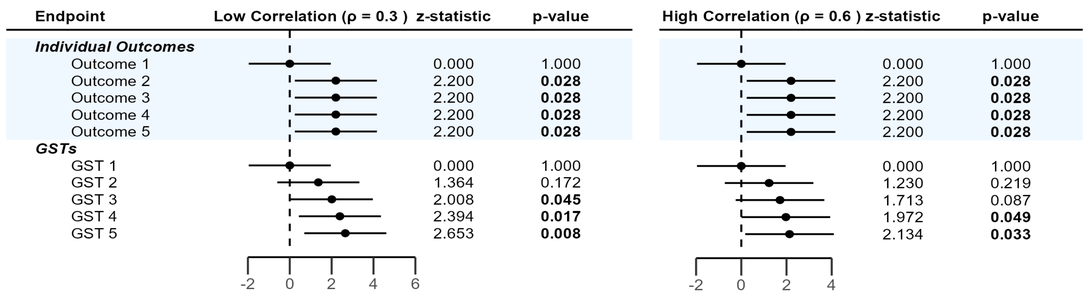

Figure 3: The sGST hierarchy begins with a non-significant endpoint, but the four subsequent secondaries show a treatment effect. This illustrates that even when the primary is not significant, having significant secondaries can provide enough cumulative evidence for the overall sGST to show significance.

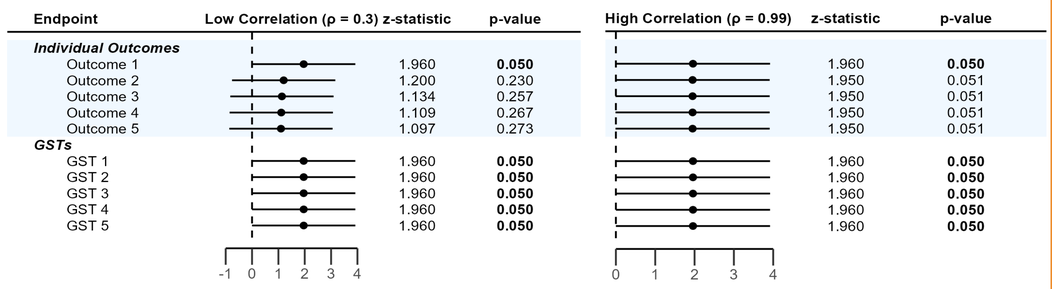

Figure 4: This scenario demonstrates the results required from each subsequent outcome to maintain significance at the next step of the sGST. When a primary endpoint is clearly significant, subsequent secondaries just need to be directionally consistent to maintain significance. However, if correlation is extremely high, subsequent endpoints are redundant and might not provide sufficient new evidence if significant.

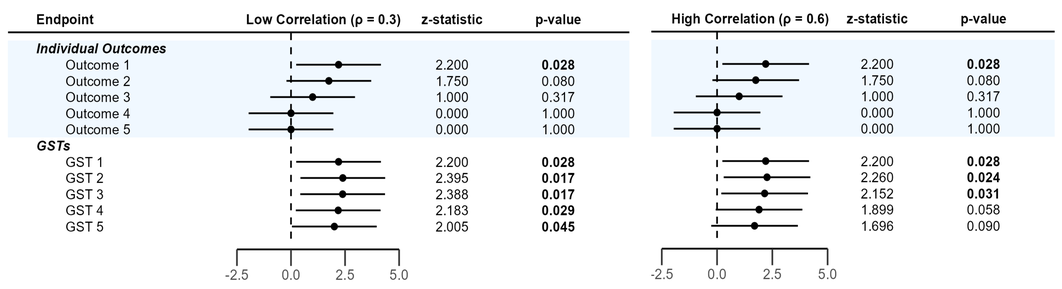

Figure 5: When primary endpoints are clinically meaningful, a weight can be applied to quantify its importance in the GST. In this demo, the primary endpoint was given half the total weight. This shows that even when secondary outcomes have insignificance, an sGST that prioritizes a clinically meaningful and significant primary can maintain an overall significance.

DISCUSSION

sGSTs are particularly useful in the context of disease modifying treatments as they allow for the assessing of evidence cumulatively rather than as separate parts. This eliminates the need for the "all-or-nothing" approach for proving significance on one specific target symptom measure. Furthermore, when prespecified, sGSTs with hierarchical gatekeeping improve the interpretability of trial results without inflating type I error or decreasing power.

In instances when correlation between endpoints is low, significant secondaries can support a significant primary endpoint. This is because when the correlation is low, there is "new" information that each secondary endpoint contains that the primary endpoint does not already capture. The flexibility of sGSTs allows stakeholders to emphasize different domains through the hierarchical arrangement and by incorporating weights based on clinical meaningfulness.

HIGHLIGHTS

- sGSTs allow for a single conclusion across multiple domains rather than assessing single endpoints as separate parts, while avoiding redundancy.
- When correlations between endpoints are low and the primary endpoint is not significant, significance can still be achieved with significant secondaries.
- Allows for quantifiable weights to be assigned based on the clinical meaningfulness of each endpoint.

REFERENCES

1. S. P. Dickson et al., J. Prev. Alzheimers Dis., vol. 10, no. 3, pp. 595–599, 2023, doi: 10.14283/jpad.2023.50
2. S. P. Dickson et al., J. Prev. Alzheimers Dis., vol. 11, no. 3, pp. 529–536, 2024, doi: 10.14283/jpad.2024.64.
3. S. P. Dickson et al., J. Prev. Alzheimers Dis., vol. 11, no. 4, pp. 992–997, Aug. 2024, doi: 10.14283/jpad.2024.55.
4. S. P. Dickson et al., Alzheimers Res Ther. 2023 May 24;15(1):98. doi: 10.1186/s13195-023-01238-1.

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