

Dose-Exposure-Response (D-E-R) Approach for Efficient Sample Size Allocation in An Exploratory Multi-Regional Trial



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Introduction

Global simultaneous drug development has become a common practice in multinational pharmaceutical companies to reduce the time lag to market and improve patient access to novel treatments. Characterization of the D-E-R relationship in a diverse population through an early Phase multi-regional trial would be beneficial to identify the potential risk of heterogeneity across different regions prior to confirmatory trials. [1] Balancing this goal with the inherent uncertainties of early drug development requires careful consideration of how to efficiently allocate sample size across regions to detect potential clinically meaningful heterogeneity.

To illustrate some of the considerations in ongoing GSK programs, we have used an established model based on data from a Phase 1 study of an anti-psoriatic drug (Drug A) (Figure 1B) [2] to design a hypothetical multi-regional Phase 2 dose-ranging trial (N=175) (Figure 1A). The objective of this study is to evaluate regional sample size allocation for the planned trial using endpoint-based approaches and model-based D-E-R approaches, assuming a minimum therapeutic improvement in the region of interest (Region X).

Methods

The primary endpoint of the Phase 2 trial was the percentage reduction from baseline in the Psoriasis Area and Severity Index (PASI) score at week 12. A PASI score reduction of 50% (i.e., PASI50) or greater was considered a clinically meaningful therapeutic improvement. [3] In this work, a minimum PASI reduction of 50% was assumed for Region X patients compared to the typical 68.4% reduction for the rest of the world (ROW) patients following the 210 mg dose at week 12 (Figures 1C). The 18.4% inter-regional difference in PASI reduction was defined as a borderline difference. An inter-regional difference greater than this borderline difference is considered a clinically meaningful difference. In the D-E-R model, the borderline difference was parameterized as 2.6-fold higher IC_{50} in Region X (Figures 1B).

- Longitudinal pharmacokinetics (PK) and clinical response data were simulated using the established D-E-R model for Drug A.
- Different proportions of patients from Region X were randomly sampled across dose levels to assess the impact of sample size allocation on the power to detect significant inter-regional differences.
- The probability of detecting inter-regional differences (Figure 2A) and the probability of the estimated inter-regional differences providing confident results (Figure 2B) were assessed.

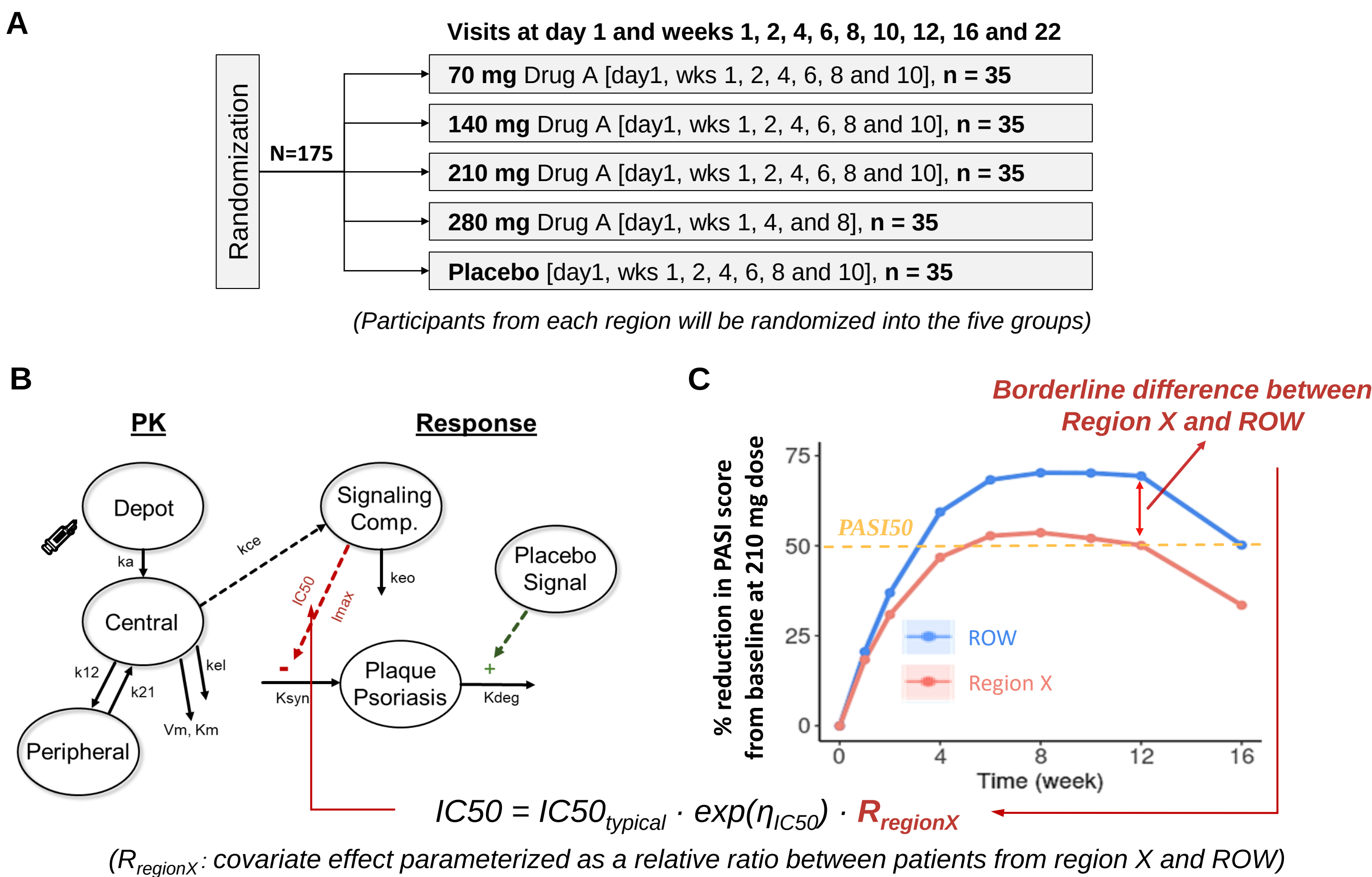


Figure 1. Trial design (A), the structure of the established PKPD model (B), and the percentage of reduction in PASI score for the patients following 210 mg dose of Drug A (C)

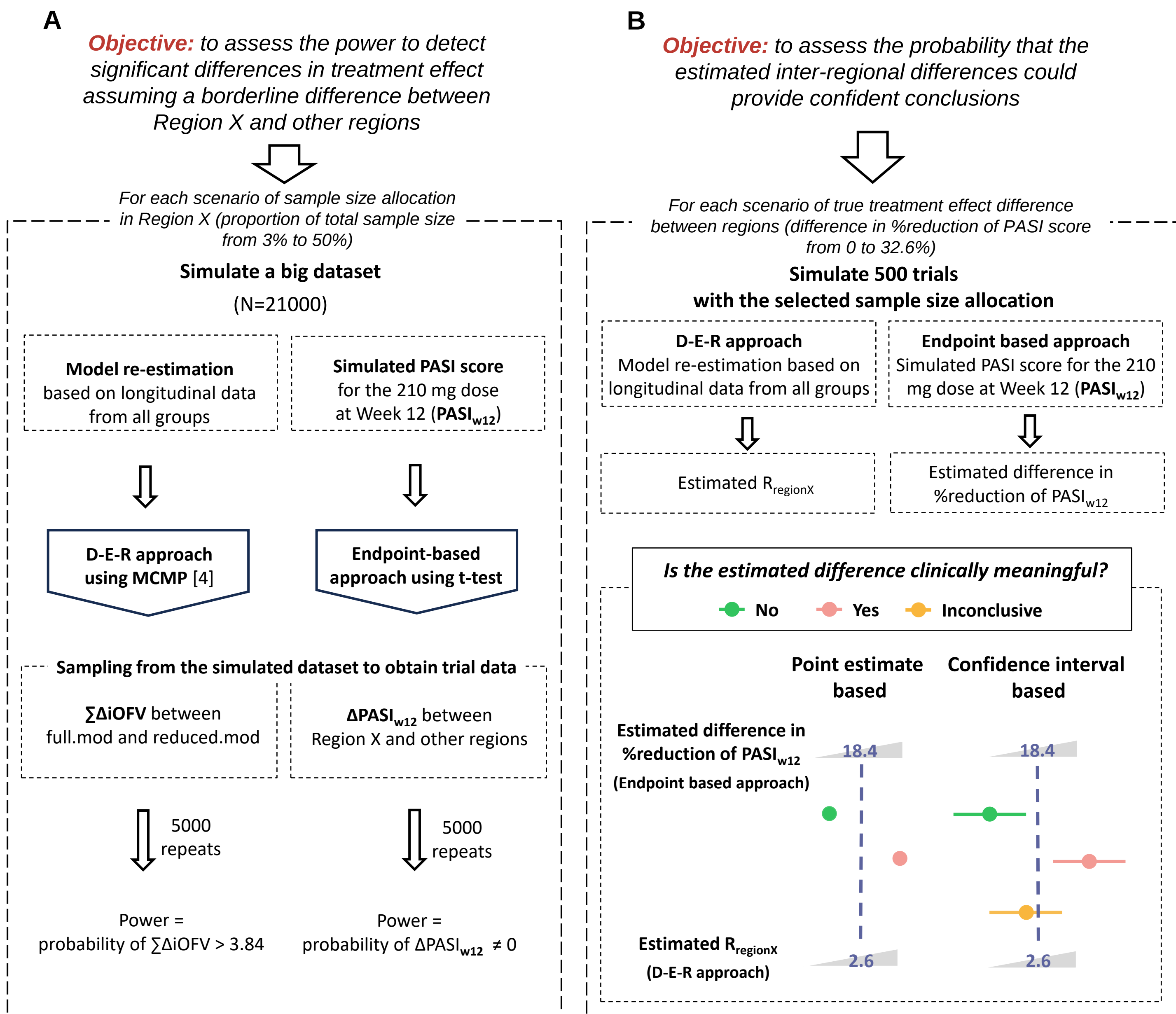


Figure 2. Procedures for assessing the impact of sample size allocation on the power to detect significant differences between regions (A) and for assessing the probability of providing confident conclusions (B)

Results

- Using the endpoint-based approach, the maximum power (when Region X takes 50% of the total sample size) to detect statistically significant treatment differences between Region X and the rest of the regions was around 40% (Figure 3A).
- With the D-E-R approach, 48 subjects from Region X, taking 27% of the total sample size, provided over 80% power to detect the borderline inter-regional difference in the treatment effect (Figure 3A).
- The power to detect a statistically significant difference between regions using the endpoint-based approach and the D-E-R approach, given different values of the true inter-regional difference, is shown in Figure 3B. It is worth noting that even when the magnitude of the inter-regional difference is not considered clinically meaningful, there is still considerable power to detect a difference.

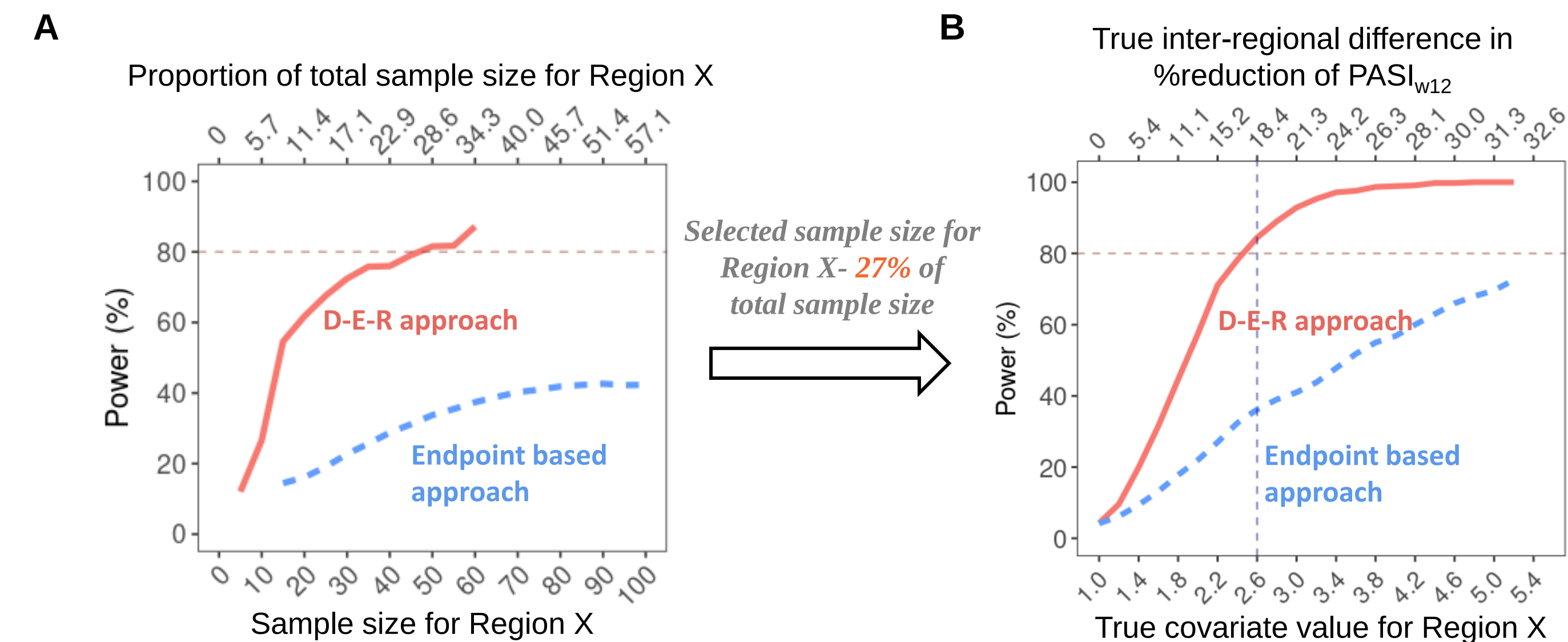


Figure 3. Power to detect a significant difference between regions assuming a borderline difference (A) and with varied true inter-regional differences (B)

- Three zones were identified using the D-E-R approach and the endpoint-based approach (Figure 4)
- Green zone: $\geq 80\%$ probability that the estimated magnitude of the inter-regional difference is below the borderline when the truth is **no clinically meaningful** difference (**zone providing confident conclusions**)
- Red zone: $\geq 80\%$ probability that the estimated magnitude of the inter-regional difference is above the borderline when the truth is **a clinically meaningful** difference (**zone providing confident conclusions**)
- Gray zone: **zone with higher probability (i.e. >20%) of being inconclusive**
- Compared to the endpoint based approach, the D-E-R approach provided larger zones of confident conclusions (green and red) and smaller zones of unconfident conclusions (grey), indicating that the D-E-R approach could better inform future trial design and decision-making for the multi-regional drug development.

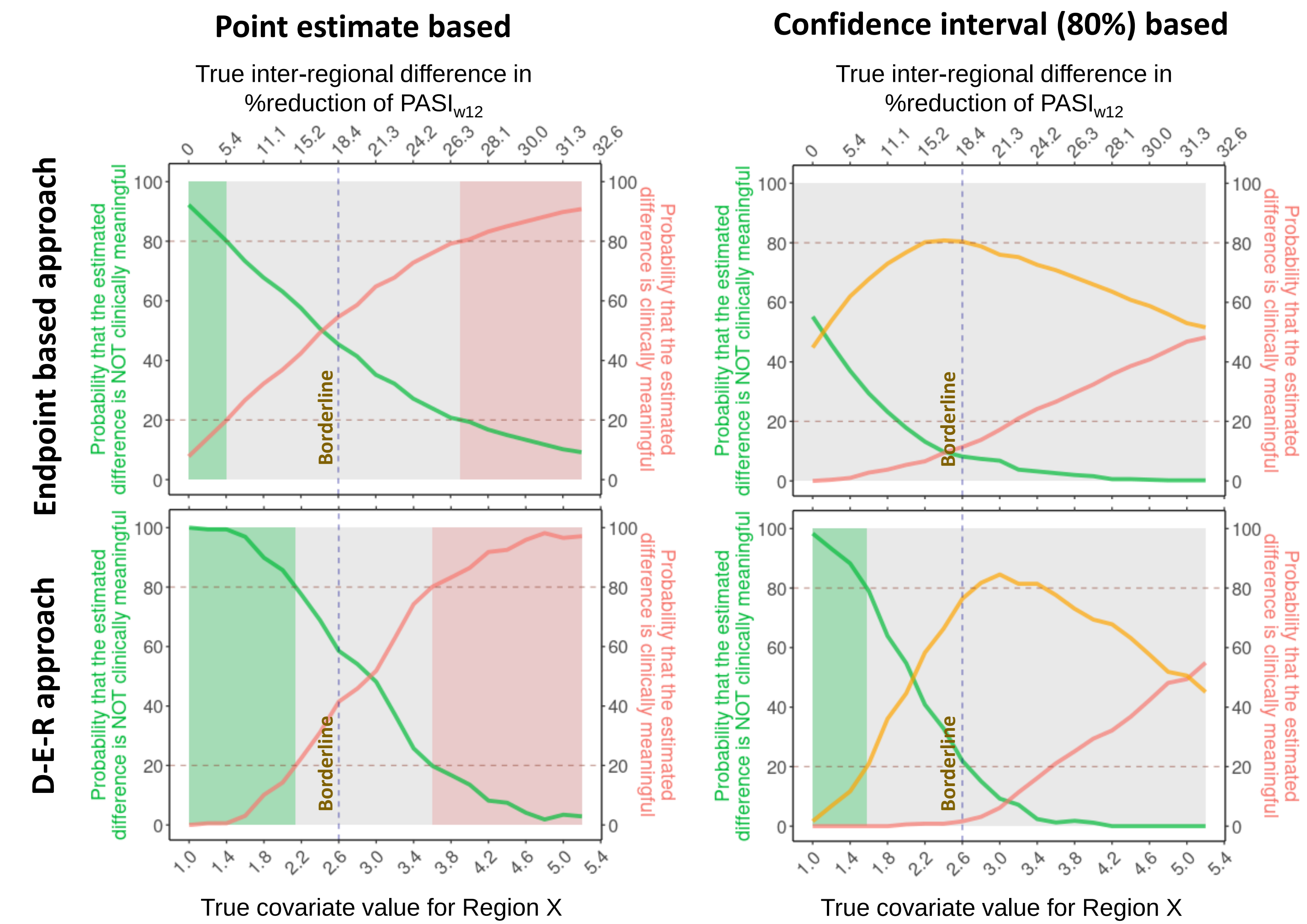


Figure 4. The probability that the estimated inter-regional differences are clinically meaningful (red lines) or not (green lines) and the zones providing confident conclusions (green and red zones) or being inconclusive (gray zones)

The yellow line indicates that it is inconclusive whether the estimated magnitude of the inter-regional difference is below or above the borderline (refer to Figure 2B).

Conclusion

This case study demonstrates that endpoint comparison based on the end-of-trial observations from one dose group is inefficient in detecting regional heterogeneity and has a high uncertainty in reaching a confident conclusion about regional heterogeneity or homogeneity in exploratory trials. In contrast, the use of a D-E-R model-based approach that utilizes data from across the dose groups and duration of the trial increases trial efficiency and importantly characterizes potential regional differences with greater confidence.

References

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