Using Contour Plots to Assess the Sensitivity of Clinical Trial Design Assumptions

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Background

- Power and sample size are extremely important topics that may not receive adequate attention
- Sufficient number of patients to detect clinically-meaningful differences… but not so many as to expose patients to unnecessary risk
- Calculations have an ethical burden in clinical trials not experienced in many subject-matter areas
- Section 3.5 of ICH E9 recommends assessing the sensitivity of calculations[1]
- Sample size should be determined using wide range of assumptions, as much data as is available, and input from clinical colleagues

Goals

- Data visualization to summarize study design
- Illustrate how contour plots can be used to better inform clinical trial design and provide greater transparency for regulators

Contour Plots

- 2D plot used to summarize 3D by using color or contour lines to describe the third dimension
- Often used in geography to communicate elevation or depth and weather patterns

Sample Data: Plaque Psoriasis

- 293 patients with moderate-to-severe plaque psoriasis[2]
- Compare multiple doses of guselkumab to adalimumab
- Results showed 36/42 (86%) guselkumab (100 mg) and 25/43 (58%) adalimumab achieved primary endpoint of 0 or 1 on global assessment at Week 16
- Treatment effect and 95% CI are 28% (9.9%, 46.1%)
- Assume minimally important clinical difference is 15%

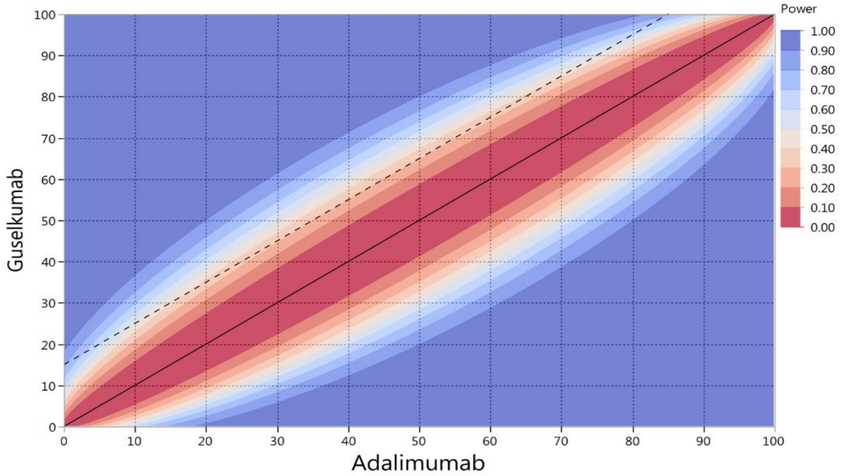

Figure 1: Power contour for all possible responses

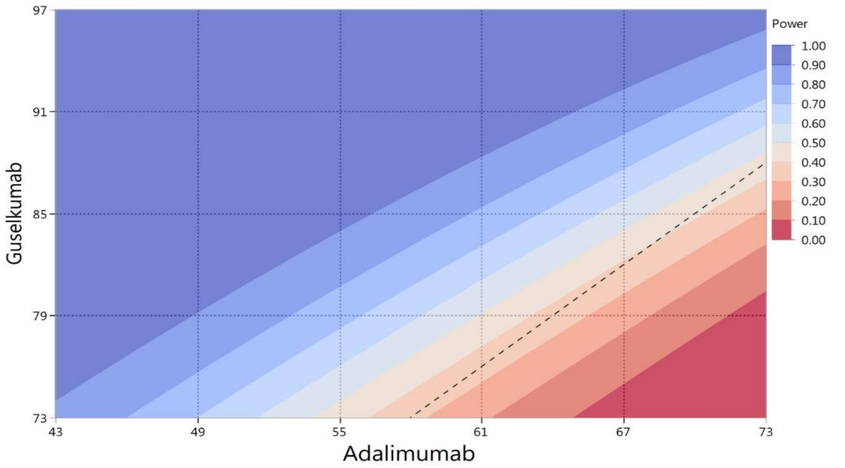

Figure 2: Zoomed power contour based on 95% confidence intervals

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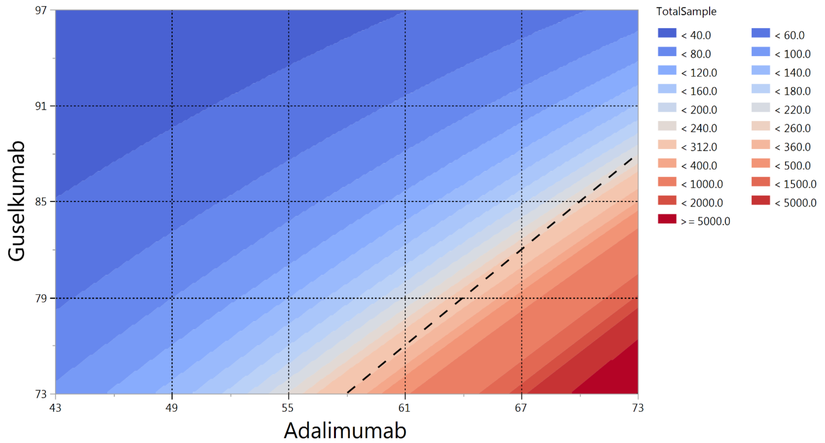

Figure 3: Zoomed sample size contour based on 95% confidence intervals

New Trial

- 86% and 58%, two-sided Pearson chi-square test at $\alpha = 0.05$ and at least 90% power will require 52 patients per arm
- A well-powered or adequately-sized trial is true under a very narrow range of assumptions

Meta-Analysis

- Conduct the trial with 104 patients

Meta-Analysis, cont.

- Results show 42/52 (81%) and 34/52 (65%) of patients met the primary endpoint for guselkumab and adalimumab, respectively
- P-value for the primary comparison is 0.077.
- How can the study team consider the results of both studies in the design of a new trial?
- Estimated treatment effect and 95% confidence interval are 20.9% (8.5%, 33.3%).
- Estimated response and 95% confidence interval for adalimumab are 62.1% (52.3%, 71.9%).

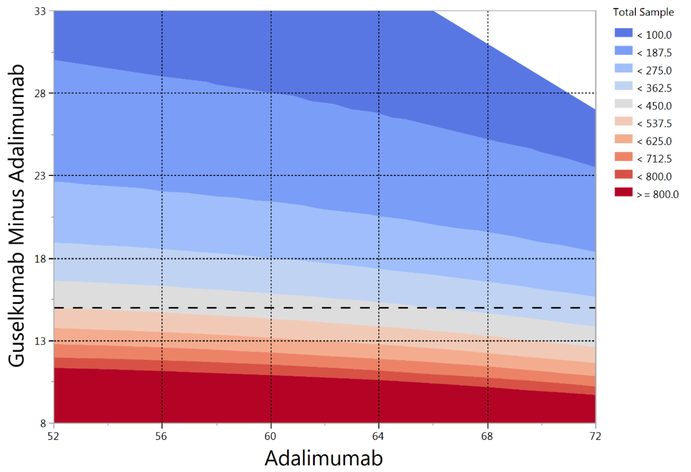

Figure 4: Zoomed sample size contour based on meta-analysis

Adaptive Designs

- Contour plots can be used to summarize the characteristics (e.g. expected sample size, stopping probabilities) of adaptive designs
- Adaptive designs allow for early stopping of a clinical trial in the presence of overwhelming efficacy or excess toxicity, or in situations when the novel compound has little chance to distinguish itself from control (i.e., futility).
- Percent predicted FEV1 for cystic fibrosis trial[3]
- Four equally-spaced stages based on O'Brien-Fleming-like boundaries

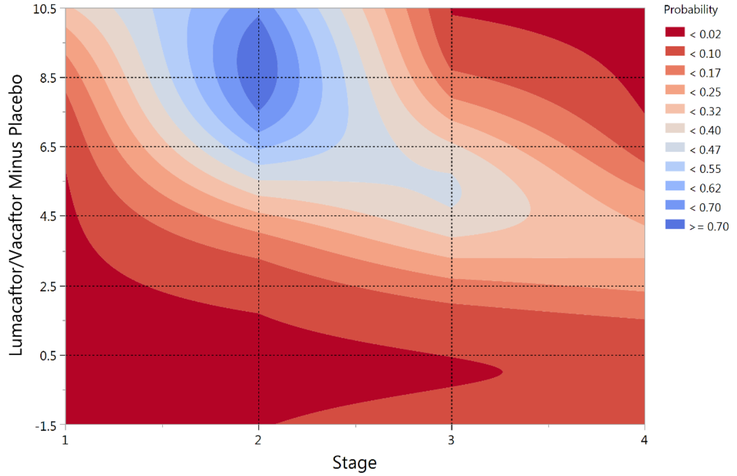

Figure 5: Stopping probability contour (efficacy only)

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Adaptive Designs, cont.

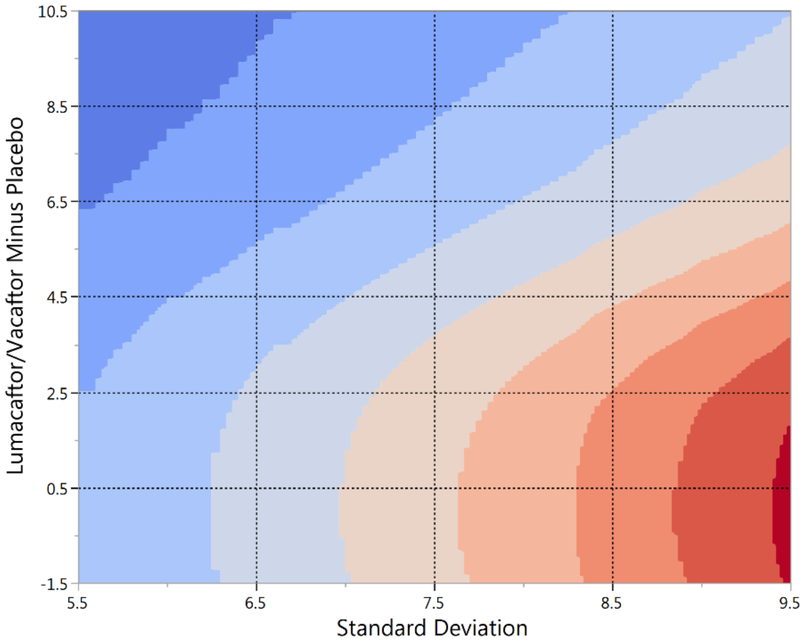

Figure 6: Sequential design with early stopping for efficacy, four stages

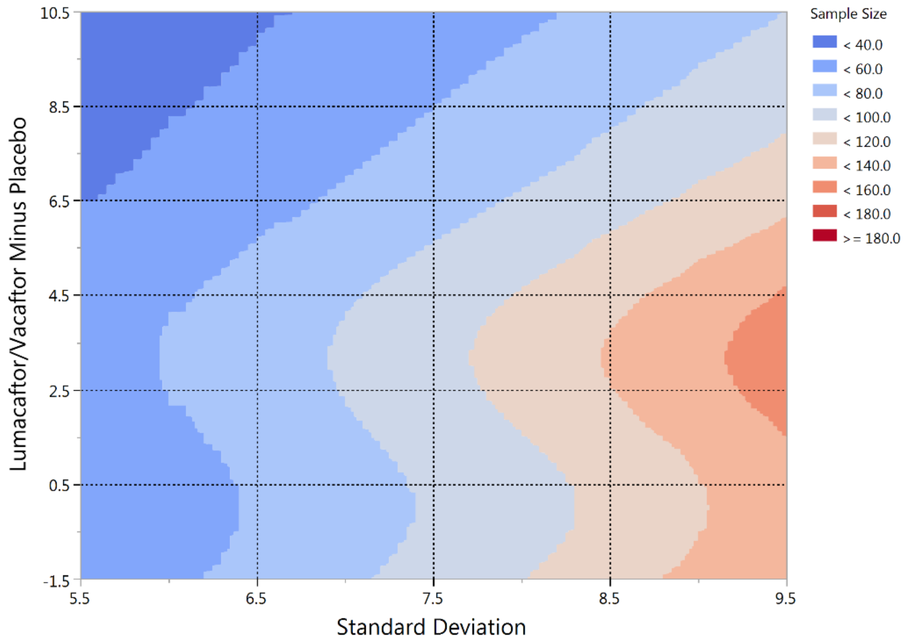

Figure 7: Sequential design with early stopping for efficacy and futility, four stages

- Figure 5 shows that for the observed treatment effect of 4.5, the trial will most likely end in the third stage. A large treatment effect will likely end in Stage 2
- Figures 6 and 7 clearly communicate the impact of adding early stopping for futility to the expected sample size of the sequential design when the treatment effect is small

Conclusions

- Recent paper summarizes examples for continuous, binary and time-to-event endpoints[4]
- Explores meta-analysis and adaptive designs
- Provides sample SAS code. Plots in this poster were produced using JMP using either **Graph Builder** or **Contour Plot**

References

1. International Conference of Harmonisation. (1998). E9: Statistical Principles for Clinical Trials.
2. Gordon KB, Duffin KC, Bissonnette R, et al. (2015). A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *New England Journal of Medicine* 373: 136-144.
3. Boyle MP, Bell SC, Konstan MW, et al. (2014). A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. *Lancet Respiratory Medicine* 2: 527-538.
4. Zink RC & Jiang X. (2016). Using contour plots to assess the sensitivity of clinical trial design assumptions. *Therapeutic Innovation & Regulatory Science* 50: 496-509.