# USING CONTOUR PLOTS TO ASSESS THE SENSITIVITY OF CLINICAL TRIAL DESIGN ASSUMPTIONS

## 2017 REGULATORY-INDUSTRY STATISTICS WORKSHOP

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# INTRODUCTION

- Power and sample size
- An extremely important topic that may not receive the attention it deserves
  - 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

# INTRODUCTION

- 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
  - Input from clinical colleagues

# INTRODUCTION

- Data visualization to summarize study design
- Introduce a sample clinical trial to
  - Motivate our discussion
  - Illustrate how contour plots can be used to
    - Better inform clinical trial design
    - Provide greater transparency for regulators
- Focus on power contour

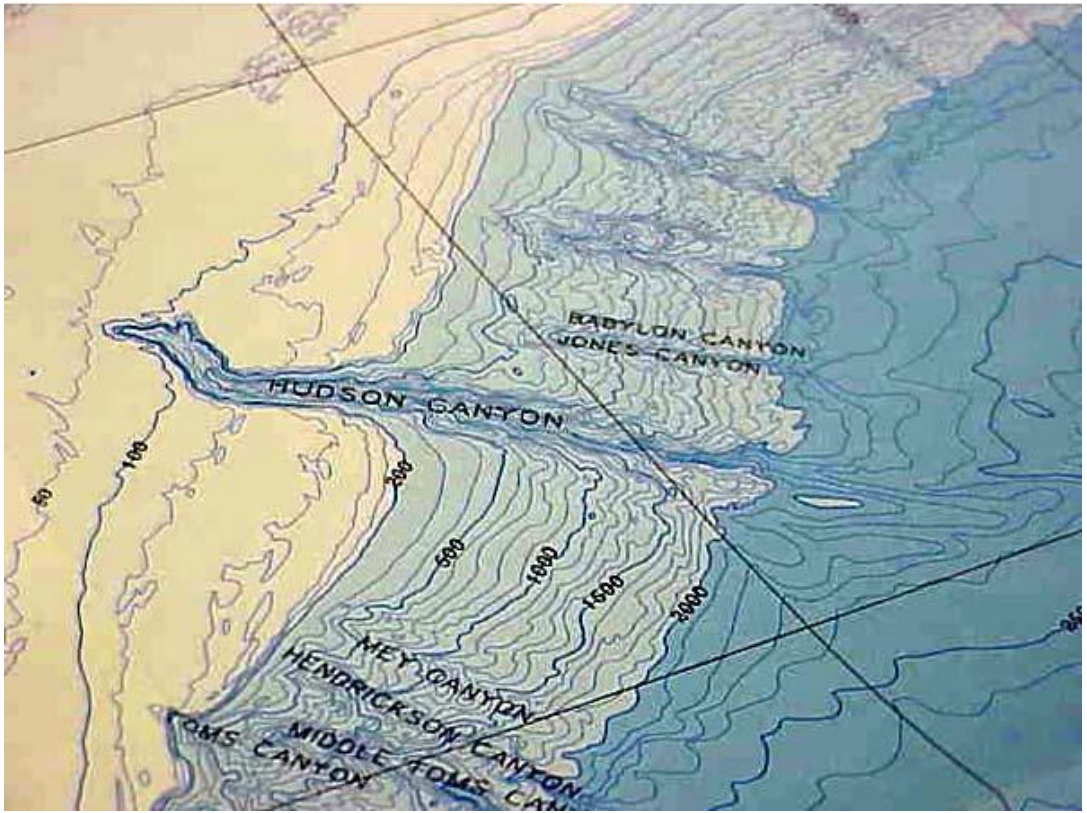
# CONTOUR PLOT

- 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
  - Weather patterns

# CONTOUR PLOTS ELEVATION CONTOUR PLOT

# CONTOUR PLOTS

# DEPTH CONTOUR PLOT



# CONTOUR PLOTS PLAQUE PSORIASIS

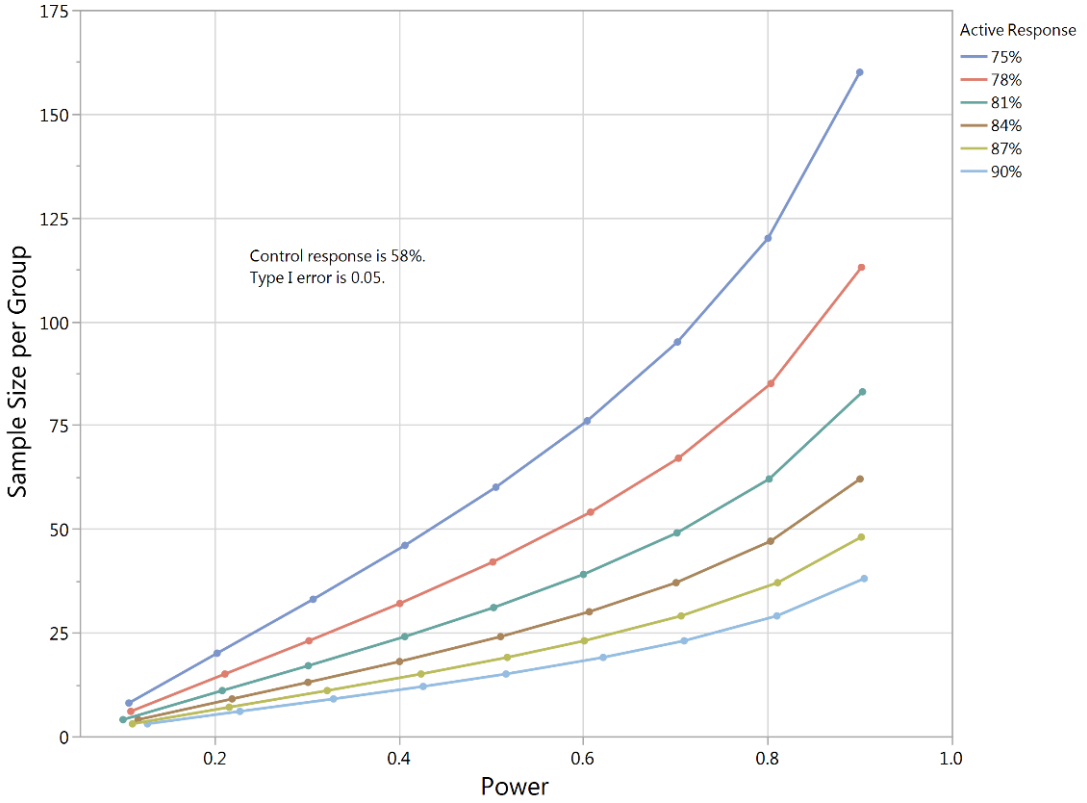
- 293 patients with moderate-to-severe plaque psoriasis [2]
- Compare multiple doses of guselkumab to adalimumab
- Results showed 36/42 (86%) guselkumab (100 mg) and 25/43 (58%) adalimumab achieved primary endpoint
- Primary endpoint: scores of 0 or 1 for physician's global assessment at Week 16
- Observed treatment difference is 28%
- 95% confidence interval is (9.9%, 46.1%)
- Assume MCID is 15%

# NEW TRIAL

- Using 86% and 58%, a two-sided Pearson chi-square test at $\alpha = 0.05$ and at least 90% power will require 52 patients per arm
- How would the power change if 86% and 58% do not reflect the unknown treatment responses?

# CONTOUR PLOTS NEW TRIAL

| Control | Active | Power |
|---|---|---|
| 58 | 73.4 | 0.378 |
| 58 | 73.5 | 0.383 |
| 58 | 73.6 | 0.387 |
| 58 | 73.7 | 0.392 |
| 58 | 73.8 | 0.396 |
| 58 | 73.9 | 0.400 |
| 58 | 74 | 0.405 |
| 58 | 74.1 | 0.409 |
| 58 | 74.2 | 0.414 |
| 58 | 74.3 | 0.418 |
| 58 | 74.4 | 0.423 |
| 58 | 74.5 | 0.427 |
| 58 | 74.6 | 0.432 |



# CONTOUR PLOTS POWER CONTOUR

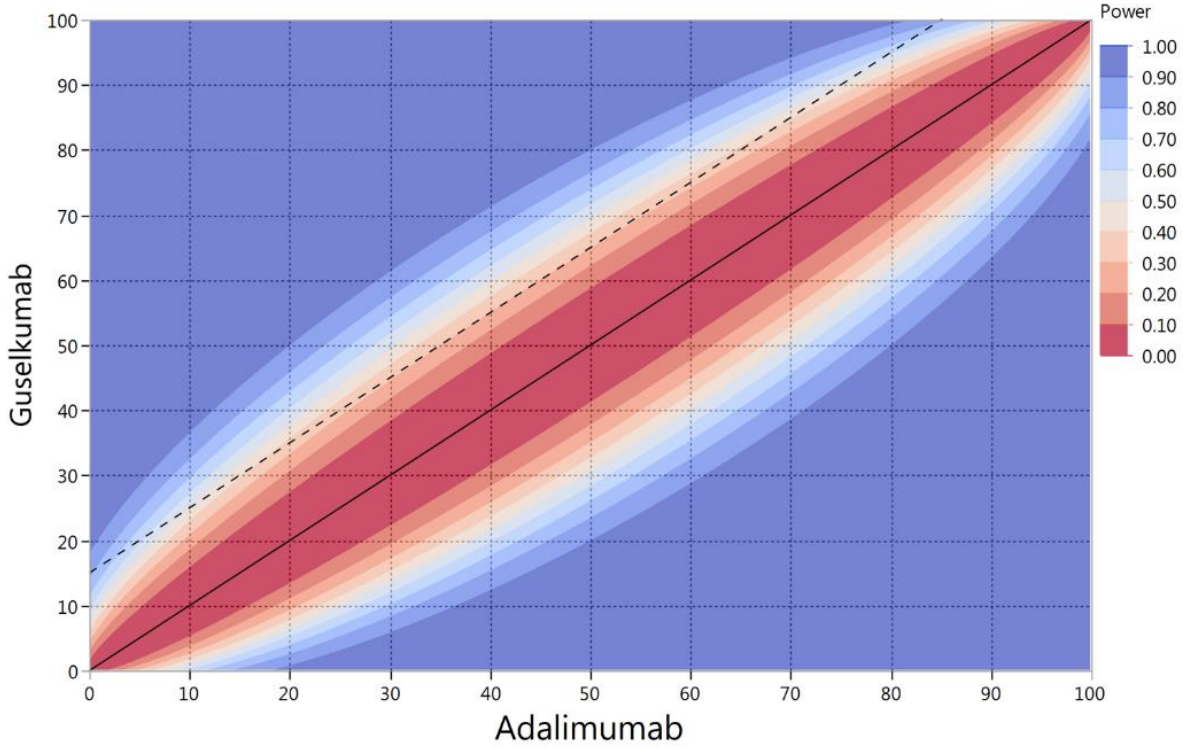



**Figure**: Power contour for all possible responses

# CONTOUR PLOTS POWER CONTOUR

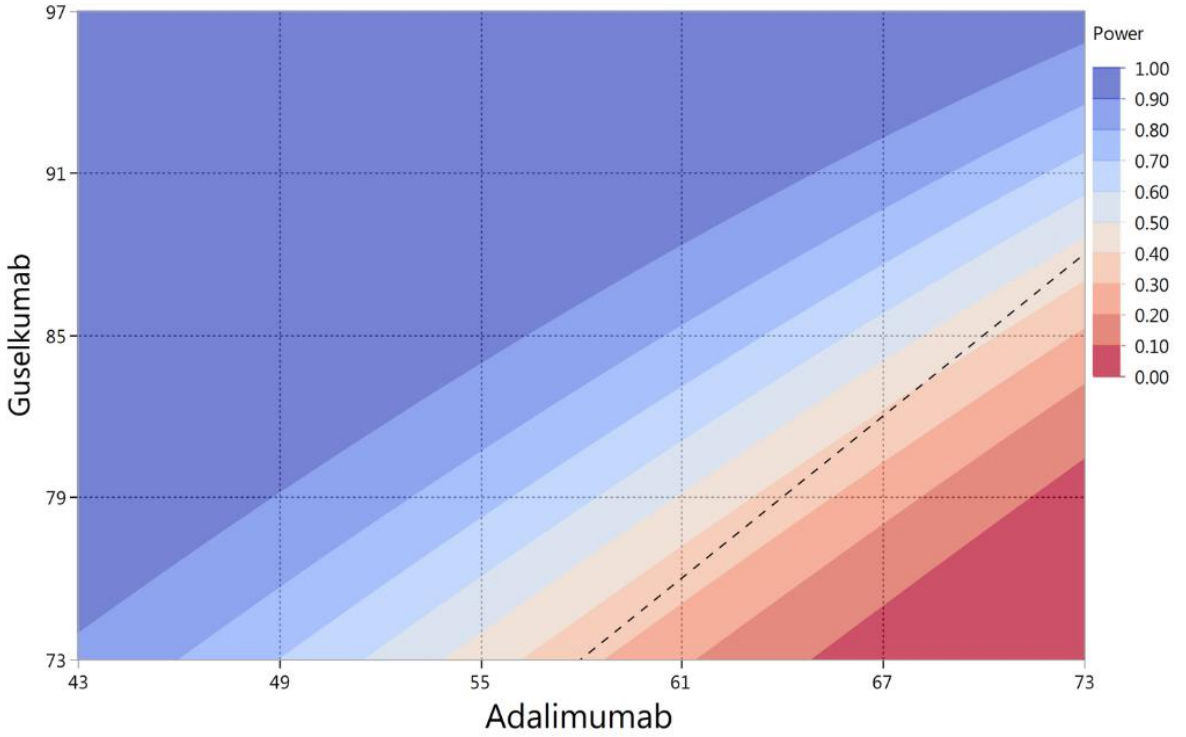



**Figure**: Zoomed power contour based on 95% confidence intervals

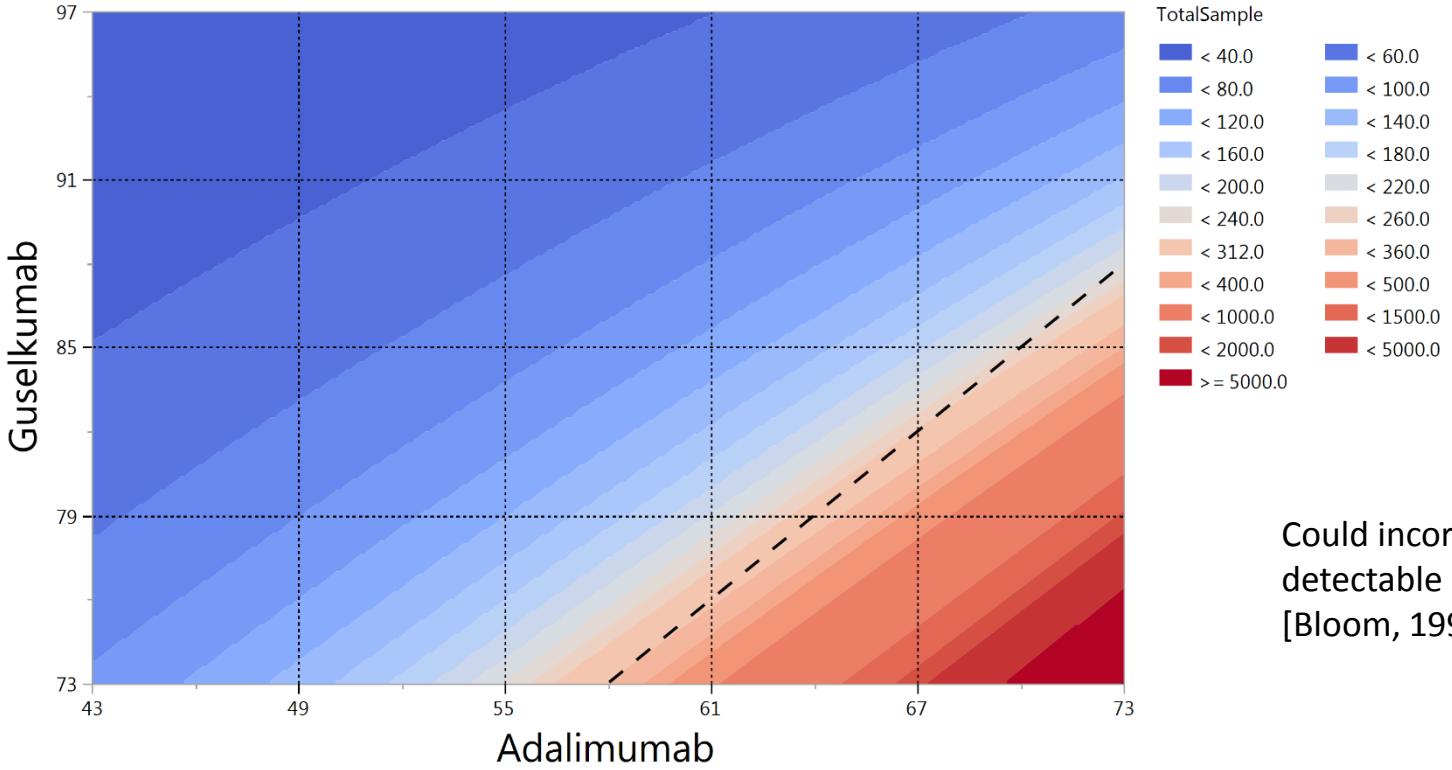
# SAMPLE SIZE

- Power contours in the examples above based upon a single calculation assuming that the observed treatment response reflected the truth.
- This approach to sample size calculations is inadequate and entirely inappropriate in practice!

# SAMPLE SIZE

- Started with power contours to illustrate
  - A “well-powered” trial is only well-powered under a very narrow range of assumptions
  - Provide sensitivity analysis for study documents based on the final selected sample size
- Invert the problem to examine sample size first

# CONTOUR PLOTS SAMPLE SIZE CONTOUR




Could incorporate minimal detectable effects [Bloom, 1995, 2005].

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

# MULTIPLE TRIALS

- Suppose we conducted trial with 104 patients
- Results show that 42/52 (81%) and 34/52 (65%) of patients met the primary endpoint for guselkumab (100mg) 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?

# MULTIPLE TRIALS

- Using meta-analysis techniques
- Estimated treatment effect and 95% confidence interval is 20.9% (8.5%, 33.3%).
- Estimated response and 95% confidence interval for adalimumab is 62.1% (52.3%, 71.9%).

# CONTOUR PLOTS SAMPLE SIZE CONTOUR

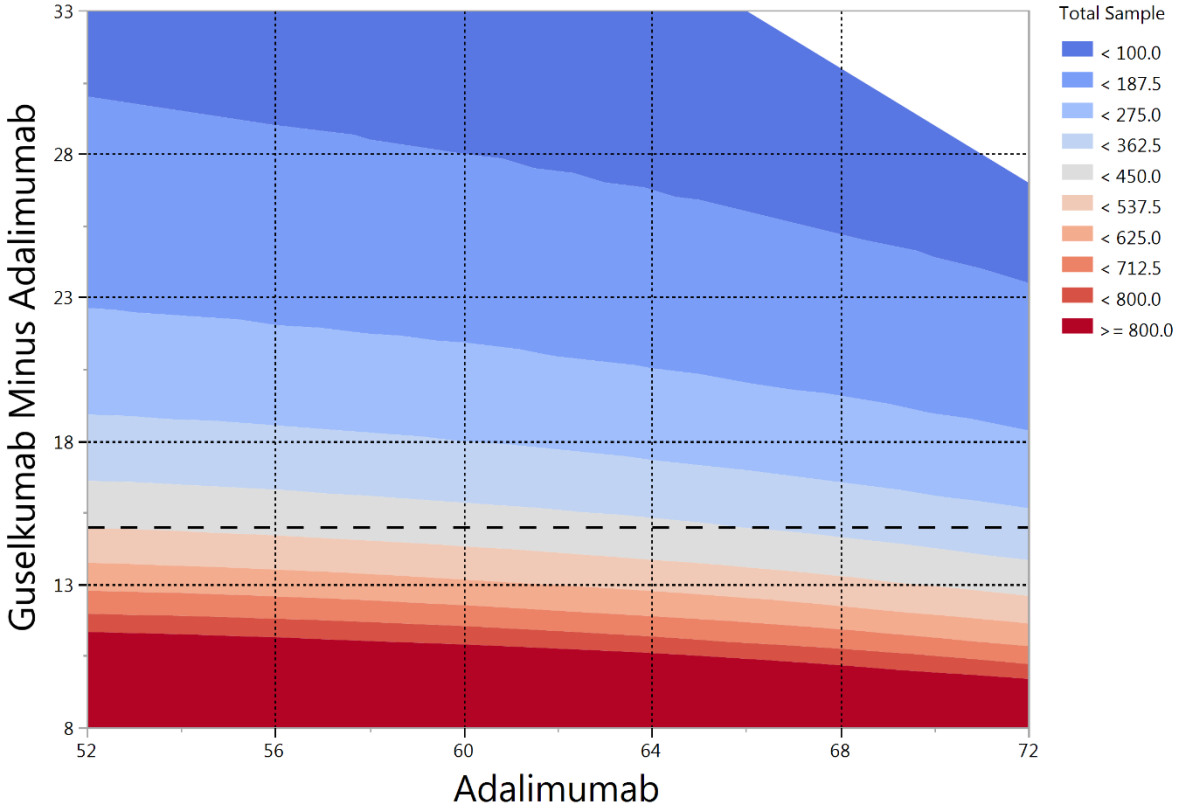



**Figure**: Sample size contour for meta-analysis

# CONTOUR PLOTS ADAPTIVE DESIGNS

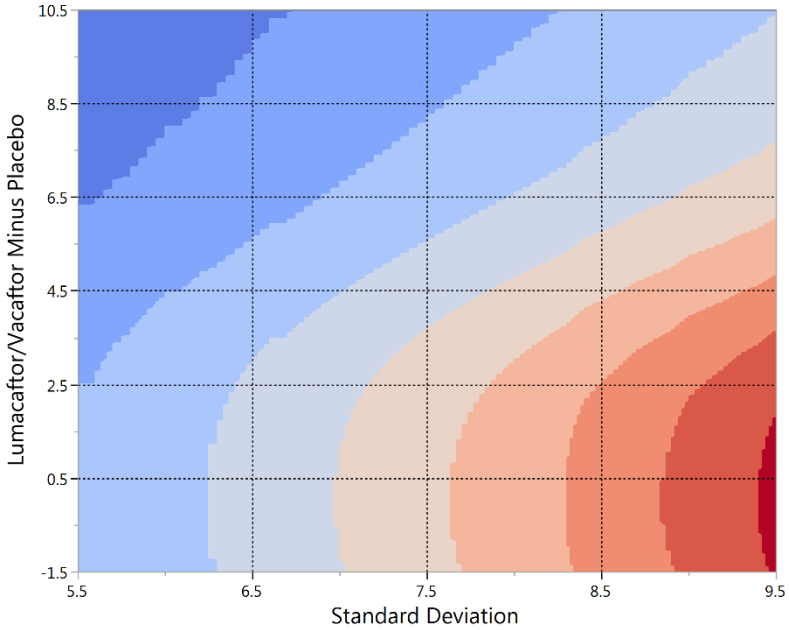



**Figure**: Sequential design with early stopping for efficacy, four stages

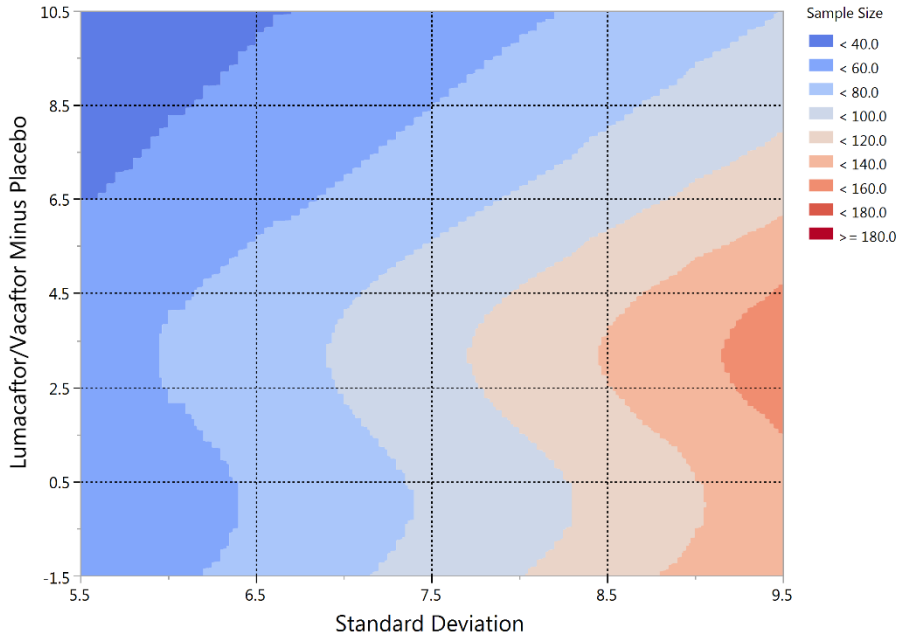



**Figure**: Sequential design with early stopping for efficacy and futility, four stages

Data from [5].

# CONTOUR PLOTS ADAPTIVE DESIGNS

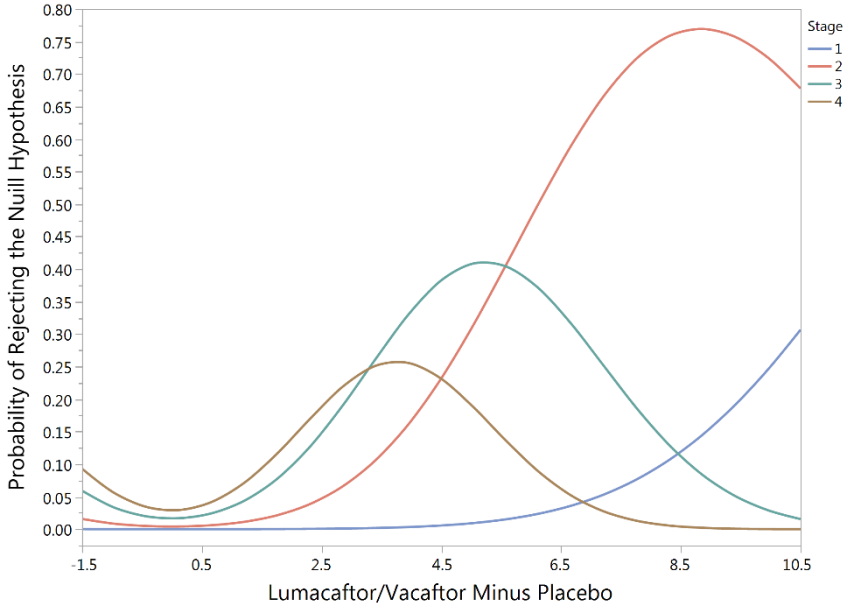



**Figure**: Stopping probability line plot (efficacy only)

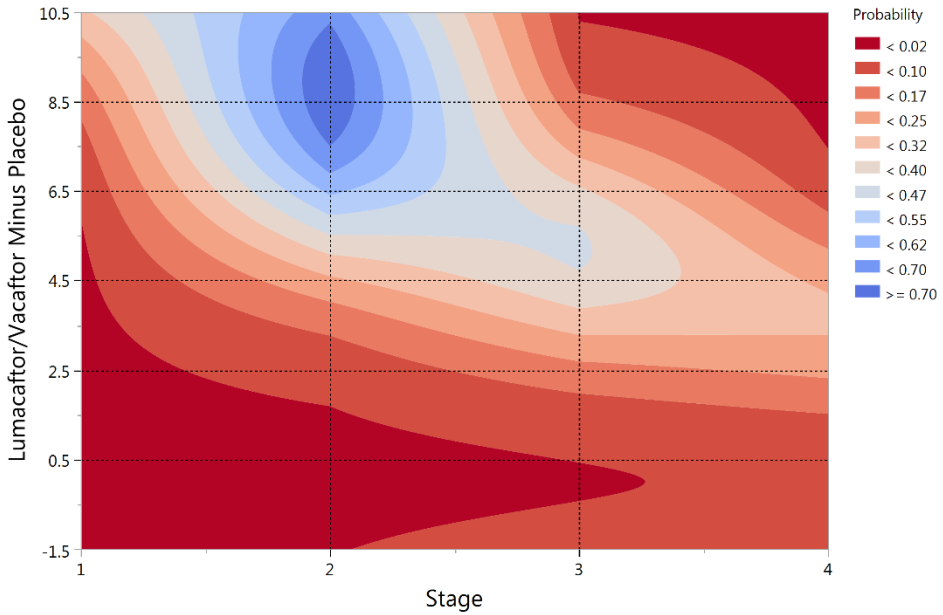



**Figure**: Stopping probability contour (efficacy only)

Data from [5].

# CONCLUSIONS

- Work is summarized in a recent *TIRS* paper [6]
- Summarizes examples for continuous, binary and time-to-event endpoints
- Explores meta-analysis and adaptive designs
- Provides sample SAS code

# CONCLUSIONS

- Our goals
  - Use data visualization to better summarize various aspects of clinical trial design
  - Improve communication with clinical colleagues
  - Provide greater transparency
- Clinical scenario evaluation

# CONCLUSIONS

- Use as much data as possible to narrow the axes
  - Placebo arm
  - Nuisance parameters (standard deviation)
- Add additional reference lines
  - To summarize results for multiple trials
- Presented cases where formulas are available
- Simulation in lower-level language for efficiency

# ACKNOWLEDGEMENTS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  - Xiaotong Jiang, UNC-Chapel Hill
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# REFERENCES


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