

Using Adaptive Designs: A Case Study and Lessons Learned

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Introduction

- We have all heard the reasons for using adaptive designs. . .
 - Save time
 - Save money
 - Approve compounds faster
- But being statisticians, we know that there are no “silver bullets” to cure all of our problems. . .
- Let’s take a realistic view of adaptive designs’ strengths and weaknesses by presenting a case study and then discussing general issues that arise in this type of study.

What is an Adaptive Design?

- Lots of different designs fall under this designation:
 - Sample size recalculation
 - Group sequential studies
 - Phase II / III
 - Treatment pruning
- We can't cover all of these types, so we've picked a case study of the treatment pruning type to use as an example to discuss challenges presented by adaptive designs.
- This case study looks at an early Phase II study, where we need to determine a dose and collect information on the outcome.

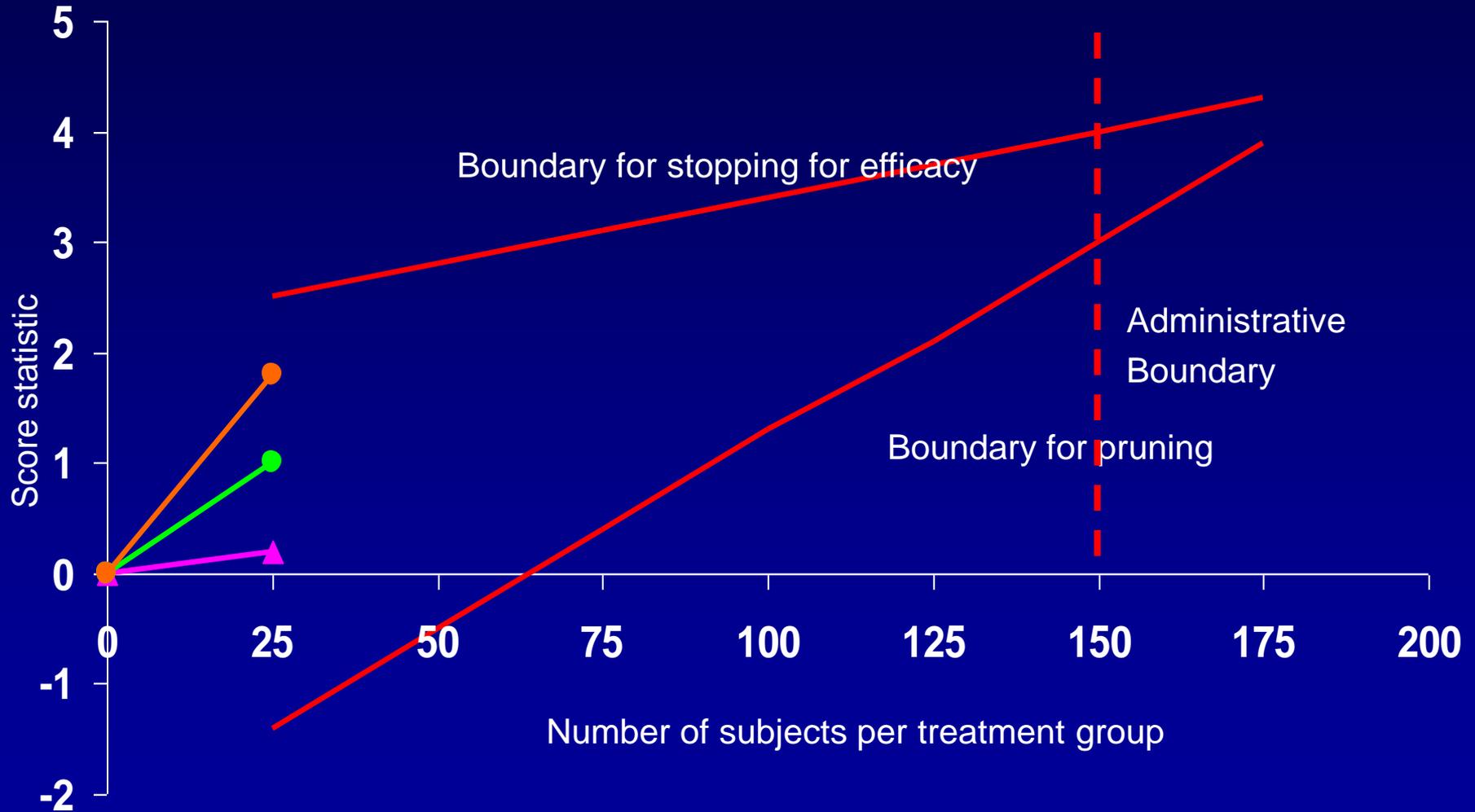
Case Study Design

- Therapeutic area: Skin infection
- Design features: Double blind, randomized, placebo controlled, multicenter, with baseline and final assessments at 2 months.
- Outcome: Percent of subjects with infection. (Log odds vs. Control)
- Safety profile (from Phase I data): Mild, but potentially unpleasant side effects (e.g., rash).
- Four dose levels to be considered: Placebo, Low, Medium, and High

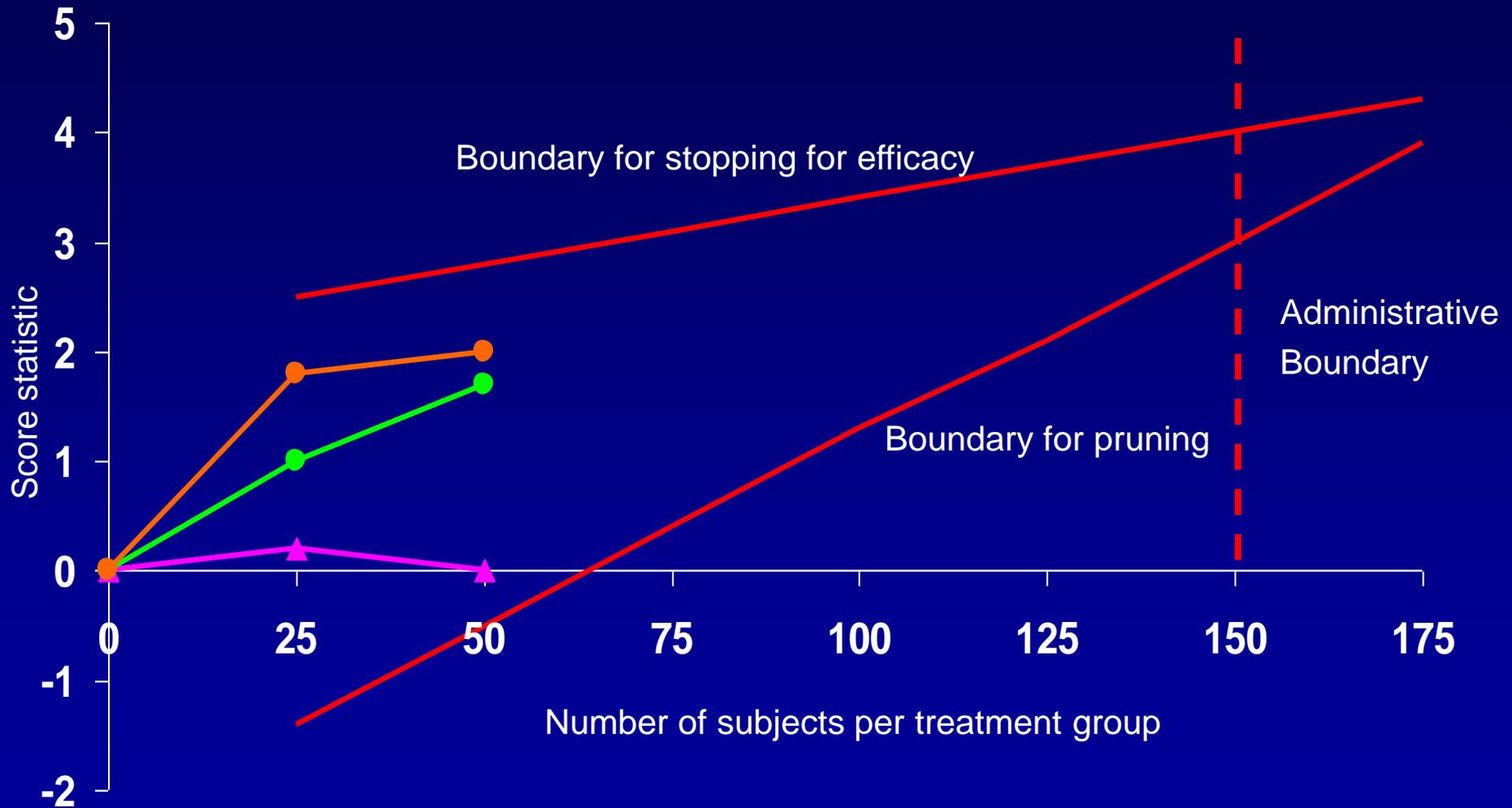
Adaptive Design

- What makes this design “adaptive” is:
 - Frequent analyses of the data (monthly, 8 total).
 - Use of a “futility” boundary to prune treatment arms.
 - Ability to stop the trial when we’ve gathered enough information to go to Phase III.
 - Ability to stop the trial and kill the compound if we’ve gathered enough information to do so.
- Other non-traditional aspects:
 - Futility boundary based on group sequential methods (Whitehead) but control of Type I error is ignored. This means that this type of study is not classified as “well controlled”.

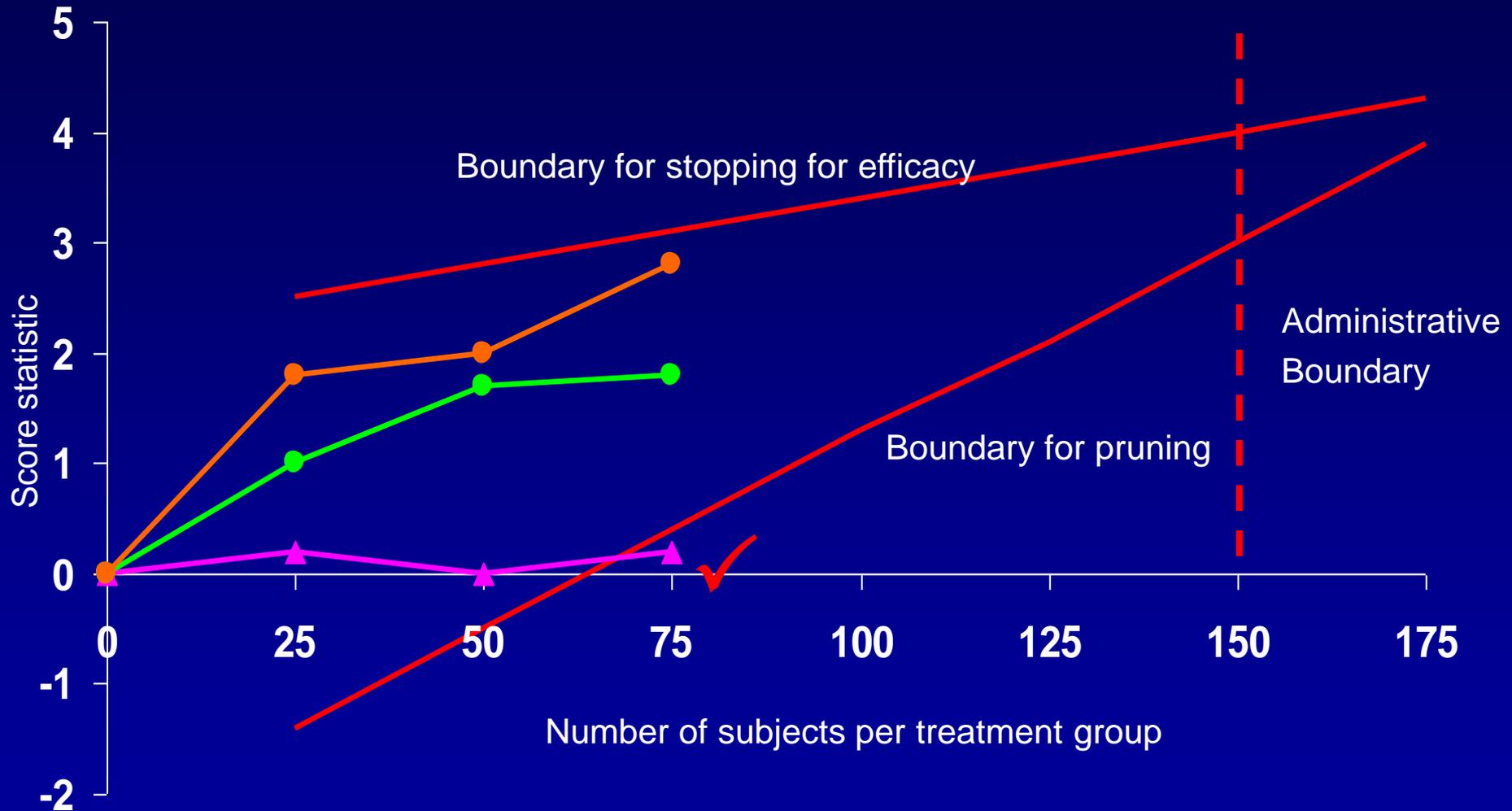
Case Study: First Interim



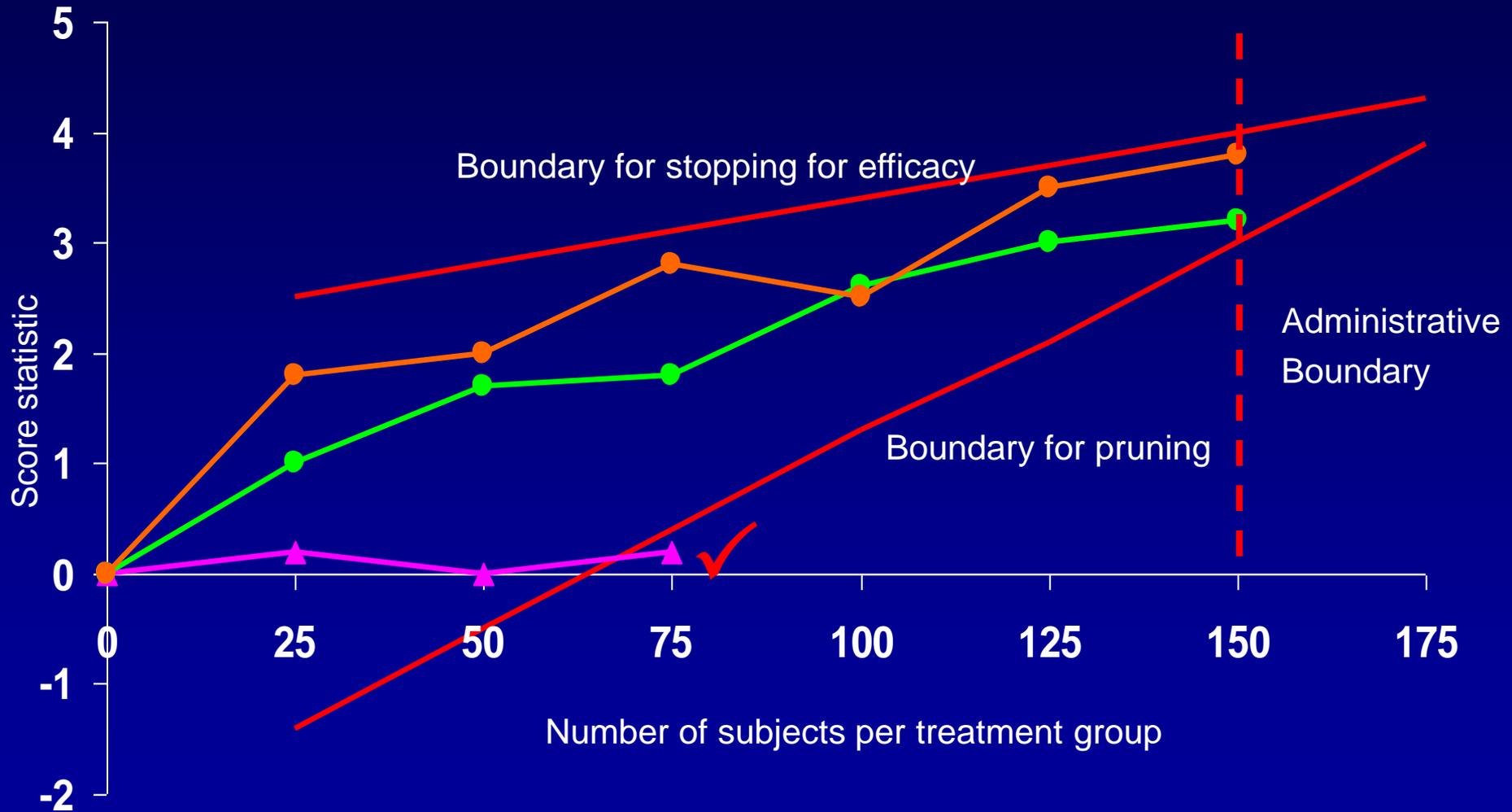
Case Study: Second Interim



Case Study: Third Interim



Example Adaptive Design: Final Analysis



Clinical Areas

What made the clinical area conducive to an adaptive design?

- A short follow-up time *relative to enrollment*
 - No benefit of stopping early if a lot more subjects have been enrolled by the time you observe your outcome.
 - Potential for surrogate endpoints, but there's a whole literature on that topic's pitfalls.
 - In our case study, we followed subjects for two months, but most infections occurred within the first two weeks.

Protocol

What changes did we need to include in the protocol?

- Set up explicit boundaries
 - These were based on group sequential design, but then altered according to probabilities of crossing the futility boundary in several clinical scenarios.
- Considered all potential outcomes
 - Explained the process for decision making, not every detail.
 - Documented statistical details and possible outcomes considered in a separate document.

Protocol

- Specified the personnel
 - Who would get to see what, when?
- Justified the alpha
 - In this case, we stated that no conclusions of efficacy would be drawn.
 - Alternatively, one could justify control of Type I error.

Project Setup

What did we do differently when setting up our adaptive design compared to classical designs?

- Informed Consent Issues
 - We should have informed subjects that some treatment arms may be dropped and their probabilities of being randomized to a treatment arm may be different than other subjects.
 - We also explained what will happen to subjects who are being treated on an arm that is pruned.

Project Setup

- FDA Approval
 - We wrote an extra memo to clarify the statistical details, potential study outcomes, and their impact on study conduct.
 - We recommend over-communication and pre-approval!
- Institutional Review Board Explanations
 - Required extra documentation to clarify the various outcomes of the study.
 - They wanted a clear outline of potential outcomes and what would happen to the study conduct in each case.

Running the Trial

What did we have to do differently in running the trial?

- Needed centralized, adaptable randomization. (IVRS)
 - When pruning arms, needed the ability to stop randomization immediately.
 - Could have hidden the pruning from the sites, ensuring an extra layer of masking. Since we didn't pre-specify the pruning in our informed consents, we needed to go back to the sites' IRBs.
- Monitoring
 - Needed fast, frequent monitoring to get the most data available for the interim analyses.

Running the Trial

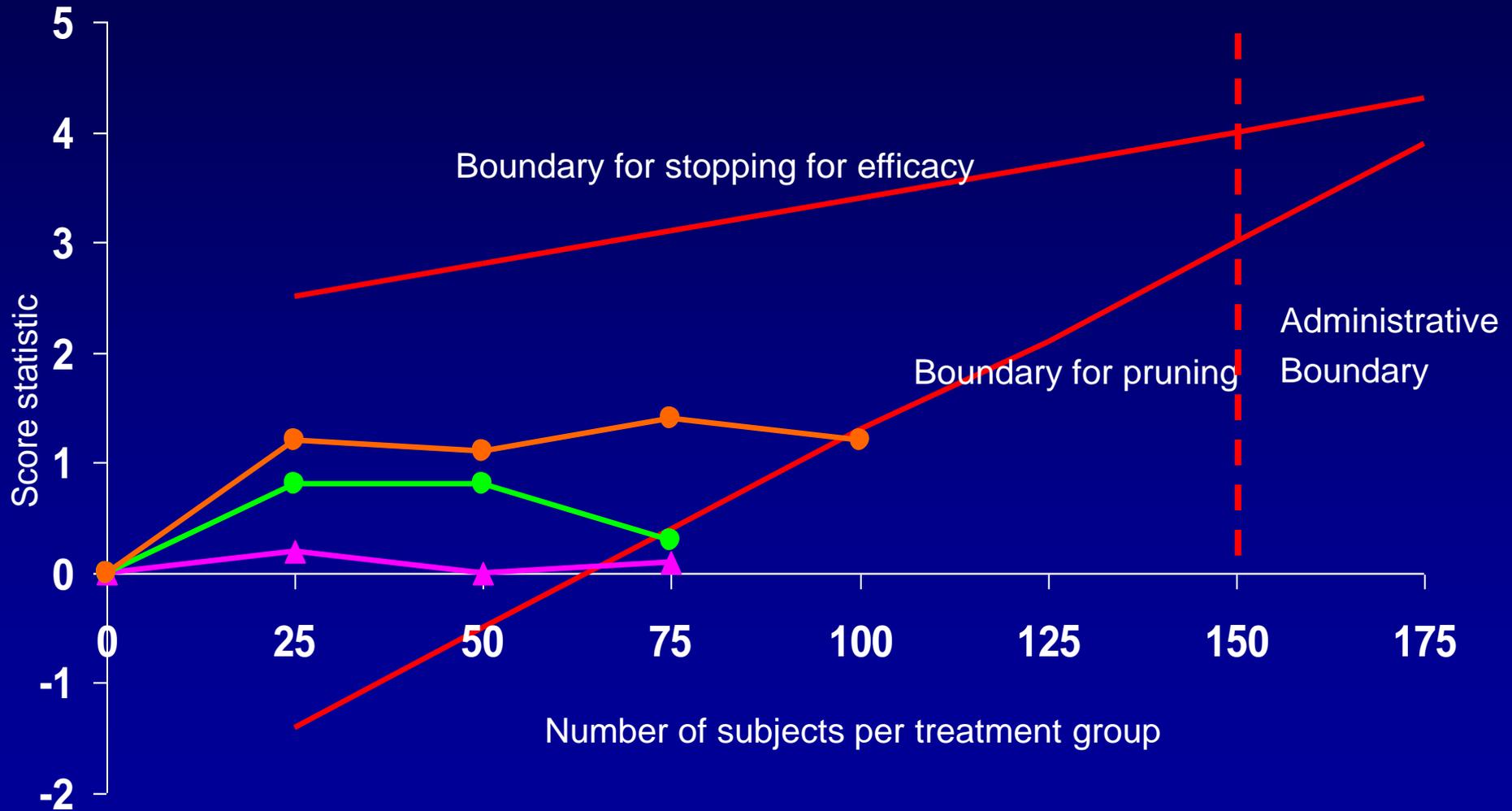
- Data Management
 - Needed fast, efficient data management in order to turn around interim analyses quickly.
 - EDC an option, although our case used traditional paper DM.
- Statistics
 - Needed pre-planned, ready-to-go analysis programs and displays to get quick interim results.
 - Strongly recommend dry runs on masked data.

Pruning Treatment Arms

How did we prune treatment arms?

- Short answer: Turned the pruned arms “off” in the randomization system.
- Statistically, decision was based on pre-specified futility boundaries.
- Ultimately, it is a clinical decision.
 - Could need more information.
 - Could be in continuation region, but safety issues.
- Let’s see what really happened. . .

Pruning Treatments



Pruning Treatment Arms: Recommendations

- Many different scenarios are possible, need to use good judgment.
 - Do not force rigid statistical rules on a potentially complex situation.
- Can continue, even if futility boundary is crossed.
- Adaptive design doesn't force you to stop, it gives you permission to stop.

Interim Analyses

Who saw the results of the interim analyses?

- For this study:
 - Lead statisticians at CRO
 - Chief Medical Officer at sponsor
- We worked to keep most people masked:
 - Site personnel—especially those determining outcomes or conducting the trial.
 - Sponsor personnel who were determining outcomes or making decisions about the conduct of subjects in the trial.
- A lot of consideration went into press releases and other communications.

The Unexpected

- We certainly didn't plan for what happened.
 - In our case study, one part of the infection definition wasn't affected by the therapy, so all treatment arms crossed the futility bound.
- We were potentially facing the worst case scenario: Compound is totally ineffective.
 - By looking at the secondary endpoints, we realized that the other part of the definition showed a big difference.
 - It may require more subjects, but adaptive designs will find this out faster.

Time to “Think”

How did we incorporate analysis and interpretation time into this faster timeline?

- Identified decision-making personnel a priori.
- Analysis trends were consistent over the course of the study.
 - By using multiple looks at the data, we saw these trends evolving and had more “what if” time.
- Planned for displays that focus on the key efficacy and safety issues.
- Performed exploratory analyses between interims based on unexpected results.

Key Statistical Challenges

What are the key statistical issues that we would consider when planning the next adaptive study?

- Boundaries
 - Efficacy AND futility—futility may be more important.
 - Specify a priori.
- Rapidity of analyses
 - Planning ahead for quick turnarounds in interim analyses.
 - Continuing exploratory analyses.
- Maintaining the mask
- Using good judgment and thinking about the results.

Conclusions

- Adaptive designs can save time and money, if appropriate to the situation.
- Need to be flexible and efficient to make them work.
- These designs are much more challenging than the classic fixed designs—need to think constantly and use good judgment.

Talk available at: www.RhoWorld.com
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