Introduction to Adaptive Designs for Clinical Operations

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Adaptive Designs: Definition

• What are adaptive designs?
  • Any multi-stage study design that uses *accumulating data* to decide how to modify aspects of the study without undermining the validity and integrity of the trial.
Adaptive Designs: An Example

• Based on an interim analysis, you decide to:
  • Stop the trial early
  • Stop a treatment arm
  • Increase sample size

KEY: Decisions about how to continue trial are based on the information gathered so far.
Why Do We Care?

- Adaptive Designs can:
  - Lead to smaller trials
  - Reduce development time
  - Allow change of direction
  - Allow us to fix bad assumptions
  - Result in more balance across treatment groups
No, Really, Why Do We Care?

• Less time in R&D → more time on patent
• Bad therapies get killed more quickly so resources can be directed to more promising areas
• Can increase sample size so trial is not a complete loss
• Makes trials more flexible when there is little info on the therapy
Classifications of Adaptive Designs

• Adaptive Designs are classified according to which decision we’re making on the accumulated data:
  • Allocation Rule: How many subjects go into which treatment arm?
  • Sampling Rule: How many subjects will we need in the next phase?
  • Stopping Rule: When do we stop the trial?
  • Decision Rule: Everything else.
Classifications of Adaptive Designs

• Of course, some designs fall into multiple categories, so we’re going to look at the usual types:
  • Adaptive Randomization
  • Sample size recalculation
  • Bayesian Dose Escalation
  • Group sequential
    • SeamlessPhase II/III
    • Pruning Designs
Adaptive Randomization

• What is it?
  • Assign treatment at randomization based on subject’s characteristics and previously randomized subjects

• Why do we use it?
  • Analysis is most powerful when even number of subjects with similar characteristics are balanced between treatment groups
What do you mean “balanced”? 

• Suppose drug works differently for men and women 
• We want an even number of subjects on Placebo and Active so we stratify the randomization 

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What’s the problem?

• If there’s more than one strata (e.g., age and sex)

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- End up with just a few subjects in each cell
Where does “adaptive” come in?

• Look at which table the subject is in
• Look at how balanced across groups it is
• Adjust probability of going to treatment or placebo
  • If more in placebo, less likely to be randomized to that arm
  • If less in placebo, more likely to be randomized to that arm
Adaptive Randomization: Name

Dropping

• Standard Randomization
  • Block
  • Stratified

• Adaptive
  • Pocock & Simon
  • Frane
  • Play-the-winner or drop-the-loser
  • Bayesian
Adaptive Randomization: Rho’s Expertise & Experience

- The part of Rho RAND that assigns treatment arms is modular and so we can plug in whatever we want (and the statisticians love new toys)
- We’ve put up 8+ of these in RhoRAND
- Done some methodologic research in this area (MS papers)
Adaptive Randomization: Points to Remember

- Most useful in Phase II when lots of influences (e.g., severity, age) and small sample sizes
- Some hesitancy to use it in Phase III as the FDA likes Phase III to be as straightforward as possible
Adaptive Randomization: Monitoring

• Short answer: It doesn’t.

• Centralized system means:
  • Can get reports of dosing if you need to check pharmacy records.
  • Can get unblinded reports if study requires it.
  • Reconciliation between RhoRAND and CDM can be performed.
Sample Size Recalculation

- Sample size calculations are based on assumptions
- When assumptions are wrong, sample size is wrong
- Leads to “close but no cigar” studies
Types of Recalculations

• Blinded vs. unblinded
  • Blinded: only check some of your assumptions
  • Unblinded: look at the treatment difference

• Paying the price
  • This always leads to needing more subjects than if we planned from the beginning
Sample Size Recalculations: Rho’s Expertise & Experience

• Blinded
• Unblinded
• Hypothetical
Sample Size Recalculations: Points to Remember

• These are almost always unplanned!
  • This is not an optimal design
  • Think “rescue”

• Usually requires **some** form of interim analysis

• Doesn’t affect monitoring except that we may be adding more subjects
Bayesian

- Philosophy: Use what you’ve learned in previous studies to direct your analyses in future studies
- Methodology: Weight results according to previous results
- Problem: Not enough structure and rules for the Pharma industry & FDA
- Only a couple of well-advertised cases of fully Bayesian designs (like an urban legend)
Bayesian Dose Escalation

• One area where Bayesian is used extensively is in dose escalation studies (esp. oncology)
• Same as a standard 3 + 3 dose escalation study, except calculate probability of toxicity (and efficacy) after each cohort instead of basing on the number of toxicities
Bayesian: Rho’s Experience

• Designed three of these studies, currently implementing two
• Only doing the statistics, in conjunction with a Phase I shop
• Expect expansion of this methodology outside of oncology
  • The benefits are big and the study logistics don’t change
Bayesian Dose Escalation: Points to Remember

- Primarily Phase I work
- Logistics are the same, so monitoring is the same as typical Phase I
Group Sequential

• Also known as “Interim Analyses”
• At prespecified times, we take all the data we’ve gathered and run the primary analysis.
• The results are then compared to boundaries to determine whether the trial can stop early
  • Efficacy
  • Futility
Example of a Group Sequential Study

Boundary for stopping for efficacy

Boundary for pruning

Number of subjects per treatment group

Score statistic
Group Sequential: Types

• Group sequential designs have been around for awhile, but not used a lot in Pharma
• Some adaptations of these are the hot new designs in “adaptive designs”
  • Seamless Phase II/III
  • Dose Finding
Phase II/III

• Aka “Adaptive Seamless Design”
• Two-stage (sometimes more) design
  • First stage has multiple doses
  • Perform an interim analysis and select the “best” dose (or best couple of doses)
  • Second stage compares only Placebo and doses selected at interim
• Final analysis uses data from both stages
Phase II/III: Example

Example NonStop Phase II-III Study

Treatment Arm

Months 'til Prune  Phase III
Dose Pruning

• Start with multiple doses to be tested
• Instead of two phases, a dose pruning design has a bunch of interim analyses and at each one, each dose is evaluated and possibly eliminated
  • Can eliminate for futility or safety or whatever
• Does not necessarily control for Type I error
GS vs. Ph II/III vs. Pruning

When do we use these designs?

• Group Sequential is generally for big studies with only two arms that you think are going to stop early for efficacy

• Seamless Phase II/III are best with a well-known class of drugs to pick a dose and get on with the Phase III quickly (“me, too” drugs)

• Pruning are good for early Phase II to pick a dose, but realizing that there’s a lot we don’t know about the compound
Group Sequential: Logistics

• **Endpoint**
  • Time to endpoint can’t be too slow, relative to enrollment rate
  • Unless there’s some good biomarkers
  • How well is it understood?

• **Recruitment**
  • Recruitment rate can’t be too fast relative to endpoint—need time to stop and look at the data

• **Position of study in development process**
  • Early is better than late

• **Who gets to see what, when?**
Group Sequential: Logistics

• Centralized Randomization
  • Either need only a few sites or centralized randomization for adaptive randomization, group sequential, or pruning designs

• Data Capture
  • Need quick capture (either EDC or paper)
  • Rho has done one on paper successfully

• Study Drug
  • Availability and cost

• Regulatory
  • Talk to the FDA early & often
Group Sequential: Logistics

• Monitoring
  • Need quick turnaround
  • Need constant monitoring
  • Need monitors to be completely on top of everything that’s going on with the site and when to go out there
  • Not easy
Group Sequential: Rho’s Experience

• Done Group Sequential Designs
  • No Phase II/III
  • No P-value Combination
  • One Pruning
Group Sequential: Points to Remember

• Need early planning
  • Buy in from all levels and depts: Clinical, Statistics, DM, PM,
  • Need to think about who’s seeing what

• Need fast, efficient teams

• Need *Lots* more statistics time and difficult DM & monitoring timelines

• Can save time not just on study, but between study—that’s the big savings
Group Sequential: Points to Remember

• Excellent for handling the unexpected
  • No client thinks their drug is going to misbehave, but it happens more often than not
• Counterintuitively, can provide more “thinking time” if observing trends over time
• Moves fast, everybody’s got to keep up
Adaptive Designs: Points to Remember

• New definitions are broad
  • Clients generally think of the Group Sequential type of designs
• Not all of these designs are “cutting edge”
  • E.g. adaptive randomization has been around for awhile
  • Artificially inflates “number of studies done”
  • Get client to ask competition how many of specific type
Adaptive Designs: Points to Remember

• There’s a lot more than fancy statistics to make these happen
  • Main thing is devoted, flexible leadership
  • And really organized, experienced people running the trial
• The adaptive designs are only useful in a few situations
  • Depends on the outcome
  • Depends on the development plan
• But, when they work, they can save lots of time and money
Adaptive Designs: References

• References
  • Group Seq: Jennison and Turnbull (“the green book with the sheep”)
  • Adaptive Rand: Rosenberger and Lachin Randomization in Clinical Trials
  • Our website: All the presentations we’ve done on the topic (heavy on pruning design)
    • Warning about “NonStop”