

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

	Pbo	Trt
M	50%	50%
W	50%	50%

What's the problem?

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

	Pbo	Trt
M	50%	50%
W	50%	50%

< 65 years

	Pbo	Trt
M	50%	50%
W	50%	50%

≥ 65 years

– 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

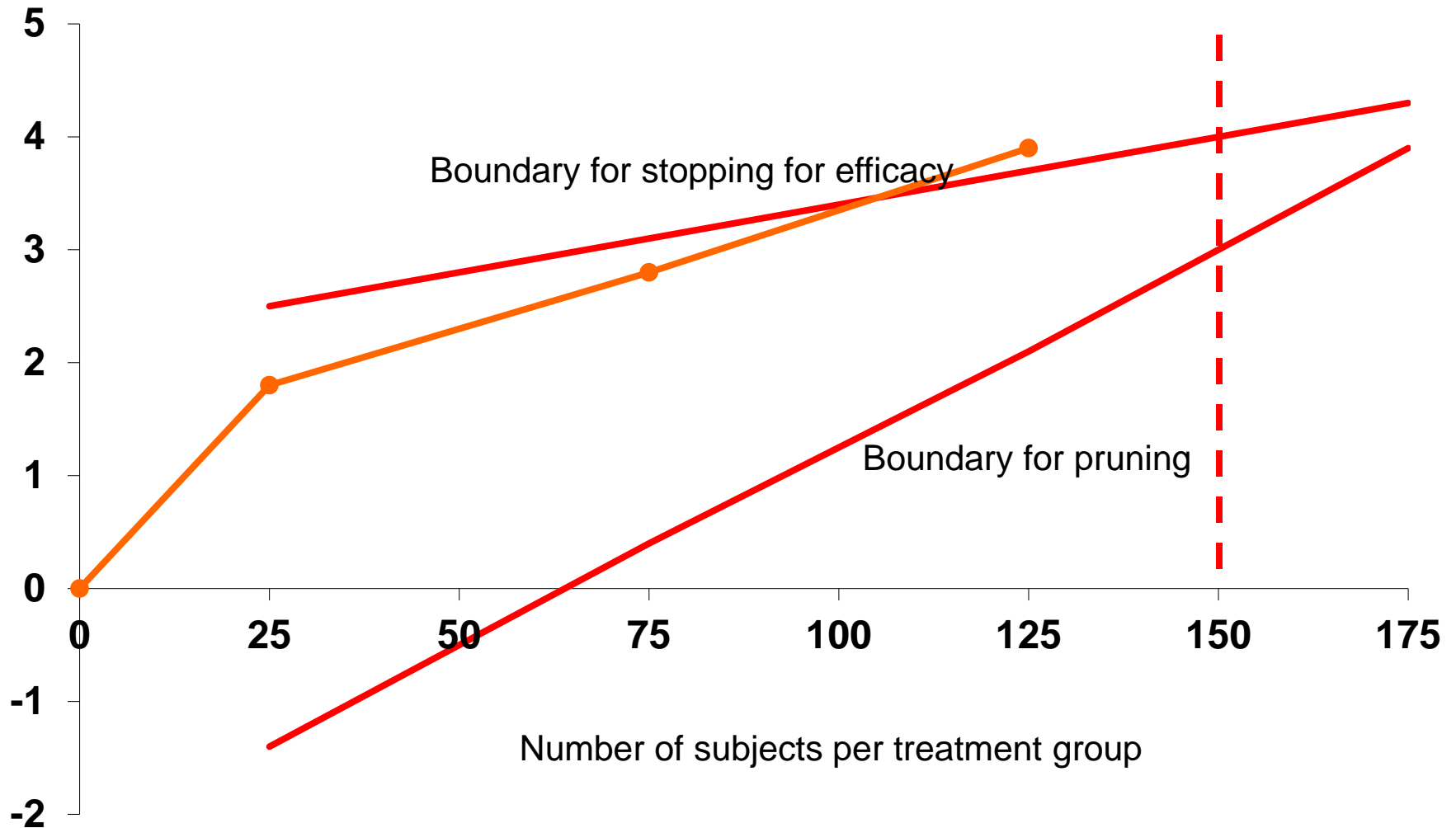
Bayesian Dose Escalation: Points to Remember

- 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



Group Sequential: Types

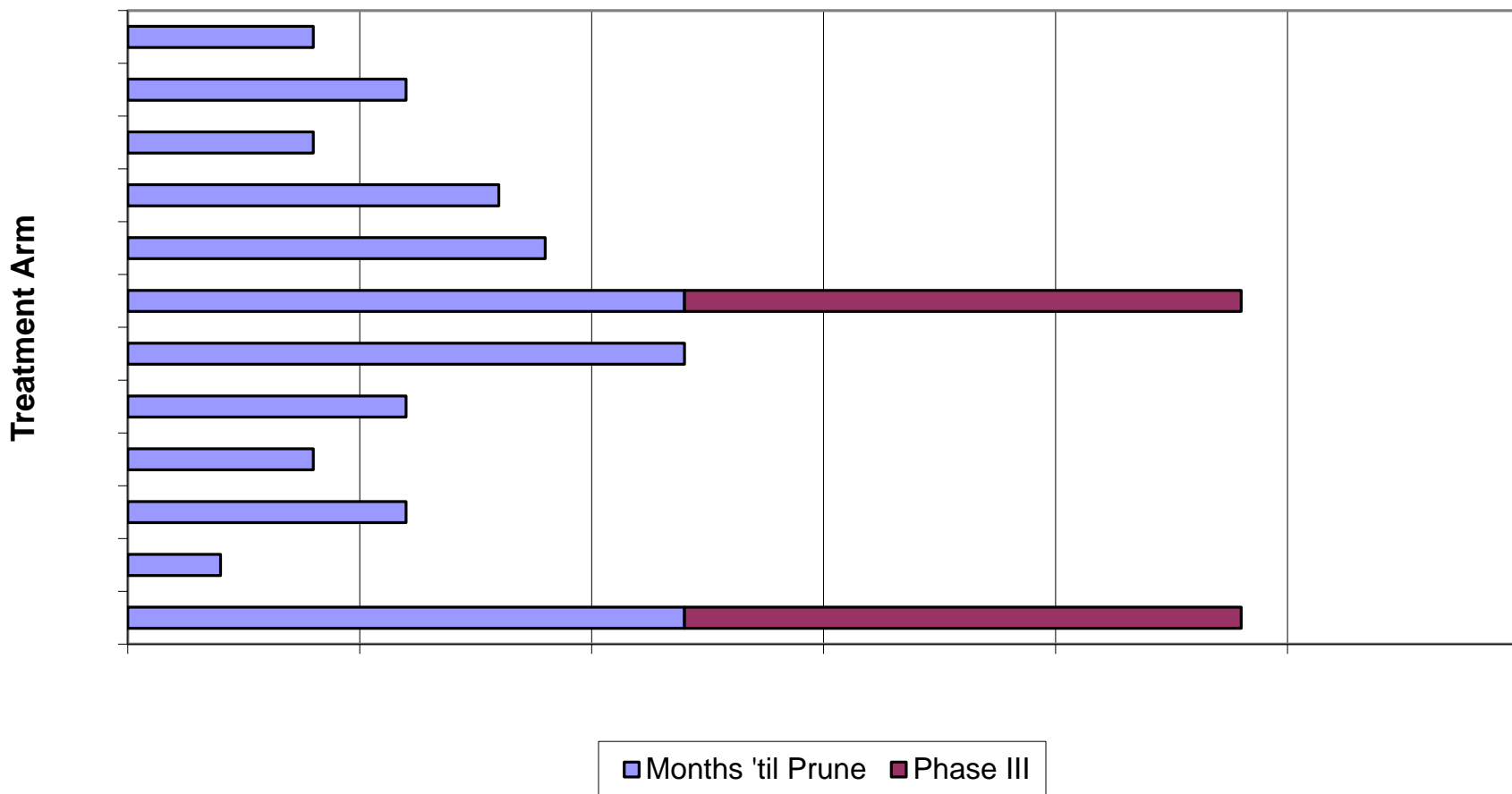
- Group sequential designs have been around for awhile, but not used a lot in Pharma
- Some adaptations of these are the hot new designs in “adaptive designs”
 - Seamless Phase II/III
 - Dose Finding

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

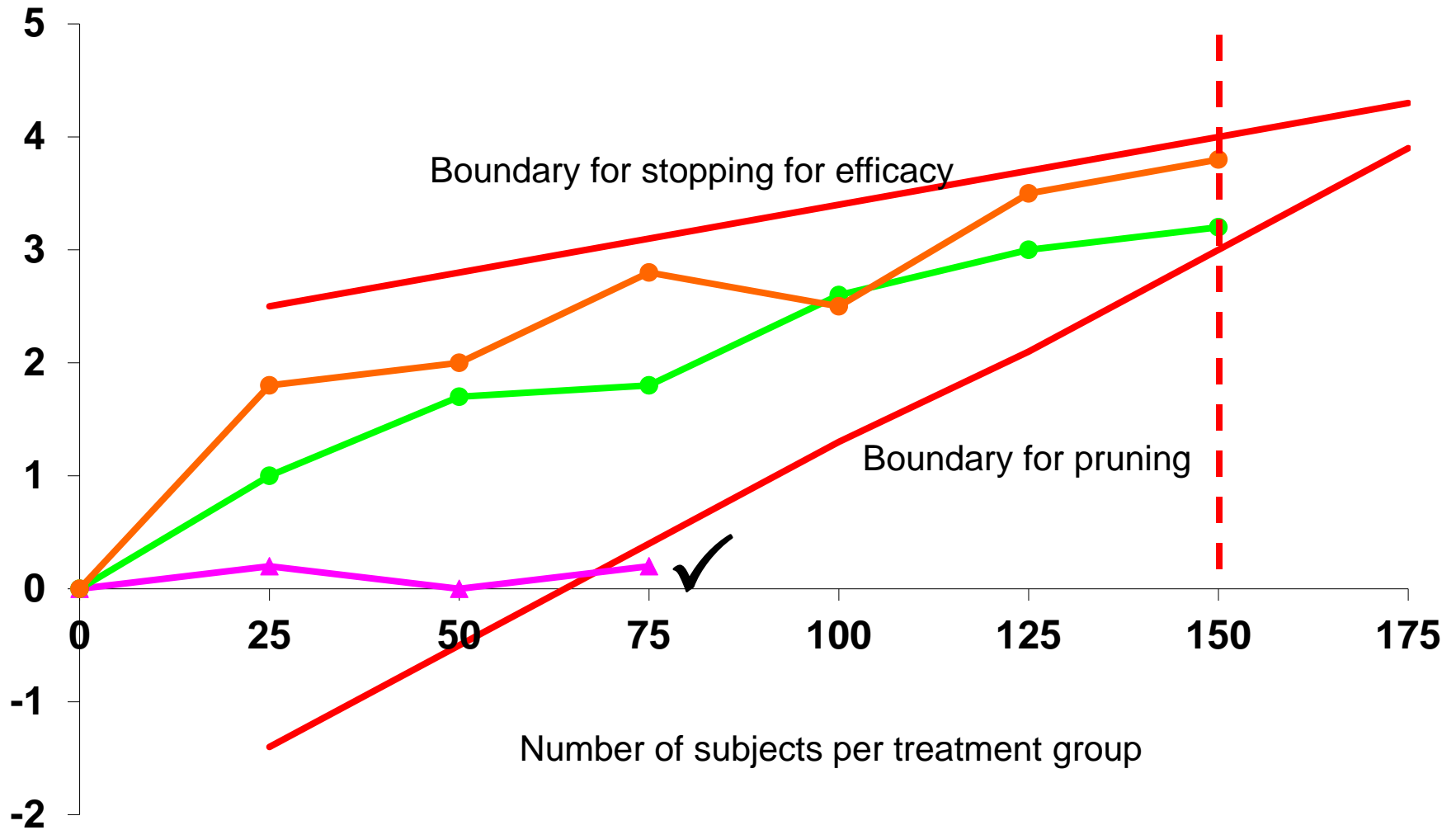
Example NonStop Phase II-III Study



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

Dose Pruning: Example



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

- Pharma White Paper: DIJ Vol. 40 (NOV2006)
- 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”