Layers of an onion: Considerations for a confirmatory, adaptive CNS trial

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Lilly

Setup

Confirmatory Trial

- 2 doses of experimental treatment (E1, E2)
- Placebo control (PL)
- 2:1:1 allocation

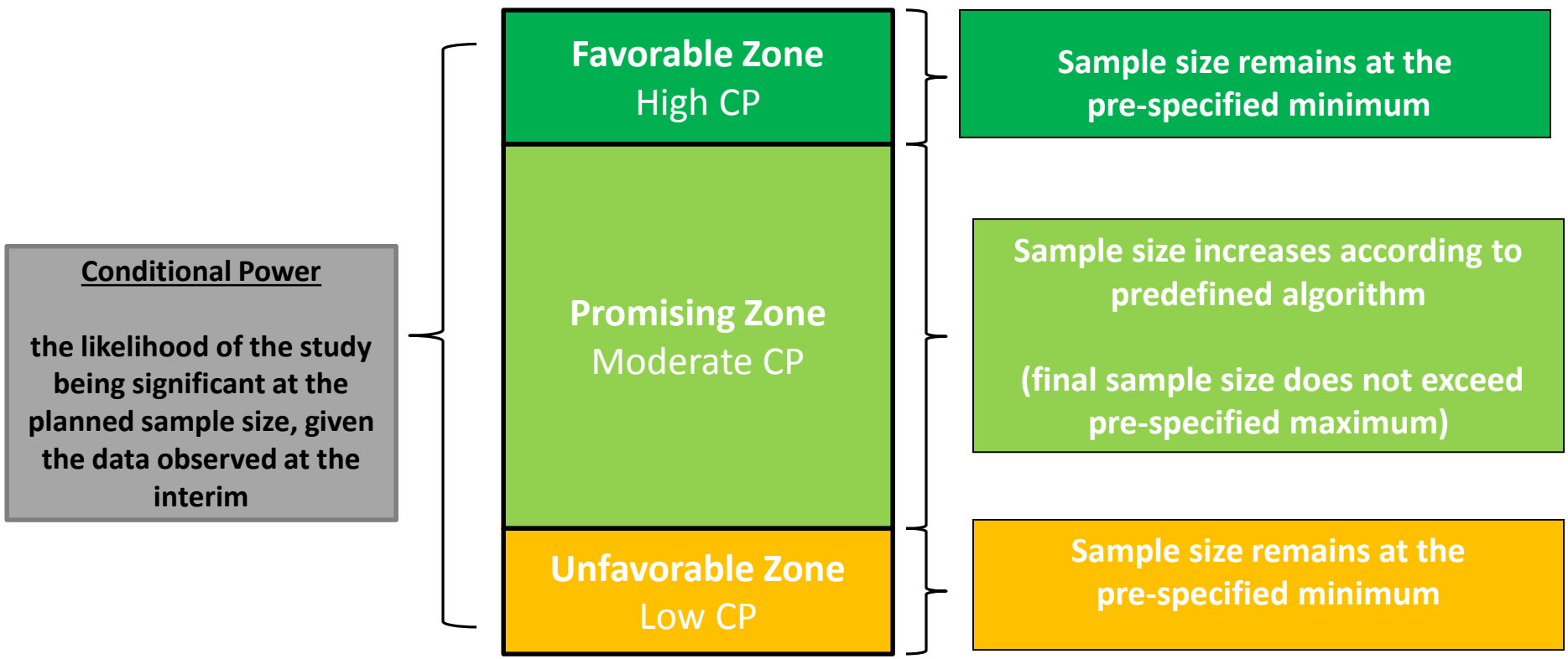
- Uncertainty:
  - Dose
  - Sample size assumptions (effect size)

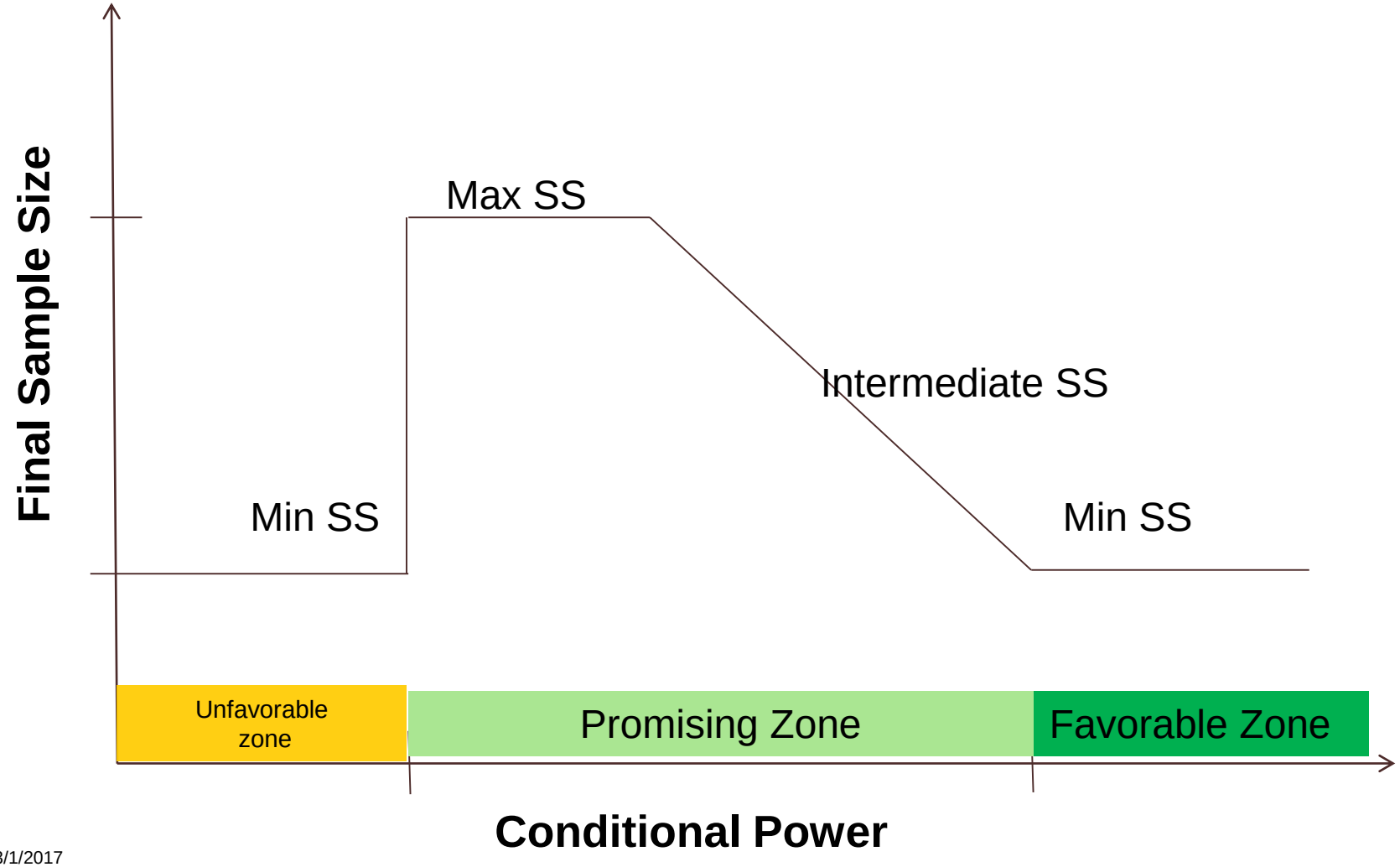
- Primary + Key Secondary Endpoints

Sample Size Adaptation Basics

- Set a min planned ss and a max planned ss
- Conduct interim analysis prior to min ss
- Using that data, decide…
  - Do we stick with current min ss or increase?
  - If increase, how much? (based on a target conditional power)

Interim Analysis Decision Rules




Final Sample Size
Max SS
Intermediate SS
Min SS
Min SS
Unfavorable zone
Promising Zone
Favorable Zone
Conditional Power

2 doses vs control

		Dose Arm E2		
		Unfavorable	**Promising**	**Favorable**
Dose Arm E1	**Unfavorable**	Maintain SS		
	Promising		Increase SS	
	Favorable			Maintain SS

- Decision regarding whether to maintain or increase sample size is obvious for these cases.
- Exactly how to increase ss is less obvious…

2 doses vs control

		Dose Arm E2		
		Unfavorable	**Promising**	**Favorable**
Dose Arm E1	**Unfavorable**			Maintain SS
	Promising			
	Favorable	Maintain SS		

- Decision for these cases is fairly obvious too
- Since maintaining ss, there is no re-estimation to do

2 doses vs control

		Dose Arm E2		
		Unfavorable	**Promising**	**Favorable**
Dose Arm E1	**Unfavorable**		Increase SS	
	Promising	Increase SS		Increase SS?
	Favorable		Increase SS?	

- In each of these cases, exactly one arm is promising, suggesting a sample size increase.
  - When one arm is favorable?
- How to increase sample size is complicated
  - Impact on allocation ratio

2 doses vs control

Summary of Decision Rules:

		Dose Arm E2		
		Unfavorable	**Promising**	**Favorable**
Dose Arm E1	**Unfavorable**	Maintain SS	Increase SS	Maintain S
	Promising	Increase SS	Increase SS	Increase SS?
	Favorable	Maintain SS	Increase SS?	Maintain SS

Now, let's look at how (or how much) the sample size is increased…

Sample Size increases

Full flexibility in ss increases?

- Does not maintain treatment allocation ratio
  - Informed consent
  - PL response
  - Operational (IWR build, packaging/shipping drug, etc)
  - Power for “many-to-one” tests (dunnett)

Impose reasonable constraints on ss adaptations

- Increase ss per original allocation ratio
- Two possibilities: Max-SS or Min-SS approach

Sample Size Increases (2)

Min-SS approach:

- Increases sample size based on the ‘best’ dose
  - If best dose is in favorable zone, no increase
  - If best dose is promising, that drives the sample size increase calculation

Max-SS approach:

- Increase sample size to the maximum ss dictated by the two ss computations
  - Sample size increases anytime at least one dose is in promising zone

Next layer…

- Possible dose actions based on interim data
  - Futility assessment for each dose
  - Discontinuing a dose arm for other reasons

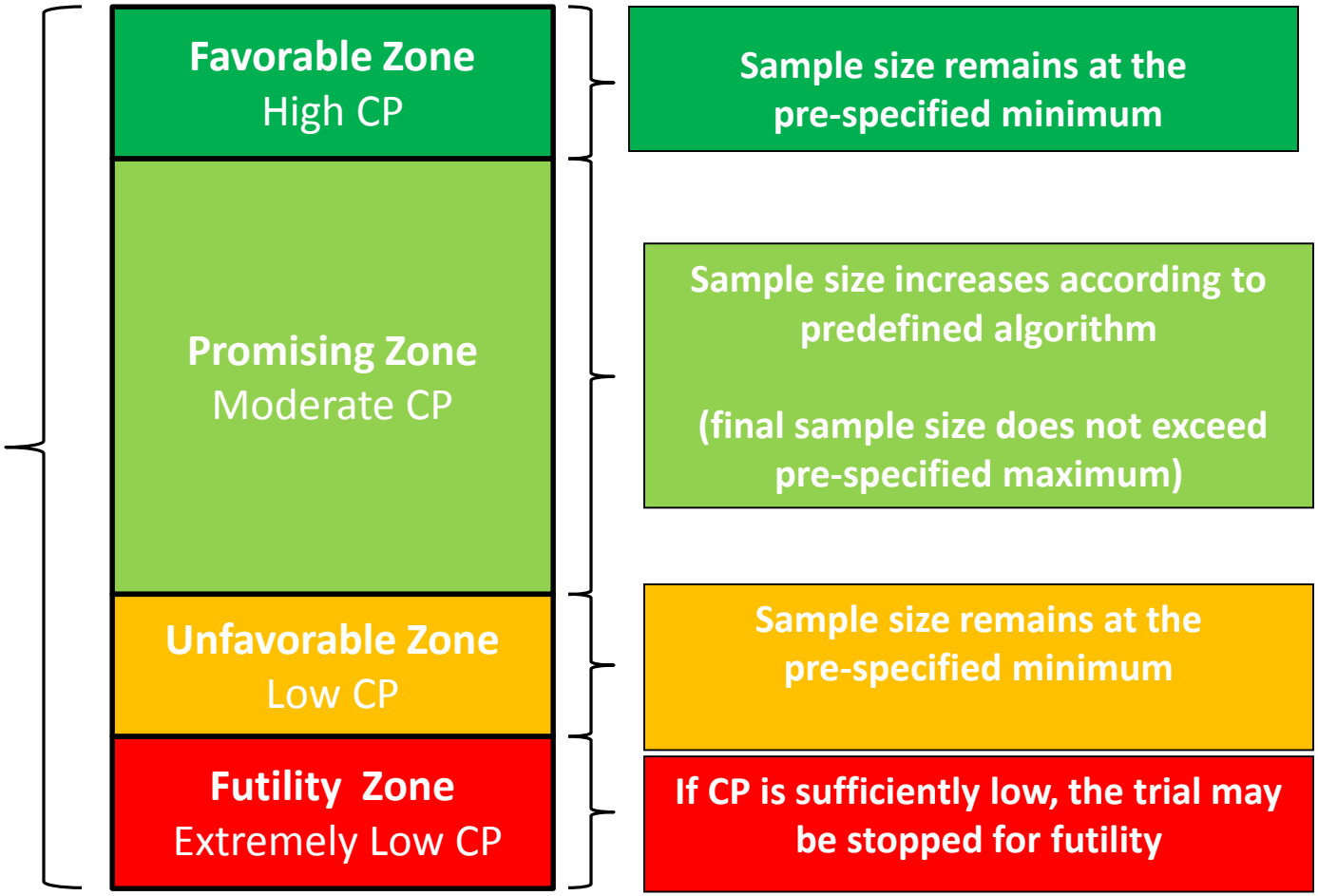
- Very Possible! Very Reasonable! Just another layer of complexity in decision making and the background mathematics

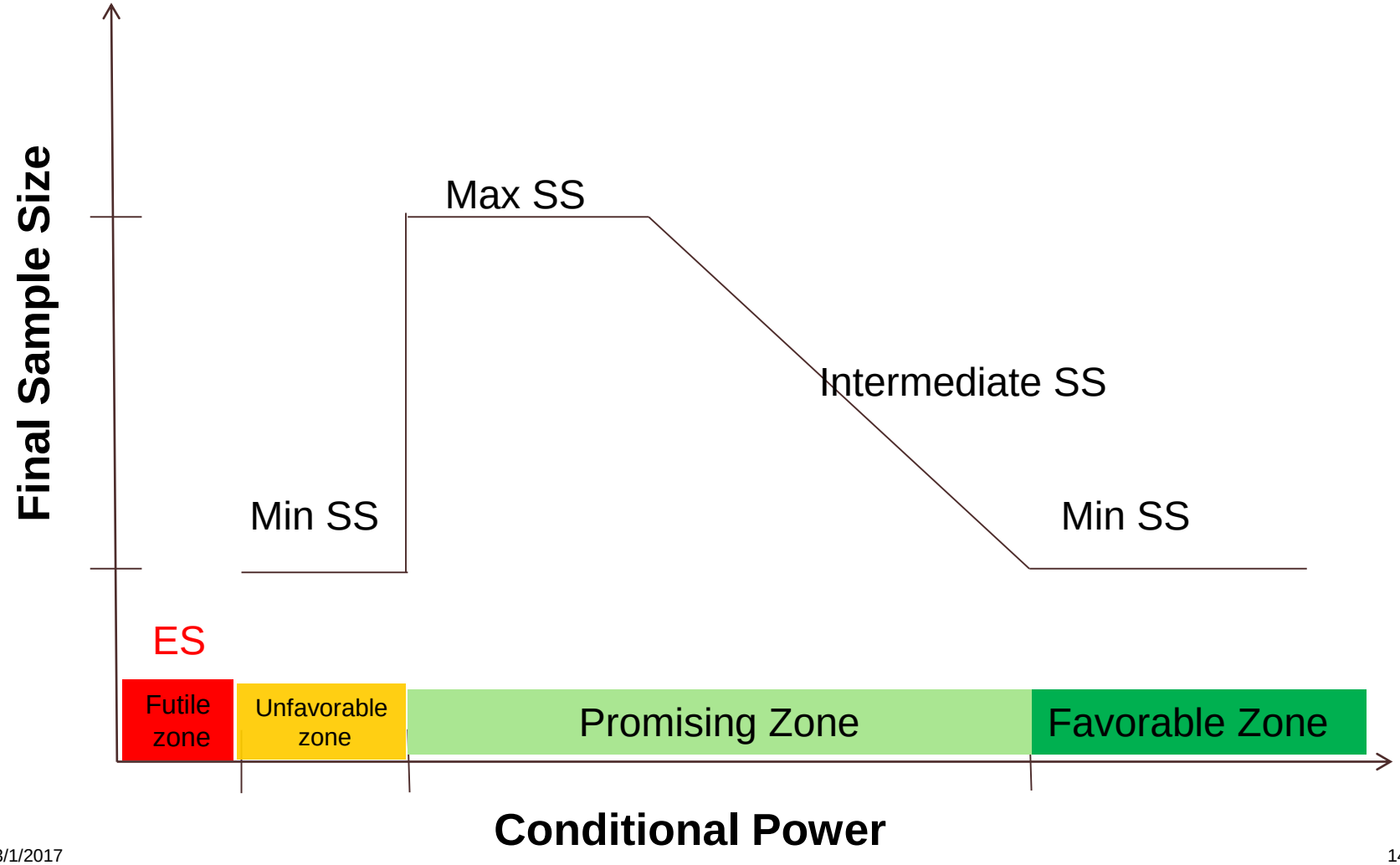
- Let's add futility assessment…

Interim Analysis Decision Rules

Conditional Power

the likelihood of the study being significant at the planned sample size, given the data observed at the interim




Final Sample Size
Max SS
Intermediate SS
Min SS
Min SS
ES
Futile zone
Unfavorable zone
Promising Zone
Favorable Zone
Conditional Power

Summary of Decision Rules:

		Dose Arm 2 (E2)			
		Futile	**Unfavorable**	**Promising**	**Favorable**
Dose Arm 1(E1)	**Futile**	Discontinue Trial for Futility	Discontinue E1		
			Maintain SS*	Increase SS*	Maintain SS*
	Unfavorable	Discontinue E2	Maintain SS*	Maintain SS	Increase SS	Maintain SS
	Promising		Increase SS*	Increase SS	Increase SS	Increase SS?
	Favorable		Maintain SS*	Maintain SS	Increase SS?	Maintain SS

* = applies to single arm only

When an arm is dropped, what about the allocation ratio?

Allocation Ratio (when arm dropped)

Original: 2:1:1

Option A: 2:1:0

Option B: 1:1:0

Operationally,

- plan IVR/IWR build for this possibility at the start of trial (flip the switch)
- Some impact on drug supply at sites.

Inferentially,

- Affects power (and final sample size)
- Affects mathematical details in computations of re-estimated sample sizes

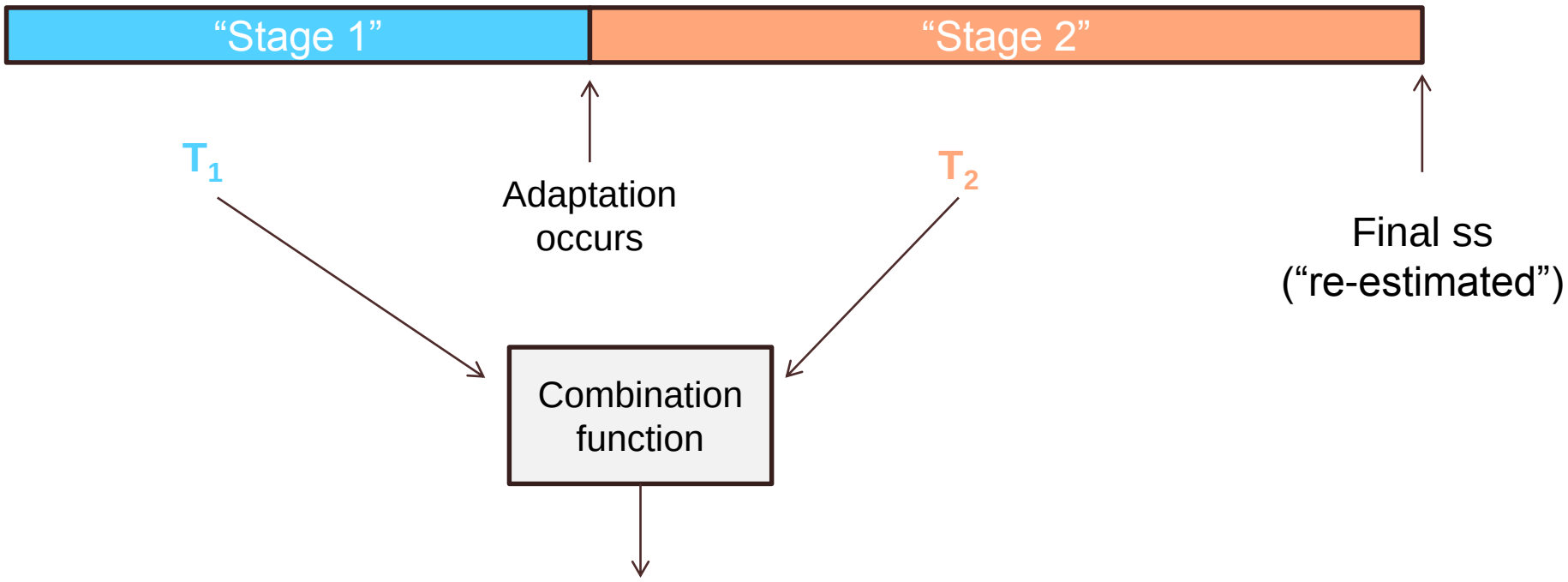
Behind the curtain: Sample Size Computations

Two (comparable) approaches:

- Using target conditional power, solve for ss
  - For each dose-PL contrast
  - Mehta and Pocock (2010) and others
  - Apply Max-ss or Min-ss
- Using conditional error, solve for ss for stage 2
  - For each dose-PL contrast
  - Muller and Schafer (2001) and others
  - Apply Max-ss or Min-ss
  - Allows use of standard ss tools

Behind the curtain: Final Analyses from Adaptive Trial

To ensure type I error control:



Example Simulation Study

- Study Design:
  - Planned min and max sample sizes: 600 and 1000
  - Interim at 300 patients
  - Placebo and two experimental arms (2:1:1)
  - Promising Zone: 20% ≤ CP < 80%
  - Futility Rule: Drop arm if CP < 10%

- Comparison of 4 Approaches:
  - Min-SS and Max-SS
  - If a dose arm is dropped, 1:1:0 and 2:1:0

Simulation Study: Power Comparisons

Effect Size for both Doses	Freq One Arm Dropped	Min-SS			Max-SS		
		Freq SS Incr	1:1:0 if Drop Dose (power)	2:1:0 if Drop Dose (power)	Freq SS Incr	1:1:0 if Drop Dose (power)	2:1:0 if Drop Dose (power)
0	23.6	15.3	2.2	2.2	16.5	2.2	2.3
0.22	31.2	29.8	74.4	73.9	50.6	76.9	76.4
0.25	26.1	26.3	84.0	83.6	50.6	86.0	85.7
0.31	15.8	17.2	94.9	94.8	44.6	95.7	95.6

- The Max-SS approach provides a power increase over the Min-SS approach.
- The 1:1:0 allocation after dropping a dose is slightly more powerful than the 2:1:0 allocation.
- The Max-SS increases more often than the Min-SS.

Next layer…. Multiple Endpoints

Adaptive Sample Size Decision Rules:

- Account for secondary endpoints or strictly on primary?

Behind the curtain:

- Sample size computations incorporating secondary endpoints, perhaps
- Apply combination functions for test statistics / p-values (type 1 error due to adaptation)
- Applying closed testing principle (type 1 error due to MT)

Take-home Messages

Adaptive Designs are powerful tools

- Reduce risk to trials due to uncertainty in key parameters at the design stage
- May offer ethical advantages vs fixed designs

Feasible (and needed) in CNS research

These designs require collaborative thought

- Each decision or flex point has implications
- Engage statisticians, clinicians, operations experts early and often on this journey

Thank you!