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Adaptive and Seamless Designs: Making the Right Decision

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Myth-busting

- Adaptive designs are **NOT** a panacea
 - they **WON'T** make treatments work, which don't work
 - They **WON'T** fix faulty designs
- Adaptive designs can often
 - increase the “information value” per \$\$ investment (crucial in today's resource-constrained environments)
 - redirect the sponsor to more promising assets
 - enable
 - earlier and better planning, decision-making
 - simulation guided clinical drug development
 - team-building
(discovery, clinical, biostatistics, IT, regulatory, project management, clinical operations, marketing)

Adapting - the principle

- **The Best Design**
 - Provides the highest information value per resource unit invested
 - Addresses the research questions at hand
- **Learning and decision making in real time**
 - Make the correct decision
 - At the earliest time point
 - Accelerate development including regulatory filings (efficacy)
 - Redeploy resources (futility)
 - In the most efficient way

Definition – adapt by design



Adaptive design is defined as a multistage study design that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial

PhRMA Working Group on Adaptive Trial Designs (Nov 2006)



Validity involves statistical properties of the trial related to inference and estimation

- Providing correct statistical inference (maintain strong control of the type 1 error, and provide adjusted p-values, estimates and confidence intervals)
- Assuring consistency between different stages of the study
- Minimizing operational bias

Integrity is primarily about transparency and trial conduct acceptable to the intended external audience

- Providing convincing results to a broader scientific community
- Preplanning, as much as possible
- Based on intended adaptations
- Maintaining confidentiality of data

Common adaptive designs

- **Dynamically change randomization ratios**
 - to achieve balance in base-line prognostic factors
 - to assign fewer subjects to doses that are too low or too high
- **Drop ineffective treatment arms after interim analysis**
- **Stop early for futility or when efficacy has been adequately demonstrated**
- **Increase sample size if observed variance is larger or effect size is smaller than expected**
- **Combine trials e.g. seamless II/III, PoC+Dose finding**

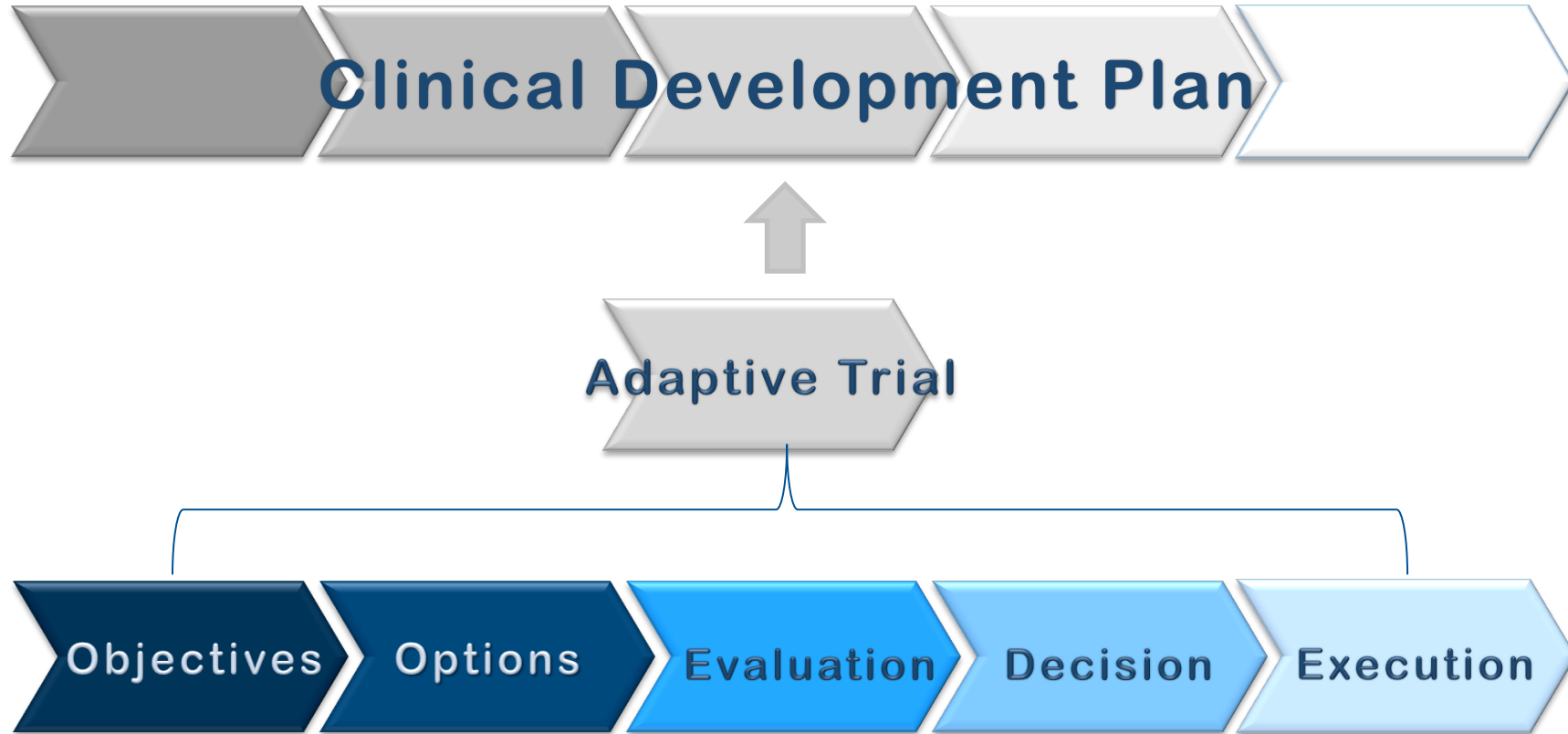
Potential benefits

- **May shorten trial duration and reduce costs**
 - End trials early for efficacy, futility or safety
 - Combine two trials into one integrated trial (eliminate “white space”, fewer subjects required)
- **Improve chances of success**
 - Increase the sample size based on interim estimates
 - Change randomization ratios dynamically to increase learning
- **Ethically Superior**
 - Fewer patients on ineffective doses, quicker identification of efficacious drugs

Gaining these requires...

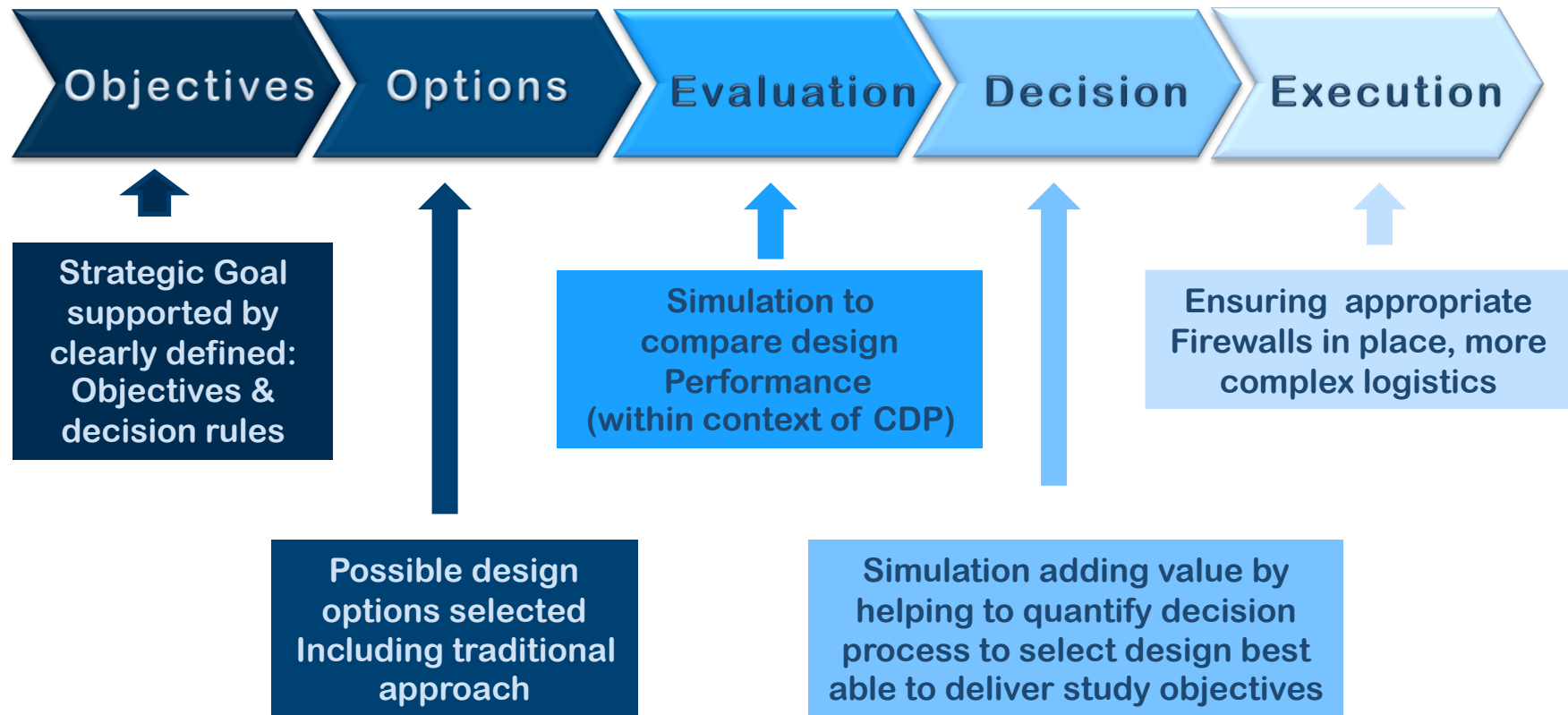
- Significant changes in the traditional process for design and implementation of clinical trials
- More up front time and effort for design,
 - e.g. cannot use formulas to calculate sample size, computer simulation needed to find an effective design, need for software tools
- More co-ordination and detailed planning,
 - e.g. randomization and drug supply

Adaptive “by design”

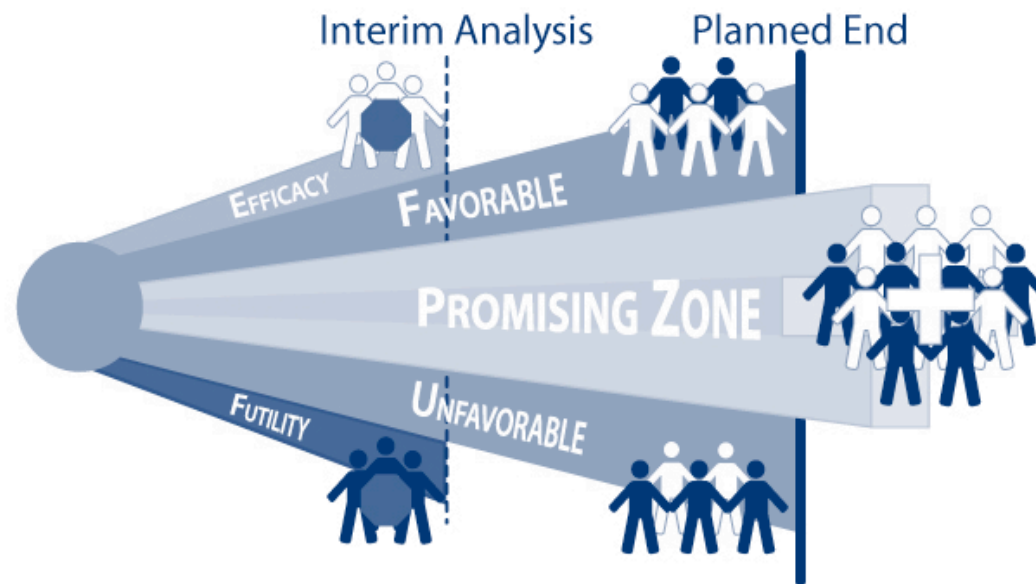


An adaptive trial like all trials, must make sense and add value within the context of the CDP

How to adapt by design



Sample size re-estimation



Preliminary design

- Primary endpoint is overall survival (OS)
- 8 months median on control arm
- 90% power to detect HR = 0.7 with $\alpha = 0.05$
- 11.43 months median on experimental arm

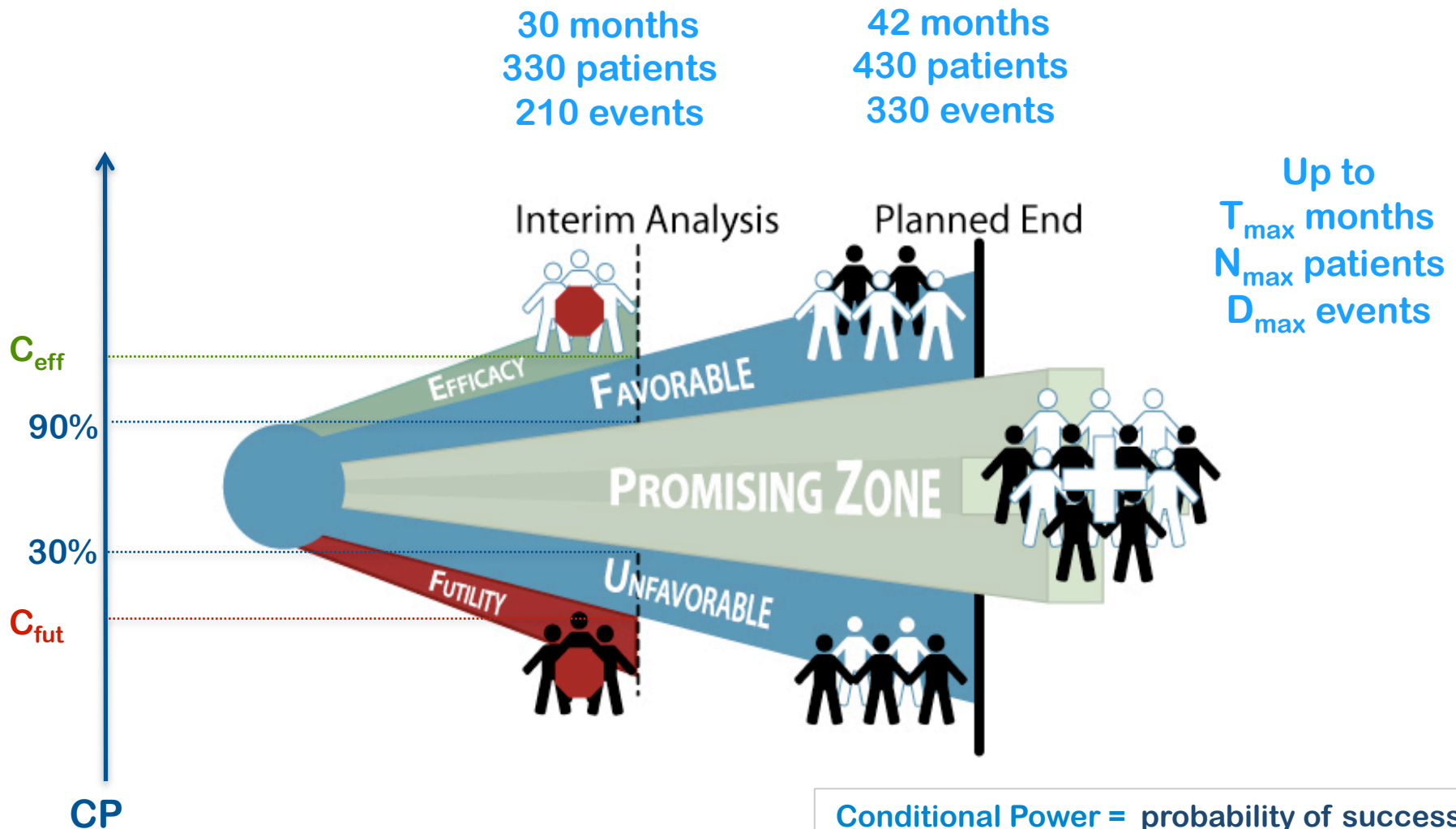
- **330 events required** to attain desired power
- Can obtain 330 events with **430 patients**, assuming 36 months enrollment and 6 months additional follow-up

Power Curve

- Considerable risk of an underpowered study if the treatment effect is smaller

Hazard Ratio	Power
0.70	90.0%
0.72	84.7%
0.74	78.1%
0.76	70.3%
0.78	61.7%
0.80	52.7%

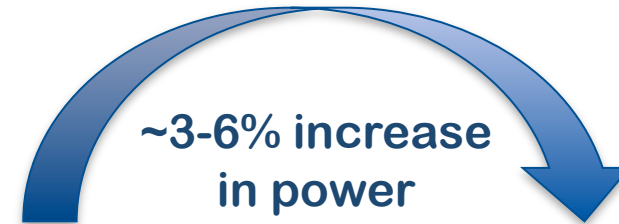
Interim analysis strategy



Conditional Power = probability of success at end of trial given current data trend

Unconditional simulation

~60 increase in events



	True HR	Non-Adaptive Power and Sample Size	Adaptive Power and Sample Size
Target Clinical Effect (TCE)	0.76	81% (387 events)	84% (443 events)
Minimum Meaningful Clinical Effect (MMCE)	0.78	72% (397 events)	77% (456 events)
	0.80	63% (404 events)	69% (467 events)

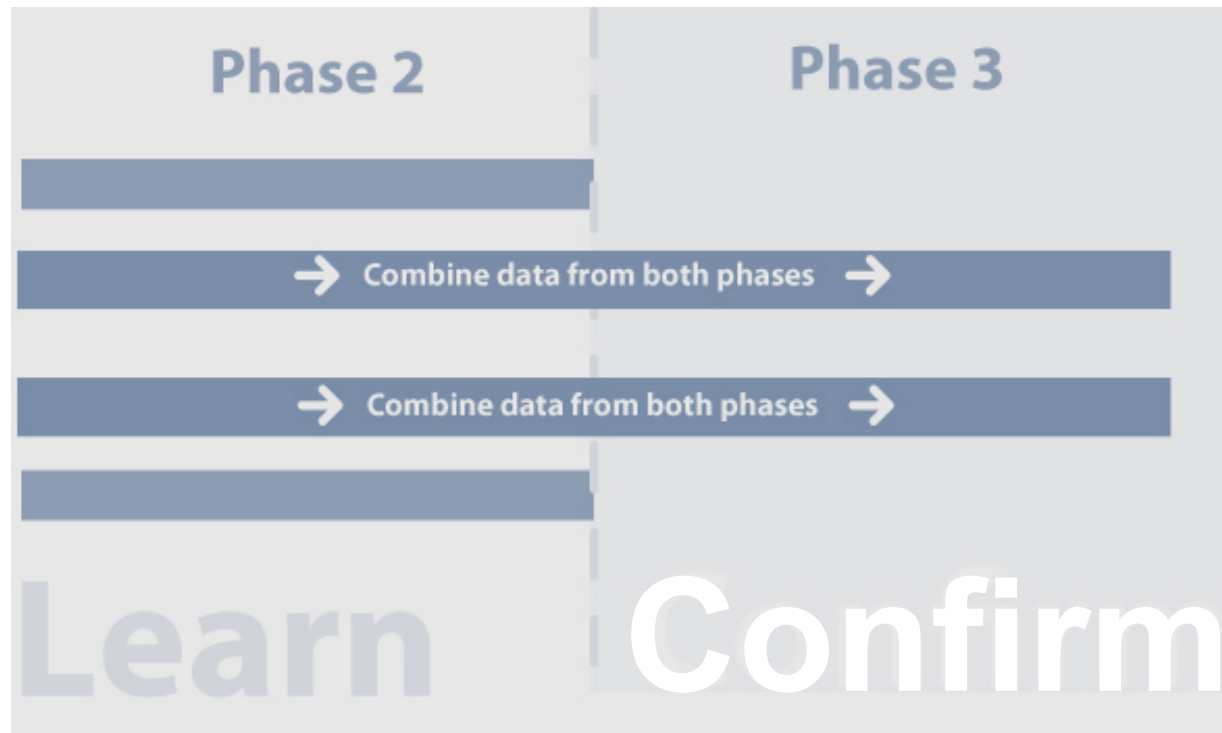
Conditional simulation results

In promising zone
~110-130 increase in events

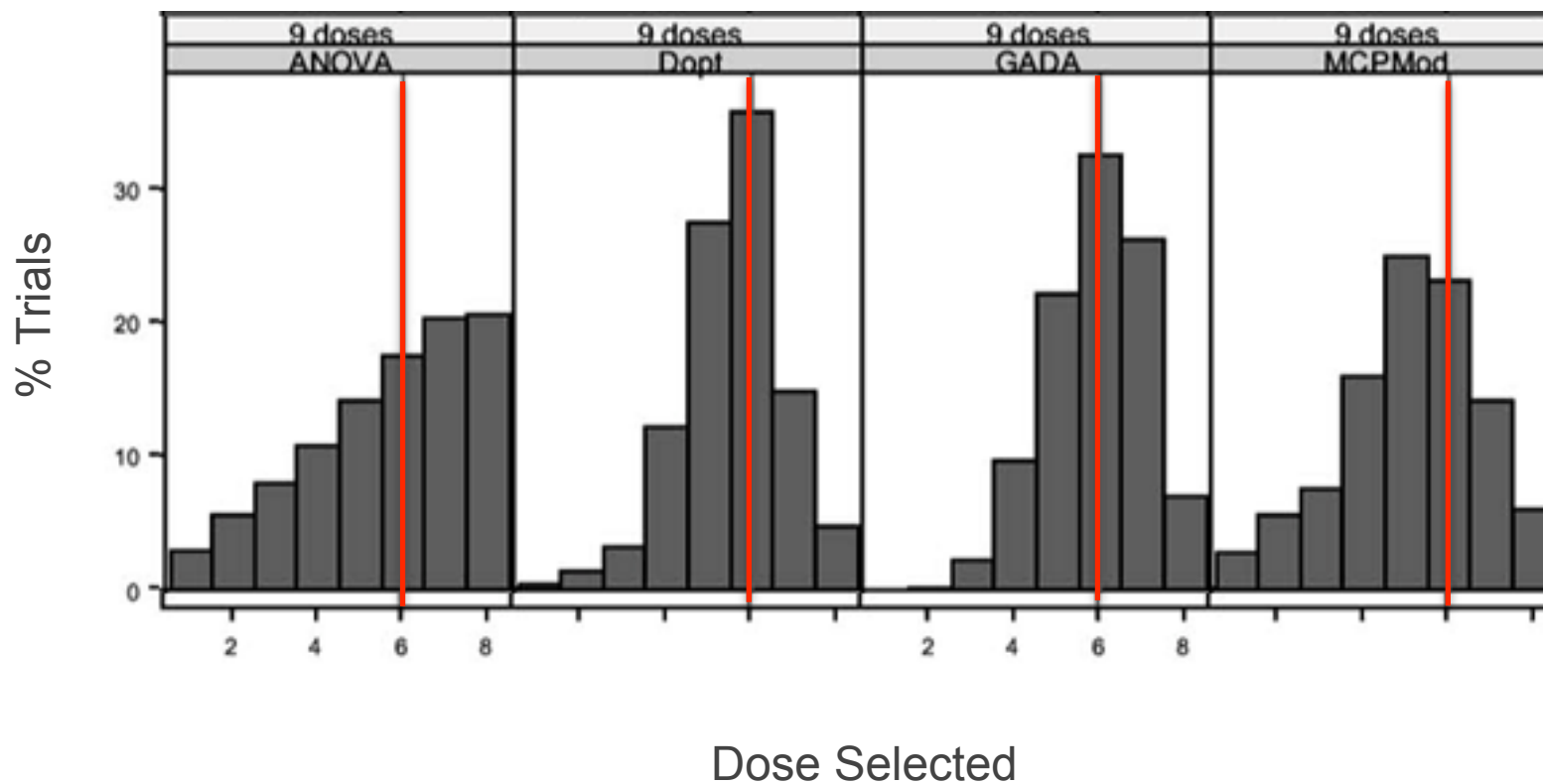


	True HR	Outcome	Prob (Outcome)	Non-Adaptive Power and Sample Size	Adaptive Power and Sample Size
TCE	0.76	Unfavorable	20%	42% (423 events)	42% (423 events)
	0.76	Promising	24%	75% (423 events)	93% (656 events)
	0.76	Favorable	57%	95% (423 events)	95% (423 events)
MMCE	0.78	Unfavorable	25%	34% (423 events)	34% (423 events)
	0.78	Promising	25%	68% (423 events)	88% (658 events)
	0.78	Favorable	50%	93% (423 events)	93% (423 events)
MMCE	0.80	Unfavorable	31%	28% (423 events)	28% (423 events)
	0.80	Promising	26%	62% (423 events)	84% (668 events)
	0.80	Favorable	43%	89% (423 events)	89% (423 events)

Dose Selection



Difficult to get the dose right



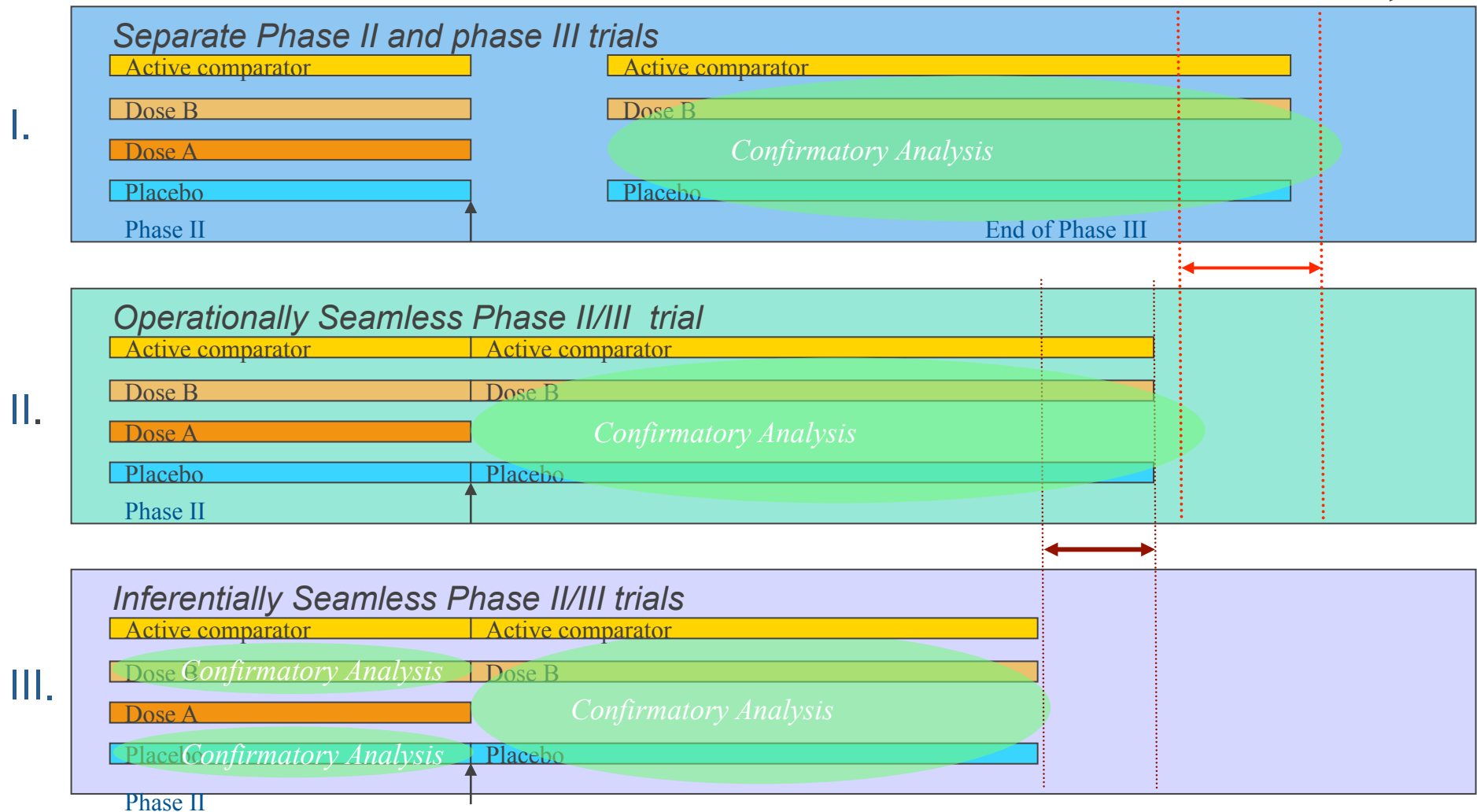
Reproduced from Bornkamp et al. J. of Biopharm. Stat. Dec2007

Learn, drop doses, confirm

- **Combines into one trial the objectives typically addressed in separate trials**
- **Reduces or eliminates time between trials and provides information efficiently earlier in development**
- **When properly conducted more efficient use of patient data**
- **Proper statistical methods must be used to minimize bias and ensure strong control of the study-wise type-1 error**

Seamless design

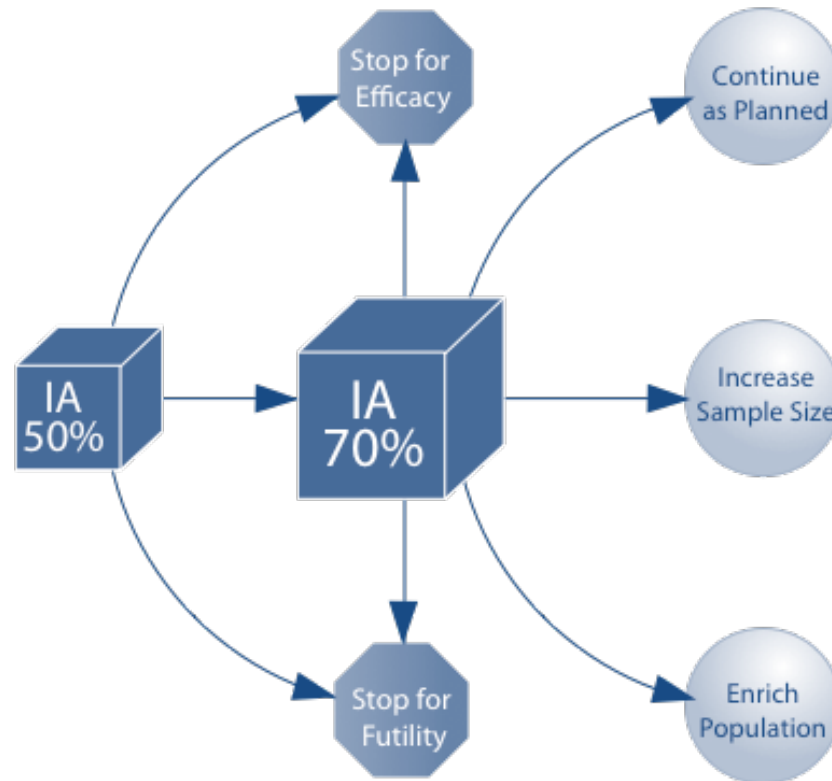
Development Timeline



Seamless phase 2/3

- Endpoints/biomarkers used for dose selection and confirmation of the efficacy of the drug must be well **understood** and **accepted/validated**
- Time needed for patient to complete the primary endpoint should be short compared to time needed to complete enrollment in the study
- Decision process and rules should be well thought out and **predefined**

Population enrichment



Population enrichment

- **Population enrichment design for Acute Coronary Syndrome**
 - Disease area with:
 - low event rates
 - Targeting tiny effects
 - Diverse population
 - Grave yard of failed trials
 - Traditionally 10K plus sample size trials
- **Group sequential with one interim population enrichment**
 - Stopping early for efficacy, futility
 - Sample size re-estimation
 - Population enrichment

Case study: PCI

- Platelet inhibition during Percutaneous Coronary Intervention (Circulation, 200?)

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Optimizing Trial Design: Sequential, Adaptive, and Enrichment Strategies
Cyrus Mehta, Ping Gao, Deepak L. Bhatt, Robert A. Harrington, Simona Skerjanec
and James H. Ware
Circulation 2009;119;597-605

Objectives

- **Composite primary endpoint – death, MI, or ischemia driven revascularization within 48 hours**
- **Placebo event rate between 8% and 10%**
- **New drug expected to reduce placebo event rate by 20%**
- **But actual risk reduction could be as low as 15%**

Pre-specifying subpopulations

- Enroll into select sub-populations based on interim results and event rates

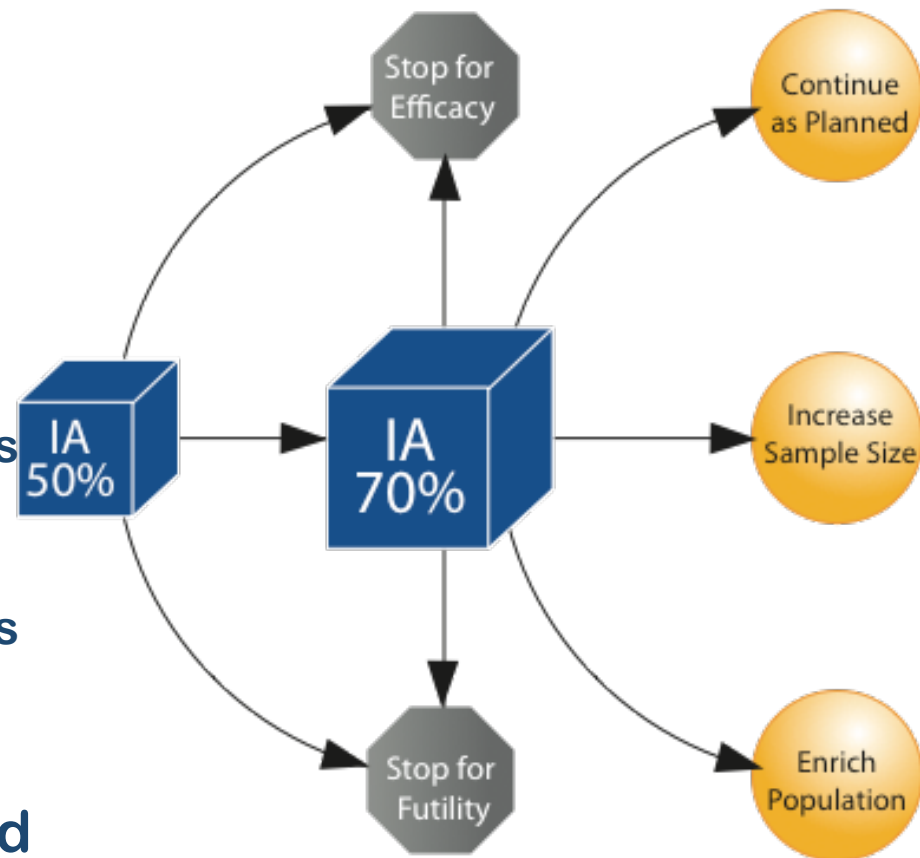
Populations	Description	% of Full Population
G0	Full population	100%
G1	High-risk	60%
G2	High-risk + treatment-naive	30%

- Subpopulations **must** be **pre-specified** or we open ourselves up to misdirection
- Goal is to try and win with G0; if not, then win with G1; if not, then win with G2

Enrichment strategy: IA2

Interim Analysis 2

- If $CP \geq 80\%$ continue as planned
- If $CP < 80\%$
 - Try for 80% with G_0 while increasing sample size
 - If unable, try for 80% by enriching with only G_1 patients and increasing sample size
 - If unable, try for 80% by enriching with only G_2 patients and increasing sample size
- Terminate for futility if $CP < 20\%$ despite enrichment and sample size increase



Role of simulation

- Adaptive designs and indeed all designs should be **simulation guided**
- Many deviations from protocol assumptions are possible and **simulations are the best tool for evaluating the impact of these deviations** on your study's operating characteristics
- Simulations can be provided to the FDA to **support and defend the study design**

Implementation challenges

- **Availability and flow of information/data** required to support adaptive decision making
- Rapid and smooth implementation of changes to the **randomization** scheme
- **Drug supply** planning and optimization
- Composition and responsibilities of data monitoring committees (**DMC**)
- **Documentation and process validation**

Regulatory considerations

- **FDA and EMEA open to adaptive designs in confirmatory settings. Some already accepted and underway**
- **Early and open discussions with regulatory agencies are critical**
- **Detailed briefing material should include briefing package, protocol, draft of the statistical analysis plan, simulation report, and DMC charter**
- **Adaptation in confirmatory trials should aim to resolve only minor amounts of design uncertainty, generally from within a small number of pre-specified possibilities**

Questions to ask yourselves

- Why and how would an adaptive solution **provide benefit?**
- Will the information provided at submission to regulatory agencies be **more informative?**
- Will regulators have an improved understanding of the **benefit-risk profile and safety** in particular?
- Will clinicians have more information to **better treat** their patients after product launch?
- Will the trialists and researchers make **best use of the information value** offered by patients agreeing to participate in this trial?

Thank you!