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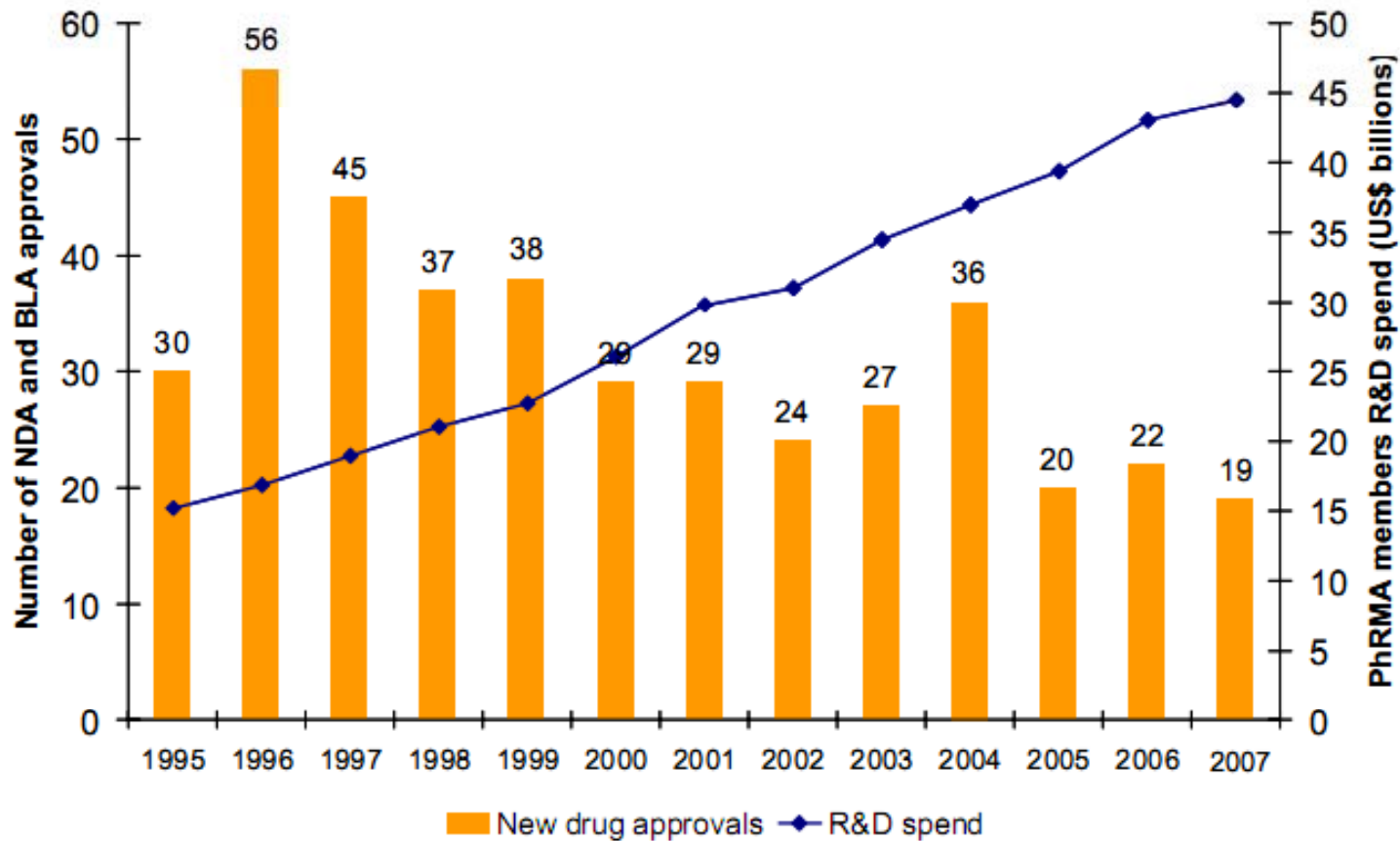
Seamless and Adaptive Designs In Late Stage Oncology Trials

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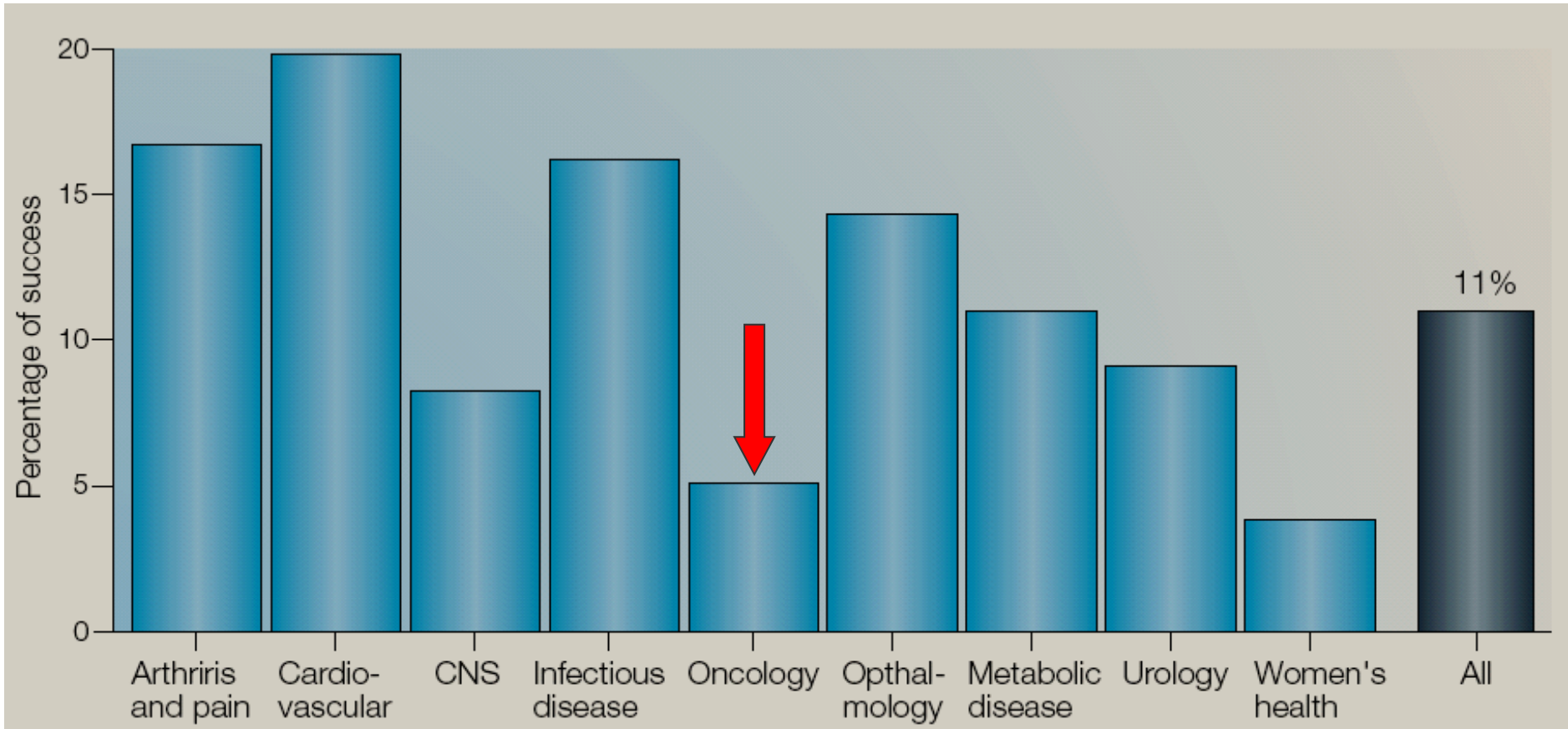
- Problems in cancer drug development
- Definition of adaptive designs
- Getting the dose right
- Seamless phase 2b/3 designs with dose selection
- Population enrichment designs
- Challenges to implementation
- Role of simulation

NDA vs. R&D costs 1995-2006



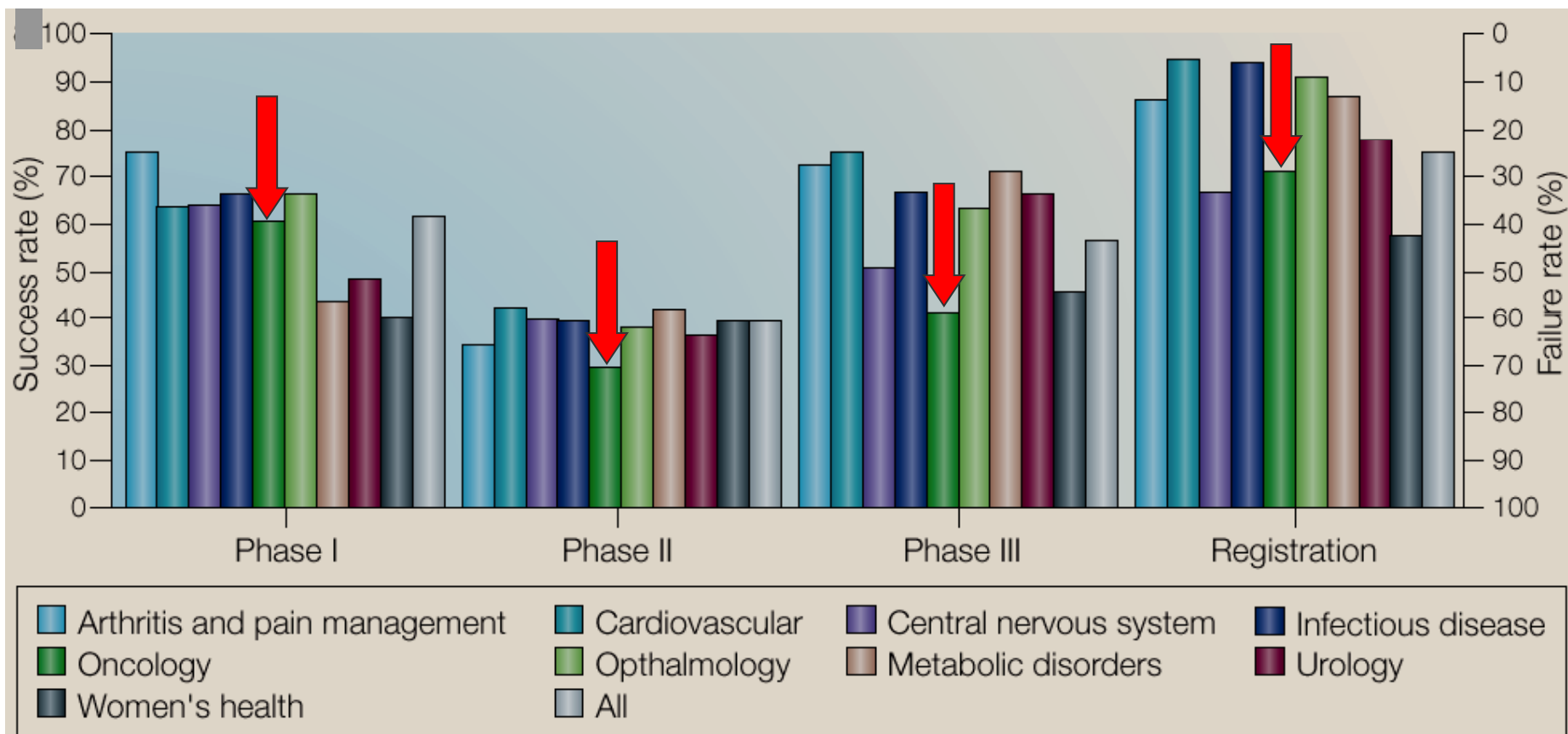
Source: www.phrma.org

Low success rate in oncology



Reproduced from *Kola and Landis Nat.Rev.Drug.Disc. Aug2004*

High failure rate even in phase 3



Reproduced from *Kola and Landis Nat.Rev.Drug.Disc. Aug2004*

Improving trial design

- Best design addresses the research questions at hand in the most efficient manner
- Earlier intimation of efficacy may accelerate development including regulatory filings
- Early signs of futility allow the sponsor to deploy resources elsewhere
- Verification of design assumptions and revision of sample size can avoid an underpowered study

How do we do a better job of establishing

- Maximum Tolerate Dose
- Proof of Concept
- Dose Selection

How can seamless and adaptive designs

- Address multiple objectives within a single trial
- Make use of early read-out biomarkers to guide decision-making

The principle

The Best Design

- Provides the highest information value per resource unit invested

Learning and decision making in real time

- Make the correct decision
- At the earliest time point
- In the most efficient way

Adaptive Design

Uses accumulating data to decide on how to modify aspects of the study

Without undermining the *validity* and *integrity* of the trial

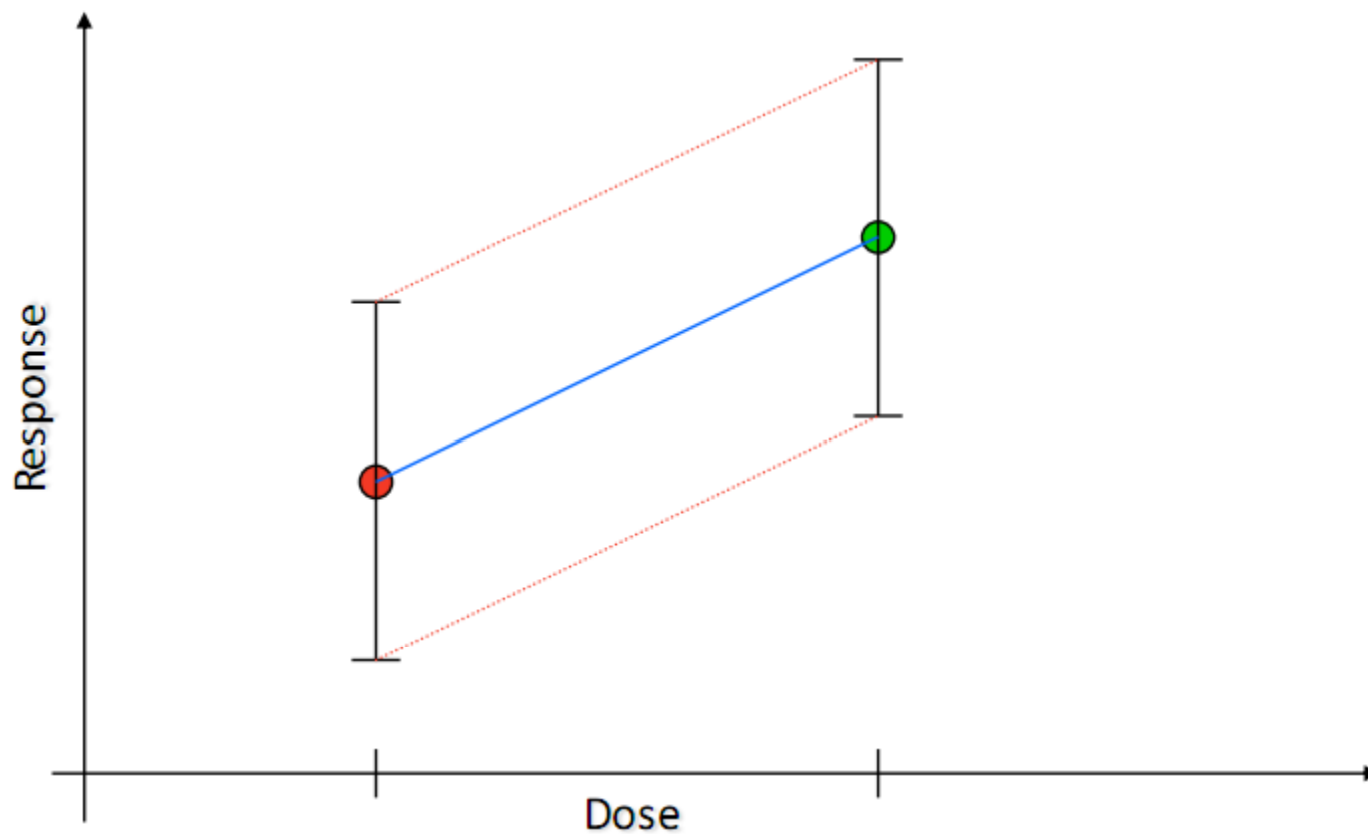
Validity means

- 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 means

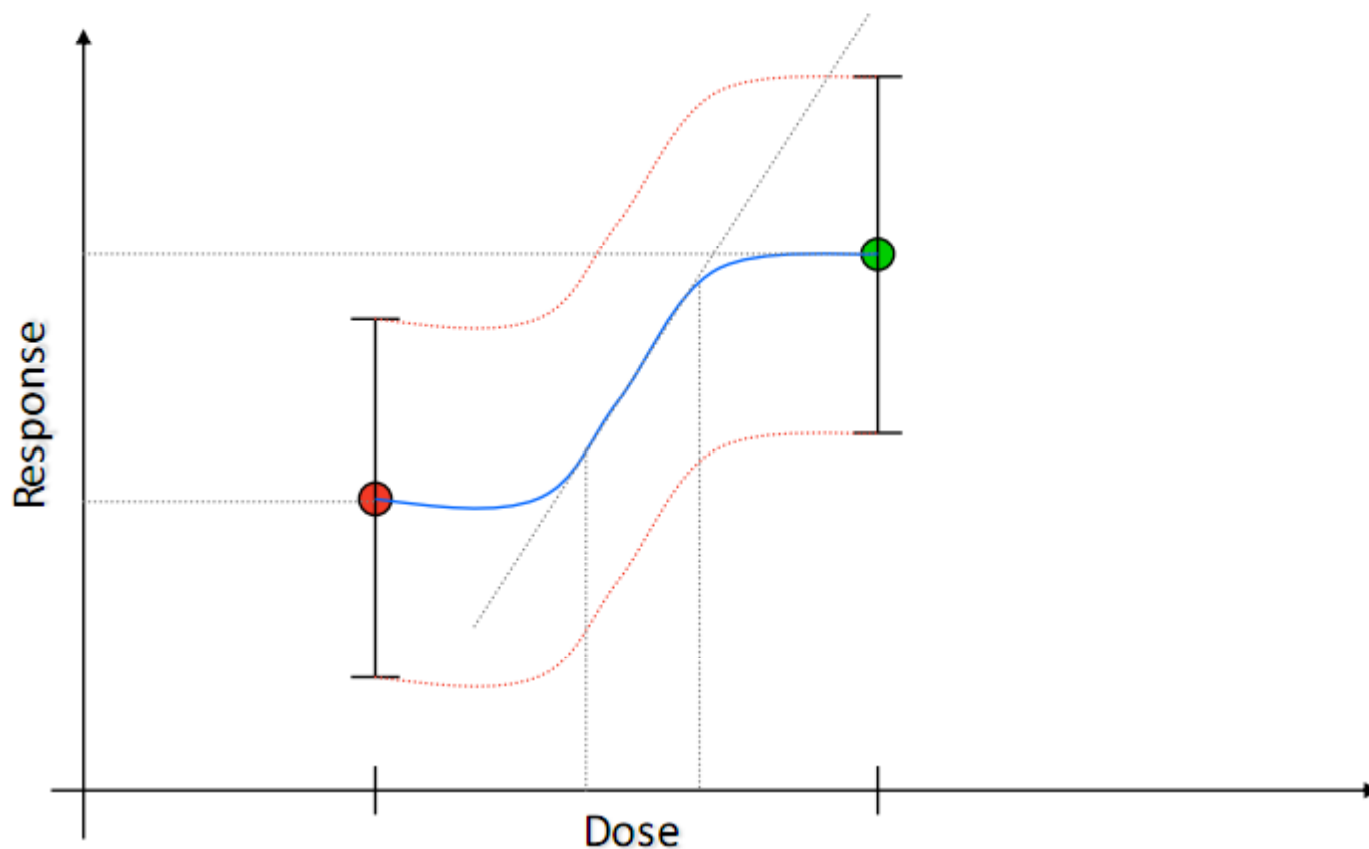
- Providing convincing results to a broader scientific community
- Preplanning, as much as possible,
- Based on intended adaptations
- Maintaining confidentiality of data

Getting the dose right



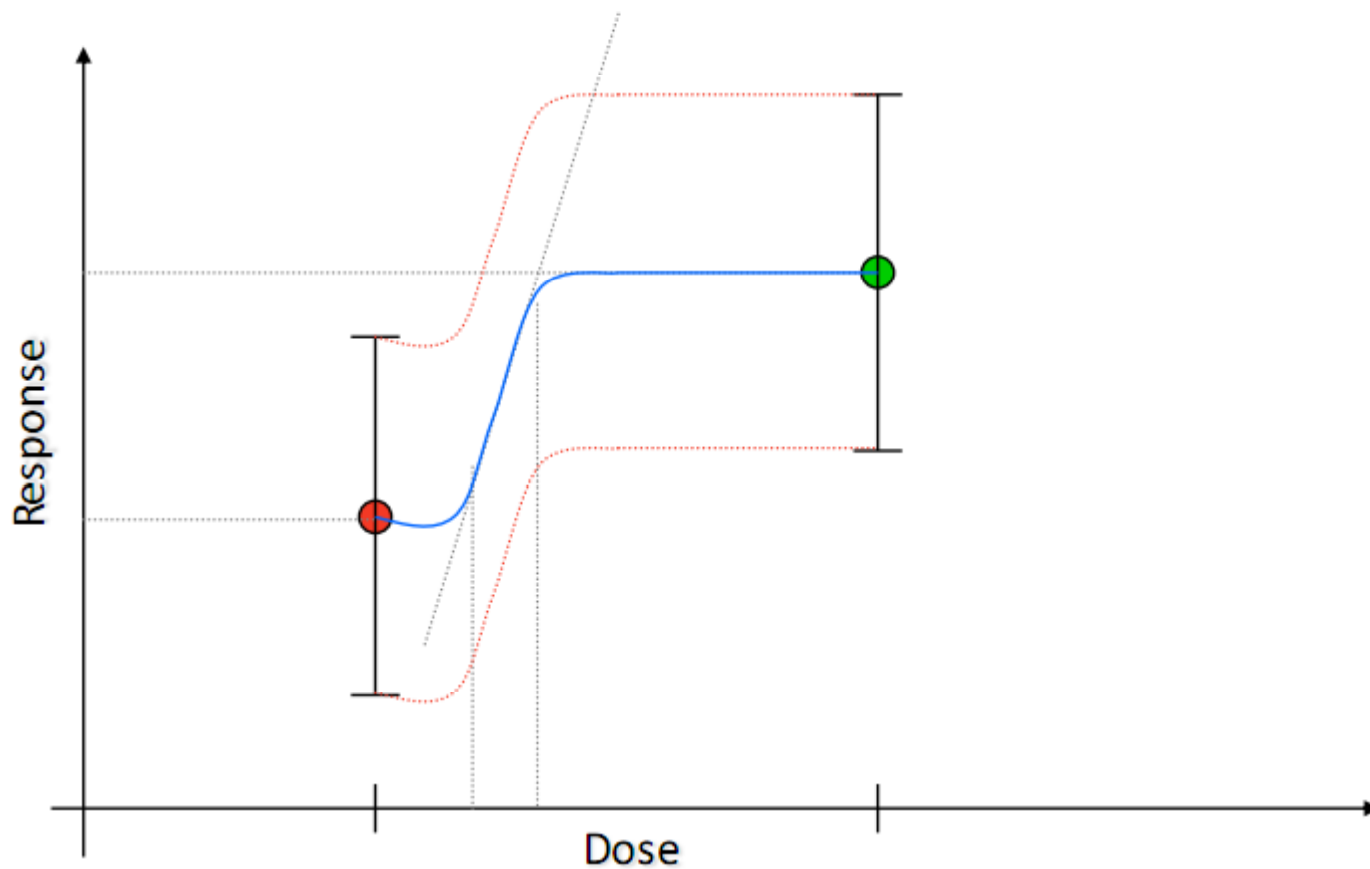
Acknowledgement : Michael Krams

Getting the dose right



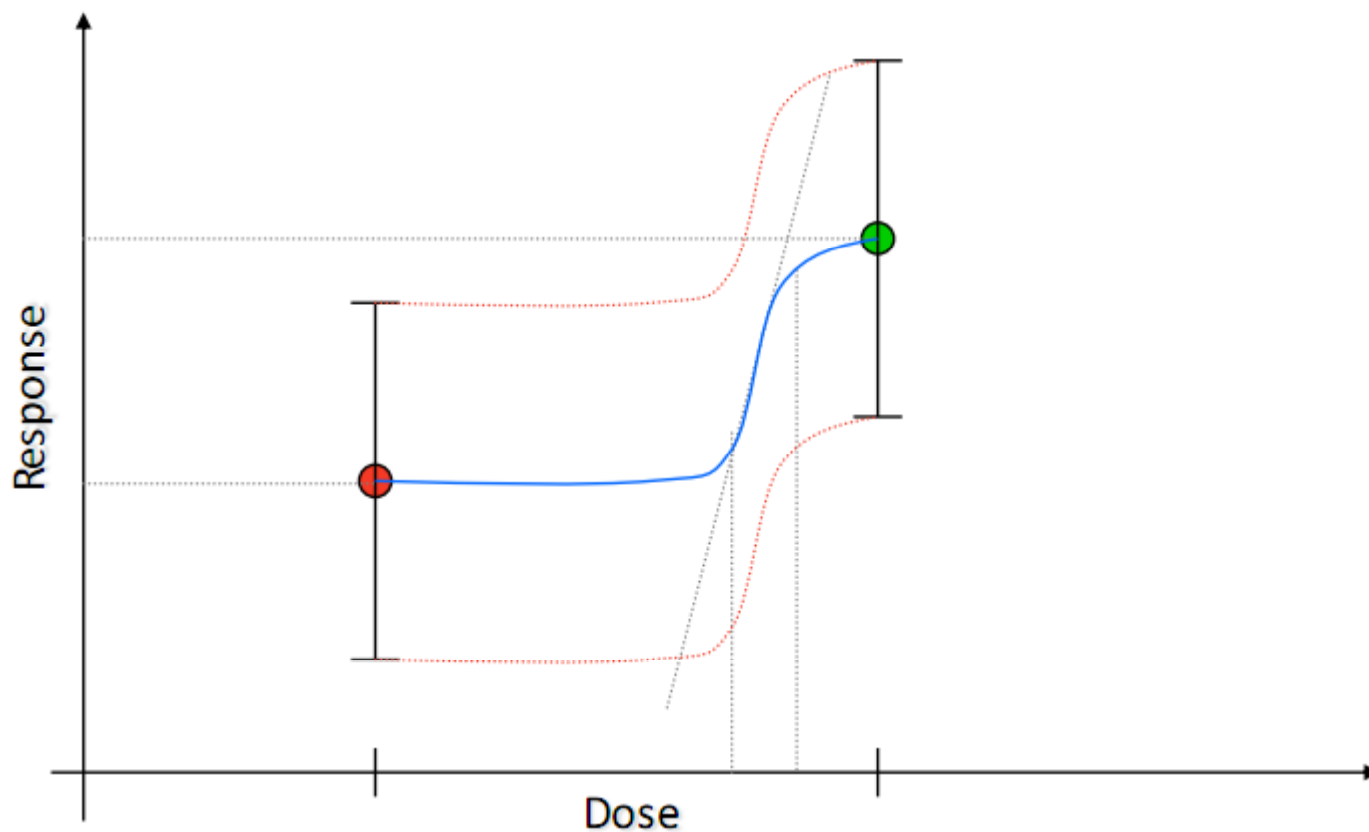
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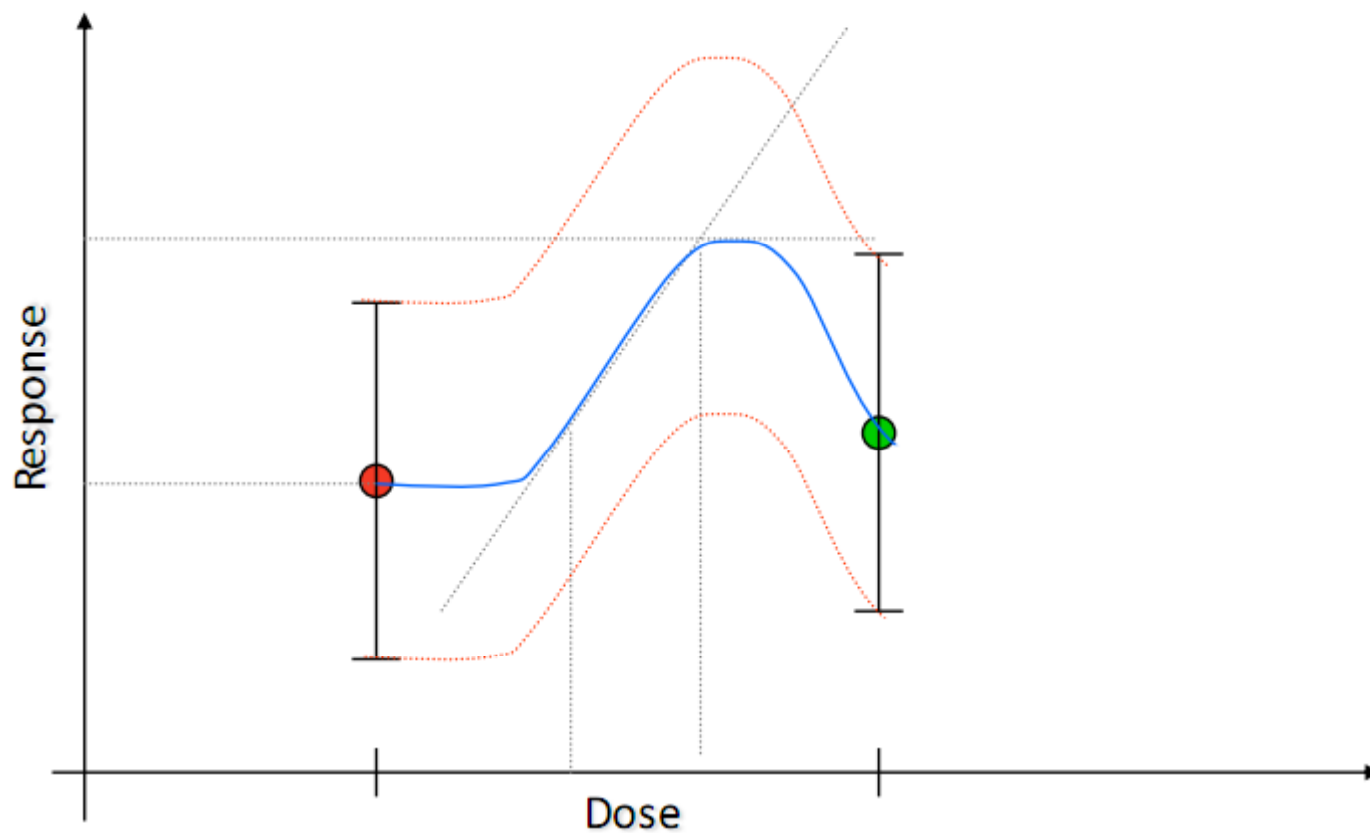
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Getting the dose right



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Getting the dose right

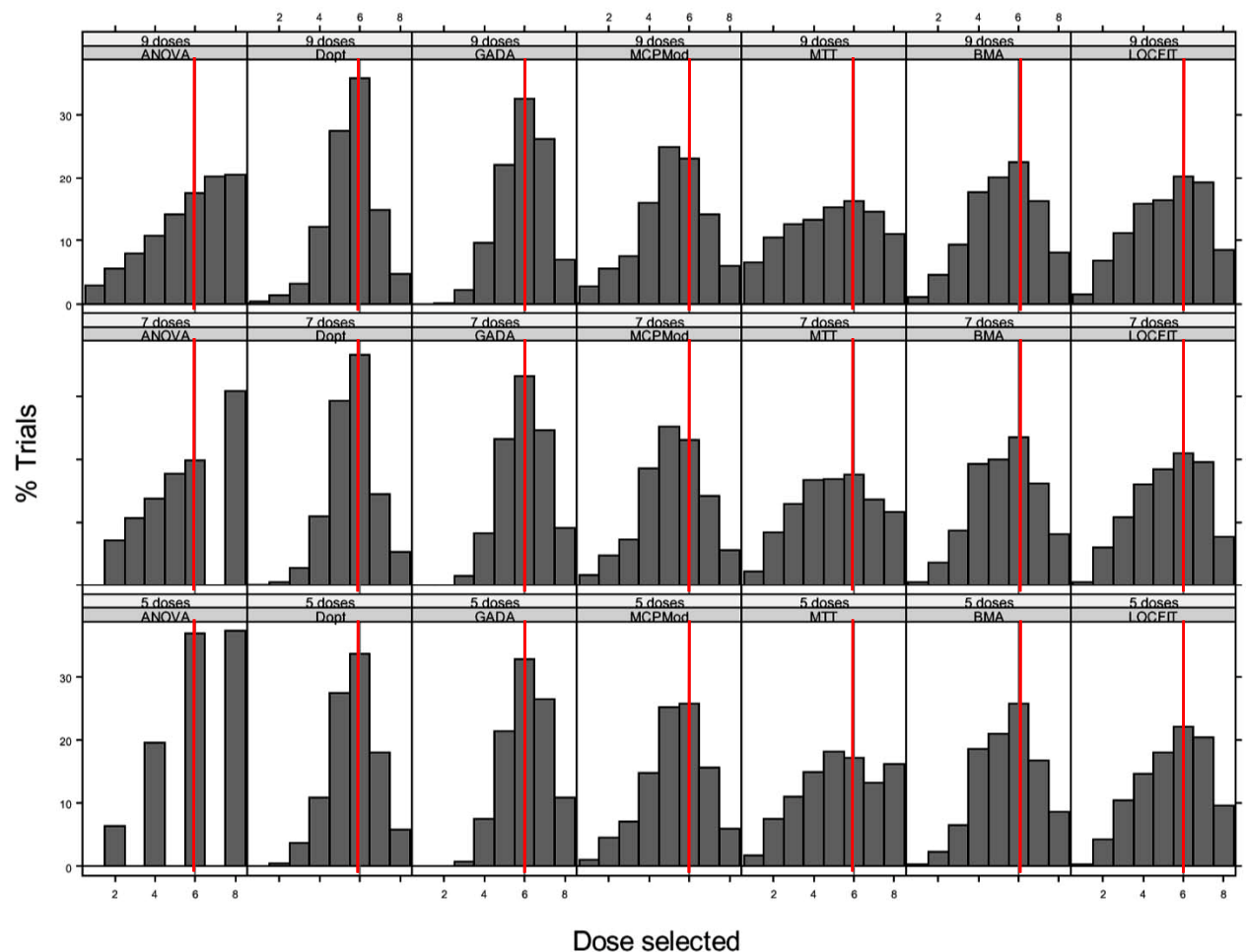


Figure 10 Histograms of estimated target doses for linear model, $N = 150$.

Reproduced from Bornkamp et al. J. of Biopharm. Stat. Dec2007, 17 (6), pp 957-964

Yannis Jemai – Seamless and Adaptive Designs in Late Stage Oncology Trials

What dose to carry forward?

Much uncertainty about optimal dose regimen to carry forward into confirmatory trials, even after all the exploratory work has been done

Uncertainty exists also about the target population or indication

What can be done to bridge the gap between the learn and the confirm stages of drug development?

Ideally

- Pre-select sensitive population using biomarkers
- Treat optimal population with targeted agent
- Monitor using PD, safety and response biomarkers
- Pick the most appropriate dose by modeling response
- Focus greater attention on patients showing clinical benefit

What is a seamless trial?

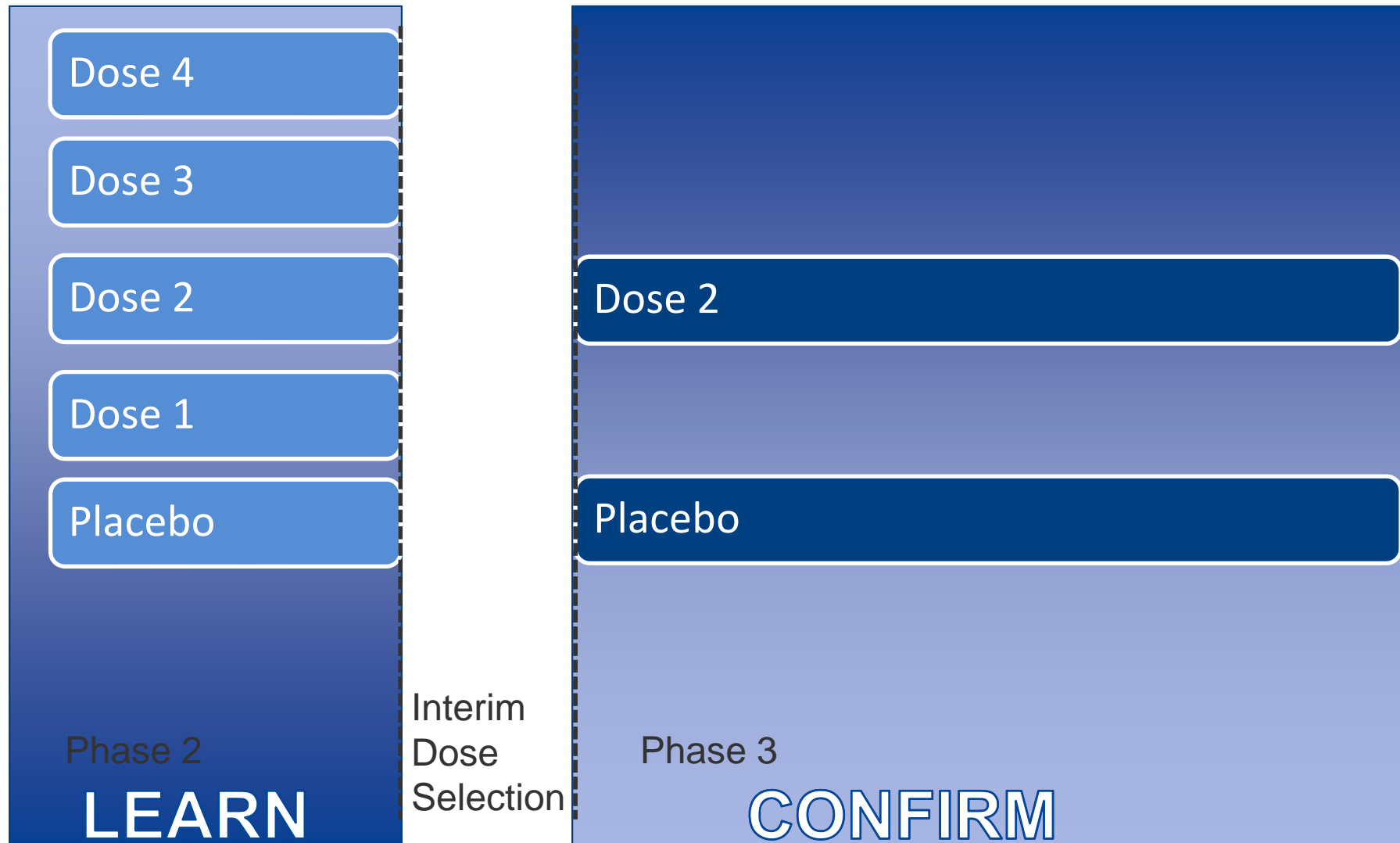
A seamless trial

- Combines within a single trial objectives that are usually achieved through separate trials in clinical development, thus combining the phases of drug development
- Uses data gathered in the first stage of the trial to guide decisions for the second stage of the trial
- May change aspects of the trial that include: the final choice of doses to be taken forward, enrichment of the population, a re-estimation of the sample size, or stopping for futility or efficacy

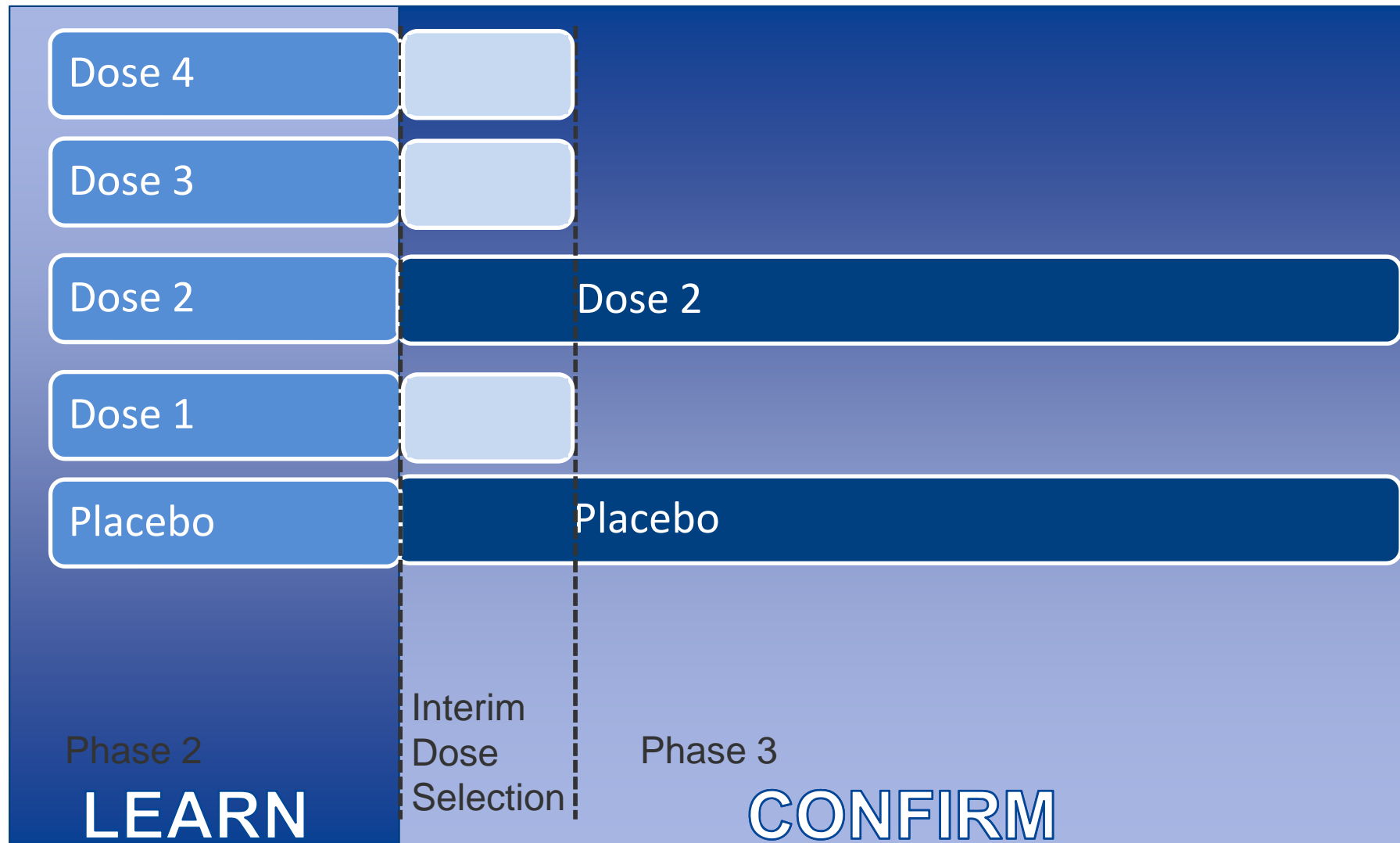
Operational vs. Inferential?

- An **operationally** seamless trial analyzes data from each stage of the study separately to address each objective
- An **inferentially** seamless trial analyzes data across stages of the study. In particular the final analysis would include all data collected in the study (e.g. phases 2b and 3) and should **strongly control the study-wise type 1 error**

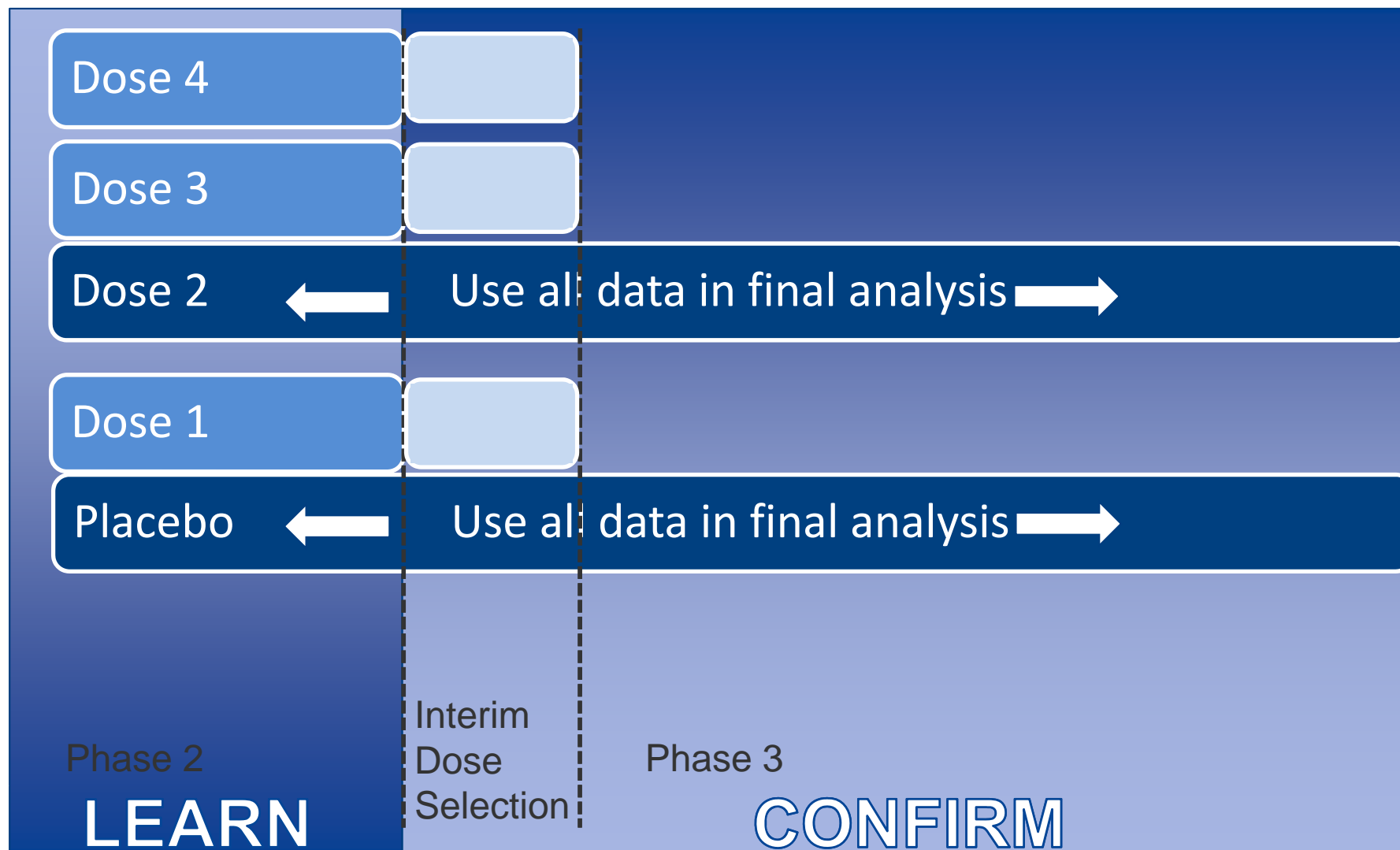
Seamless phase 2/3 designs



Seamless phase 2/3 designs



Seamless phase 2/3 designs



Many rules can be used to carry doses forward

- Futility: drop dose arms that have low probability of success
- Efficacy: keep dose arms that are doing well based on probability of success, size of treatment effect, or formal statistical test
- Carry forward single dose arm or multiple doses
- Bayesian decision rules based on predictive probabilities

Final analysis must ensure strong control of the study-wise type 1 error

- Generally through p-value combination tests or use of a conditional error function
- Combined with closed testing of hypotheses

Simulations help to characterize sensitivity of the design to deviations from assumptions

Personalized medicine?

In addition to dose selection, adaptive designs can be used to select sub-populations in so-called population enrichment trials

In other words we may change the eligibility criteria for the study population based on accumulating evidence

These subpopulations **must** be pre-specified or we open ourselves up to misdirection

Population enrichment designs

Acute Coronary Syndrome Trials present major challenges to design

- Low event rates
- Tiny effect sizes
- Diverse patient population

Such trials require enormous sample size commitments (on the order of 10,000 patients)

Acknowledgements: Cyrus Mehta, Ping Gao, Jim Ware, Aniruddha Deshmukh, Stuart Pocock, Misha Salganik

Platelet Inhibition during PCI

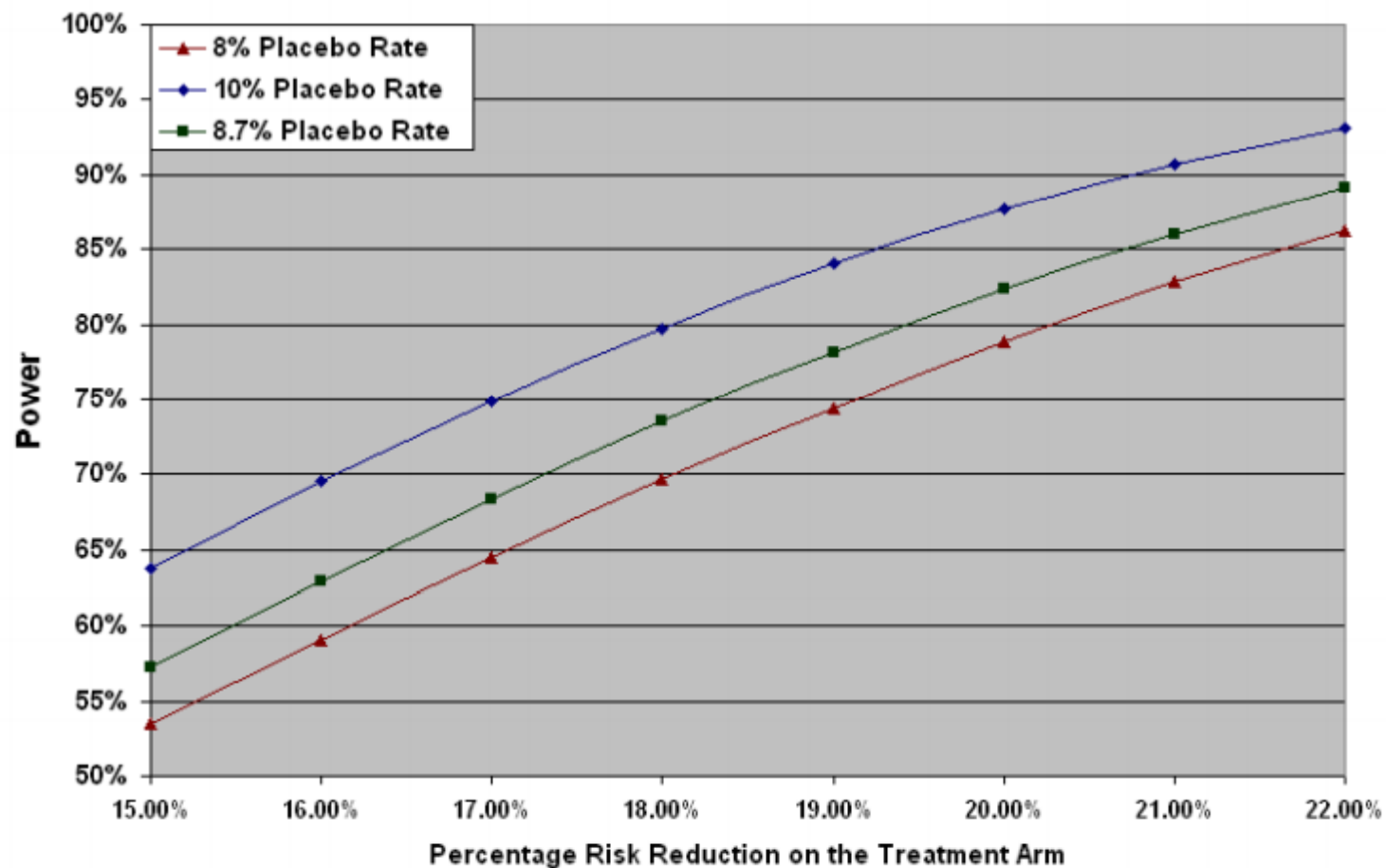
- Composite primary endpoint – death, MI or ischemia driven revascularization within 48 hours
- Placebo event rate uncertain, between 8% and 10%
- New drug expected to reduce placebo event rate by 20%
- Actual risk reduction could be as low as 15%
- Clinical team suspects higher reduction of event rate may be achieved in sub-populations that are at risk for diabetes and/or treatment naive

Conventional design

- Initial commitment of **N = 8000** patients
- This sample size provides more than 80% power if both
 - **Risk reduction $\geq 18\%$**
 - **Placebo event rate $\geq 10\%$**
- Were these parameter estimates to be off by just a few percentage points, study might be underpowered

Power curves for fixed design

**Power Curves with Three Different Placebo Event Rates
Fixed Sample Designs (N = 8000)**



Pre-specified subgroups

1. Using clinical judgment, four non-overlapping partitions of the overall population

Non-overlapping Partition	% of Population
High-risk and clopidogrel naïve	30%
High-risk and pre-treated with clopidogrel	30%
Low-risk and clopidogrel naïve	20%
Low-risk and pre-treated with clopidogrel	20%

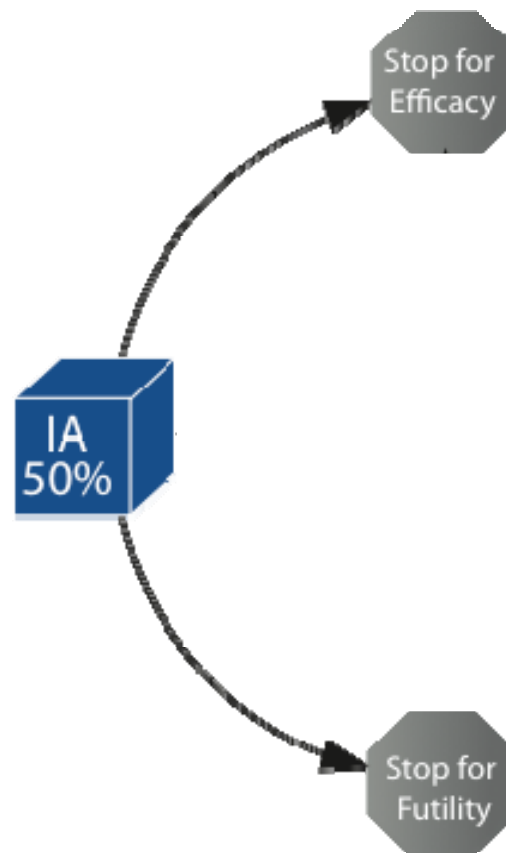
High risk patients are those with diabetes and a troponin+ marker

2. Form three nested subgroups from these four non-overlapping partitions
 - G_0 = full population (100%)
 - G_1 = high-risk subgroup (60% of G_0)
 - G_2 = high-risk, clopidogrel-naïve subgroup (50% of G_1 ; 30% of G_0)

3. Goal is to try and win with G_0 ; if not, then win with G_1 ; if not, then with G_2

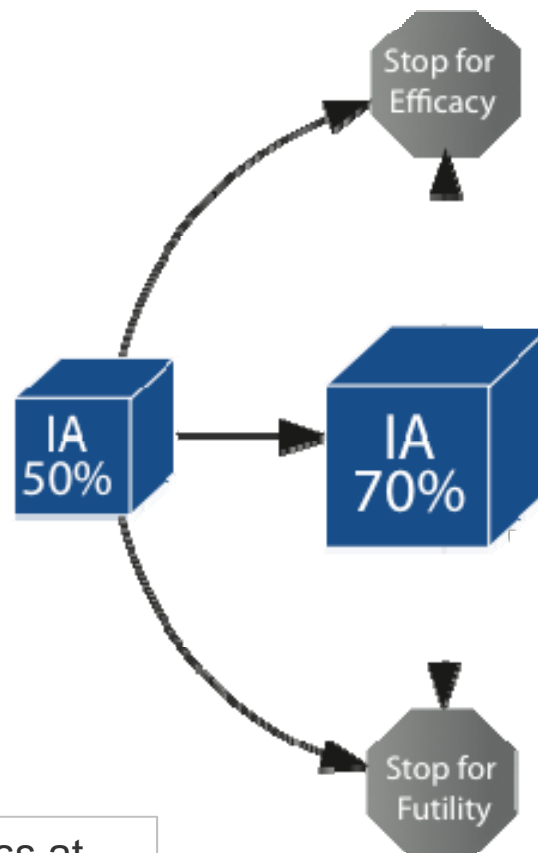
Interim Analysis 1

- 50% of targeted events observed
- Stop for efficacy if 27.7% or greater **decrease** in observed event rate
- Stop for futility if 1% or greater **increase** in observed event rate



Interim Analysis 2

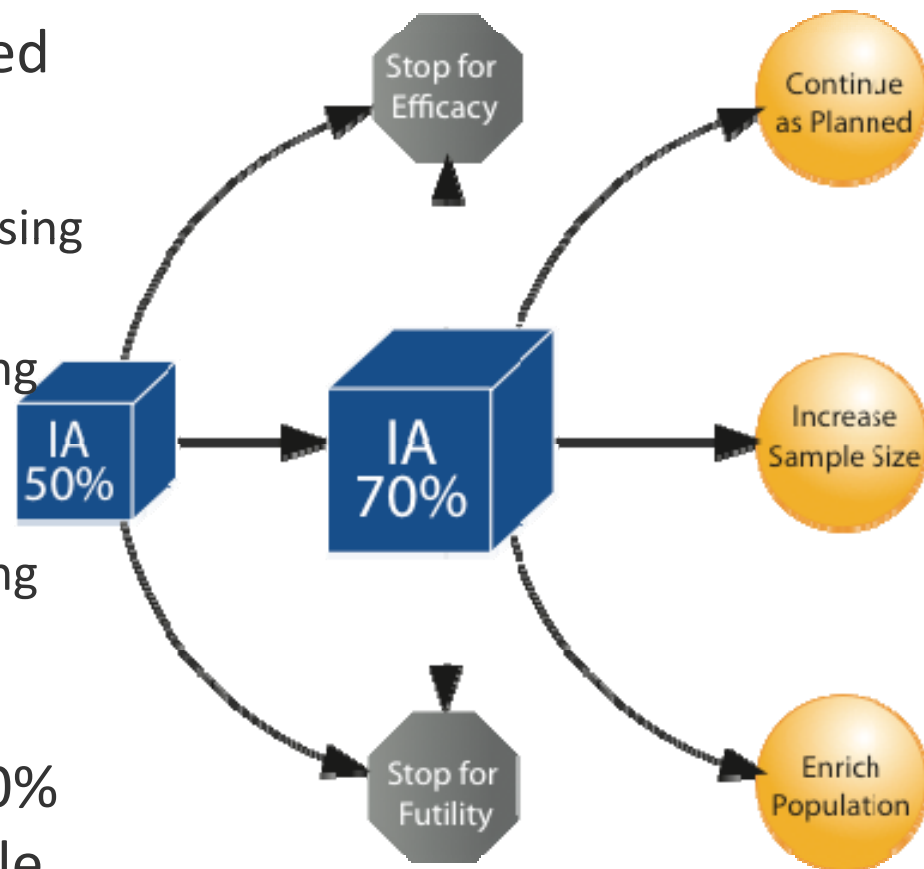
- 70% of targeted events observed
- Stop for efficacy if 20.3% or greater **decrease** in observed event rate
- Compute **conditional power (CP)**
- Stop for futility if CP less than 20%



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

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



Challenges to implementation

- 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
- Documentation and process validation

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

- Adaptive designs are not a panacea, but they can help us improve the way we develop drugs by increasing the information value return on invested resources
- With careful planning and simulation guided design, seamless adaptive trials can help answer multiple questions in an efficient manner

Thank you