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Innovative Drug Development at a Glance – The Concepts, The Vision, & The Factors to Consider

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Introduction to Complex Innovative Trial Design Webinar Series

Innovative Drug Development at a Glance – The Concepts, The Vision, & The Factors to Consider

Agenda:

Complex innovative design can increase return on R&D investment

Adaptive designs can increase trial efficiency or increase probability of technical success

Master protocols reduce administrative burden and accelerate phase transitions

Pharmaceutical frameworks for assessing trial designs in a larger context

Innovative designs can accelerate COVID-19 therapy development

Summary

Q&A

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Complex Innovative Design Can Increase Return On R&D Investment

Complex Innovative Trial Design Can Increase R&D Efficiency & Productivity

Inefficiencies And Missed Commercialization Opportunities Are Costly.

Patients wait for therapies or receive suboptimal therapies.

Millions to billions in revenue sacrificed by delays to market, competitive shutouts, unfavorable product profiles, & unproven treatments.

Promising programs go unfunded as budgets fund unnecessarily large trials.

Advanced Designs Have The Potential To

- Improve The Probability Of Commercial Success
- Accelerate Delivery Of Therapies To Patients In Need
- Improve Return On R&D Investment

Integrating CID with other drug development tools and best available technology can **save a program 20-30% in time and cost.[3]**

Sources: [1] Tufts research published in Journal of Health Economics, 2016, https://doi.org/10.1016/j.jhealeco.2016.01.012.
[2] PhRMA, http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf, accessed 29-Apr-2020.
[3] Presentation at DIA Conference on CID by Richard Moscicki, MD, March 2020.

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A Hole In One Is Highly Unlikely Even For The Pros

At the outset, even the best planned trials face uncertainties:

- Treatment effect
- Subpopulation responsiveness
- Dose selection

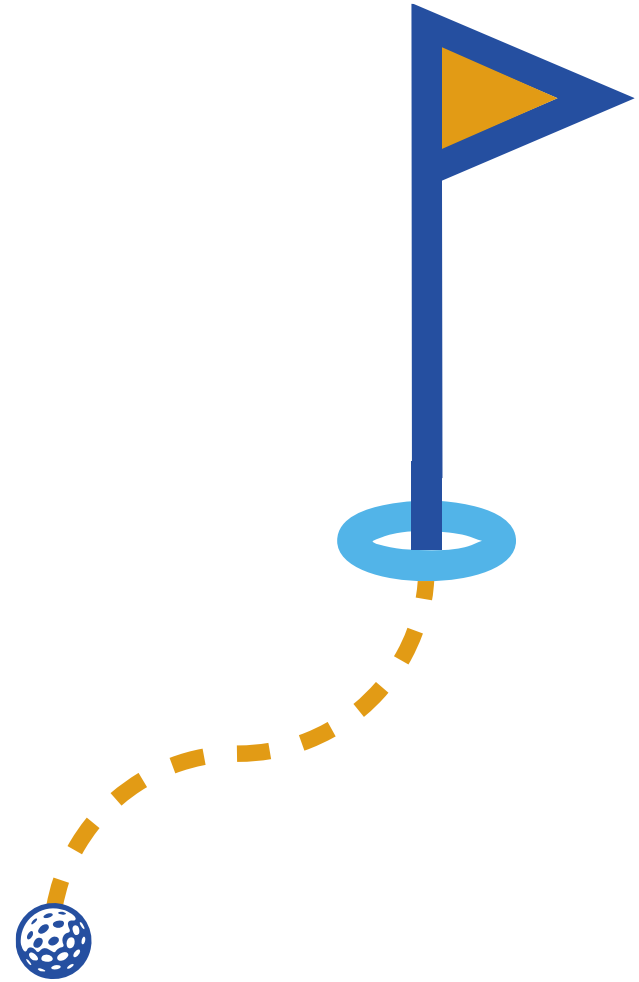
Researchers using fixed trial designs either:

- Over-engineer designs (large sample size, trial duration) >> increase cost of trial and delay time to market

OR

- Risk failing to draw a meaningful conclusion >> repeat trials or abandon promising therapies

Complex innovative designs enable researchers to mitigate uncertainty by pre-planning ways to adapt as they learn.



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Complex Innovative Designs Can Increase R&D Return On Investment In Exchange For Modest Operational Complexity

ADVANTAGES

Increase R&D Return On Investment

REDUCE

- Cost
- Time of Development

IMPROVE

- Probability of Success
- Expected NPV

COSTS

Operational Complexity

INCREASED SET UP TIME

- Require more up-front discussion
- Increased statistical resource at the planning stage such as simulations
- Operationalize the processes among multiple parties

Increased Spend & Complexity

- Additional manufacturing costs for some designs
- Increased drug supply & trial site management complexity

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Uncertainties & Adaptive Insurance Solutions

Uncertainty About Treatment Effect Or Variability Of Data • **Early stopping for futility** • **Sample size re-estimation**	Uncertainty about dose • **Advanced dose escalation designs** • **Adaptive dose response** • **Seamless 2/3**	Uncertainty about (sub)population, indication • **Population enrichment** • **Master protocol: Basket**
Uncertainty about most promising therapy • **Master protocol: Umbrella**	Uncertainty about dose, indication, and/or therapy • **Multi-arm, multi-stage** • **Master protocol: Continuing**	Drug simply doesn't work • **Early stopping for futility**

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Poll Question

Do you use complex or adaptive trial design?

A: No

B: Yes, but only group sequential

C: I use group sequential and other advanced trial designs

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Long-standing Complex Designs Already Have Regulatory Acceptance, And Regulators Are Paving The Way For More Innovation

Draft FDA Guidance 2019
Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

The primary focus is on FDA and sponsor interactions for CID proposals for trials intended to provide substantial evidence of effectiveness.

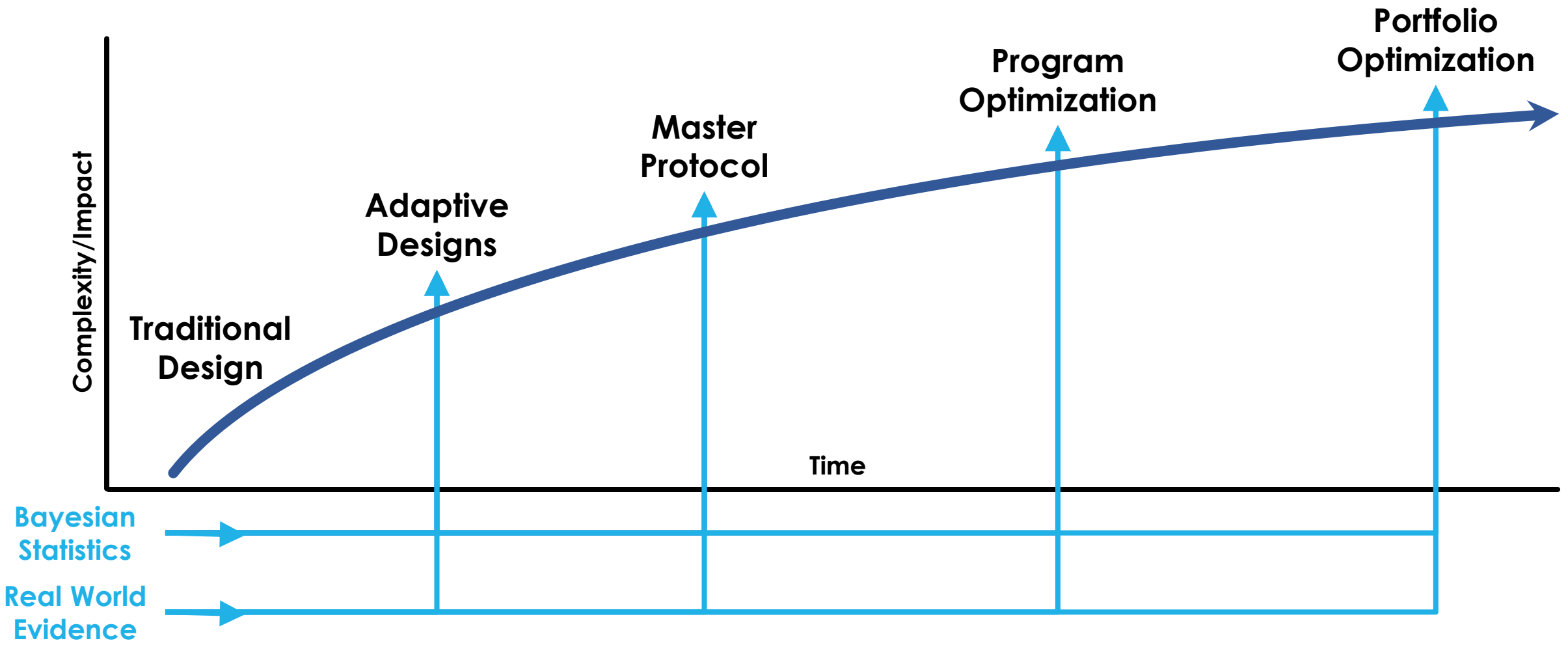
A common feature of many CIDs is the need for simulations because the trial operating characteristics cannot be calculated directly.

This guidance does not indicate whether specific novel designs are or are not appropriate for regulatory use.

Determinations to be made on a case-by-case basis depending on:

- The reasons the design is being proposed,
- Its validity in the specific setting, and on factors unique to a given development program.
- A CID proposal that may be appropriate for one product class in one indication may not be appropriate for another product class or in another indication.

Journey from Traditional Designs to Portfolio Optimization



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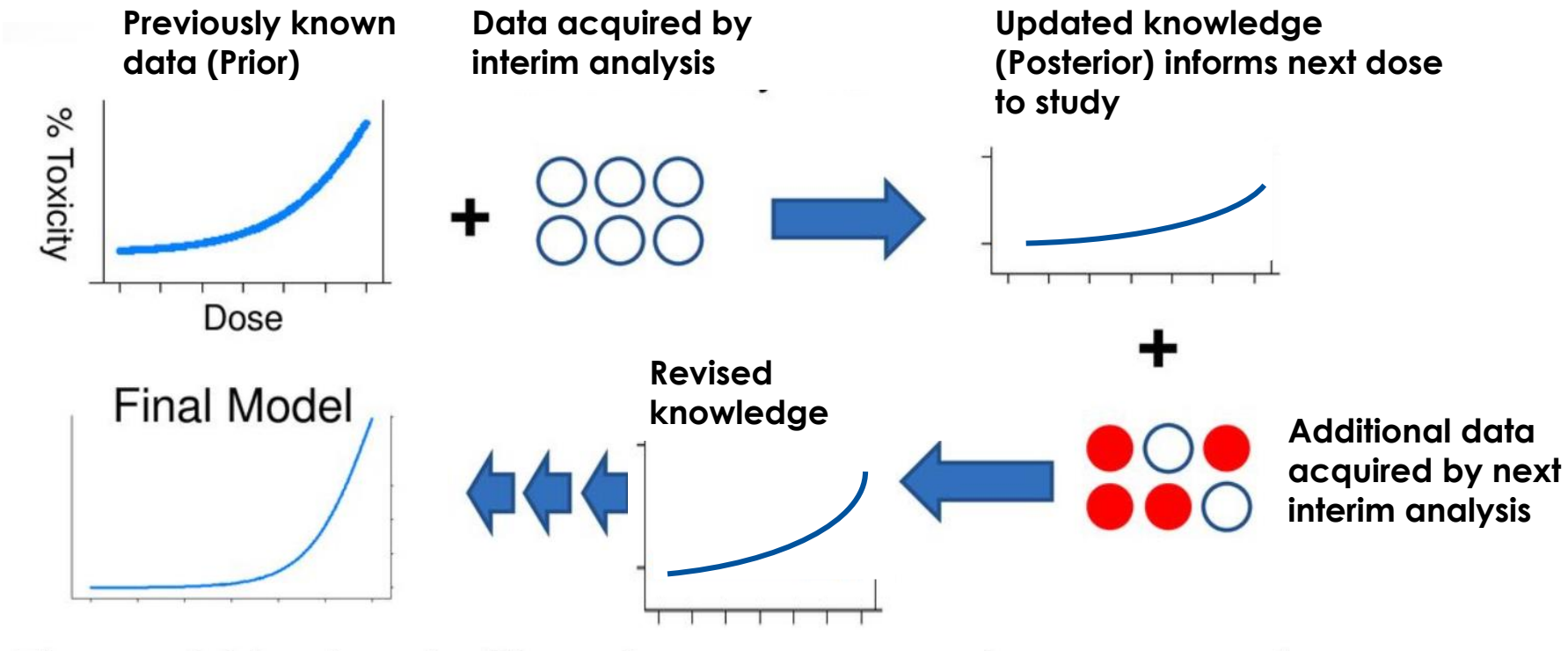
Adaptive Designs Can Increase Trial Efficiency Or Increase Probability Of Technical Success

Advanced Dose Escalation Better Characterizes Maximum Tolerated Dose

Continuous Reassessment Method (CRM) and Bayesian Logistic Regression Module (BLRM)



The Model Leads To Significant Improvement On The Accuracy Of The Dose Identification Over The Conventional Approach

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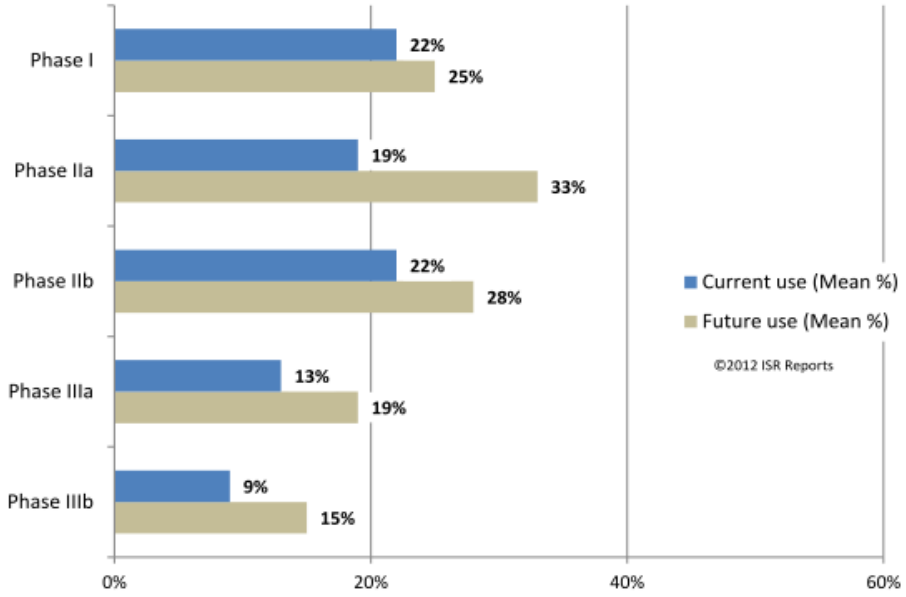
Adaptive Dose-Finding Improves Probability of Success

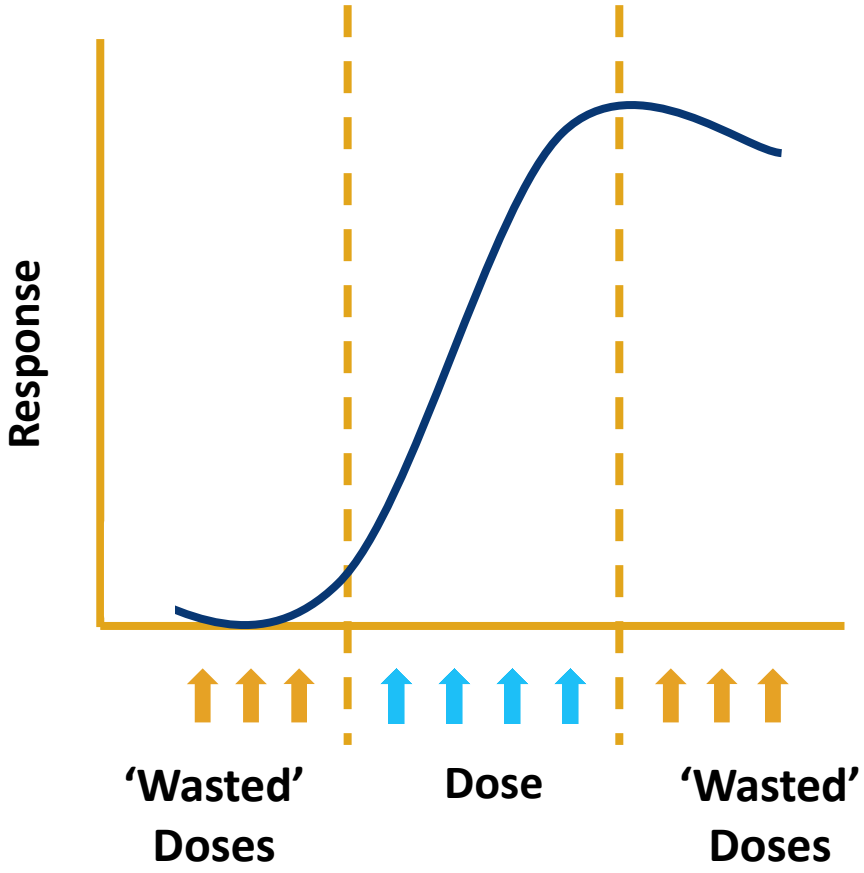
Inappropriate dose selection remains the main reason for failure at Phase II and III

The greatest uptake of adaptive trials will be in exploratory development (Phase IIa/IIb) to improve dose selection and Phase II decision-making



ISR Report December 2012

Increased number of doses + adaptive allocation



The strategy is to initially include few patients on many doses to determine the dose-response, then to allocate more patients to the dose-range of interest – this reduces allocation of patients to 'non-informative' doses ('wasted doses').

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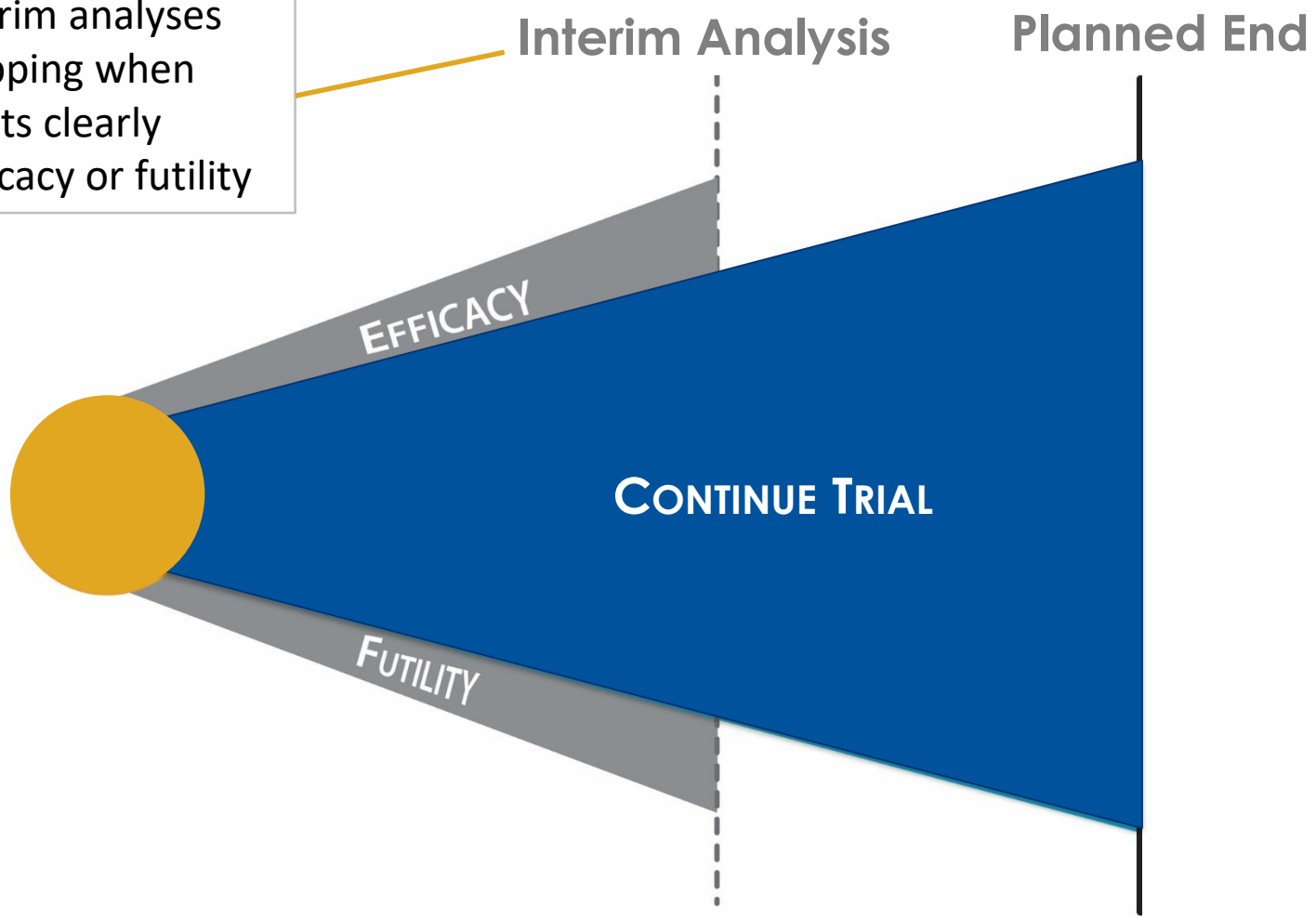
Group Sequential Design Can Reduce Sample Size And Duration, Conserving Resources And Accelerating Development

Pre-planned interim analyses enable early stopping when preliminary results clearly demonstrate efficacy or futility



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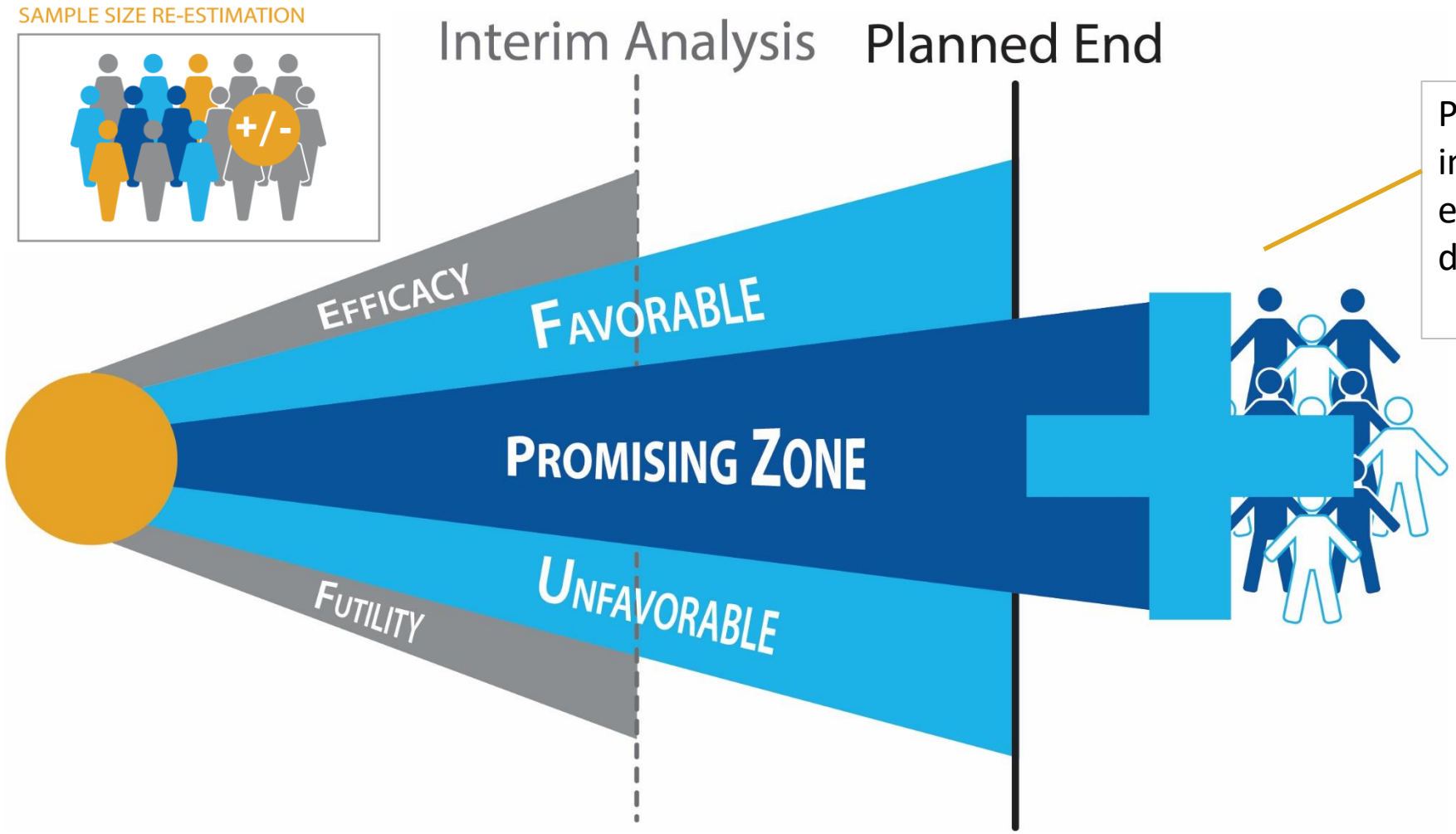
Adaptive Sample Size Re-estimation Can Increase Probability of Success When Treatment Effect is Less than Expected



Pre-planned criteria for increasing enrollment when expected trial end would not draw meaningful conclusion

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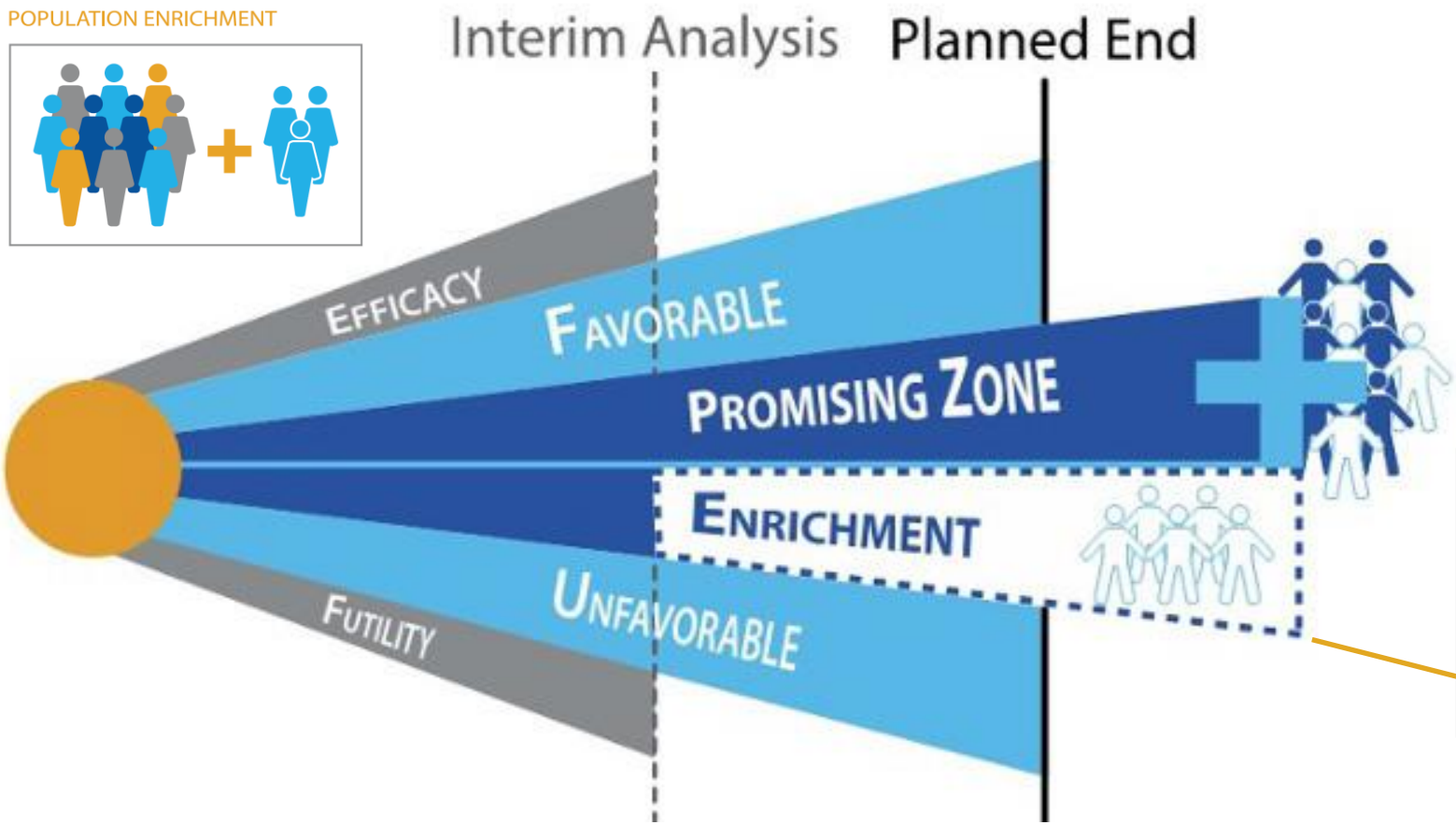
Adaptive Population Enrichment Can Increase Probability Of Success When Treatment Effect Is Different For Subpopulations, Diluting Signal



Pre-planned criteria for increasing proportion of promising subpopulation when expected trial end would not draw meaningful conclusion

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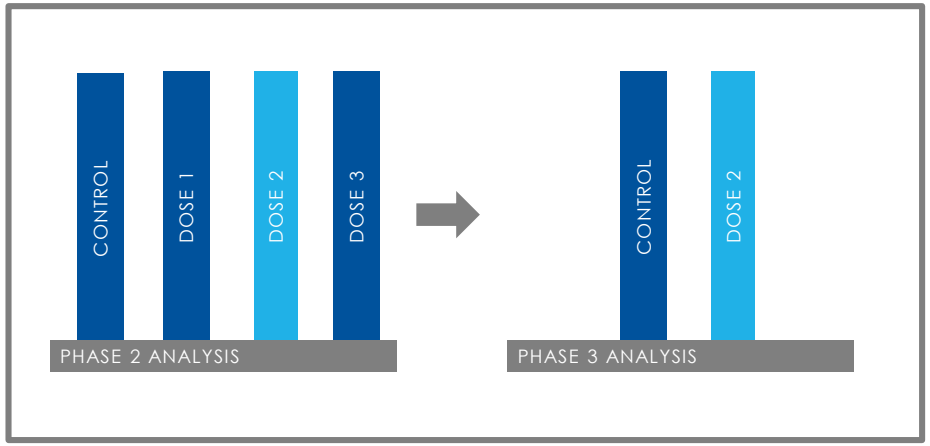
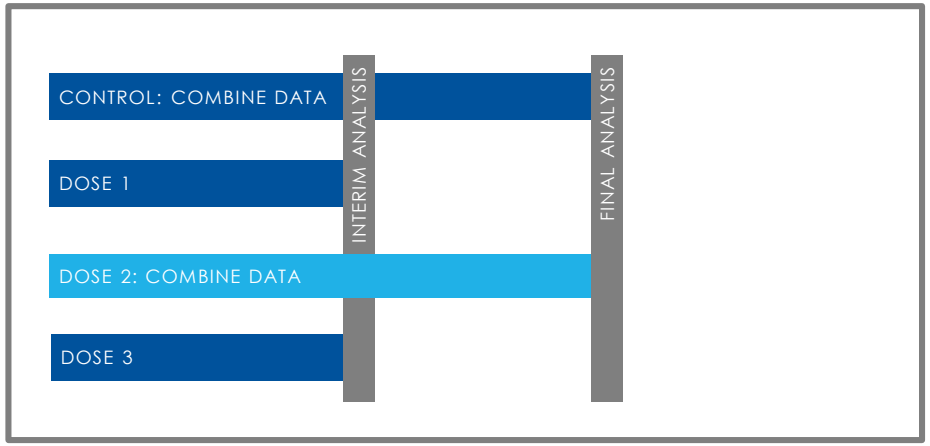
Seamless Phase 2/3 Can Increase Development Efficiency

TRADITIONAL



- Dose selection at Phase 2 analysis
- Phase 3 analysis uses data from Phase 3 only

SEAMLESS PHASE 2/3



- Dose selection at interim analysis
- Final analysis combines the data from both stages utilizing the method of Posch et. al. (Statistics in Medicine, 2005)

Some seamless phase 2/3 studies can achieve dose selection and confirmatory data at the same power with **30% fewer patients**[1] over other traditional designs and avoid time lost between trials.

[1]Cytel analysis.

Master Protocols Reduce Administrative Burden And Accelerate Phase Transitions

Master Protocols

Operational Efficiencies

- Patients, central laboratories and reading centers are shared
- Common investigators' training and screening platforms
- Master databases are compiled

Statistical Efficiencies

- Shared Control
- Information "borrowing"
- Adaptive randomization can be applied to accrue patients to the best treatments

Strategic Benefits

- Protocols continue even after drug candidates exit – new trials need not be started each time
- Standardization implemented at the platform level
- Decisions made in the broader context

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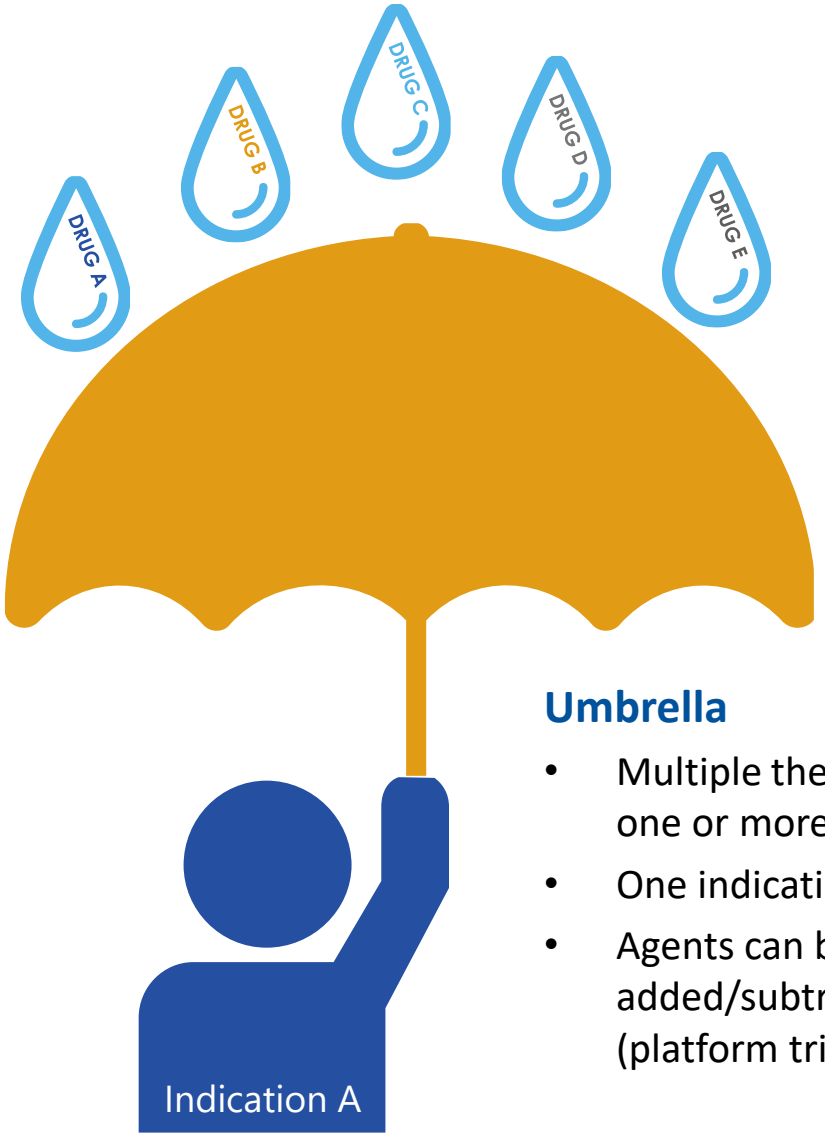
Two Types of Master Protocols



Umbrella

- Multiple therapies (from one or more sponsors)
- One indication
- Agents can be added/subtracted (platform trials)

Basket

- One therapy from one sponsor
- Multiple indications
- Indications can be added/subtracted (platform trials)

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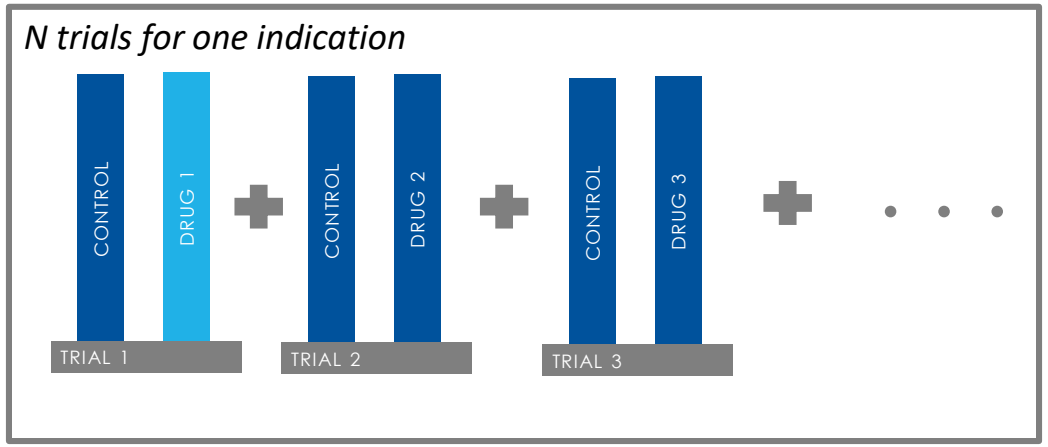
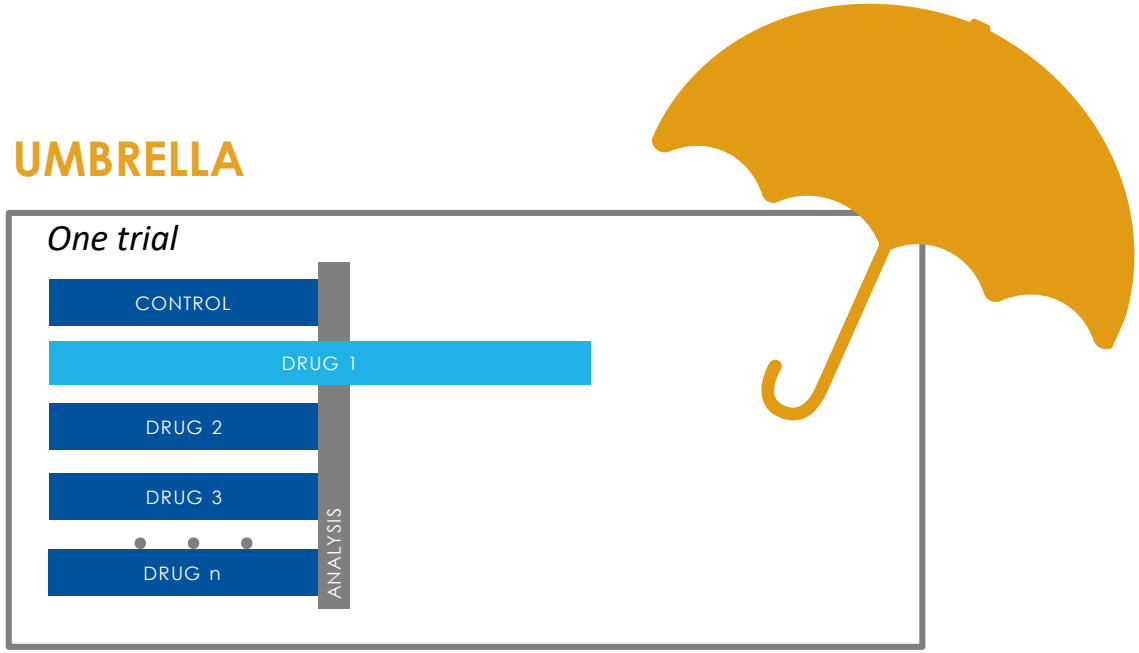
Umbrella Trials Increase Administrative and Control-group Efficiency When Exploring Drugs for an Indication

TRADITIONAL



UMBRELLA



(Adaptively Randomize)

- Control groups are shared (control is minimized)
- Patients are not wasted on ineffective treatments
- New drugs can be added while the trial continues (platform trial)

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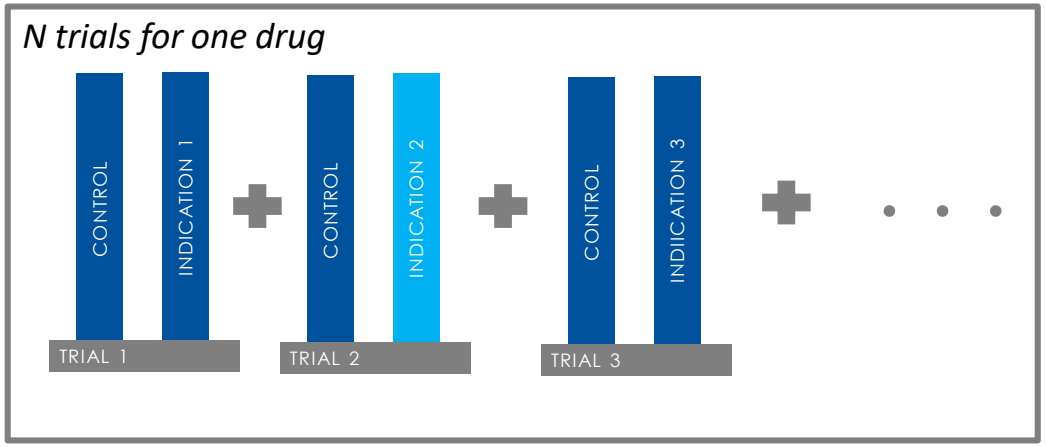
Basket Trials Increase Administrative & Control-group Efficiency When Exploring Indications for a New Drug

TRADITIONAL



BASKET

(Adaptively Randomize)

- Control groups are shared (control is minimized)
- Efficiently screen new drugs against numerous indications
- New indications can be added while the trial continues (platform trial)

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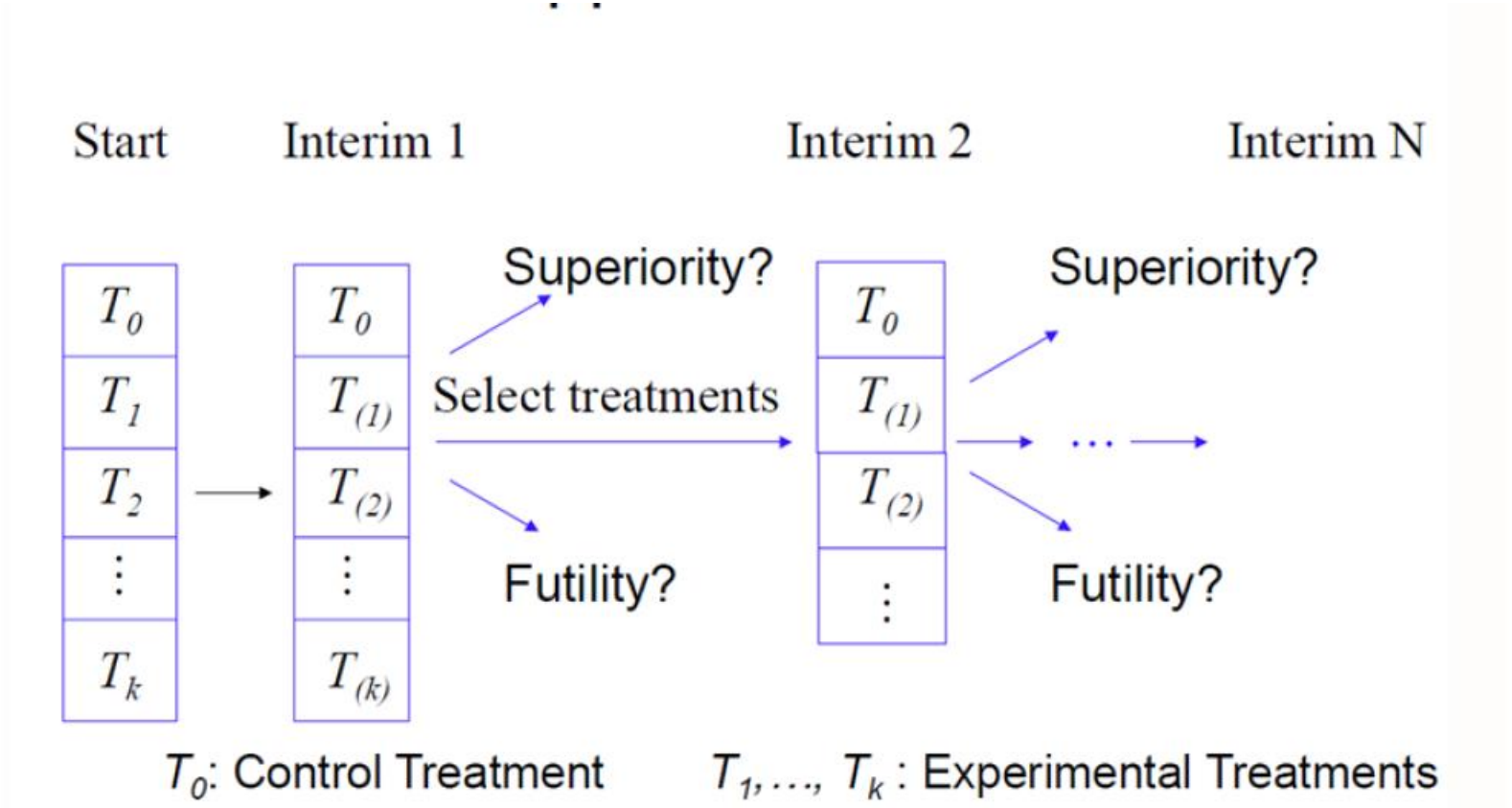
Multi-arm Multi-stage (MAMS) Design Increases Development Efficiency

DROP-THE-LOSER AND GRADUATE-THE-WINNER DESIGNS



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Chapman & Hall/CRC Biostatistics Series
Platform Trials in Drug Development
Umbrella Trials and Basket Trials
SELECTION
PRUNING (External Data)
PRUNING (Surrogate endpoints)
Consistent trend in definitive endpoint
Accelerated Approval
FULL APPROVAL (Pooled analysis of definitive endpoint)
Edited by
Zoran Antonijevic
Robert A. Beckman
CRC Press
Taylor & Francis Group
A CHAPMAN & HALL BOOK

Pharmaceutical Frameworks For Considering Trial Designs

Pharmaceutical Frameworks

Perceived Risk vs. Objective Risk

Development Options and Operating Characteristics

- Define Context
- Frame the Problem
- Specify Options
- Run Simulations

Bayesian Updating

Objective Decision Criteria

- Evidence-driven
- Prospectively Defined
- Optimality

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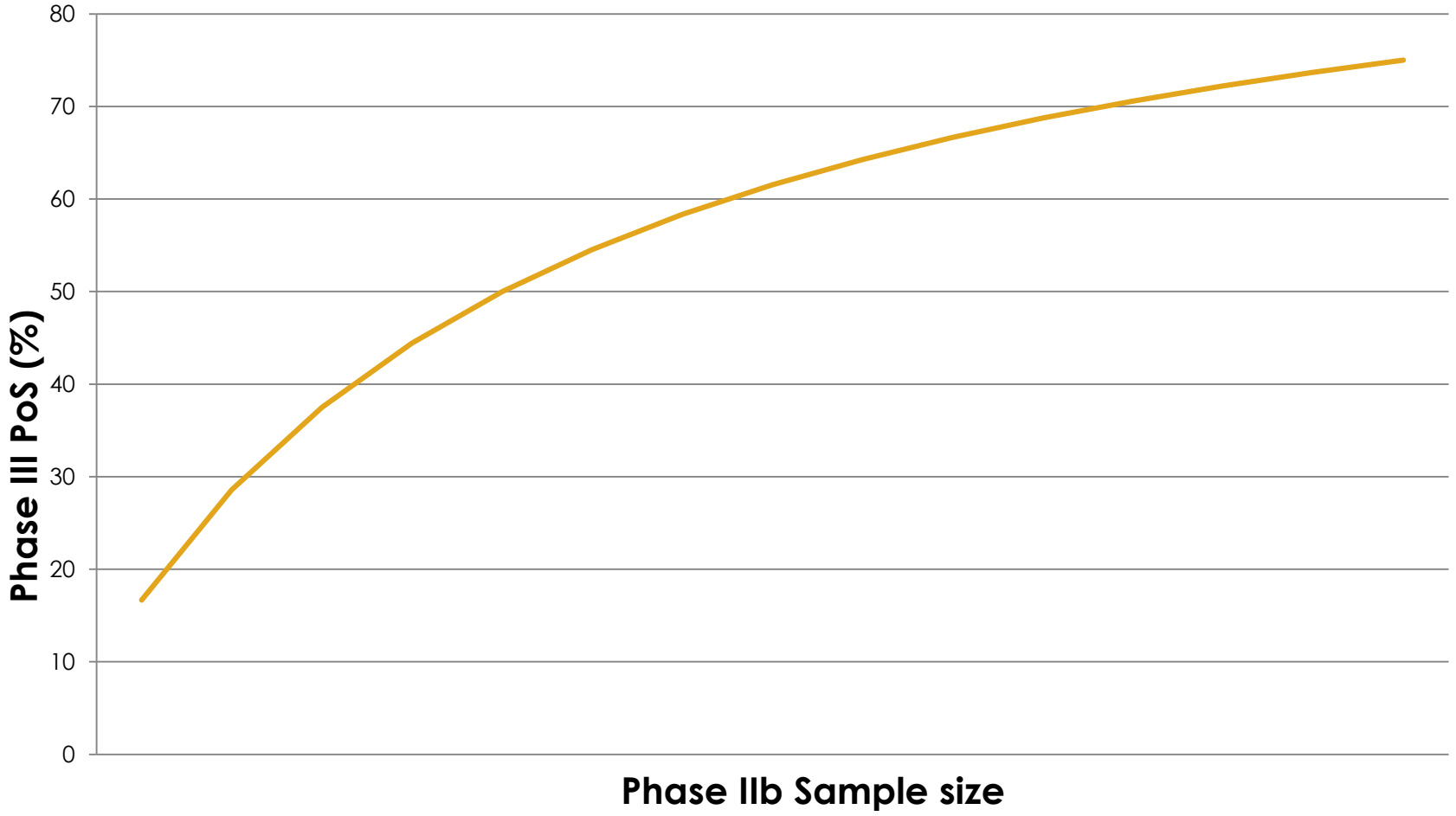
Relationship Between the Size of Phase IIb and the Probability of Success in Phase III



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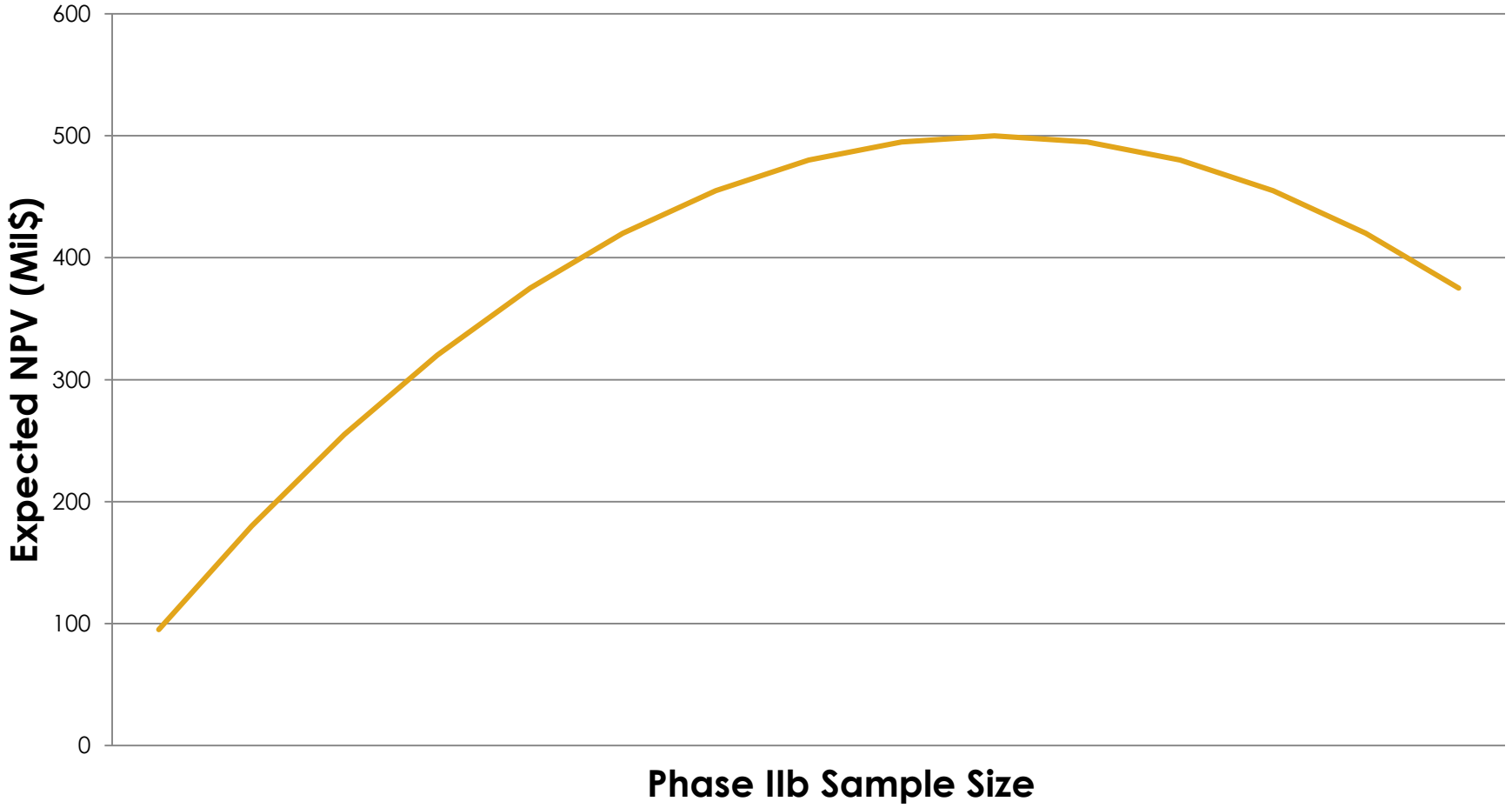
Relationship Between the Size of Phase IIb and Product's Expected NPV



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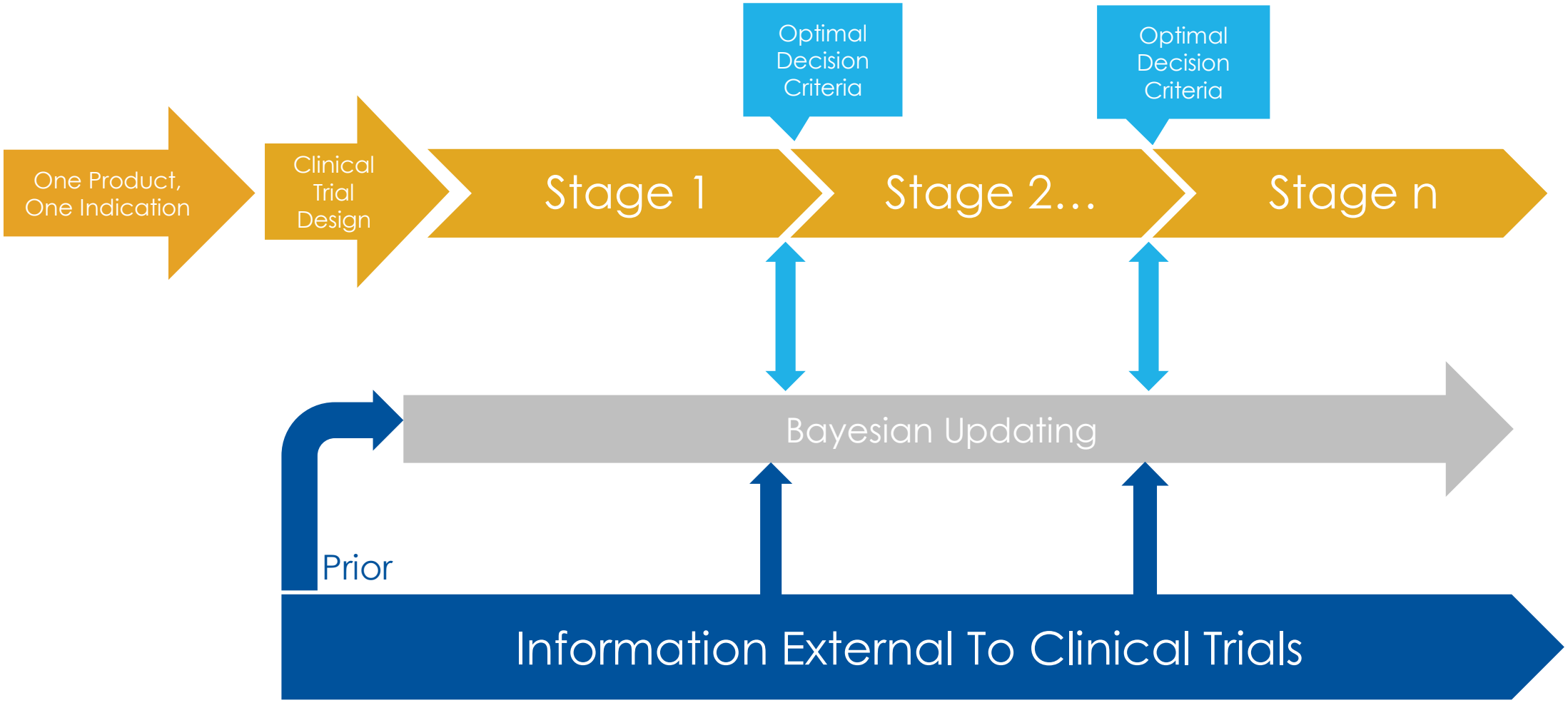
Program Level Framework



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Types of Error in Drug Development

Type I Error

- Incorrectly continue development of a truly negative treatment

Type II Error

- Incorrectly stopping development of a good treatment

Type III Error (Beckman, Chen) portfolio only

- Missed opportunity to invest into trials that might have identified good treatments

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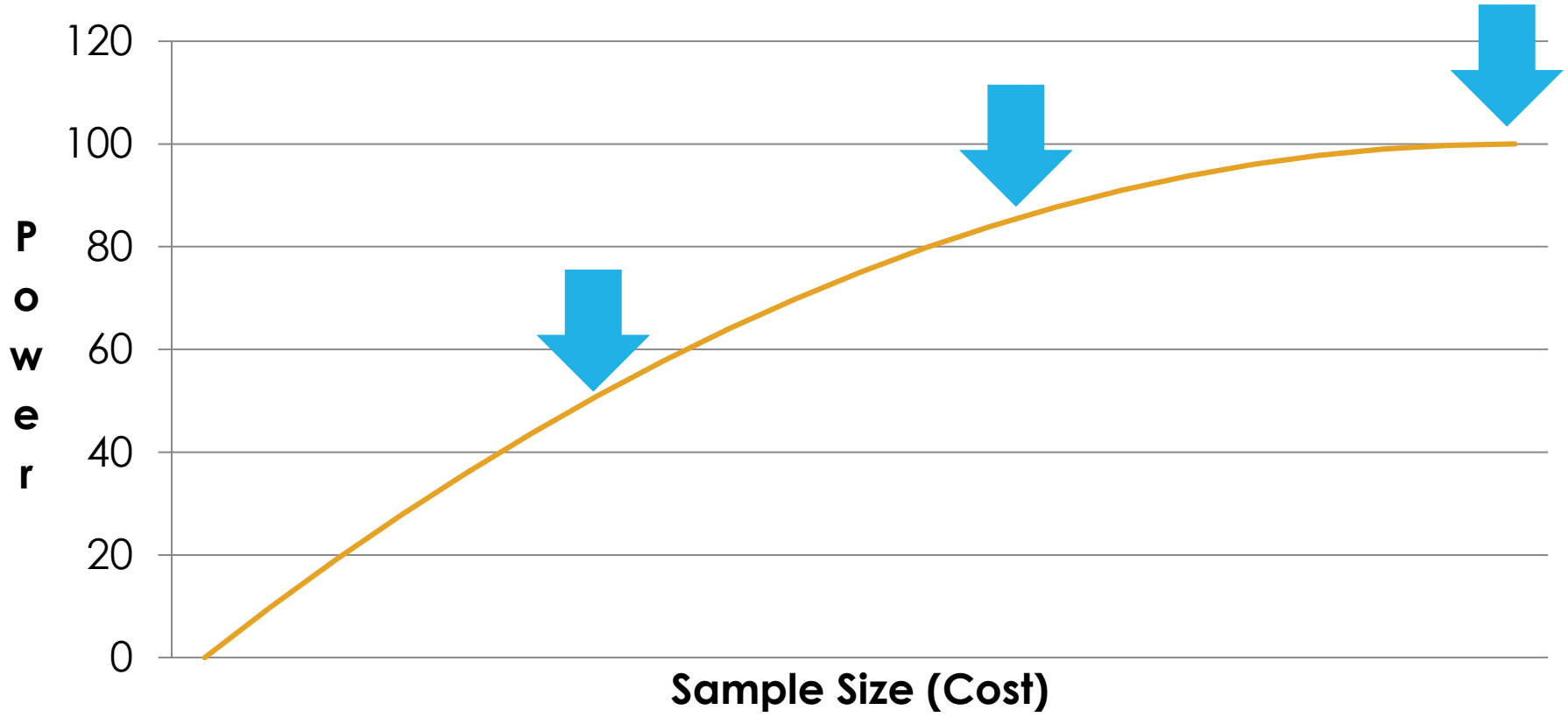
What is the Problem with not Optimizing at the Portfolio Level



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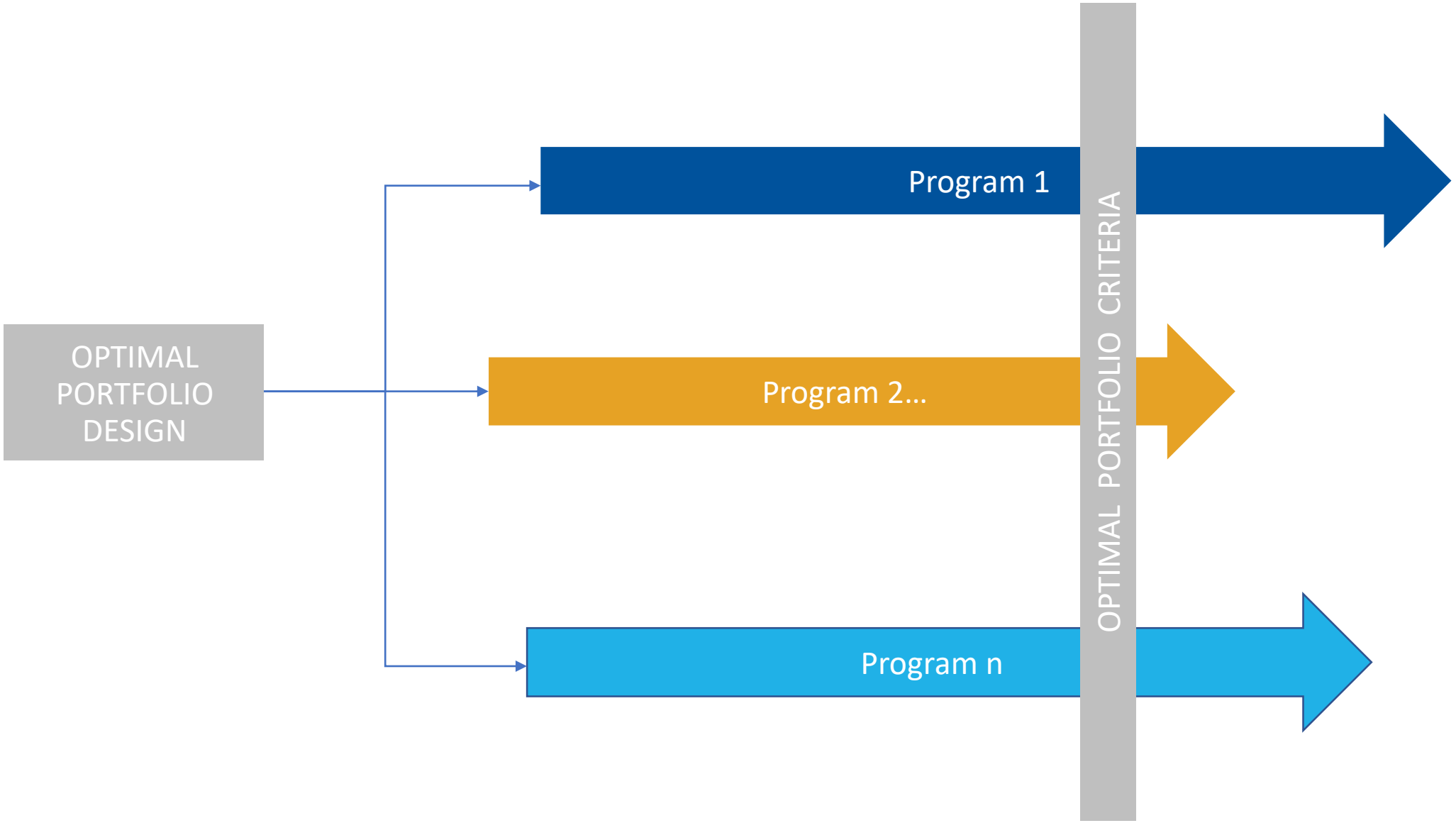
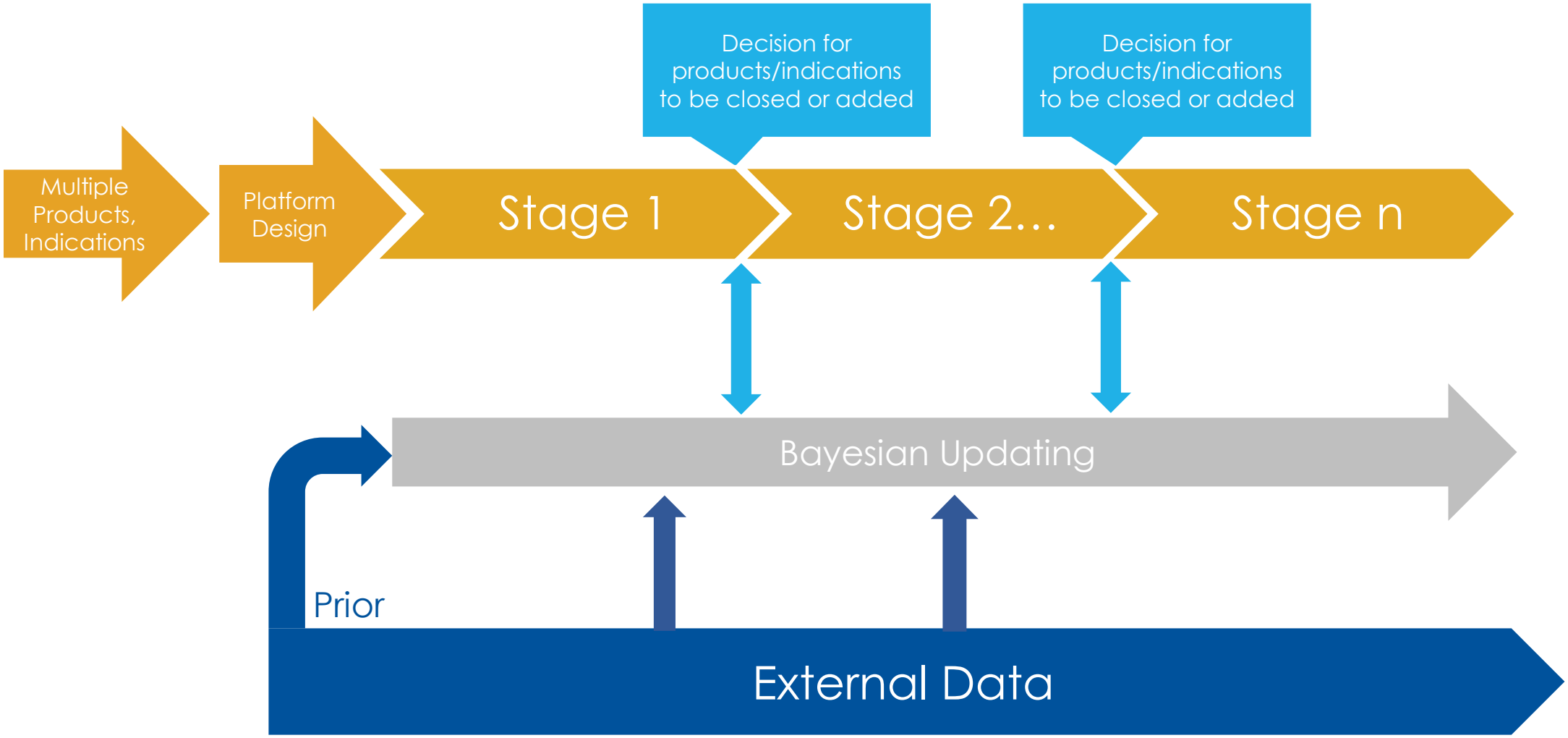
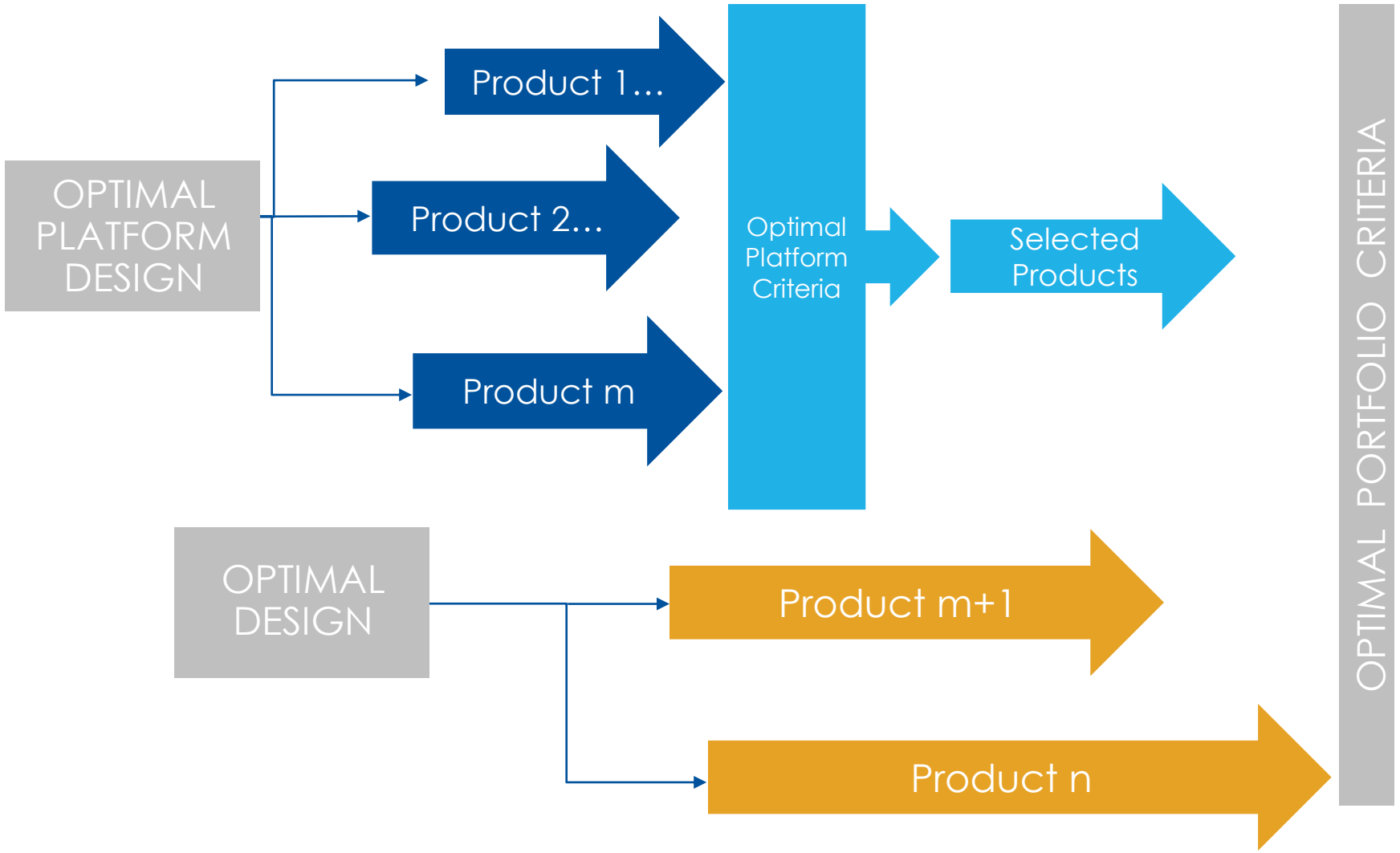

OPTIMAL PORTFOLIO DESIGN
Program 1
Program 2…
Program n
OPTIMAL PORTFOLIO CRITERIA

Platform level Framework



Portfolio Level Framework That Includes A Platform



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Innovative Designs Can Accelerate COVID-19 Therapy Development

COVID-19

Scientific rigor in drug development vs. the acute urgency for treatment. Three innovative approaches merit consideration:

Platform trials, with multiple therapies tested, possibly at staggered times, with potential to share control patients. Examples:

- SOLIDARITY, WHO-sponsored
- Adaptive COVID-19 Treatment Trial (ACTT), NIH-sponsored
- REMAP-CAP, a global platform trial adaptively testing many therapies

Alternative data sources and Bayesian designs, utilizing external data to minimize control patient numbers

Multi-stage seamless trials, with adaptive selection of doses and acceleration between phases

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Summary

Summary

Innovative designs can increase the value of our programs by reducing time and cost and/or by increasing PoS.

- Usually they will increase the eNPV

It is critical to define the framework within which one can develop and assess alternatives.

Optimal decision criteria can further improve the quality of development at program, platform, or portfolio level.

- Decision making at trial or program level an obstacle in getting the most out of Platforms and Portfolios

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East

Easy Access to the Adaptive Designs That Matter

Delivered by the Thought Leaders Behind the Methods

Software that is Faster & Easier to Use

Popular Fixed and Adaptive Designs at your Fingertips

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Global Products and Services

Statistical Software

Industry standard for trial design, including CID adaptive (East, EOD)

Leader in exact statistical solutions (Xact: StatXact, LogXact, Procs)

Operations software (e.g. ACES, EnForeSys, FlexRandomizer)

All 25 top biopharma companies, the FDA, EMA & PMDA use our software

Strategic Consulting

PhD statisticians expert in innovative design & complex statistical questions

Experts in Data Science, PK/PD, Enrolment & Event Forecasting, Portfolio/Program Optimization (NPV)

Project-Based Services

Reliable Biometrics service provider delivering high quality, on time

Lead staff with over 15 years industry experience on average

Including biostatistics & programming, ISC, data management, PK/PD analysis, medical writing

Functional Services Provision (FSP)

Creation of dedicated teams operating within/as an extension of the client's own biostatistics & programming, data management and PK/PD teams

Leader in offshoring of Biometrics competencies

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Q&A

Conclusion

Upcoming Webinars

Topic	Date	Time	Speaker	
Complex Innovative Trial Designs at a Glance – The Concepts, the Promise, and the Factors to Consider	Wednesday, May 20, 2020	11:00AM EDT | 16:00 GMT	Zoran Antonijevic	✓
Group Sequential Designs and Sample Size Re-estimation – Modern Uses	Wednesday, June 3, 2020	11:00AM EDT | 16:00 GMT	Christopher Jennison	
Practical Model-based Approaches for Phase I Oncology Trials	Wednesday, June 17, 2020	11:00AM EDT | 16:00 GMT	Satrajit Roychoudhury	
Introduction to Population Enrichment	Wednesday, July 15, 2020	11:00AM EDT | 16:00 GMT	Thomas Burnett	

Other Topics Planned for Series: Introduction to Adaptive Dose Finding, Seamless Phase 2/3 Trial Designs, Basket Trial Designs, Umbrella Trial Design, Multi-arm Multi-stage Trial Design, and Program/Portfolio Designs

Recordings will be posted to www.cytel.com.

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Thank you

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Thank you

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