

***Good Practices for Adaptive Clinical
Trials in Pharmaceutical Product
Development***

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Content

Part I (Brenda Gaydos)

- Background
- Strategic points to consider
- Trial simulations
- Documentation

Part II (Keaven Anderson)

- Statistical considerations
- Bayesian methods
- Final data analyses & Inference
- Data Monitoring Committees

Background

PhRMA Adaptive Design Working Group

- **Initiated Q1 2005**
- **Vision 2006**
 - To **establish a dialogue** between statisticians, clinicians, regulators and other lines within the Pharmaceutical Industry, Health Authorities and Academia,
 - with a **goal to contribute to developing a consensus position** on when and how to consider the use of adaptive designs in clinical drug development.
- **Vision 2007**
 - To turn adaptive designs into a respected approach across all phases of clinical drug development
 - To **educate, set expectations for high quality standards, and share experiences** on case studies
 - To **continue to develop consensus positions through dialogue**

Background

Executive Summary of the PhRMA Working Group (2006)

- *Journal of Biopharmaceutical Statistics*; 16:275-283, 2006
- *Japanese Journal of Clinical Pharmacology*; 40:303-310, 2009

Full White Paper (2006)

- *Drug Information Journal*; 40(4), 2006
 - Terminology and Classification
 - Logistics and operational considerations
 - Adaptive dose-response studies
 - Adaptive seamless phase 2/3 designs
 - Sample-size reestimation
 - Confidentiality and trial integrity issues

Good Practices Paper (2009)

- **Goal:** Good adaptive practices for the industry based on experiences to date
 - Regulatory discussions: **FDA, EFPIA / EMA, Health Canada, PMDA / JPMA**
- **Audience:** Anyone involved in planning and executing clinical trials

Strategic Points to Consider

- Assessing design alternatives
- Scope of adaptations within confirmatory trials
- Operational considerations
- Regulatory considerations
- Clinical considerations

Assessing Design Alternatives

Clearly articulate & quantify benefits and risks

- Must consider the overall development plan and information value per resource unit
- When developing adaptive design alternatives, consideration should be given to the following questions
 - 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?

Assessing Design Alternatives

Recommended to perform a formal assessment analysis

- Establish conventional base case plan (*anchor*)
- Describe the pros/cons of alternative adaptive designs for all affected stakeholders relative to the base case
 - Patients, investigators, researchers, trialists, health authorities, ethics committees, sponsors, and payers
- Assess scientific & business considerations
 - Assess the level of certainty for which the research questions are addressed
 - Assess the earliest time point at which sufficient information is acquired or uncertainty is reduced to drive decisions
 - Understand the costs, including drug supply material and management costs
- Assess strategies based on faster to patient
 - NOT faster to traditional project benchmarking milestones (e.g. faster to first efficacy dose, or first registration dose)

Scope of Adaptations within Confirmatory Trials

Situation dependent

Number of ***trial aspects*** adapted should be small (1 or 2)

- “...aim to resolve only minor amounts of design uncertainty, generally from within a small number of pre-specified possibilities.”

Proper adjustments to maintain type I error rate control

(e.g.) Inferentially seamless phase 2/3 designs

- with Treatment or Population selection at interim
- All potential effect hypotheses pre-specified
- Analyses must account for all groups
- Propose NO limit on # treatment arms or populations (adapting only 1 trial aspect), but caution on efficiency

Scope of Adaptations within Confirmatory Trials

Could consider operationally seamless 2/3 design if desirable to generate hypotheses from data analysis within the trial

- Similar to 2 studies in one protocol
- Stage 2 specified up to the selection to be made in stage 1
- e.g. exploration of data from stage 1 to select endpoints
- Data from stage 1 would not be combined in final analysis with data from stage 2
- **Cautions:**
 - Loss of *think time* that would typically occur between phase 2 and phase 3 study
 - AND Loss of efficiency from combining data to make inference

Regulatory input should be sought in advance for adaptive confirmatory trials

Operational Considerations

Resources

- Planning pulled forward
- Additional resources may be required
 - At design stage for scenario creation & simulation
 - Accelerated activities in areas of clinical monitoring, data management
 - Interim data analysis activities
- Trial execution budgets need to be considered over a range (e.g. min to max sample size) to account for adaptive features

Impact of enrollment rate on the adaptive design needs to be carefully considered

- Faster enrollment may NOT be faster to patient
- Enrollment rate can be an adaptive aspect of the trial (e.g. open up other sites if futility is not declared following an interim)

Use the best available information, including NOT fully cleaned data, when deciding on adaptations

- Balance data quality and timeliness to optimize decision making

Operational Considerations

Minimize time required from data extraction to analysis

- Automate as much as possible to reduce manual intervention

Randomization requires close integration between data analysis and allocation of treatment assignment.

- Develop process jointly with data analysis

Develop a communication plan to effectively manage adaptations and mitigate potential for operational bias

Assess drug supply early (pre-IND)

- More dosage strengths and greater quantities of drug available may be required
- For seamless Phase II/III, accelerated commercial formulation and/or a material bridging strategy may be needed.

Developed drug management plan to address changes in study design.

- Trial simulation can help to minimize risk of lack of material availability and waste

Regulatory Considerations

For Confirmatory Trials (see FDA draft guidance)

- Early discussions with regulatory agencies can be critical
- Must consider the adaptive trial in context of full clinical plan
- Review packaged detailed enough to allow a critical review
- Some important questions to consider:

What are the benefits and risks of making decisions based on interim analyses?

Is there a clear rationale for the benefit of the adaptive design?

Are there any potential concerns by regulators based on the analysis criteria proposed to make decisions?

Have we clearly described who will see what data, and how information will be disseminated?

Have all the key stakeholders within the health authority been invited to provide input to the proposed study design?

Clinical Considerations

Determine an explicit goal for the adaptive design: e.g.

- treating as effectively as possible patients in the trial
- minimizing trial sample size for specified power
- minimizing overall drug development cost
- identifying the best doses to take forward as efficiently as possible

Develop quantitative decision criteria

- No trial design will be globally optimal

Identify key (minimum) endpoints to drive decisions

- Reduce complexity

Maintain control group throughout the trial

- Enhance trial interpretability

Clinical Considerations

Compare drug development strategies, NOT trial design strategies

- A single adaptive trial may take the place of more than one conventional trial
- Consider alternative strategies as well as alternative trial designs
- Some considerations:
 - Strength of evidence in overall development package (# fixed, # adaptive A&WC)
 - Overall development time
 - Total number of patients
 - Number of patients exposed to potentially ineffective therapies
 - Total resources

Procedures *fit for purpose*

- Statistical methods & operational processes vary from early to late phase

Trial Simulation

Trial simulation improves design and is recommended independent of designs under consideration

At minimum, both the adaptive design and an analogous fixed design should be simulated and compared

- Leverage information from disease state and exposure response models
- Assess operating characteristics under a variety of scenarios (including the Type I error rate)

Assess impact of enrollment rate

- Benefits of fast enrollment should be weighed against benefits of controlled enrollment

Incorporate the appropriate lag in information

- Lag should include time to realization of clinical outcome and time until data and data analysis are available

Assess impact of missing data

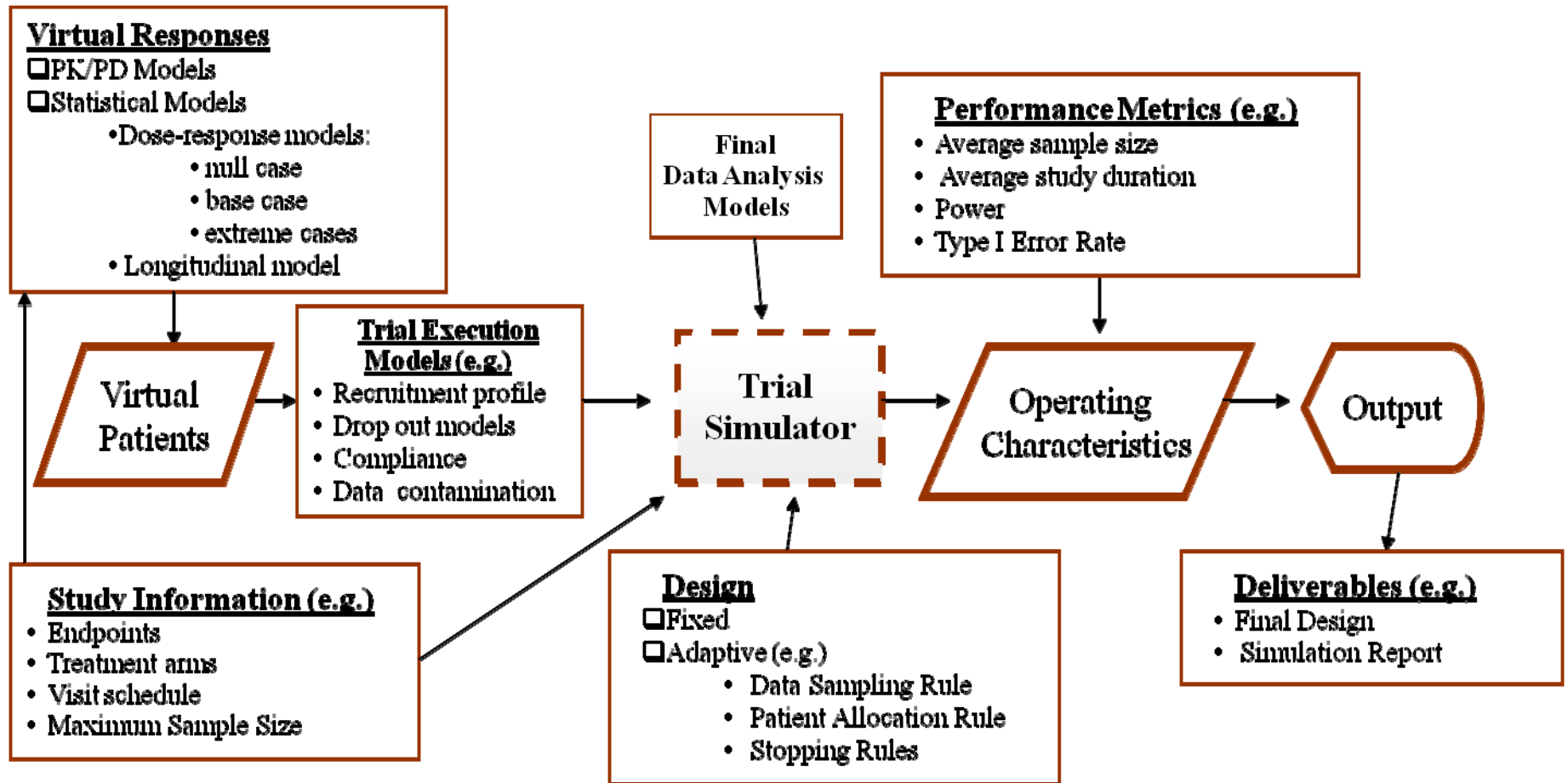
- Bias due to adaptation can be confounded with bias that may be inherent in the conventional design/analysis approach (e.g. LOCF)

Components of Trial Simulation



Exemplifies the
need for cross-
disciplinary
involvement

Trial Simulation Framework



Final Data Analysis Models

Performance Metrics (e.g.)

- Average sample size
- Average study duration
- Power
- Type I Error Rate

Trial Execution Models (e.g.)

- Recruitment profile
- Drop out models
- Compliance
- Data contamination

Trial Simulator

Operating Characteristics

Output

Study Information (e.g.)

- Endpoints
- Treatment arms
- Visit schedule
- Maximum Sample Size

Design

- ☐ Fixed
- ☐ Adaptive (e.g.)
 - Data Sampling Rule
 - Patient Allocation Rule
 - Stopping Rules

Deliverables (e.g.)

- Final Design
- Simulation Report

From: Good Practices for Adaptive Clinical Trials in Pharmaceutical Product Development. *Drug Information Journal* 43(5) 539-556.

Documentation

Operational bias should be mitigated through design,
NOT through post-trial analysis

- Operating procedures should be well documented
- Pre-specify the type of adaptation

To minimize operational bias, some details of the adaptive design may best be deferred to an IRB supplement or statistical analysis plan, e.g.

- How dose allocations are made in an adaptive dose finding trial
- Details of calculations for unblinded sample size re-estimation

Written clarity on adaptive algorithm in both exploratory and confirmatory trials facilitates:

- Ethical Review
- Implementation
- Maximizing Information

Recommend including in the protocol some justification of why an adaptive approach has been selected over a more conventional design

Documenting Trial Simulations

Purpose & timing of report can differ

- **Internal decision to select design**
 - Should contain performance comparisons of alternative design options, including a traditional design as a benchmark
 - Prior to protocol writing
- **Regulatory agency approval of study protocol**
 - Should contain main operating characteristics of the selected design
 - Prior to submitting documents for regulatory review & updated as needed to incorporate feedback
- **Increase understanding of design for DMC**
 - Should include clarity of decision rules
 - Prior to finalization of charter
- **Increase understanding of design for IRB review**
 - Should include examples of possible trial conduct
 - Submitted with the protocol

Documentation: Trial Simulation Report

Format depends on complexity of the adaptive design and the purpose of the simulation study

- Separate document, part of the Protocol, the IRB Supplement, or the Statistical Analysis Plan (SAP)

Why a separate report versus SAP?

- **Objective:** Trial simulation is for design justification, not detailed description of analyses of all data in the trial
- **Content:** Simulation of different scenarios to assesses the likelihood of design changes and the impact on 1 or a few endpoints. May include 2 or more designs for comparison purposes (fixed vs adaptive)
- **Timing:** All simulations need to be complete before protocol design finalized. Due to aggressive timelines, the simulation report is typically finalized after the protocol.
- **Audience:** Simulation report has a different and sometimes broader audience

General Outline of Report

- Differs depending on adaptive design type and phase of development
- White paper under development
 - General practices for conducting and reporting trial simulations
 - Special considerations for
 - dose escalation designs
 - dose ranging designs
 - sample size reestimation with or without early stopping
 - multistage confirmatory designs

Summary

Adaptive BY DESIGN

- Prospectively planned adaptations
- Written clarity on the adaptive mechanism
- Operating procedures should be well documented

Value across the clinical development paradigm

- Provide clarity on benefits over conventional approach
- Different requirements may apply in the setup of infrastructure for adaptive designs in exploratory VS confirmatory

Routinely use trial simulation to optimize trial design

- For Adaptive OR Fixed trial designs
- Recommend separate companion report for more extensive simulations

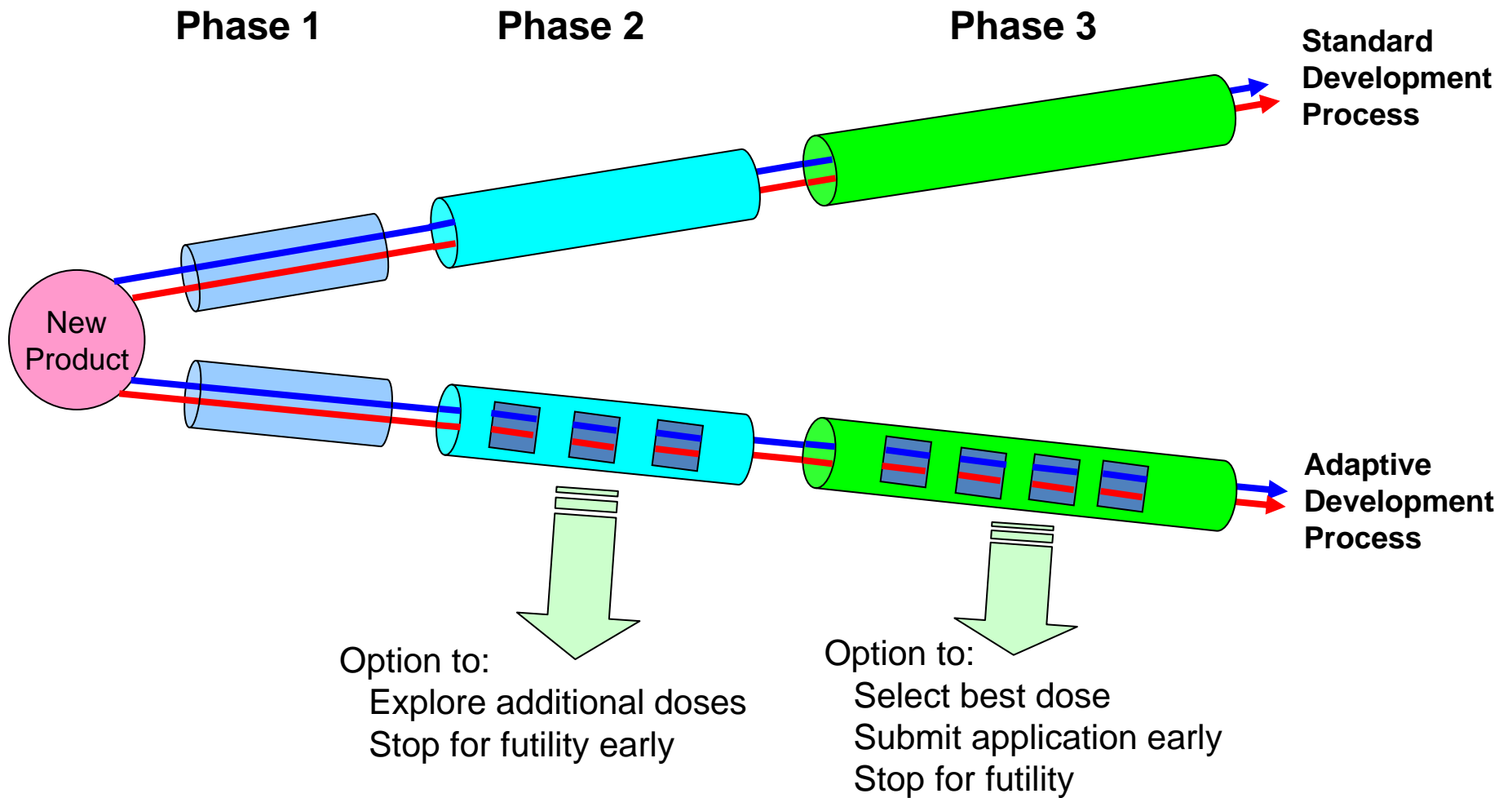
Scientifically and operationally more complex

- BUT issues are resolvable
- **Proper planning is essential**
- Simplifies as we gain experience & move toward standards

Part II Outline

- Statistical considerations
 - Designs
 - Dose finding
 - Group sequential design
 - Sample size re-estimation
 - Seamless Phase 2/3
 - Bayesian methods
 - Final data analyses
 - Inference and estimation
- Data Monitoring Committees
- Conclusions

Clinical Development Process



Source: J. Schindler

Dose-finding

- Adaptive dose-finding (DF) can characterize dose response more fully and efficiently than fixed-dose designs
 - Encouraged during “learning phase” by FDA
 - see Bornkamp et al. (often cited by FDA)
- Simulate design performance
 - include impact on confirmatory phase
 - may wish to carry more than 1 dose forward
 - Sample size should account for precision of target dose estimates and accuracy of decisions to be made
 - Engage DMC early engage in simulation prior to protocol approval
- DMC monitors design performance during study

Group sequential design

- On FDA's list of well-understood adaptive designs
- Large sample size with possible early stopping to adapt
- Information-based design allows sample size adaptation for event rates or incorrect variance assumptions
- Disadvantage: may not work when trial cannot stop promptly due to
 - long follow-up
 - slow data collection or cleaning
 - time to produce analysis

Sample size re-estimation

- Blinded sample size re-estimation
 - Encouraged by FDA draft guidance
 - Useful when nuisance parameters such as variance or control event rate uncertain
- Unblinded sample size re-estimation
 - Not on FDA “well-understood” list
 - Some think it should be
 - Type I error control well-understood
 - Estimation options available
 - Careful design selection required to be efficient

Seamless Ph II/II Design

- Seamless design combines objectives from 2 stages
 - Data from 1st stage must be available to determine final form of 2nd stage
- Multiple possibilities; e.g.,
 - Proof-of-concept + dose-finding
 - Dose-selection + confirmation
- Inferentially seamless
 - Combines data from both stages in inference
- Operationally seamless
 - Inference separate for each trial stage
 - May be preferred over inferentially seamless if there are “more unknowns” at the time of study design

Inferentially Seamless II/III

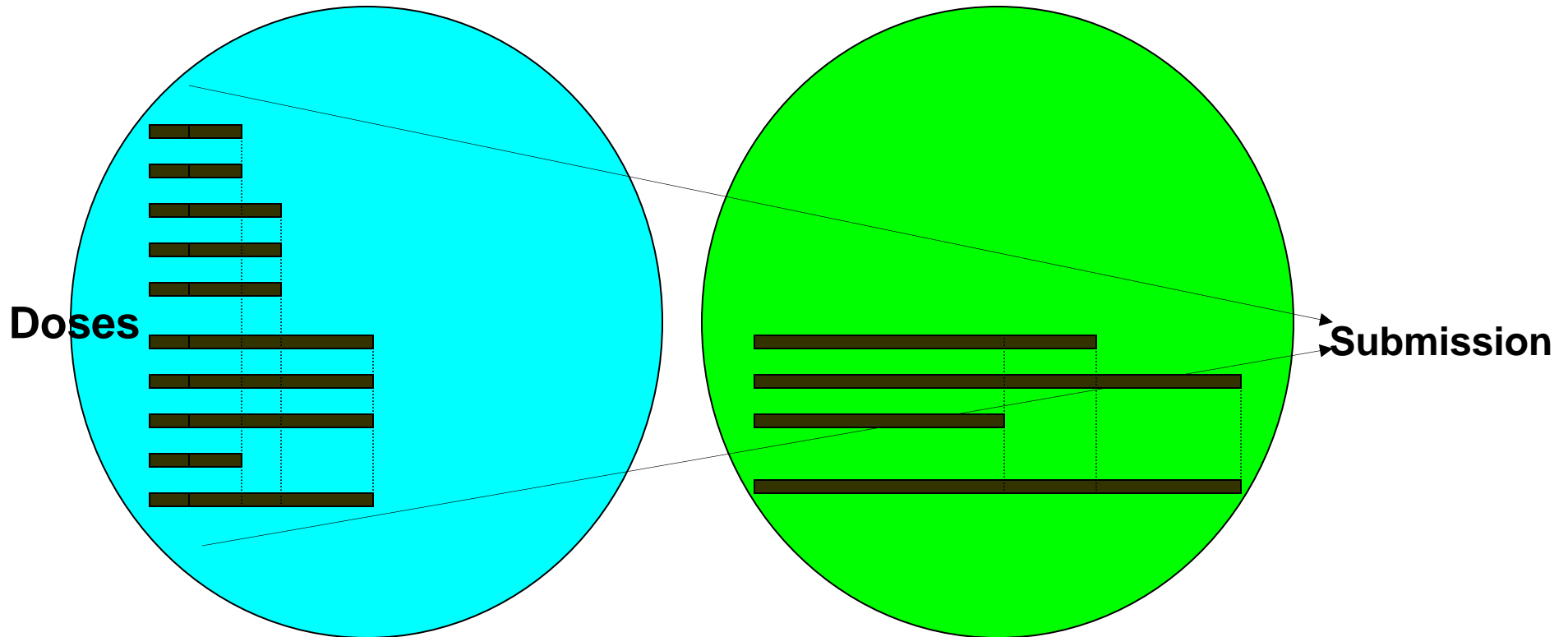
- Advantages
 - Reduces or eliminates time between trials
 - Allows an additional chance for limited learning during confirmatory trial (e.g., dose, population)
 - Substantial understanding of these designs has been developed
 - Combination of data from 2 stages possibly reduces number needed for pivotal trial

Inferentially Seamless II/III

- Disadvantages

- Limits incorporation of external considerations changing during trial
- Full evaluation of learning may not be possible before confirmatory stage
- Potential for long review cycles (internal and external)
- Careful planning and execution required
- Decision process for adaptation will be scrutinized
- Consistency between stages likely to be scrutinized
- Commercial formulation of product desirable
- Combining 2 trials into 1 may eliminate a separate, “2nd supportive trial”

Tandem Adaptive Clinical Trials



1. Adaptive Phase II Trial
POC/Dose Response Estimation
Early Development

2. Adaptive Phase III Trial
Registration Development

Bayesian Methods

- Can be ideal for learning stage of development
 - Excellent data integration capabilities
- Simulation a good idea for documentation of frequentist properties
- Full potential not yet realized due to lack of experience

Statistical considerations

- Assessing homogeneity
 - some knowledge of interim results may be conveyed through adaptations
 - recommend as 2ndary analysis

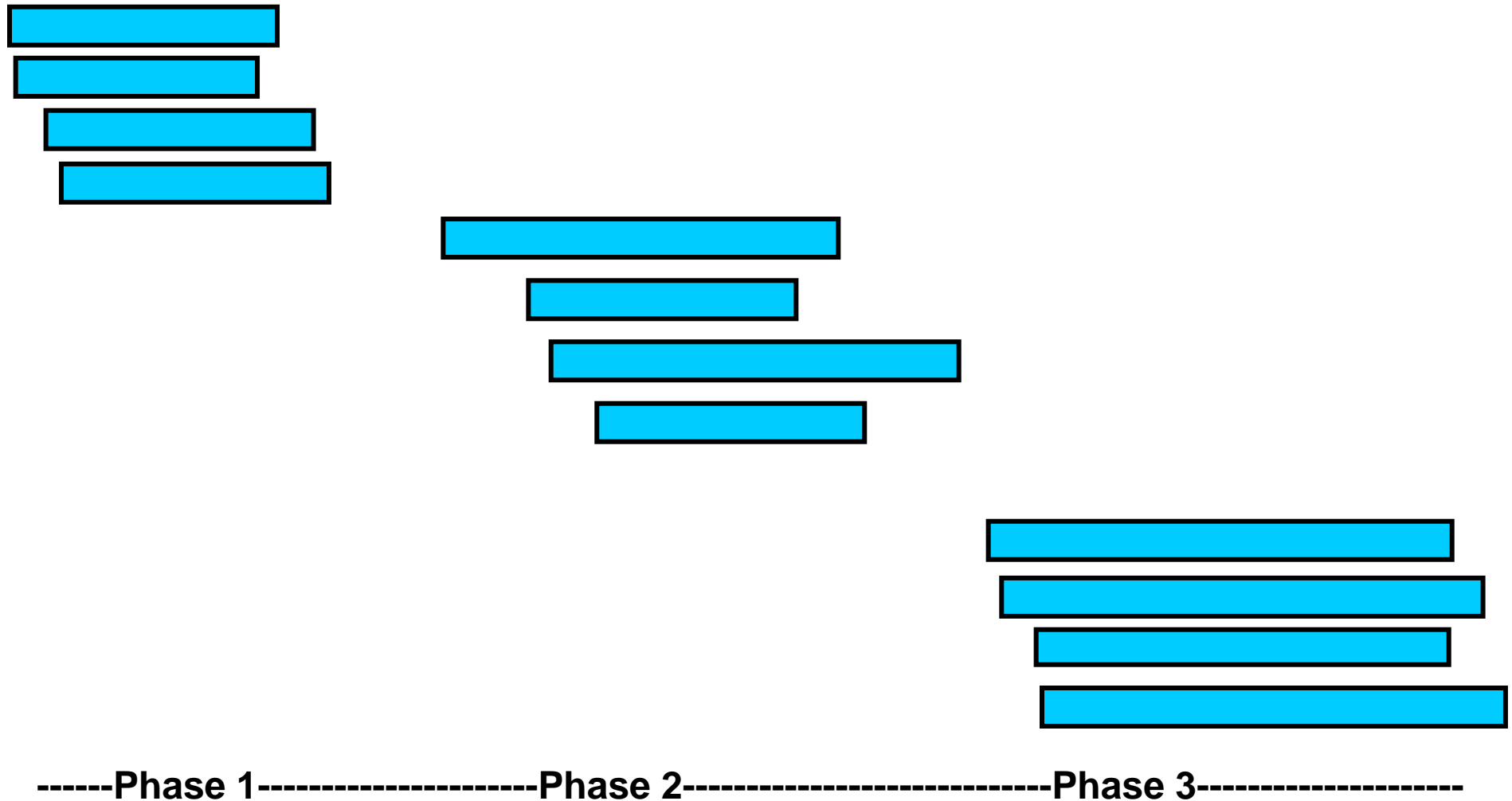
Statistical considerations

- Confirmatory trials
- Protect Type I error rate for all possible conclusions
 - Pre-specify all possible primary hypothesis
 - Simpler for operationally seamless trials
 - Inference for “part II” separately specified at end of “part I”
- Potential for estimation bias should be considered
 - Several methods cited

Data monitoring committees

- Access to interim results should be controlled
 - Especially for confirmatory trials
- Monitor interim analyses in both learn and confirm studies
 - Develop appropriate fit-for-purpose process (learn versus confirm)
- Plan for additional challenges in making and implementing decisions
 - Consider the composition and structure of the decision-making group
 - Difficult decision on whether or not to involve sponsor in any way
- Critical documentation
 - DMC charter (paper provides link to a model)
 - Documentation of information flow
 - Regulators may audit!

Classical clinical development



Adaptive Clinical Development

(possibly saves years)



---Early development-----Registration Development-----

Conclusions

- Adaptive design have potential to improve drug development
 - when appropriately applied
 - careful evaluation required for risk/benefit
- Many issues with adaptive trials exist for others
 - Recommend that similar standards apply
- Paper provides substantial practical guidance for those interested in designing and conducting adaptive trials