# Adaptive Trials: Unlocking the Opportunity and the Competitive Advantage

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# Acknowledgements


- **Contributors to ideas presented today**
  - Thanks to Keaven Anderson, Jim Bolognese, Nicole Dossin

# Adaptive Trials - Definition

- A clinical trial process that: uses accumulating trial data **not** available at study start, as a basis for modifications to the trial design.

- Adaptive trials are part of an **Adaptive Drug Development Process**
  - Incorporates **early review** of clinical data
  - Option for **modifications** to a trial in progress
  - All data from the trial are used in the analysis

- Statistical Methodology enables Adaptive Trials
  - Bayesian methods
  - Group sequential methods (classical & new)
  - Adaptive' methods
  - Combining p-values

# Why do we need Adaptive Trials?

- High failure rate of new products in development
- Approximately:
  - 1 out of 13 products entering clinical trials enter the market
  - 1 out of 2 products in phase 3 enter the market

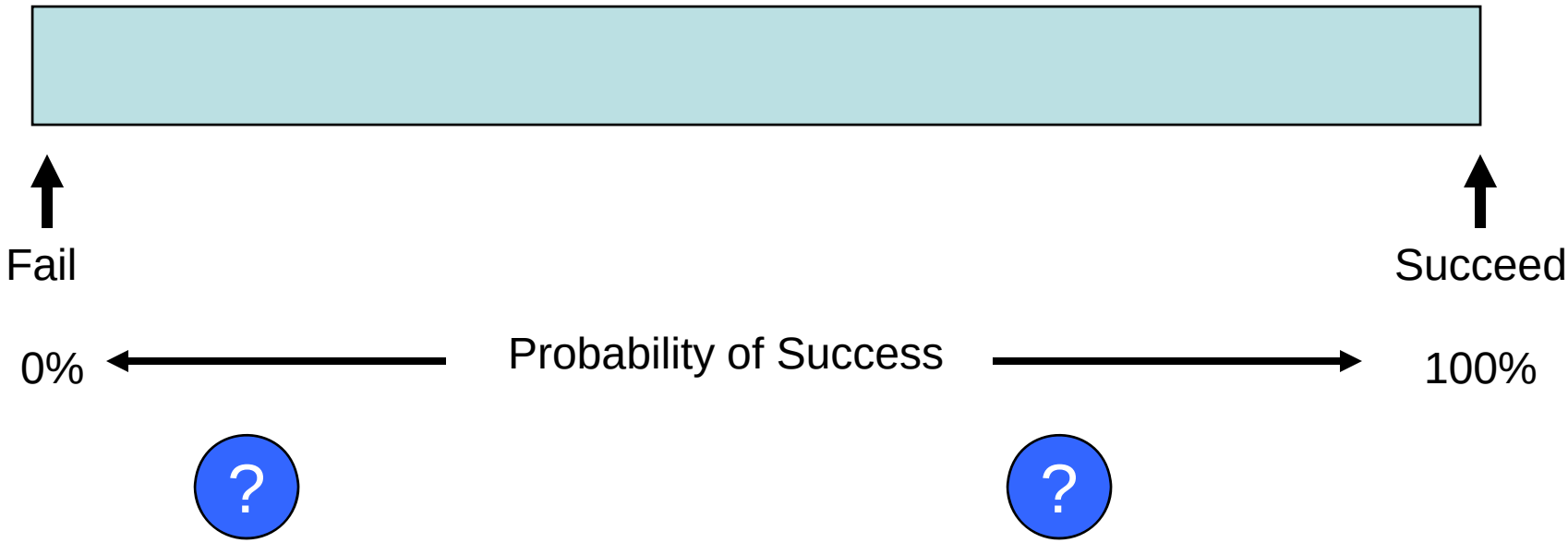
# Why do we need Adaptive Trials?

- High failure rate of new products in development
- Approximately:
  - 1 out of 13 products entering clinical trials enter the market **(92% fail)**
  - 1 out of 2 products in phase 3 enter the market **(50% fail)**

# Adaptive Decisions


Where is a drug in this continuum?

# Adaptive Decisions

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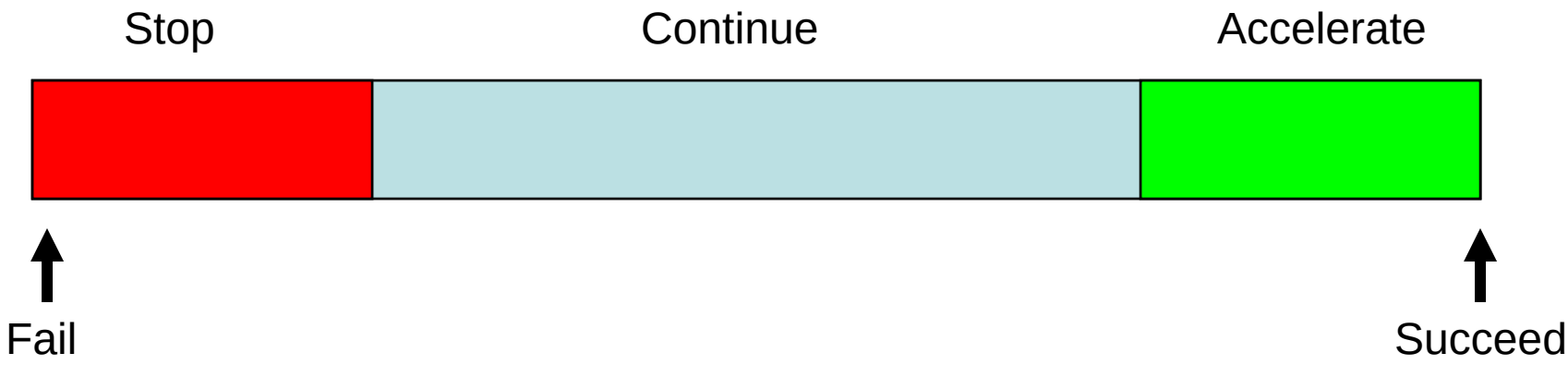


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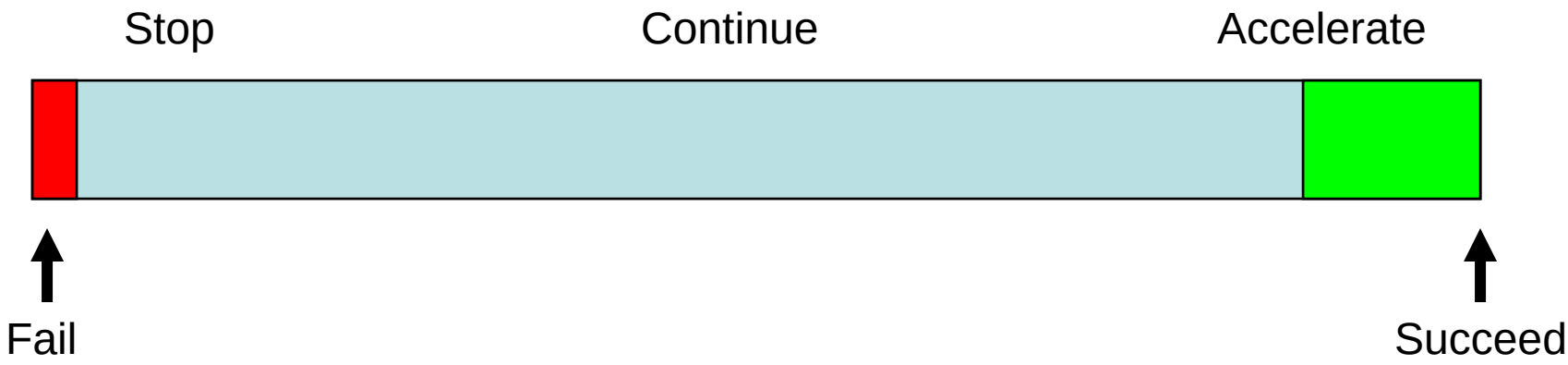


Where is a drug in this continuum?

May be different for different companies

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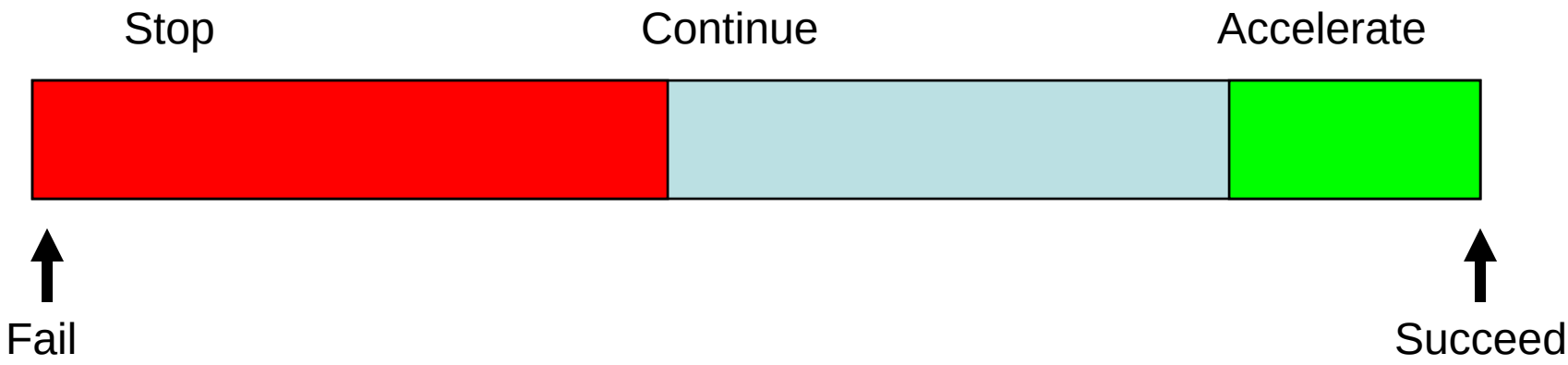


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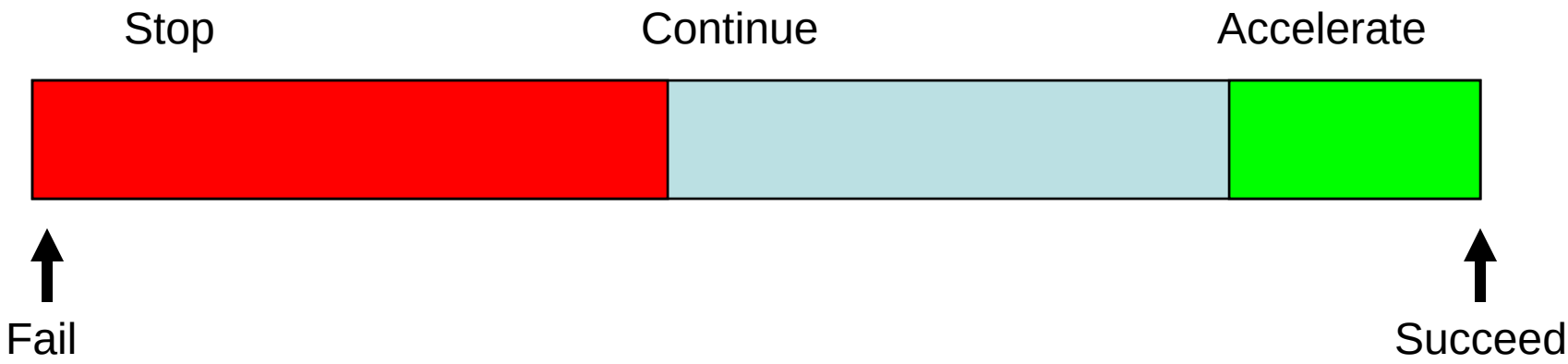


How can the statistician help?

Create a framework for decision making during the course of the trial

Estimate probabilities of success (or failure) based on early data

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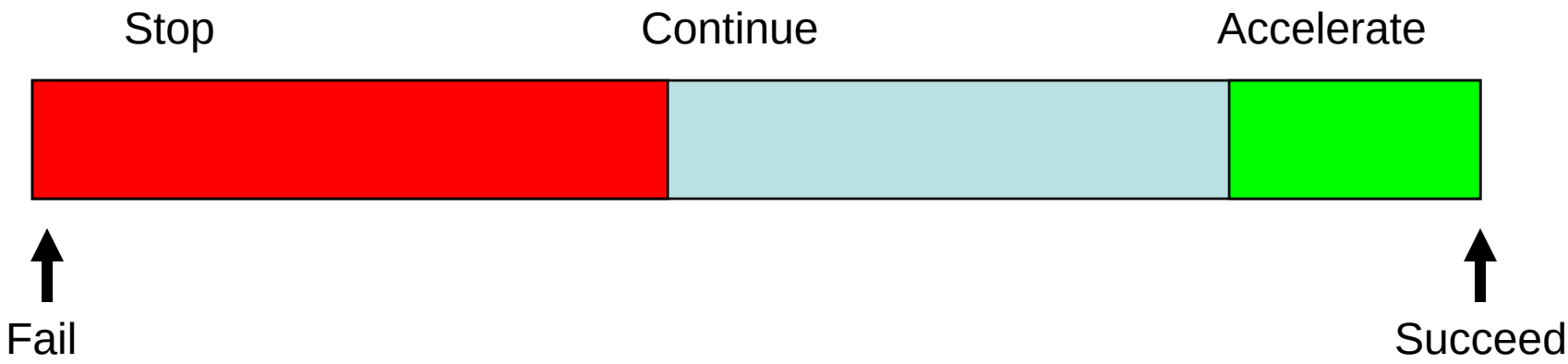



How can the statistician help?

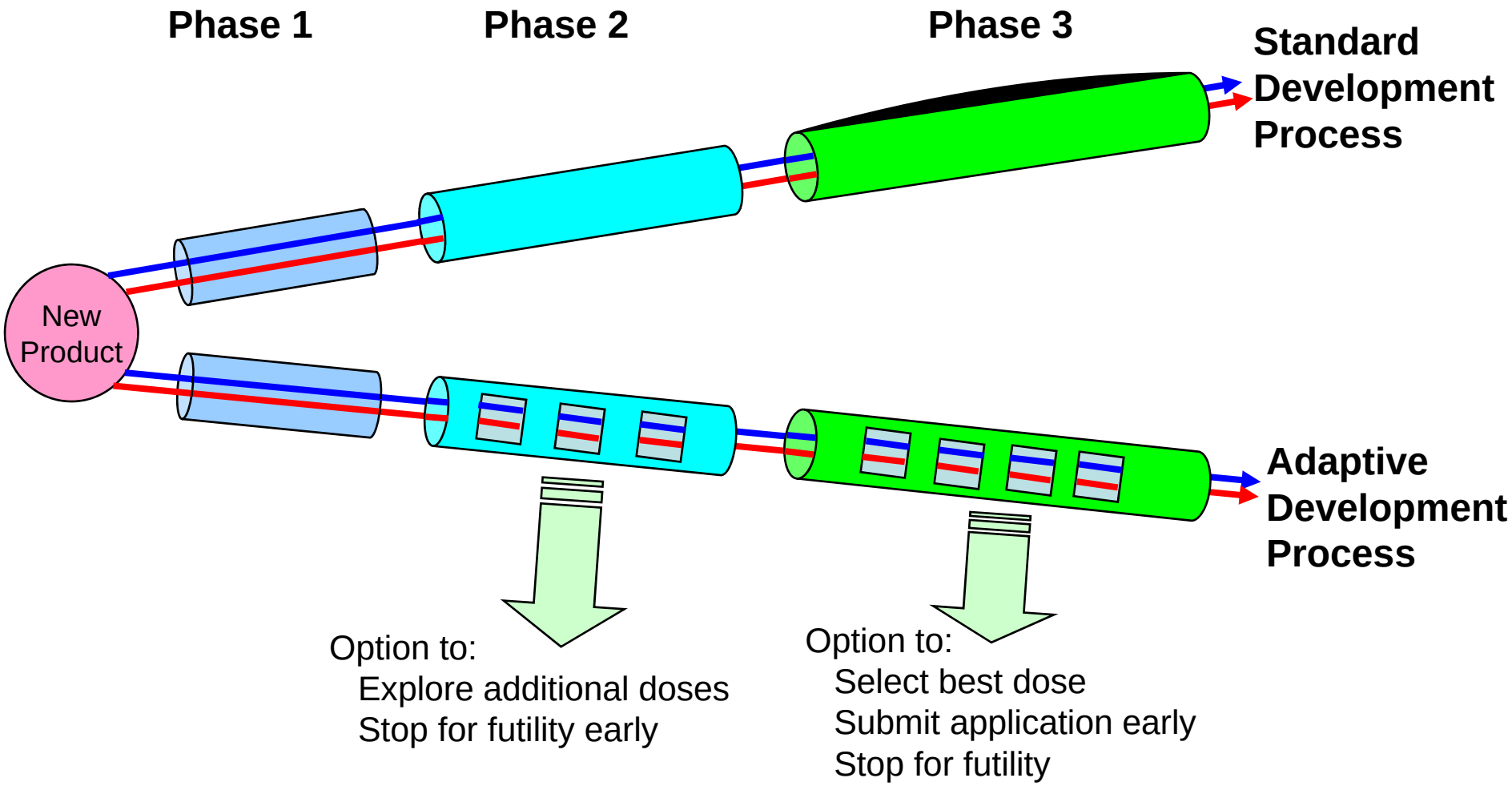
Create a framework for decision making during the course of the trial

Estimate probabilities of success (or failure) based on early data **Remember: >50% of all products fail**

# Advantages of Adaptive Trials

- More efficient, faster trials
  - Midcourse correction for trials that are off target
  - Fewer patients enrolled into ineffective treatment arms
  - Shorter trials – smaller overall sample size required
  - Increased quality of results – more patients enrolled into successful treatments
  - Better for patients – greater chance of receiving an effective treatment
- Reduce timeline by combining phases
  - Reduce white space between phases
  - Reduce overall time of Clinical Development
- Reduce costs by stopping unsuccessful trials

# Clinical Development Process



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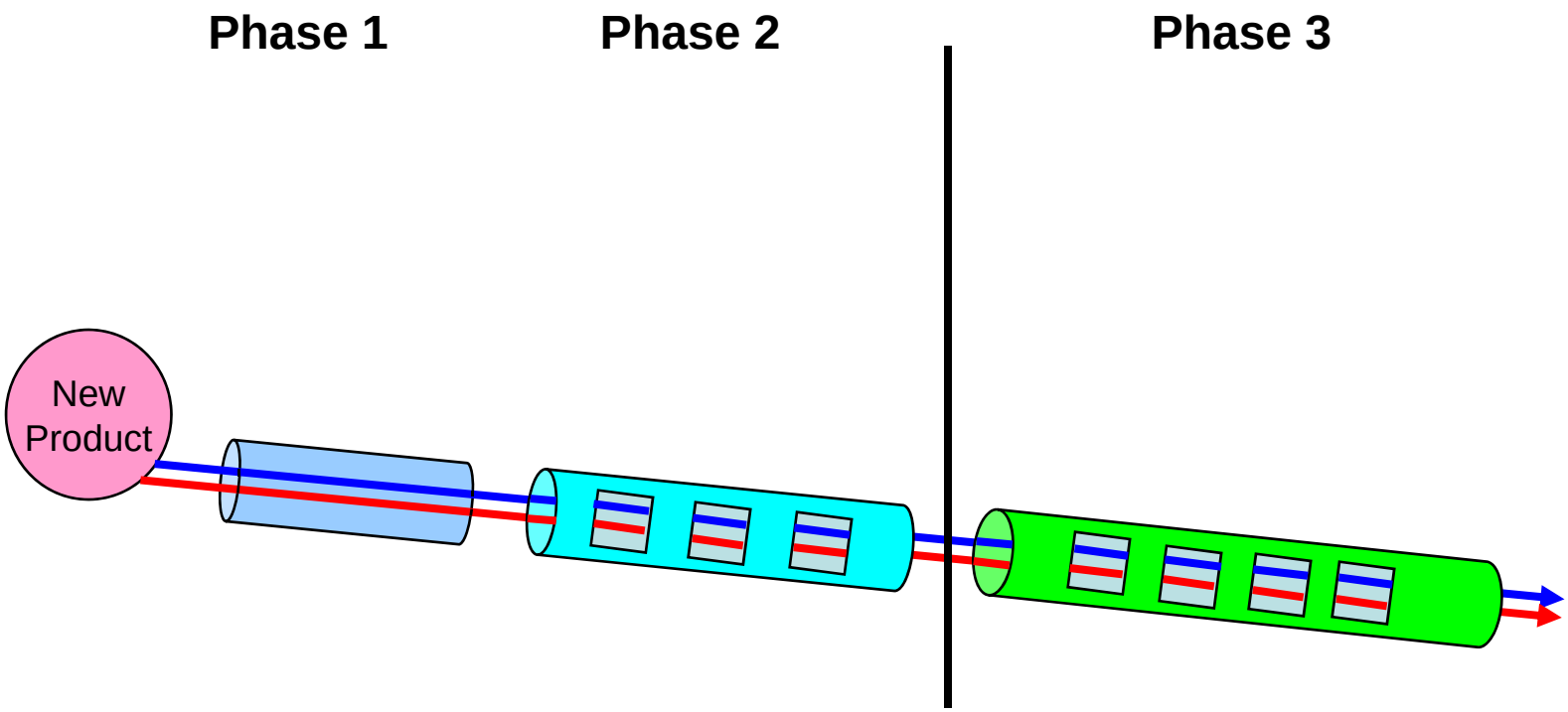
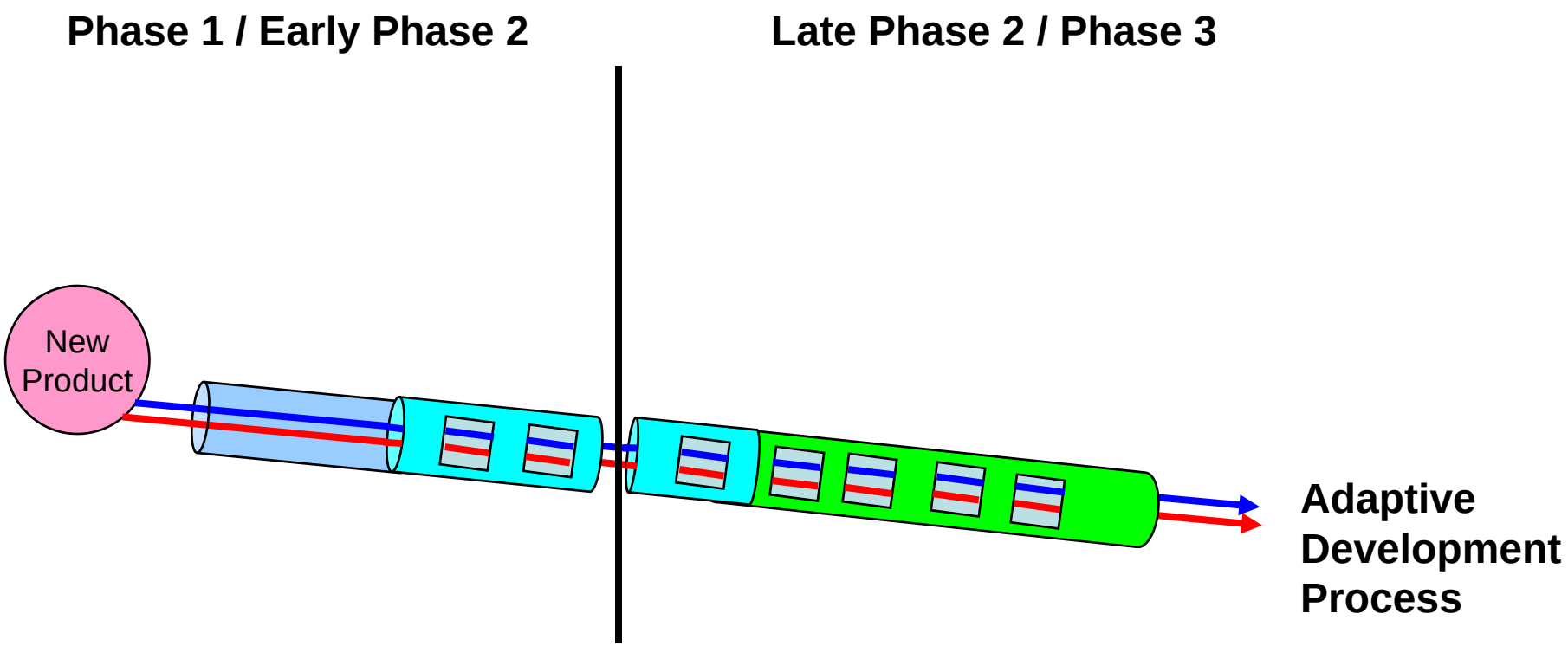



There is a natural division between Phase II and Phase III
Driven by need for: 1) Double masked designs
2) Highest quality clinical data

# Clinical Development Process



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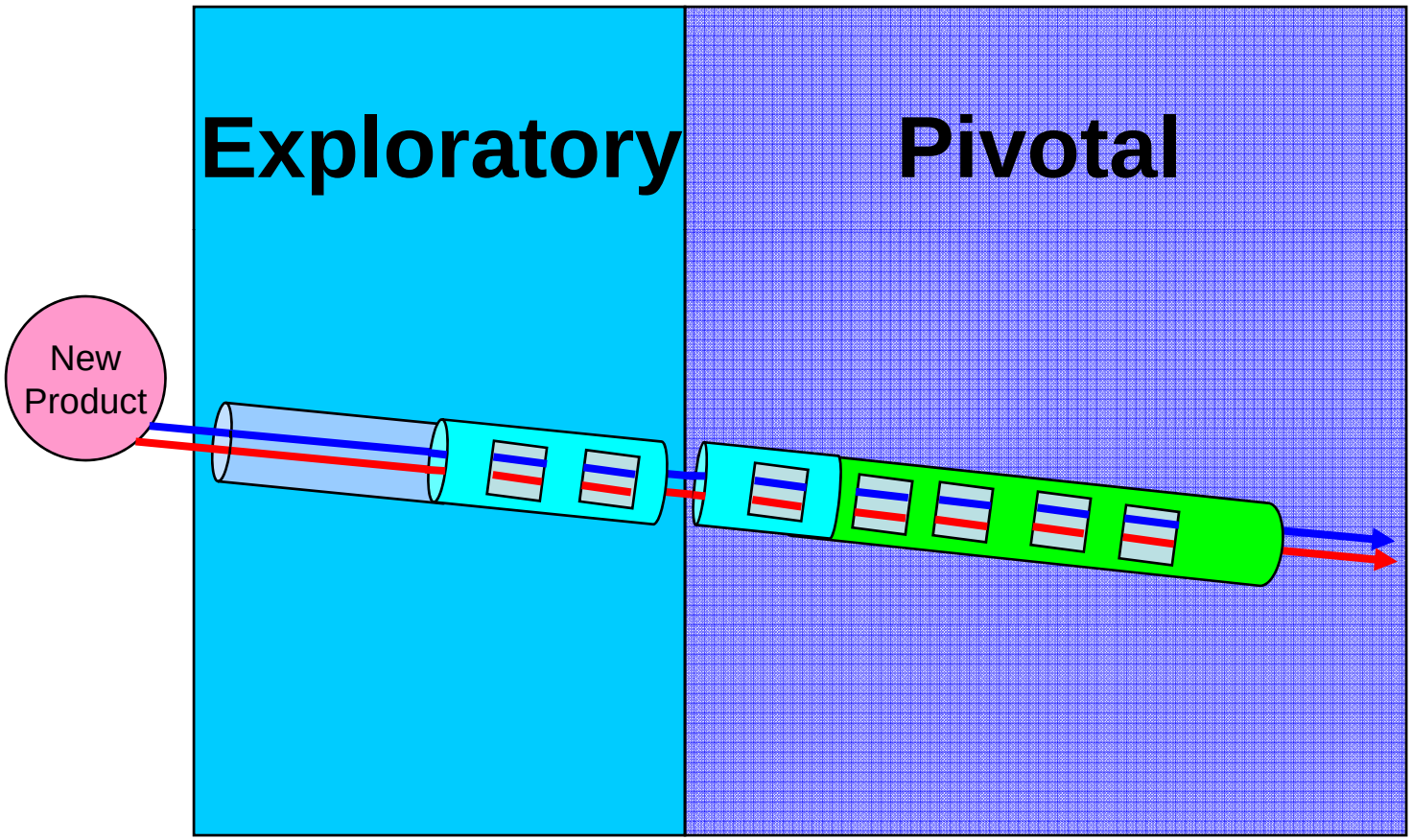
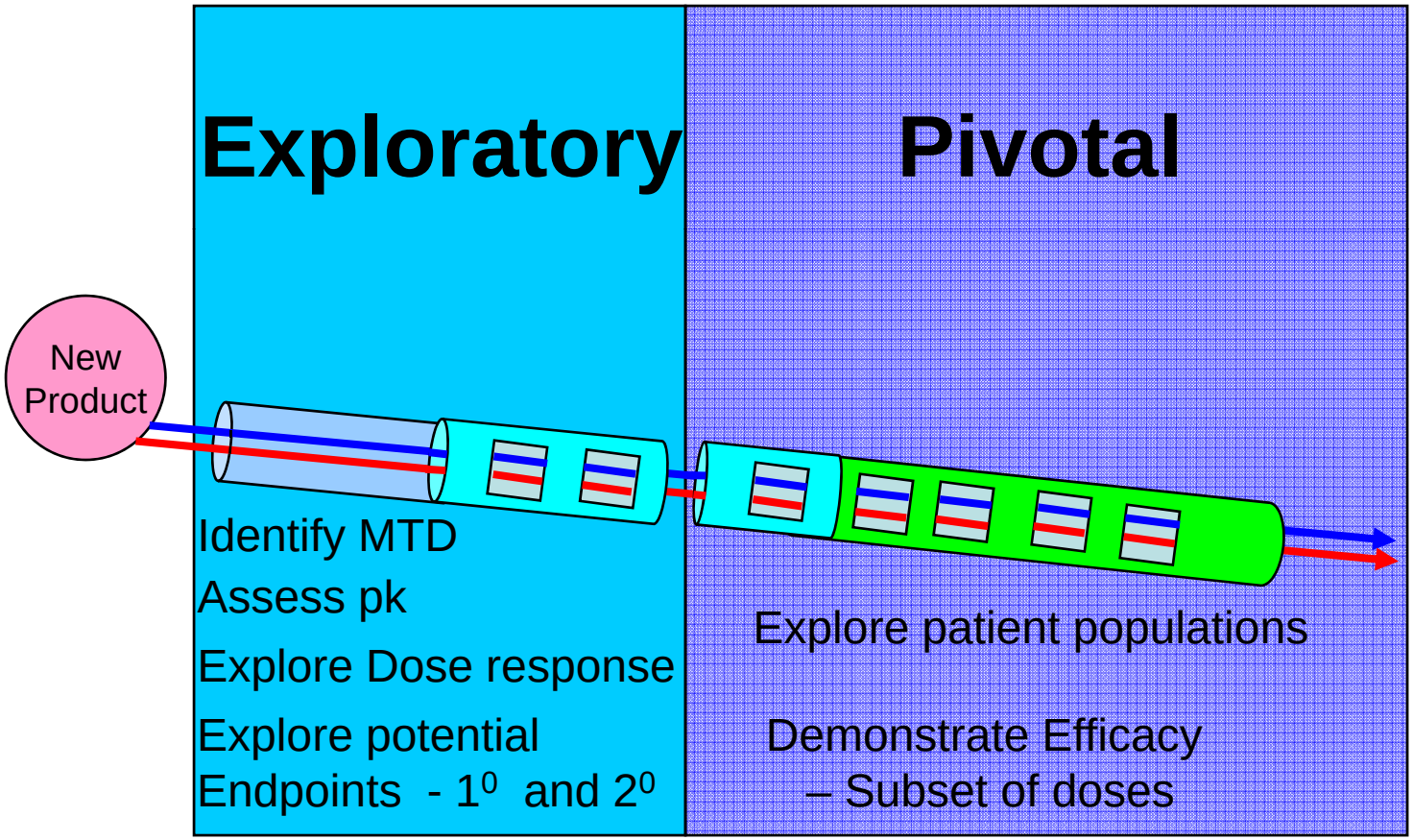


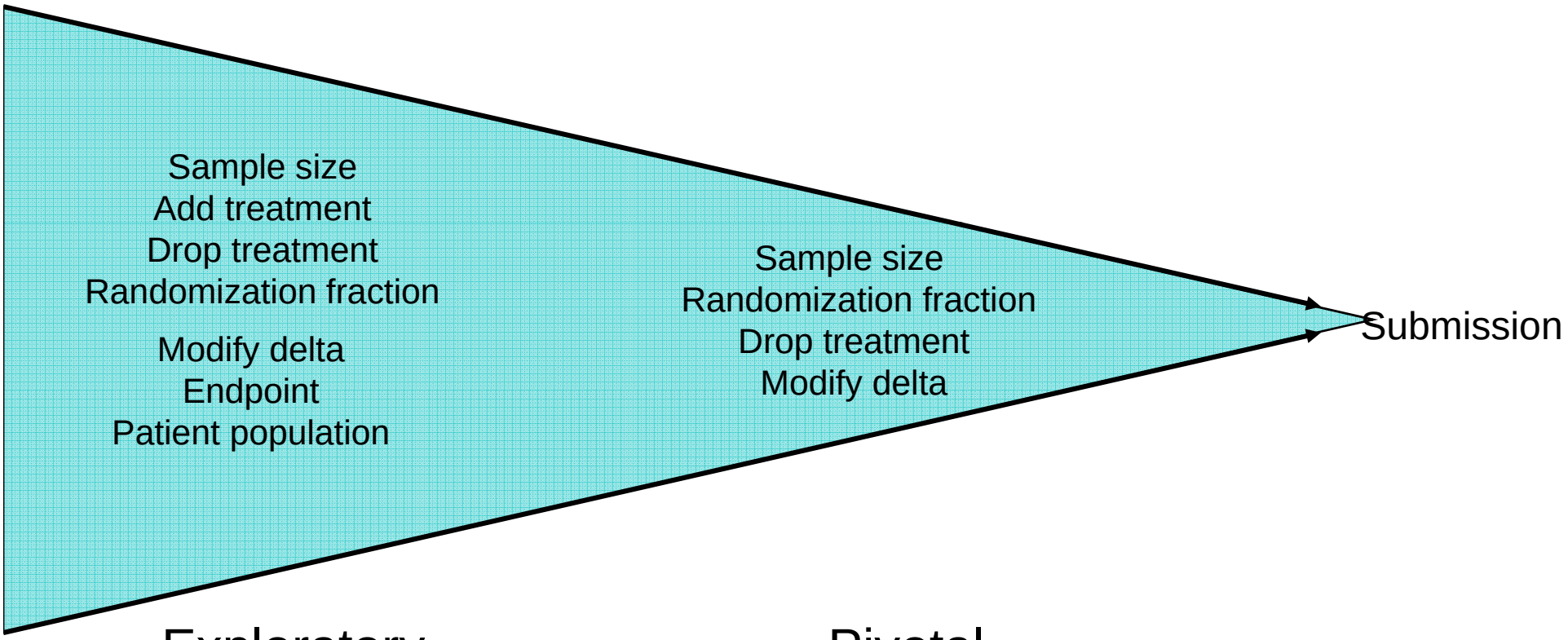

**Adaptive Development Process**

# Adaptive Clinical Development Process




**Adaptive Development Process**

# Constrained Adaptive Options




Exploratory

Adaptive Phase II

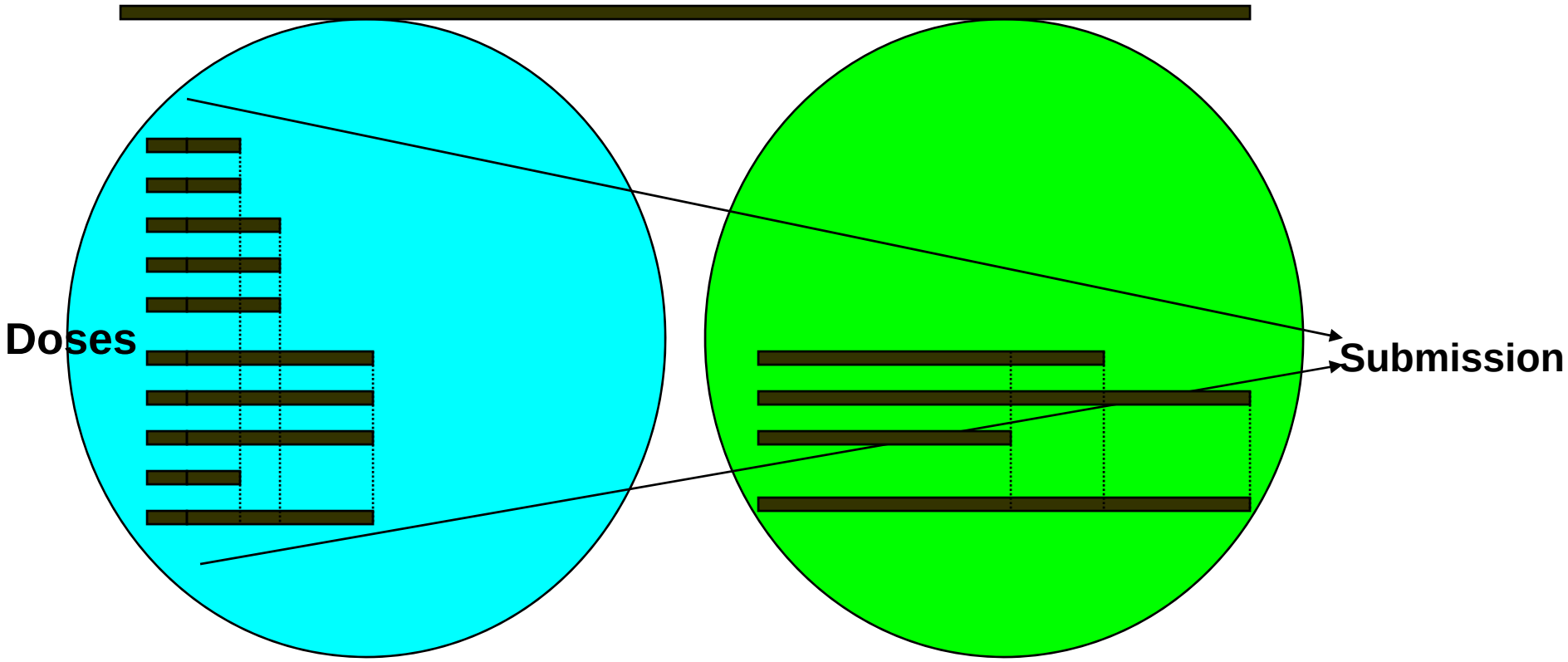
Pivotal

Adaptive Phase III

# Tandem Adaptive Clinical Trials

- Exploratory trial: Combined POC/Dose Response Studies
  - Evaluate many doses for dose response
  - Adaptively allocate doses for better estimation at the ‘steep’ part of the curve
- Pivotal Trial
  - Evaluate a few doses with larger sample sizes
  - Adaptive allocate to ‘best’ subset of doses

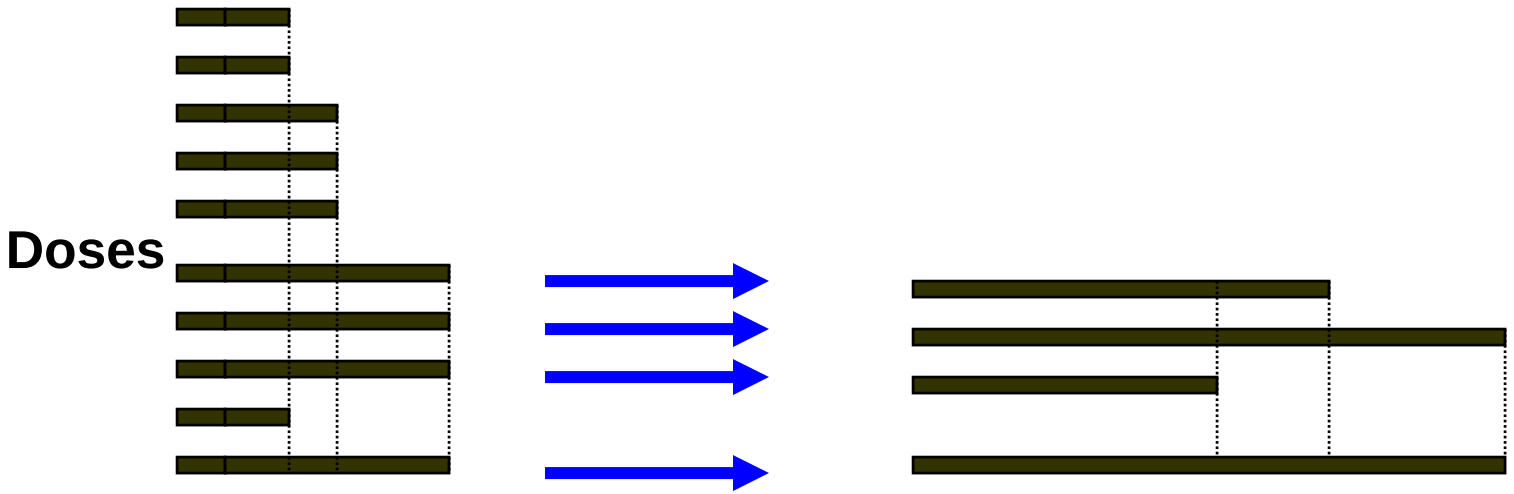
# Tandem Adaptive Clinical Trials




**1. Adaptive Phase II Trial**
**POC/Dose Response Estimation**

**2. Adaptive Phase III Trial**

# Tandem Adaptive Clinical Trials




**1. Adaptive Phase II**
**POC/Dose Response Estimation**
Exploratory

**2. Adaptive Phase III**

Pivotal

# Issues to Consider

## Identify if you are in Confirmatory or Exploratory

| Exploratory | Confirmatory |
| --- | --- |
| • Masking often discretionary<br>• IDMC optional<br>• Flexible decision process<br>• Consider many options<br>• "Start many – finish few" or<br>• "Start few – add new" | • Masking often necessary<br>• Use IDMC<br>• Decisions driven by algorithms<br>• Limited options<br>• Sample size re-estimation<br>• "Start many – finish few" |

# Example: Prevention of Pre-cancerous Cervical Lesions with GARDASIL®

*Thanks to Lisa Lupinacci, Christine Gause*

# FUTURE II Trial (NEJM 2007;356:1915-27)

- Population: 15-26 year-old women
- Treatments
  - Placebo
  - GARDASIL – quadrivalent vaccine against human papillomavirus (HPV) types 6/11/16/18
- Endpoint: Pre-cancerous lesions (CIN 2/3)
  - Variable follow-up (up to 4 years; 3 years, on average)
  - Primary population
    - Per protocol
    - Free of infection with vaccine virus types at baseline
- Sample size (event-driven analysis)
  - N=12,167
  - Designed to get 29 primary endpoints during the course of the study

# FUTURE II Trial

- Interim analysis plan
  - Wang-Tsiatis boundary
    - $\Delta$=0.2, between O'Brien-Fleming and Pocock bound
  - One interim analysis
    - 19 events, nominal $\alpha$=0.0102, one-sided
  - Final analysis
    - 29 events, nominal $\alpha$=0.02055, one-sided
- Overall Type I error: 2.5%, one-sided
- Power statement
  - Powered for 80% to 90% vaccine efficacy
  - 80% to 90% power at interim
  - At least 90% at final analysis

# Designing an event-driven trial

- Merck usually wants a trial to complete within a fixed time
- Base sample size on
  - Assumed accrual rate (may vary with time)
  - Assumed control rate (may vary with time)
  - Assumed event rate reduction (constant over time!)
  - Assumed dropout rates
    - May vary by time and treatment
- Use these design parameters to design a trial with
  - Desired fixed accrual period
    - Estimate sample size to enroll in this period
  - Desired fixed final analysis time

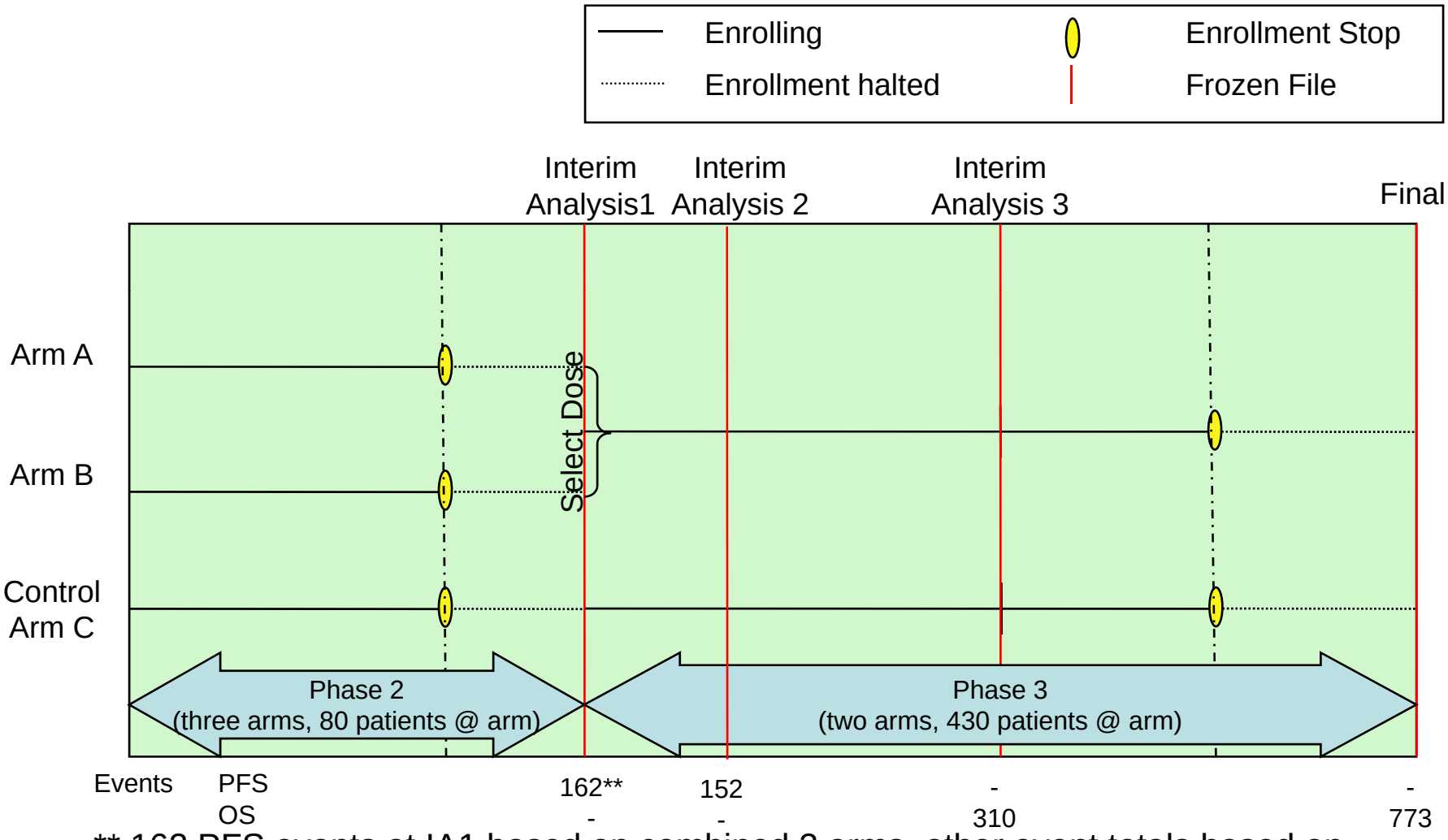
# Example:
# Phase II/III Adaptive Design for an Oncology Trial

*Thanks to Jason Clark*

# Phase II/III Oncology Trial

- Two possible doses versus control
  - Early dose-selection followed by confirmation
- Dual primary endpoints
  - Progression-free survival (PFS, $\alpha$=0.005)
  - Overall survival (OS, $\alpha$= 0.02)
  - No assumptions on correlation structure needed
- Why dual primaries?
  - Early selection, futility and efficacy decisions based on PFS
  - Later efficacy confirmation and futility based on OS
- Trial is powered for
  - >90% if $HR_{PFS}$ <0.63 (2.4m inc in PFS)
  - >80% if $HR_{OS}$ <0.80 (2m inc in OS)

# Phase II/III Oncology Trial




** 162 PFS events at IA1 based on combined 3 arms, other event totals based on cumulative events in two continuing arms only

# Phase II/III Oncology Trial

- Sponsor is blinded to interim results
  - Dose selection decisions are left in hands of DSMB
  - Clear rules for continuation of study in protocol and DSMB charter
  - DSMB instructed that trial only continues with a VERY positive signal; otherwise, this turns into a Phase II trial that can be carefully scrutinized before Phase III decision
    - Sponsor risks that DSMB may not decide as sponsor would!
- Dose selection could introduce upward bias
  - Testing requires adjustment to control Type I error
    - Multiple doses
    - Multiple endpoints
  - Estimation requires adjustment to reduce bias
  - Regulators specifically interested in these issues

# Phase II/III Oncology Trial

- Interim analysis objectives
  - Interim 1
    - Proof of concept (futility testing for PFS)
    - Dose selection – this is early!!
    - Enrollment held to limit Phase II investment prior to proof of concept
  - Interim 2
    - Confirm proof of concept to confirm value of Phase III investment
  - Interim 3
    - Possible accelerated approval based on PFS
    - Possible trial stop for positive survival result
  - Final analysis
    - Final confirmation of survival benefit

# Statistician's Role

- "Just give me a standard Phase 2/3"
  - There are no standard Phase 2/3 trials
  - All of the confirmatory software for my trial was developed by the statistician
- Issues
  - These trial designs may have large financial implications
  - We don't press a button & get results
  - The trial designs often require weeks of programming to verify the operating characteristics
    - This design required 80-120 hours of total programming time

# Lots of Review & Process Time

- Clinical protocol reviews
  - Twice for concept sheets
  - Twice for full protocol
- Statistics reviews
  - 2 trips
  - 1 ex-committee review
- Executive review of proposal
- Program review
- Start to finish
  - 6 months
  - At least a dozen designs considered

# Phase II/III Oncology Trial

**Strategic Issues**

- Team understanding – few opportunities for "course correction"
  - Trial design changes after study start initiated by sponsor may invalidate statistical conclusions
  - Sponsor may not get opportunity to see unblinded analysis until study is stopped
    - No separate Phase II trial
  - Entire competitive landscape may change while trial is ongoing
- Information inferred from interim
  - Bounds designed to be informative, continuing trial may be enough signal to allow other program decisions
  - Information needs to be limited enough to NOT compromise the trial

# Phase II/III Oncology Trial -Conclusions

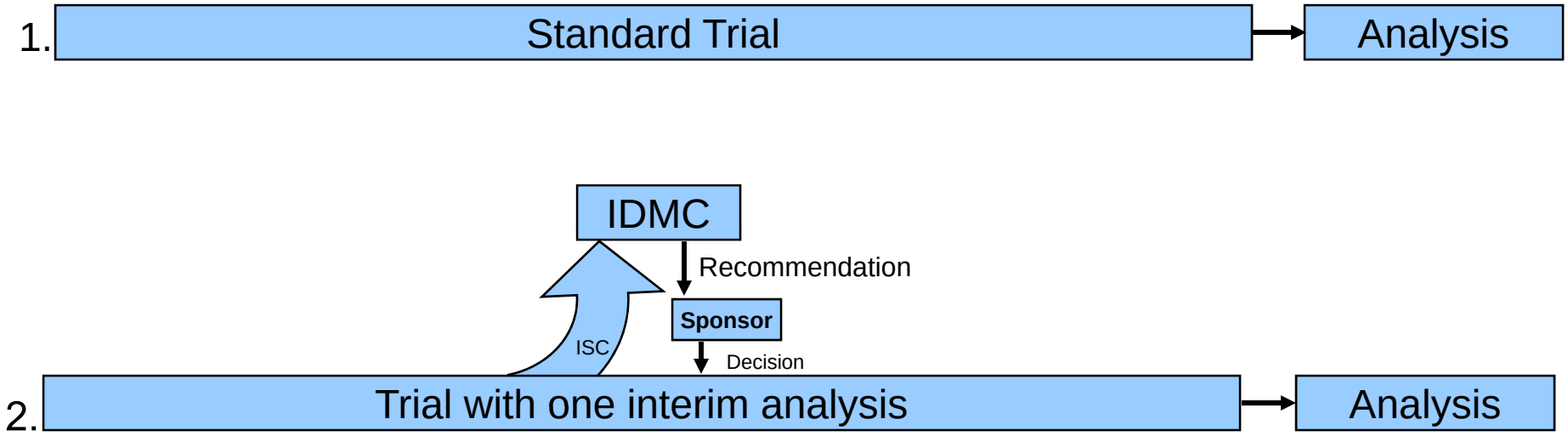
- P2/3's require far more preparation time
  - Negotiation between clinical, statistics, drug supplies, regulatory, etc
  - No luxury of "silo"-ed thinking – requires good x-functional team
  - Understand strategic needs of compound
  - eCRF's & SAP for pivotal trial based on less trial experience
- P2/3 may not be for you
  - With extra work, will you "save" any time
  - Risk inherent with not seeing data – confident about your endpoints & design?
  - Pre-investment required to get realize full benefit of P2/3
- DSMB member selection & charter very important
- FDA doesn't guarantee rest of world will follow
- Will you need a 2nd trial?

# Process Requirements

# Clinical Trial Strategies

1. 

# Clinical Trial Strategies



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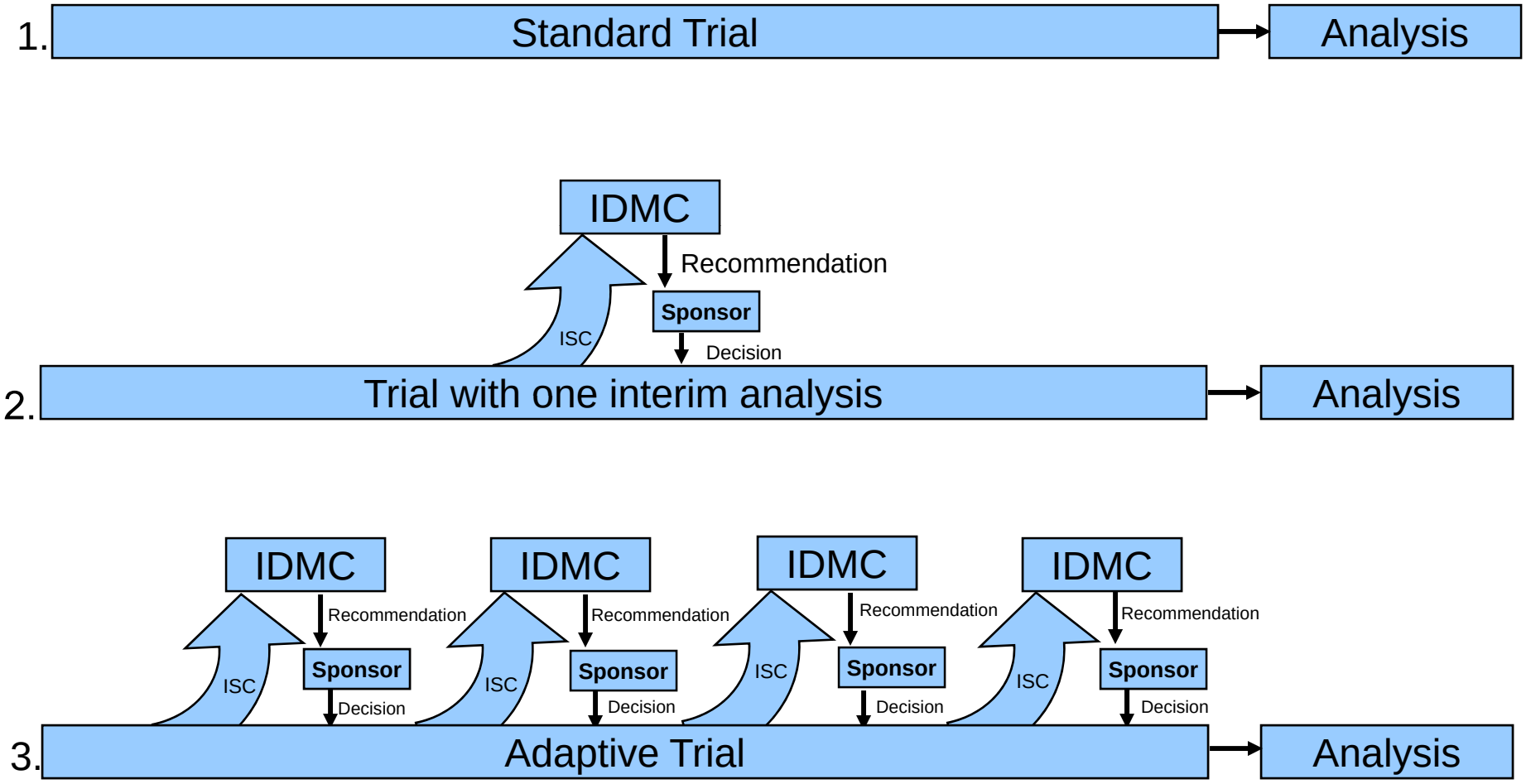


# Dose-Adaptive Design - Each weekly cohort of patients (after first 3) adaptively assigned dose based on 1wk Biomarker (BMX) data or 4-week key endpoint data

| Cohort of patients | WK 1 | WK 2 | WK 3 | WK 4 | WK 5 | WK 6 | WK 7 | WK 8 |
|---|---|---|---|---|---|---|---|---|
| 1 | Dose by Design | | 1 wk BMX data | | | 4wk KEY data | | |
| 2 | | Dose by Design | | 1 wk BMX data | | | 4wk KEY data | |
| 3 | | | Dose by Design | | 1 wk BMX data | | | 4wk KEY data |
| 4 | | | | Adaptive Dose | | 1 wk BMX data | | |
| 5 | | | | | Adaptive Dose | | 1 wk BMX data | |
| 6 | | | | | | Adaptive | | 1 wk |

# Definitions

- IDMC
  - Independent Data Monitoring Committee
  - Biostatistical and Medical Staff not involved with the study conduct
  - Usually outside the pharmaceutical company
- ISC
  - Independent Statistical Center
  - Usually outside the pharmaceutical company
  - Prepares the subset of data and the analysis for the IDMC
  - Creates briefing document for discussion at the IDMC meeting
- Trial Steering Committee (Sponsor)
  - Senior management in the pharmaceutical company
  - Interpret IDMC recommendations and decide on modifications

# Adaptive Trial Process (1)

1. Protocol specifies which adaptive options will be considered and decision process is outlined
2. ISC obtains subset of data to be reviewed at the interim time point
3. Unmasked treatment codes are added to the interim data subset
4. Analysis and tables/reports are generated by the ISC as outlined in the protocol (briefing document)

# Adaptive Trial Process (2)

5. IDMC reviews briefing document
6. High level summary of IDMC conclusions communicated to Steering Committee
7. Steering committee then decides appropriate trial modifications (if any) based on IDMC recommendations.
8. Modifications are made and process is repeated at next interim time point.

Decision-making process may be more simply structured for non-pivotal trials!

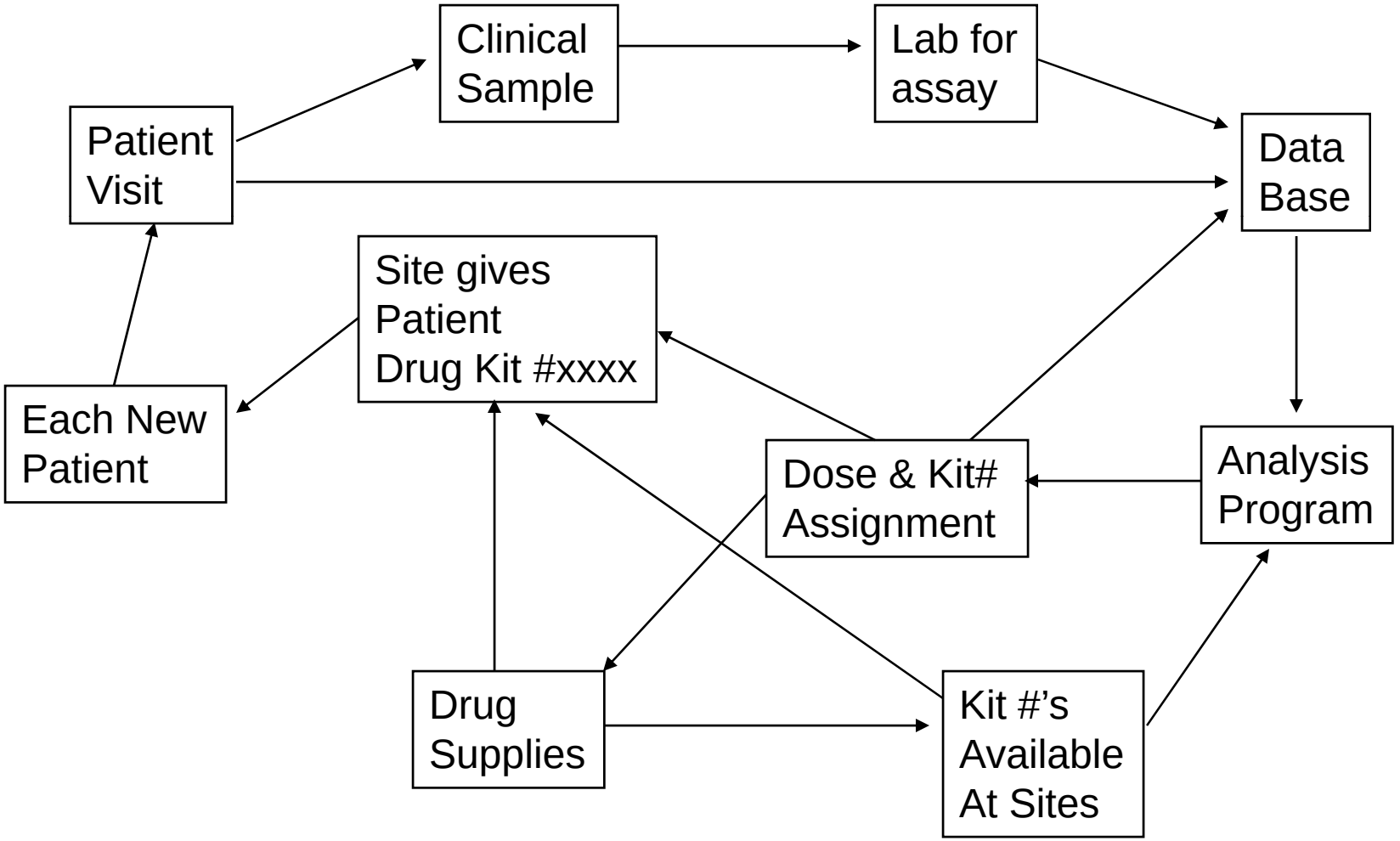
# Data Access - Implementation Capability

EDC

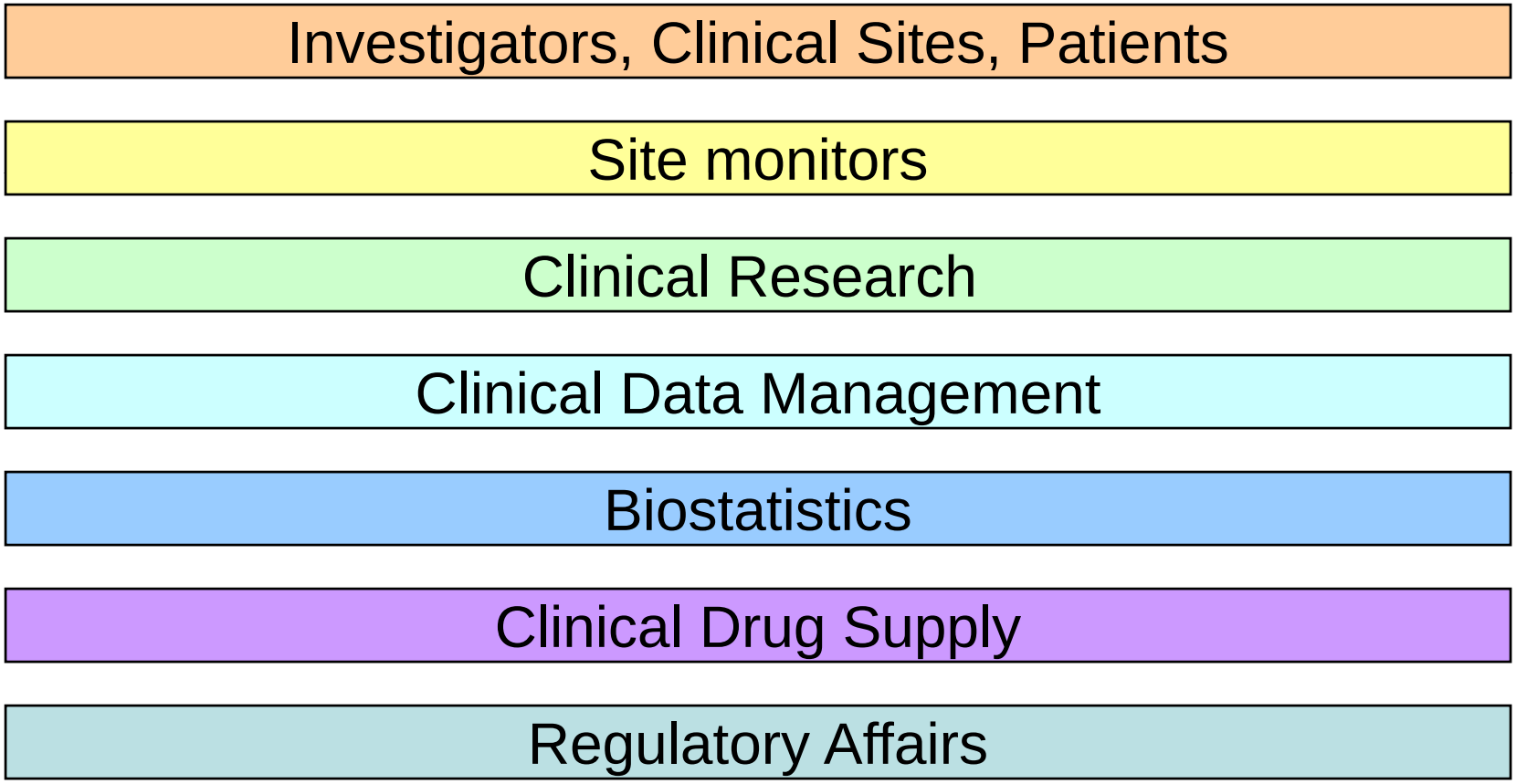
eClinical
Online review

IVRS, Drug supply,
Randomization
Integration

# Adaptive Design with Continuous Information Flow



# Frequent Interactions



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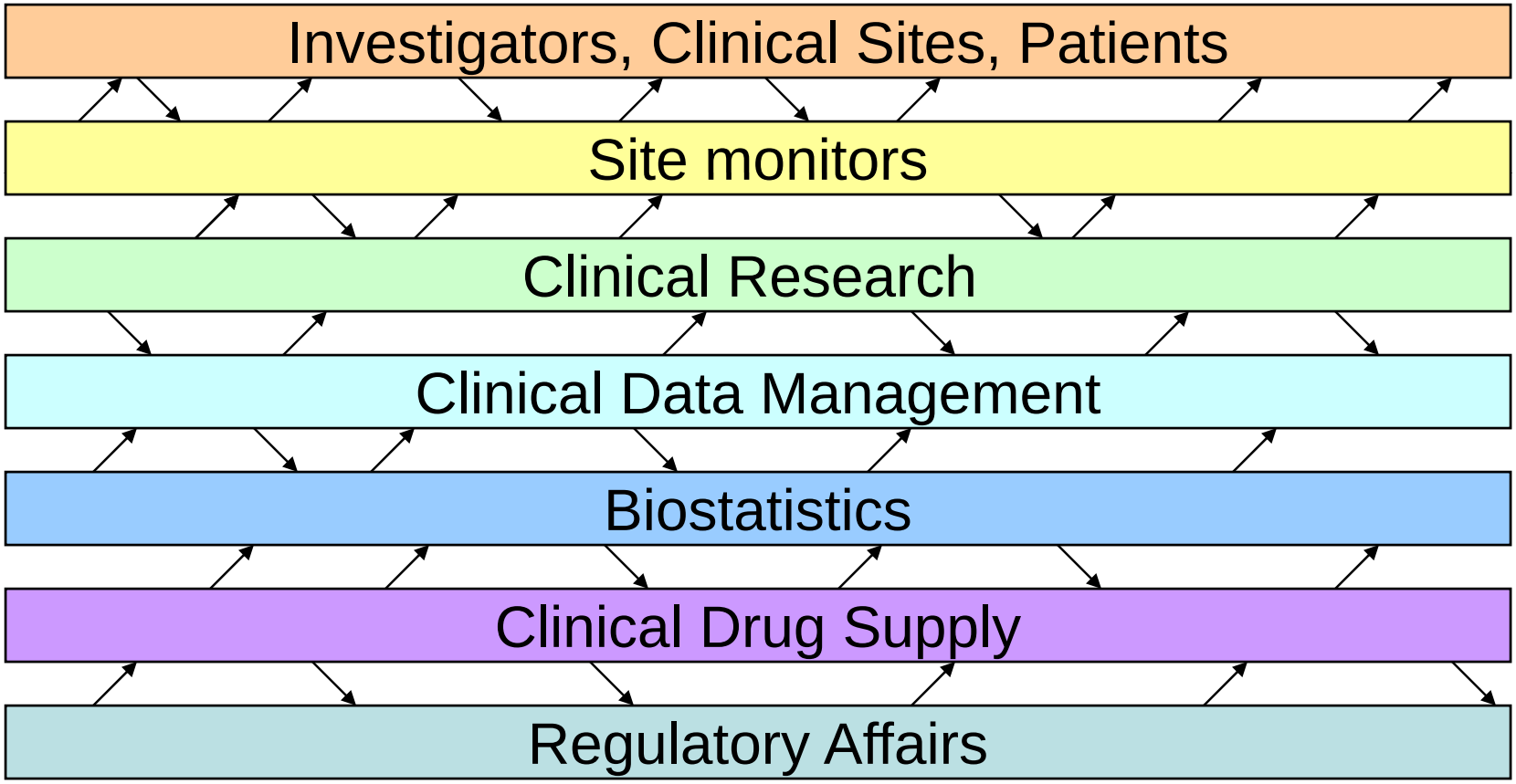


# Process Requirements for Adaptive Trials

- **Simulations/Modeling**
  - Simulate options before protocol is written
- **Protocol**
  - Adaptive trial described in protocol
- **Set up interim review process**
  - Establish IDMC, ISC
- **Set up Decision making process**
  - Rapid action on interim results is essential
  - Select decision makers (steering committees) in advance

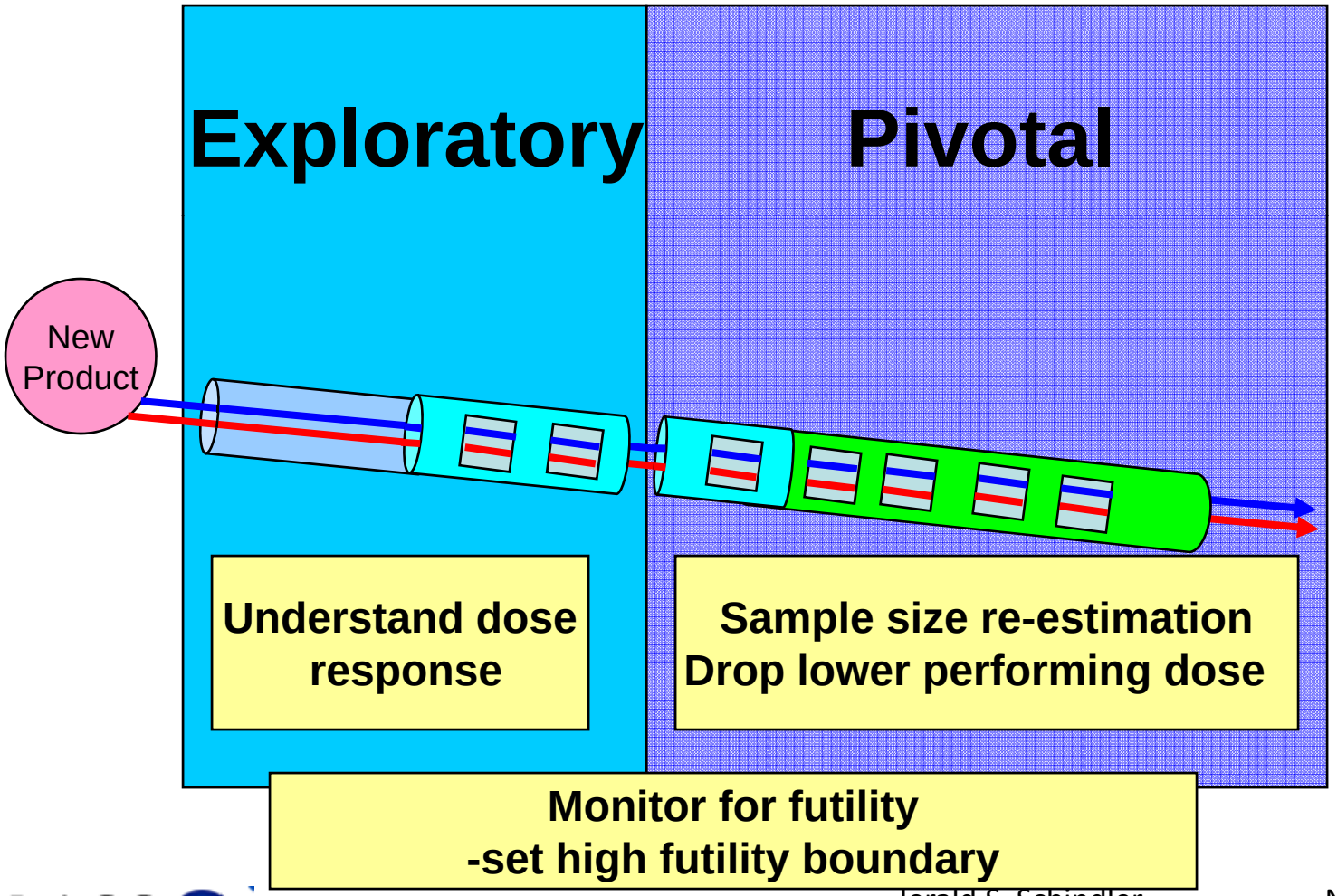
# Infrastructure Requirements for Adaptive Trials

- **eClinical System**
  - Bring information from many different systems into one place
  - Easy access and reporting
- **Live, “real time” data**
  - The more current the data are the more powerful the result will be
- **Ability to review and analyze the data often**
  - Acquire software to support sophisticated analyses
  - Train and develop staff to acquire additional statistical skill
- **Ability to implement the desired changes quickly**
  - Adjust randomization probabilities
  - Link between randomization system/ drug supplies tracking

# Standards

- Standard tools allow
  - Quick protocol development
  - Significant adaptation
    - Early decision making
    - Event-based analysis timing
- Custom tools
  - Allow more significant adaptations, possibly greater benefit and/or earlier conclusion
  - Cost is
    - More effort (design and review)
    - Longer time to start
    - More likely to have regulatory issues

# Adaptive Clinical Development Process




**Adaptive Development Process**

# Simple and Easy Rules for Success In Adaptive Clinical Development

(For Low Risk and Maximum Benefit from the Adaptive Process)

1. Separate development into Exploratory and Pivotal phases
2. Constrain adaptive options over time
3. Exploratory – Explore MTD, pk, dose response, potential outcome variables adaptively
4. Pivotal - Explore patient populations, final dose selection or sample size required; then demonstrate efficacy adaptively
5. Masking, IDMC
   - Exploratory – optional
   - Pivotal – often required
6. Sponsor involvement in IDMC
   - Exploratory – yes
   - Pivotal – no
7. Decision making
   - Exploratory – flexible, some rules stated in advance
   - Pivotal – driven by algorithms, rules stated in advance
8. Extra planning required for statistics and logistics!