Adaptive Designs
Terminology and Classification

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Wyeth Research

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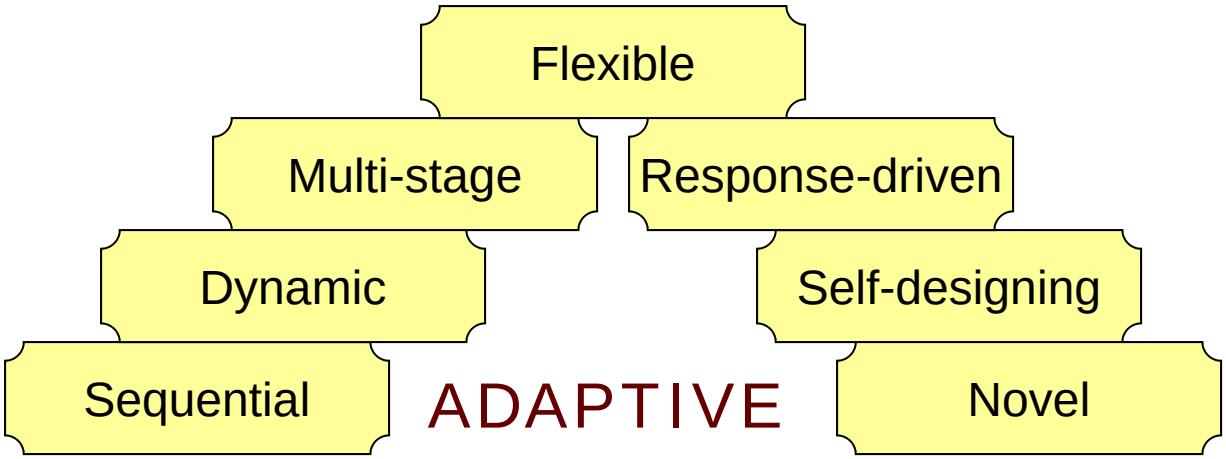
Outline

- Definition and general structure of adaptive designs
- Classification of adaptive designs in drug development
- Achieving the goals

What are Adaptive Designs?



- An adaptive design should be adaptive by "design" not an *adhoc* change of the trial conduct and analysis
- Adaptation is a design feature, not a remedy for poor planning

What are Adaptive Designs?

Definition

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 (such as adjusted p-values, adjusted estimates and confidence intervals, etc)
- is about credibility, interpretability and persuasiveness to a broader scientific community

Integrity means

- preplanning, as much as possible, based on intended adaptations
- minimizing operational bias
- assuring consistency between different stages of the study
- maintaining confidentiality of data

General Structure

- An adaptive design requires the trial to be conducted in several stages with access to the accumulated data
- An adaptive design may have one or more rules:
  - **Allocation Rule**: how subjects will be allocated to available arms
  - **Sampling Rule**: how many subjects will be sampled at next stage
  - **Stopping Rule**: when to stop the trial (for efficacy, harm, futility)
  - **Decision Rule**: the final decision and interim decisions pertaining to design change not covered by the previous three rules
- At any stage, the data may be analyzed and next stages redesigned taking into account all available data

Examples

- Group Sequential Designs: only **Stopping Rule**
- Response Adaptive Allocation: only **Allocation Rule**
- Sample Size Re-assessment: only **Sampling Rule**
- Flexible Designs:
  - Adaptive AR: changing the randomization ratio
  - Adaptive SaR: the timing of the next IA
  - Stopping Rule
  - Adaptive DR: changing the target treatment difference; changing the primary endpoint; varying the form of the primary analysis; etc

Allocation Rules

- Fixed (static) AR:
  - Randomization used to achieve balance in all prognostic factors at baseline
- Adaptive (dynamic) AR:
  - Response-adaptive randomization uses interim data to unbalance the allocation probabilities in favor of the “better” treatment(s): urn models, RPW, doubly adaptive biased coin design
  - Bayesian AR alters the allocation probabilities based on posterior probabilities of each treatment arm being the “best”
- Covariate Adjusted Response Adaptive (CARA) AR

Sampling Rules

- Sample size re-estimation (SSR)
  - Restricted sampling rule
  - Blinded SSR or Unblinded SSR based on estimate of nuisance parameter
- Traditional Group Sequential Designs
  - Fixed sample sizes per stage
- Error Spending Approach
  - Variable sample sizes per stage (but do not depend on observations)
- Sequentially Planned Decision Procedures
  - Future stage sample size depends on the current value of test statistic
- Flexible SSR uses also the estimated treatment effect

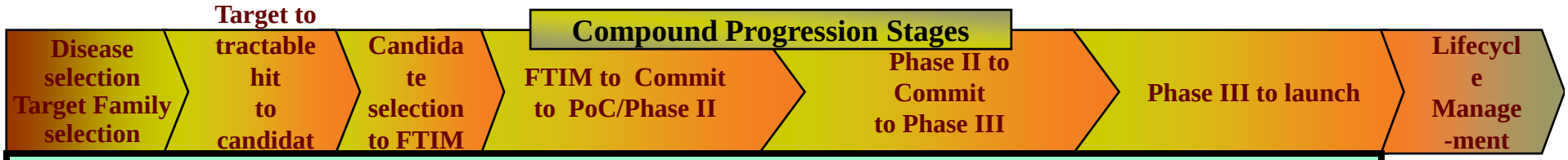
Stopping Rules

- Early Stopping based on Boundary Crossing
  - Superiority
  - Harm
  - Futility
- Stochastic Curtailment
  - Conditional power
  - Predictive power
- Bayesian Stopping Rules
  - Based on posterior probabilities of hypotheses
  - Complemented by making predictions of the possible consequences of continuing

Decision Rules

- Changing the test statistics
  - Adaptive scores in trend test or under non proportional hazards
  - Adaptive weight in location-scale test
  - Including a covariate that shows variance reduction
- Redesigning multiple endpoints
  - Changing their pre-assigned hierarchical order in multiple testing
  - Updating their correlation in reverse multiplicity situation
- Switching from superiority to non-inferiority
- Changing the hierarchical order of hypotheses
- Changing the patient population
  - going forward either with the full population or with a pre-specified subpopulation

Classification



SINGLE ARM TRIALS
Two-stage Designs
Screening Designs
TWO-ARM TRIALS
Group Sequential Designs
Information Based Designs
Adaptive GSD (Flexible Designs)
MULTI-ARM TRIALS
Bayesian Designs
Group Sequential Designs
Flexible Designs
DOSE-FINDING STUDIES
Dose-escalation designs
Dose-finding designs (Flexible Designs)
Adaptive Model-based Dose-finding
SEAMLESS DESIGNS
Dose-escalation based on efficacy/toxicity
Learning/Confirming in Phase II/III

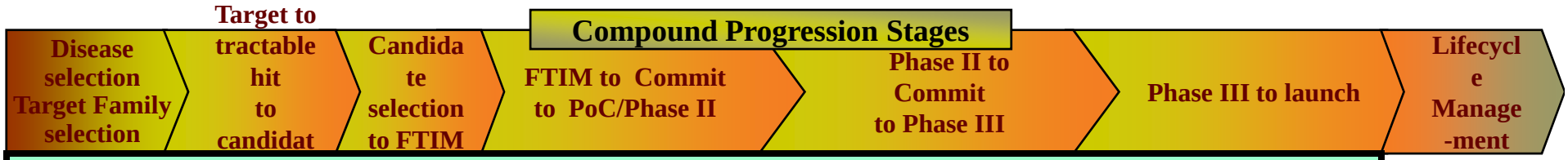
Two-Stage Designs

- **Objective:** single-arm studies using short-term endpoints; hypothesis testing about some minimal acceptable probability of response
- Gehan design: early stopping for futility; sample size of the 2nd stage gives a specified precision for response rate
- Group sequential designs: Fleming (1982), Simon (1989)
- Adaptive two-stage design: Banerjee&Tsiatis (2006)
- Bayesian designs: Thall&Simon (1994)

Screening Designs

- **Objective:** adaptive design for the entire screening program
  - Minimize the shortest time to identify the “promising” compound
  - Subject to the given constraints on type I and type II risks for the entire screening program
    - type I risk = Pr(screening procedures stops with a FP compound)
    - type II risk= Pr(any of the rejected compounds is a FN compound)
- Two-stage design (Yao&Venkatraman, 1998)
- Adaptive screening designs (Stout and Hardwick, 2002)
- Bayesian screening designs (Berry, 2001)

Classification



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Group Sequential Designs

- **Objective:** testing two hypotheses with given significance level and power at the specified alternative, prefixed maximum sample size

  - **AR:** fixed randomization
  - **SaR:** after a fixed number (a group) of observations,
    - or using error-spending function,
    - or using “Christmas-tree” adjustment
  - **StR:** boundary crossing
    - Haybittle, Pocock, O’Brien-Fleming type
    - linear boundaries
    - error-spending families
    - conditional power, stochastic curtailment
  - **DR:** final decision - to accept or reject the null hypothesis

- **References:** Jennison&Turnbull (2000); Whitehead (1997)

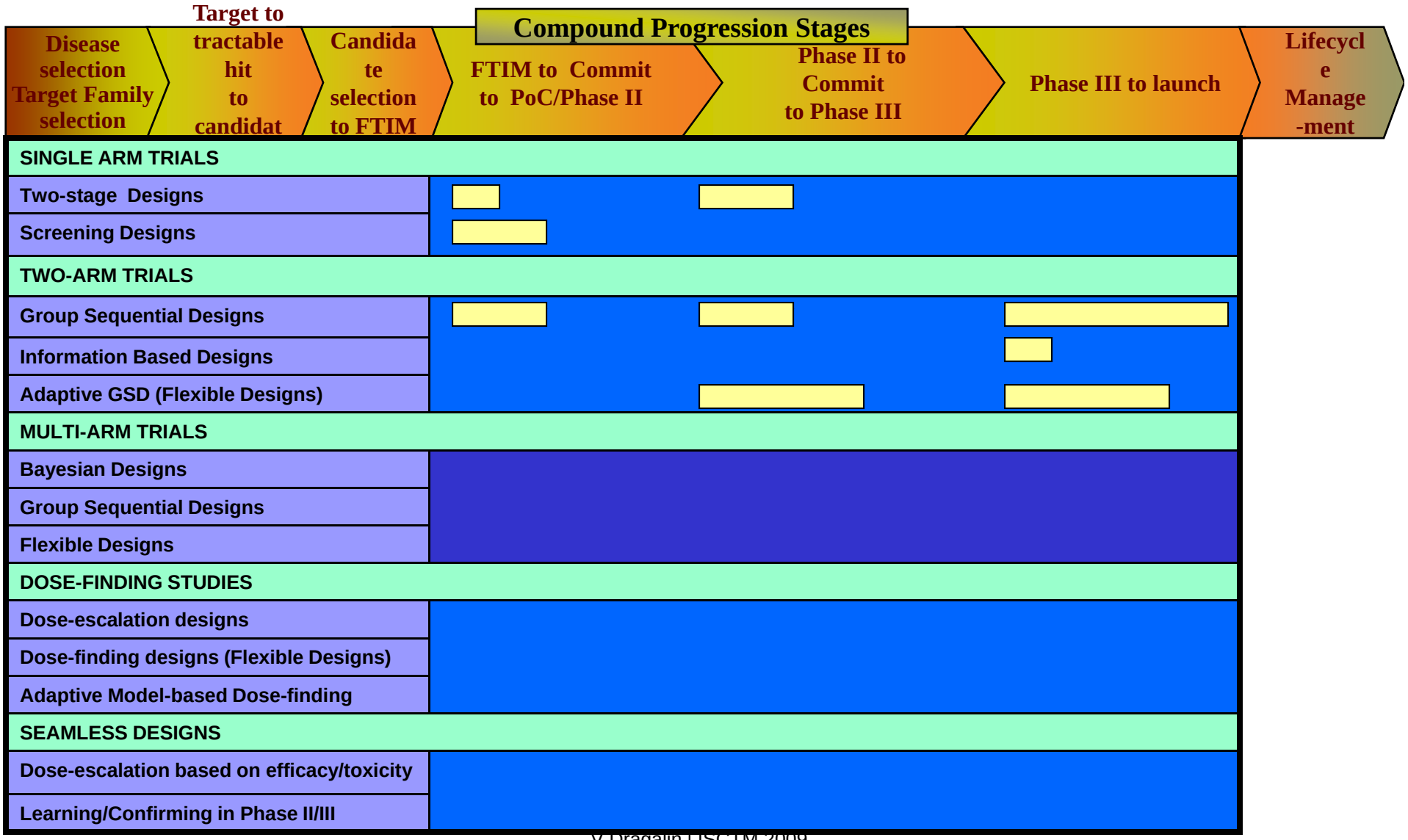
Adaptive GSD (Flexible Designs)

- **Objective:** testing two hypotheses with given significance level and power at the specified alternative or adaptively changing the alternative at which a specified power is to be attained

  - **AR:** fixed or adaptive randomization
  - **SaR:** sample size of the next stage depends on results at the time of interim analysis
  - **StR:** p-value combination, conditional error, variance-spending
  - **DR:** adapting alternative hypothesis, primary endpoint, test statistics, inserting or skipping IAs

- **References:** Bauer; Brannath et al; Müller&Schäfer; Fisher

Classification



Bayesian Designs

- **Objective:** to use the posterior probabilities of hypotheses of interest as a basis for interim decisions (*Proper Bayesian*) or to explicitly assess the losses associated with consequences of stopping or continuing the study (*Decision-theoretic Bayesian*)

  - **AR:** equal randomization or *play-the-winner* (next patient is allocated to the currently superior treatment) or *bandit designs* (minimizing the number of patients allocated to the inferior treatment)
  - **SaR:** not specified
  - **StR:** not formally pre-specified stopping criterion, or using a *skeptical prior* for stopping for efficacy and an *enthusiastic prior* for stopping for futility, or using *backwards induction*
  - **DR:** update the posterior distribution; formal incorporation of external evidence; inference not affected by the number and timing of IAs

- **References:** Berry (2001, 2004); Berry et al. (2001); Spiegelhalter et al. (2004).

Pairwise comparisons with GSD

- **Objective:** compare multiple treatments with a control; focus on type I error rate rather than power

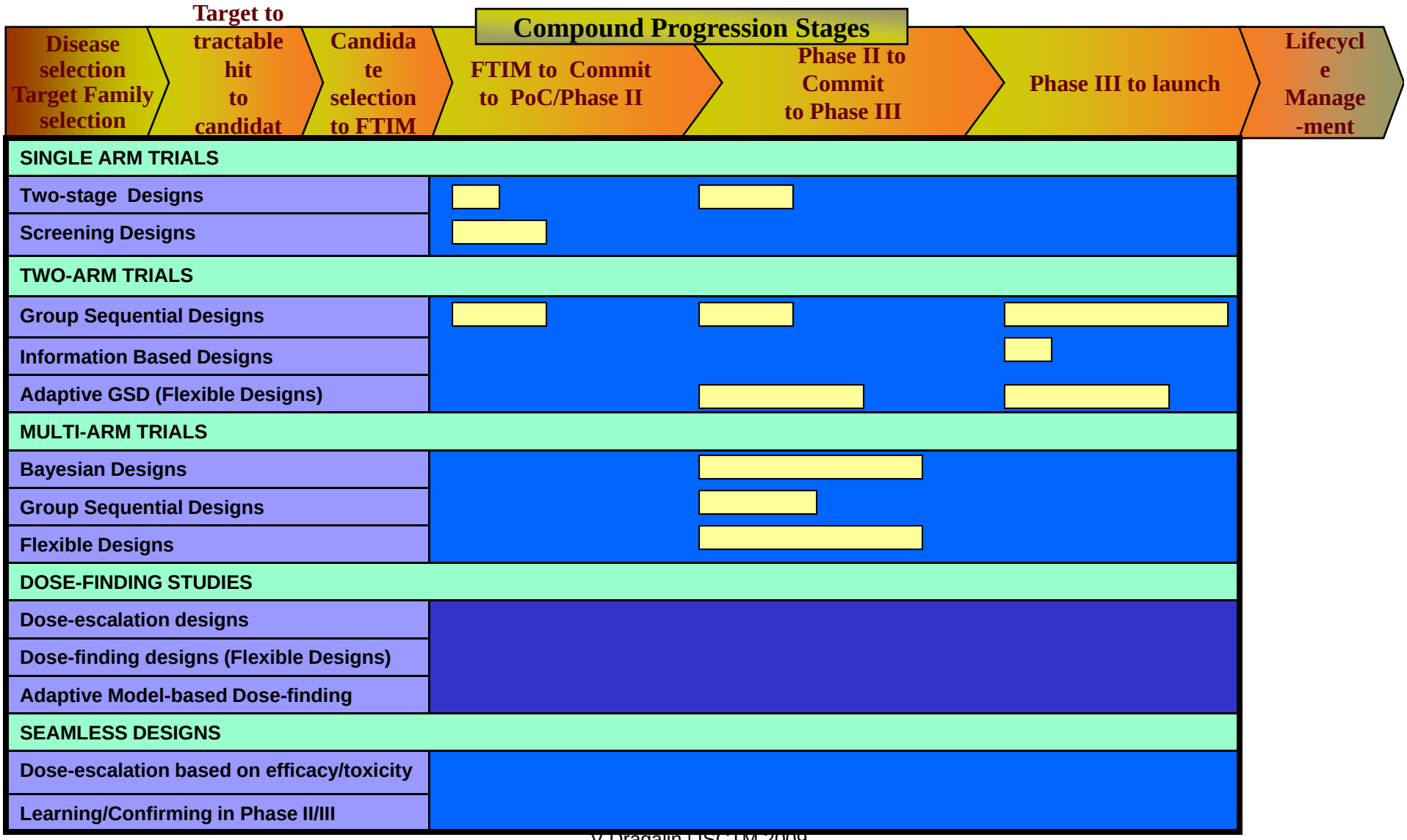
  - A simple Bonferroni approximation is only slightly conservative
  - Treatments may be dropped in the course of the trial if they are significantly inferior to others
  - “Step-down” procedures allow critical values for remaining comparisons to be reduced after some treatments have been discarded

- **References:** Follmann et al (1994)

p-value combination tests

- **Objective:** compare multiple treatments with a control in a two-stage design allowing integration of data from both stages in a confirmatory trial
- **Focus:** control of multiple (familywise) Type I error level
- **Great flexibility:**
  - General distributional assumptions for the endpoints
  - General stopping rules and selection criteria
  - Early termination of the trial
  - Early elimination of treatments due to lack of efficacy or to safety issues or for ethical/economic reasons
- **References:** Bauer&Kieser (1994)

Classification



Dose-escalation designs

- **Objective:** target the MTD (Phase I) or the best safe dose (Phase I/II) or find the therapeutic window

  - **AR:** non-parametric (3+3 rule, up-and-down)
    - or model-based (Continual Reassessment Methods)
    - or Escalation With Overdose Control (EWOC)
    - or Bayesian Decision Design
    - or Bayesian Optimal Design
    - or Penalized Adaptive D-optimal Design
  - **SaR:** cohorts of fixed size or in two stages (Storer design)
  - **StR:** no early stopping or stopping by design (e.g. 3+3 rule)
  - **DR:** update model parameters (for model-based AR)

- **References:** O'Quigley et al.; Babb et al.

Adaptive Model-based Dose-finding

- **Objective:** find the optimal dose; working model for the dose-response; dose sequence identified in advance

  - **AR:** *Bayesian* (based on predictive probabilities: smallest average posterior variance) or *frequentist* (based on optimal experimental design: maximum information per cost)
  - **SaR:** cohorts of fixed size or after each observation
  - **StR:** stopping for futility or when the optimal dose for confirmatory stage is sufficiently well known (estimation!)
  - **DR:** update model parameters, Bayesian predictions of long-term endpoint using a longitudinal model

- **References:** Berry et al. (2001); Dragalin&Fedorov

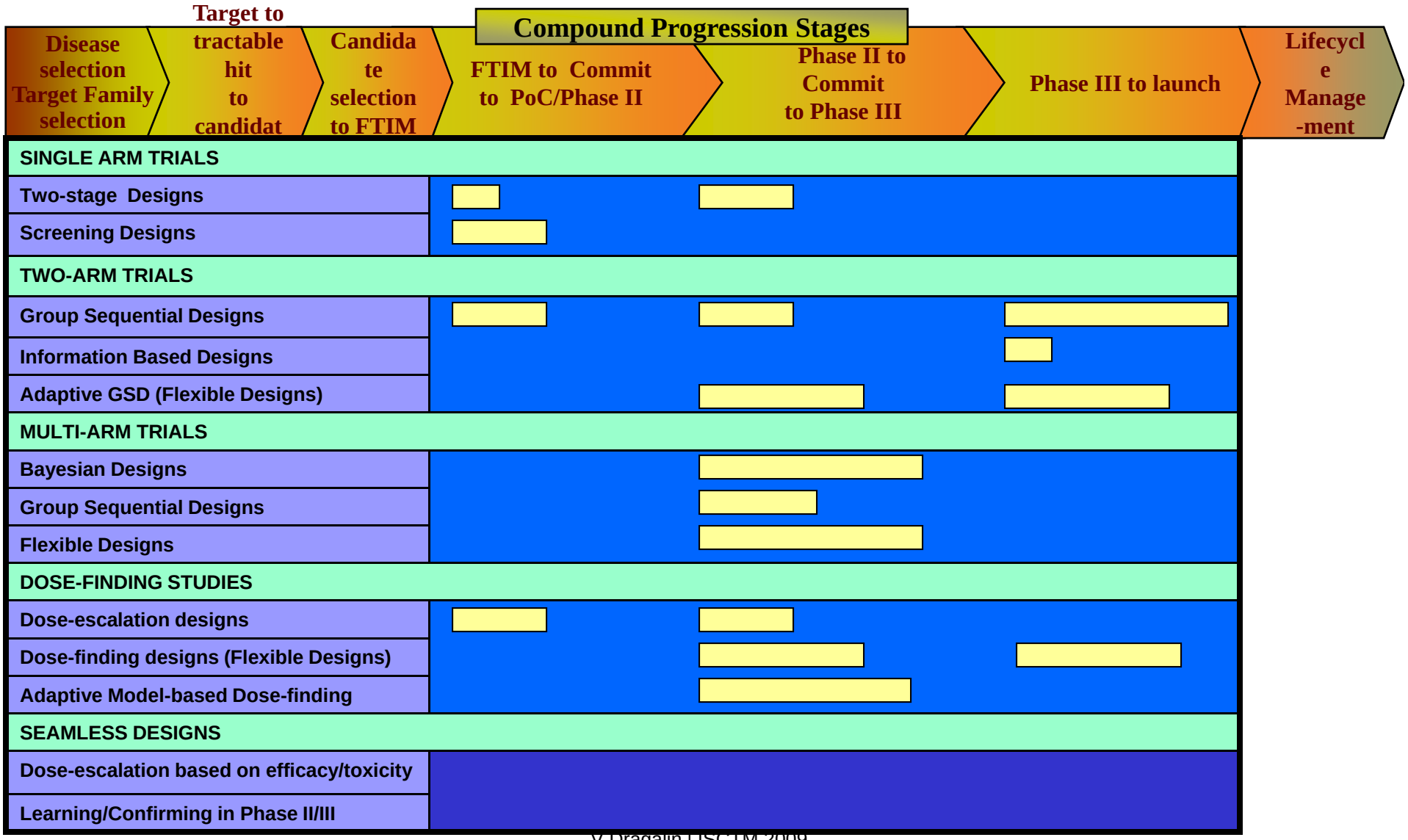
Adaptive Dose-finding (Flexible Designs)

- **Objective:** establishing a dose-response relationship or combining Phase II/III using p-value combination tests

  - **AR:** drop or add doses
  - **SaR:** sample size reassessment for the next stage
  - **StR:** early stopping for futility or early termination of some inferior doses
  - **DR:** adapting hypotheses, primary endpoint, test statistics, inserting or skipping IAs

- **References:** Bauer&Kohne

Classification



Seamless Designs: Definition

Seamless design

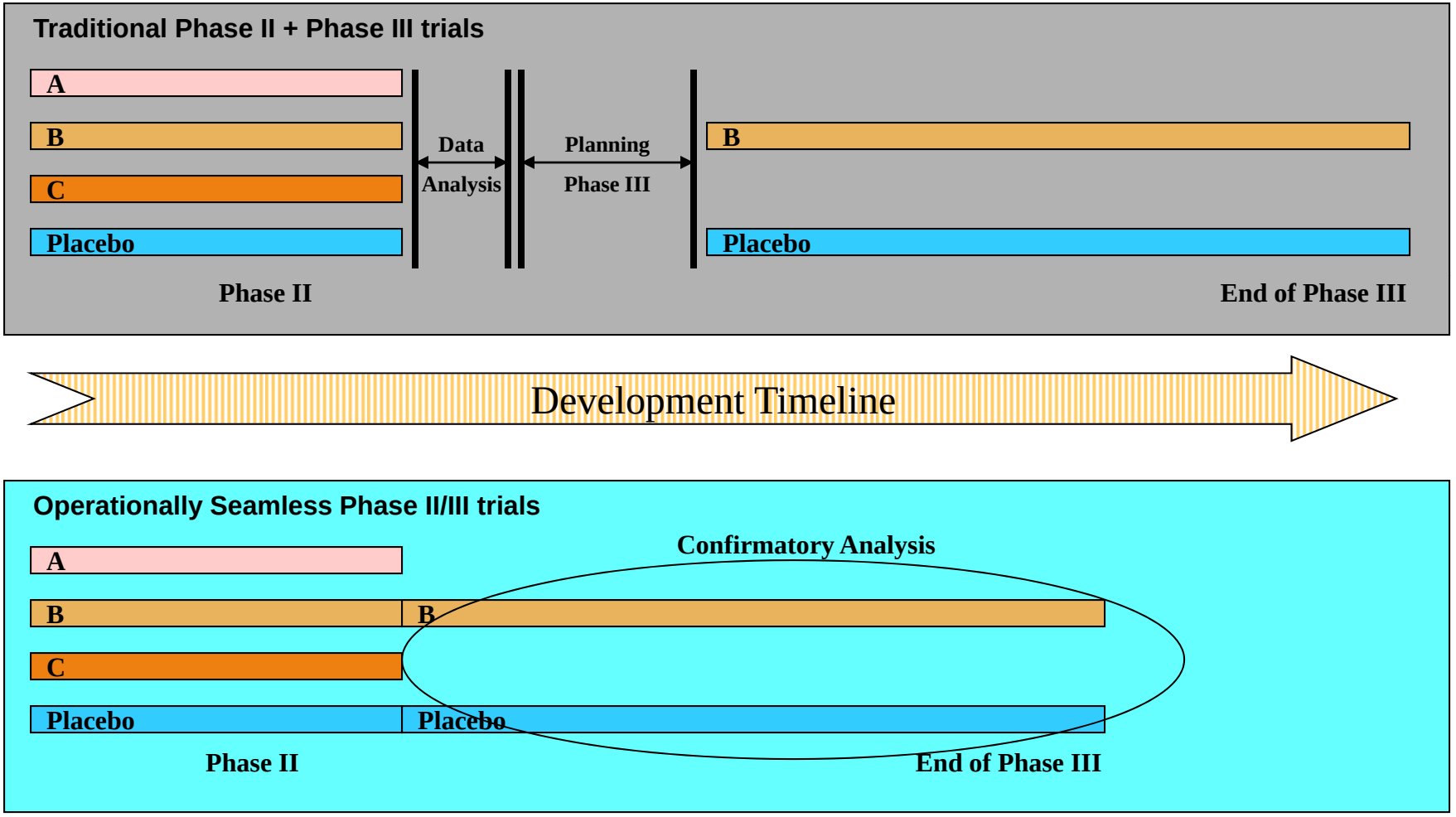
- A clinical trial design that combines into a single trial objectives which are traditionally addressed in separate trials (*operationally* seamless)

Adaptive Seamless design

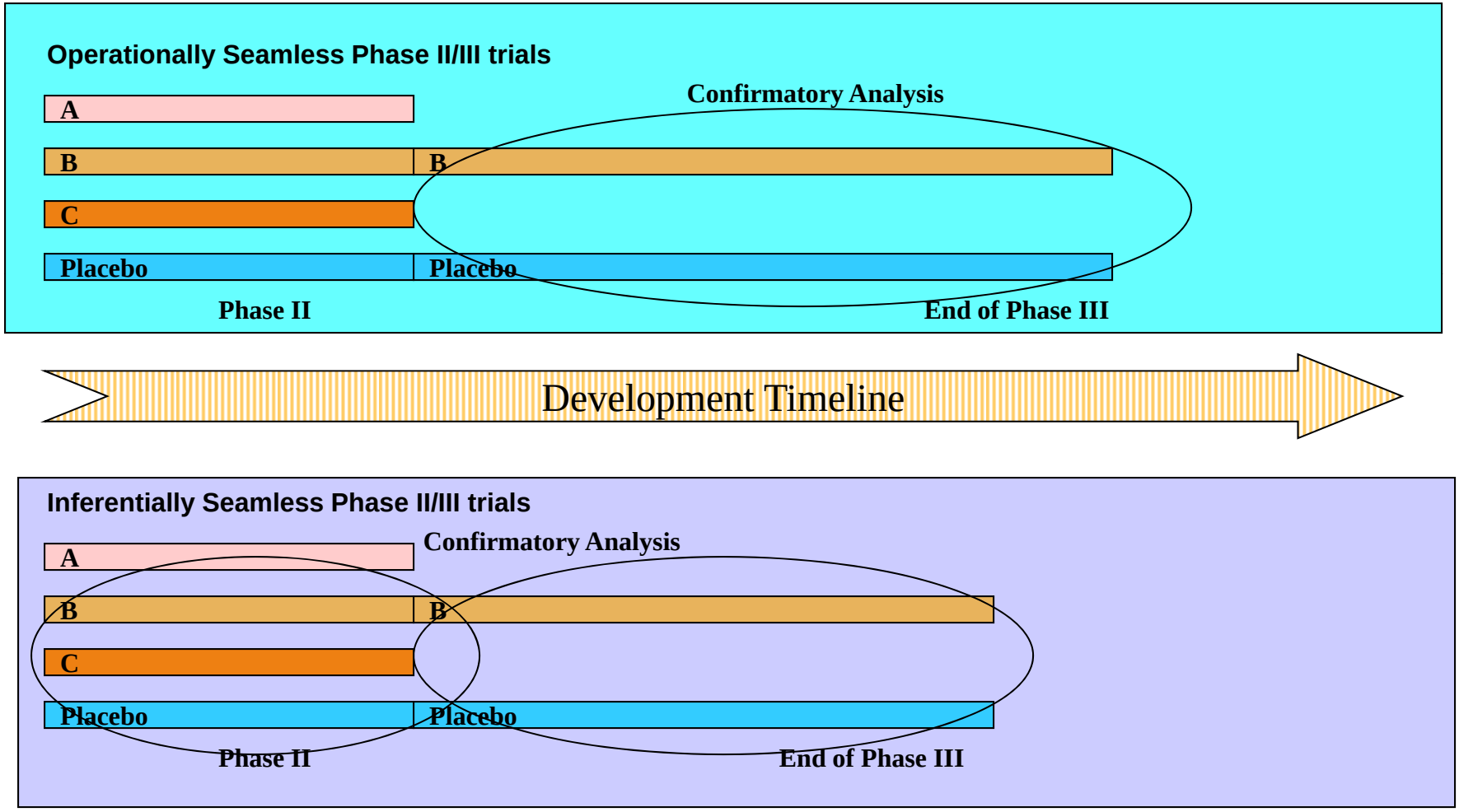
- A seamless trial in which the final analysis will use data from patients enrolled before and after the adaptation (*inferentially* seamless)

References: Maca et al. (2006)

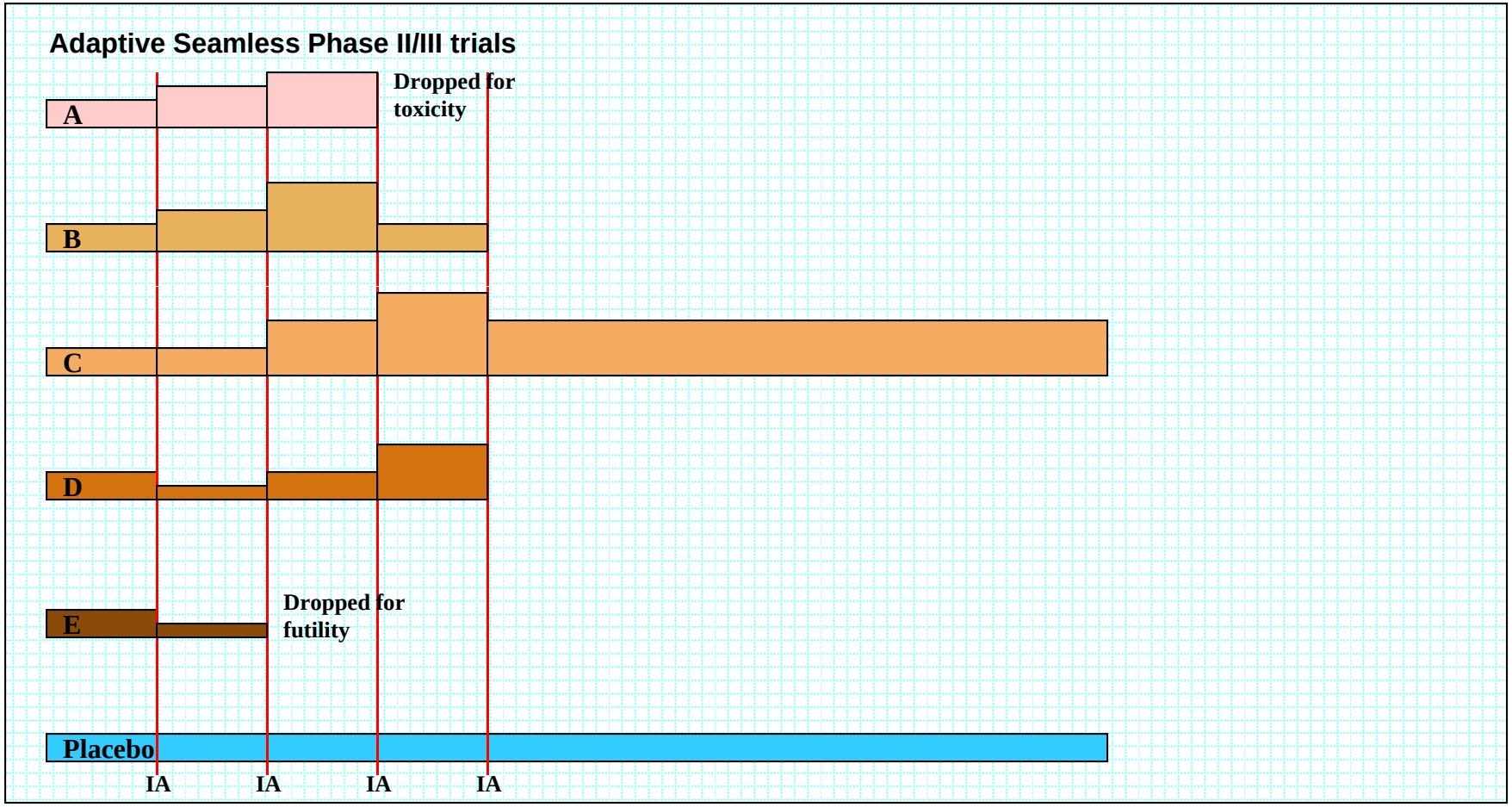
Faster: Operationally Seamless



At lower costs: Inferentially Seamless



Better: Adaptive Seamless

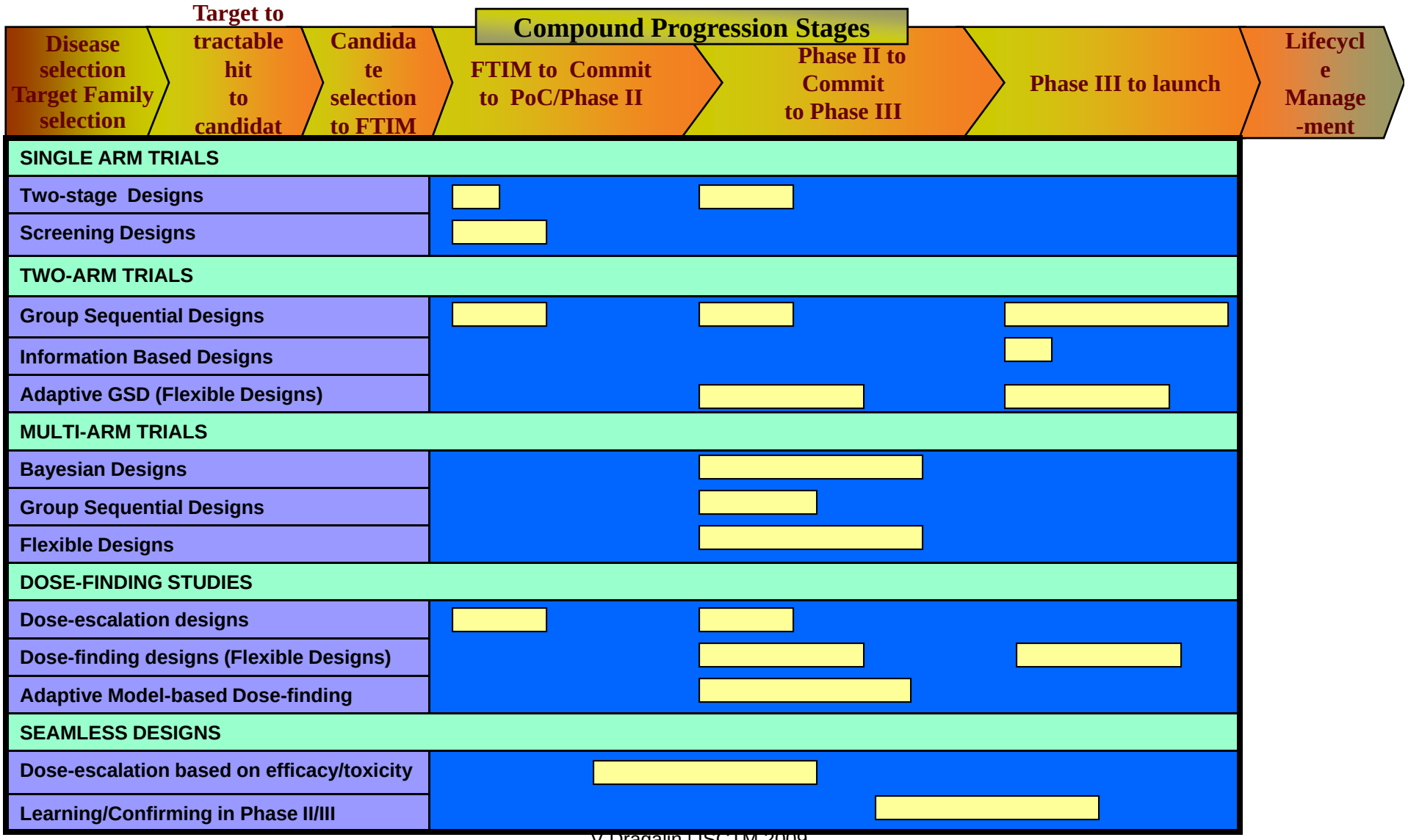


Development Timeline

Bayesian model-based designs

- **Objective:** adaptive dose ranging within a confirmatory trial
- **Focus:** efficient learning, effective treatment of patients in the trial
- **Method includes:**
  - **AR:** to maximize information about dose response
  - **SaR:** Frequent analysis of the data as it accumulates
  - Seamless switch to confirmatory stage without stopping enrollment in a double-blind fashion
  - Use of longitudinal model for prediction of the clinical endpoint
- **References:** Berry et al

Classification



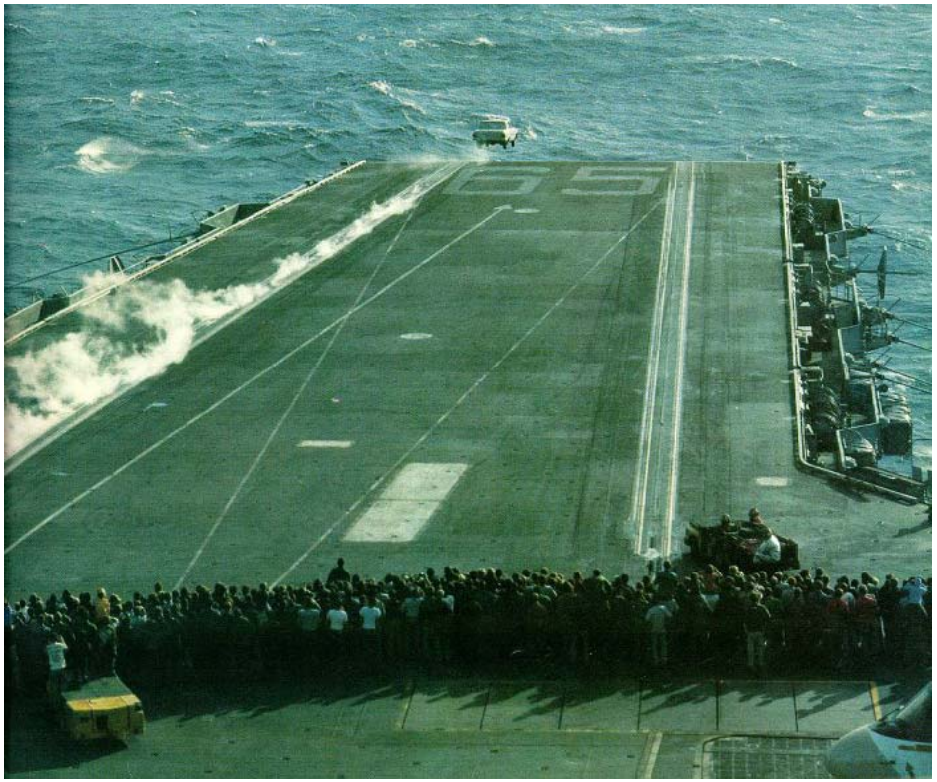
Achieving the goals

- The objective of a clinical trial may be either
  - to target the MTD or MED or to find the therapeutic range
  - or to determine the OSD (Optimal Safe Dose) to be recommended for confirmation
  - or to confirm efficacy over control in Phase III clinical trial

- This clinical goal is usually determined by
  - the clinicians from the pharmaceutical industry
  - practicing physicians
  - key opinion leaders in the field, and
  - the regulatory agency

Achieving the goals

- Once agreement has been reached on the objective, it is the statistician's responsibility to provide the appropriate design and statistical inferential structure required to achieve that goal



Achieving the goals

- There are plenty of available designs on statistician's shelf
- The greatest challenge is their implementation

- Adaptive designs have much more to offer than the rigid conventional parallel group designs in clinical trials

References

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