Discussion

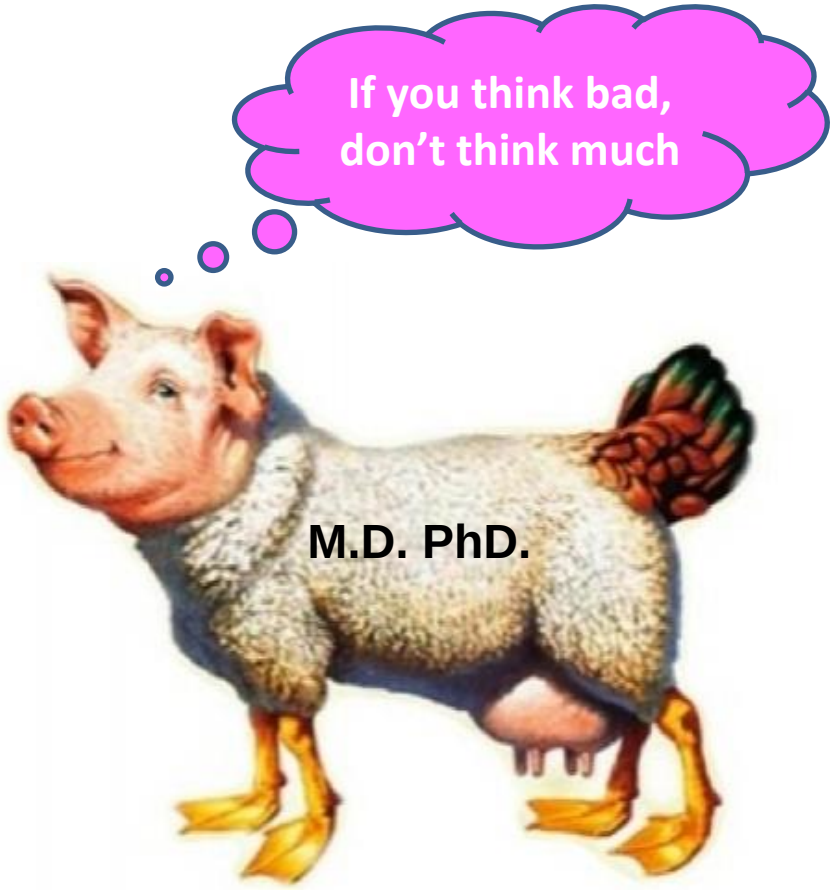
Design of Experiments in Healthcare,

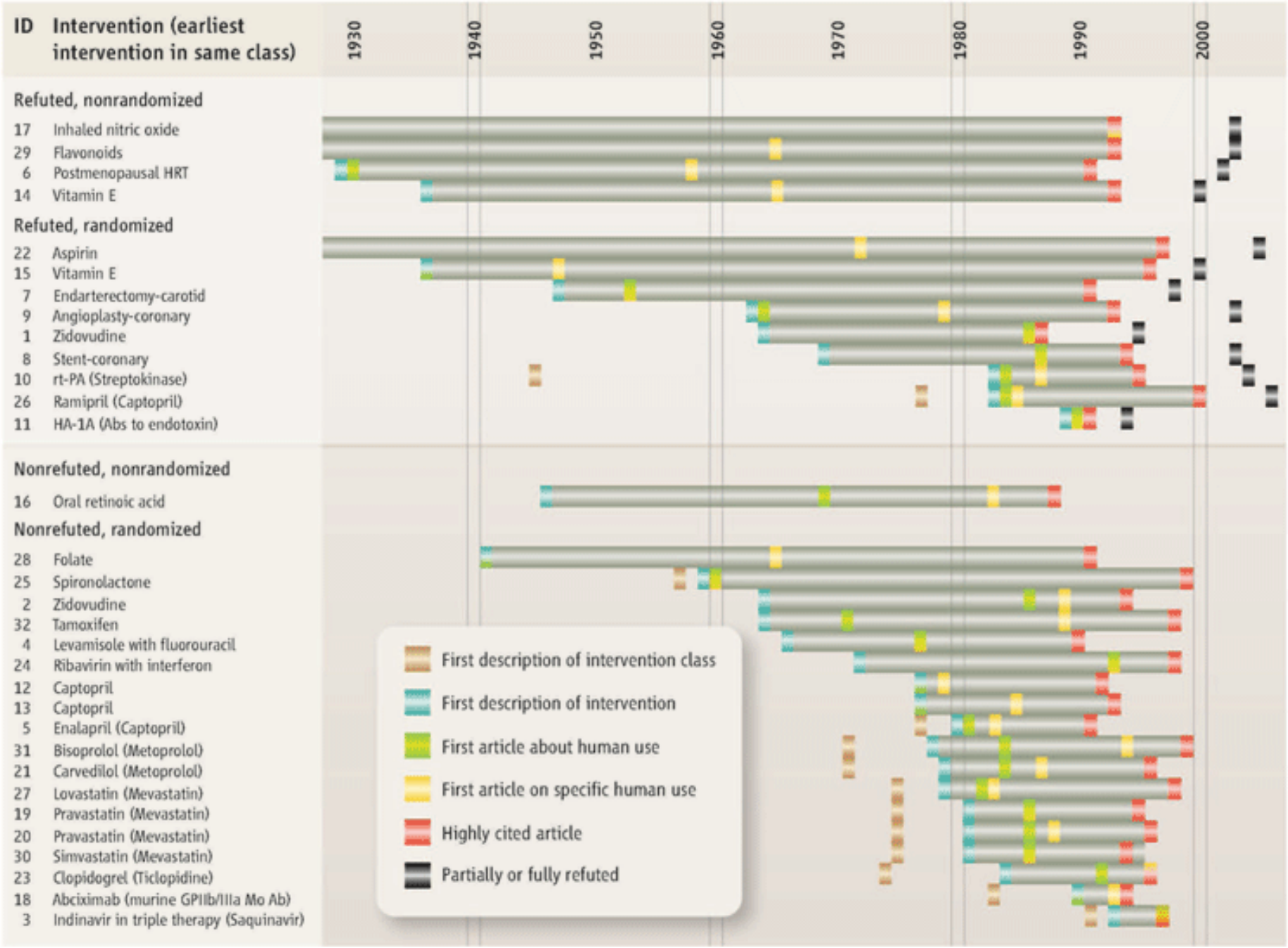
dose-ranging studies,

astrophysics

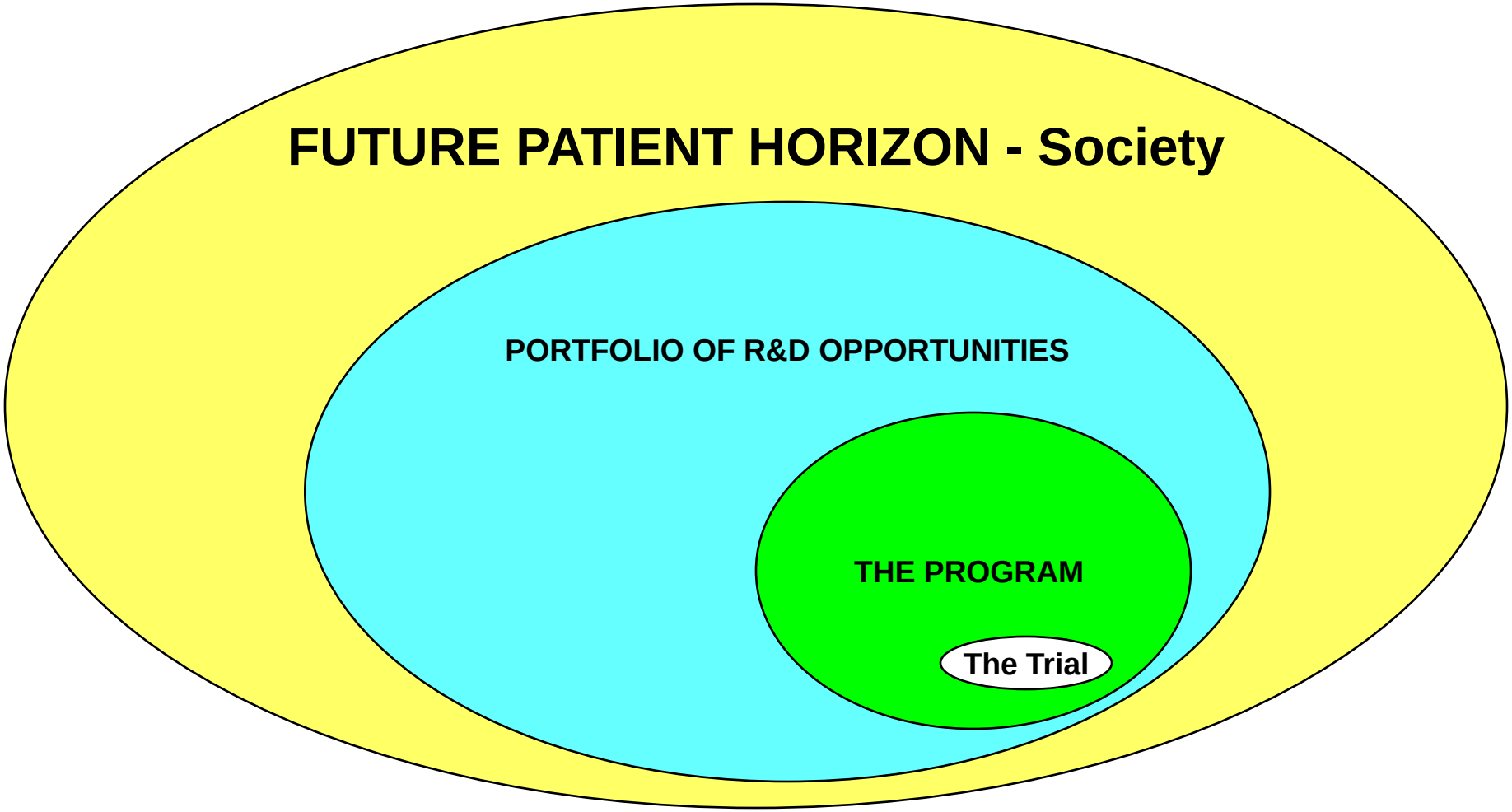
… and other dangerous things

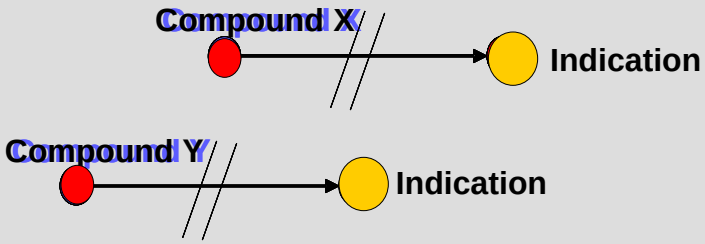
1.





Contopoulous-Ioannidis et al. Life Cycle of Translational Research for Medical Interventions. *Science 2008;321(5894) 1298-1299*


FUTURE PATIENT HORIZON - Society
PORTFOLIO OF R&D OPPORTUNITIES
THE PROGRAM
The Trial

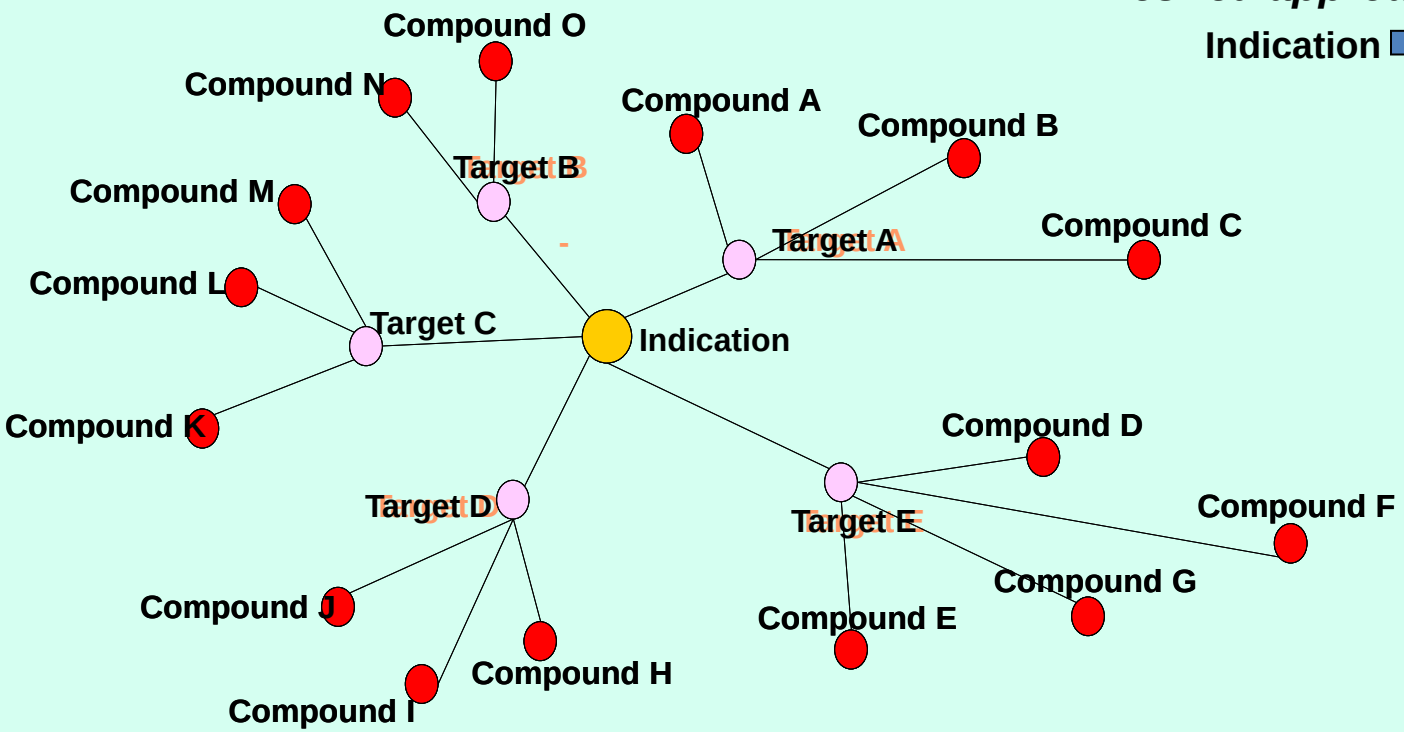


Traditional “mapping” is one-dimensional

Compound ⇨ Indication

Desired approach is multi-dimensional

Indication ⇨ Target ⇨ Compounds



- Aligning utilities
  - Society/Industry/Patients in general/Patients in the trial
  -
- What drives decision making?
  - Time-to-milestone
  - Time-to-high quality information
  - Time-to-future patient horizon

- Key requirements
  - Fundamental understanding of biology
    - Match molecular fingerprint of the disease with characteristics of the drug
  - Translational science
  - Clinical trial methodology
  - Regulatory science

"3 Bucket" Approach

1. What is acceptable?
   - In a "Confirmatory" setting:
     Blinded sample size re-estimation, group sequential designs
   - In a "Learn" setting: *Adaptive BY Design*, e.g. adaptive exploration of treatment strategies, learning about the dose-response
   - What is required?
     - Correct statistical inference; Controlling operational bias

2. What is definitely unacceptable?
   - Poorly planned, unsubstantiated, undocumented proposals
   - Post-hoc adaptations

3. What requires case-by-case consideration?
   - *Adaptive BY Design* in the "confirmatory phase"
     - Seamless adaptive phase II/III
   - Purely Bayesian approaches in a confirmatory setting
   - Can we identify aspects that we can move into Bucket #1 or #2

A modern review process for adaptive designs

- Should we plan for an intensified and sufficiently early and continuous interaction between FDA and sponsor to facilitate high quality planning and implementation of adaptive designs?
  - What is the process to move this forward?
- What is the method for sponsor and regulatory interaction for case-by-case issues?
  - Special Protocol Assessment Tool may not be enough

2010 Regulatory guidance documents

- Food and Drug Administration (2010), *Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics (Draft Guidance). Silver Spring, MD: US Food and Drug Administration. Available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf

2007 Regulatory guidance documents

- EMEA (2007), *Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design. EMEA Doc. Ref. CHMP/EWP/2459/02. Available at* http://www.emea.europa.eu/pdfs/human/ewp/245902enadopted.pdf

2.

“Articulate and Quantify”

What is the value proposition? “Differentiation”

Label

What are the decision problems?

What are the research questions?

What is most efficient approach to answer research question(s)?

Assumption log, Issue log

……..

Sheiner L. Learning versus confirming. Clin Pharmacol Ther 1997;61-275-91

LEARN

The Good, The Bad and the Ugly

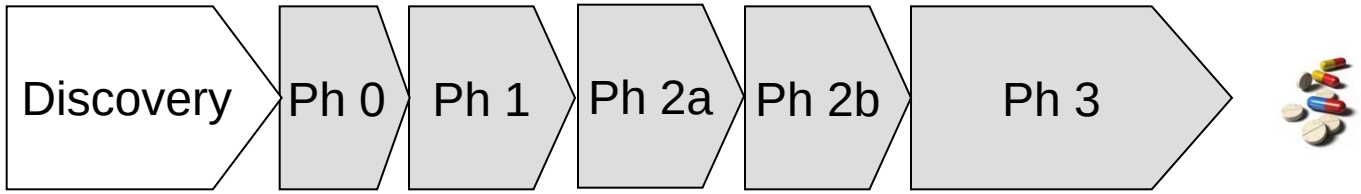
FAIL EFFICIENTLY

CONFIRM

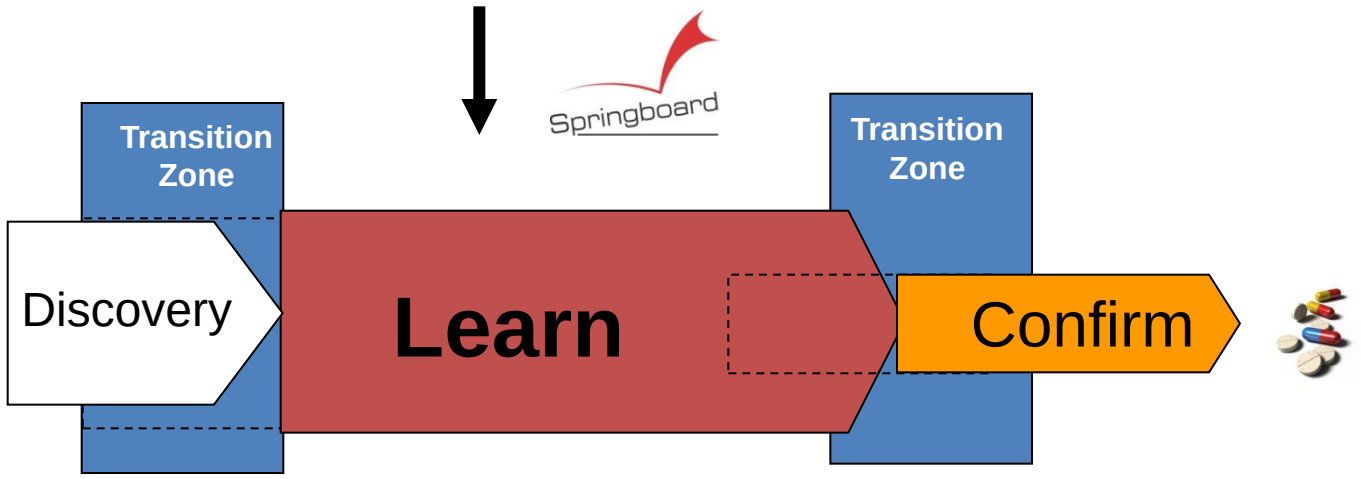
SUCCEED EFFICIENTLY

- **The principle: Learning and decision making in real time**
  - Make decisions based on data
  - At the earliest time point
  - In the most efficient way
  - On a program basis
  - **The "best" design: highest information value per resource unit invested**

Old



New

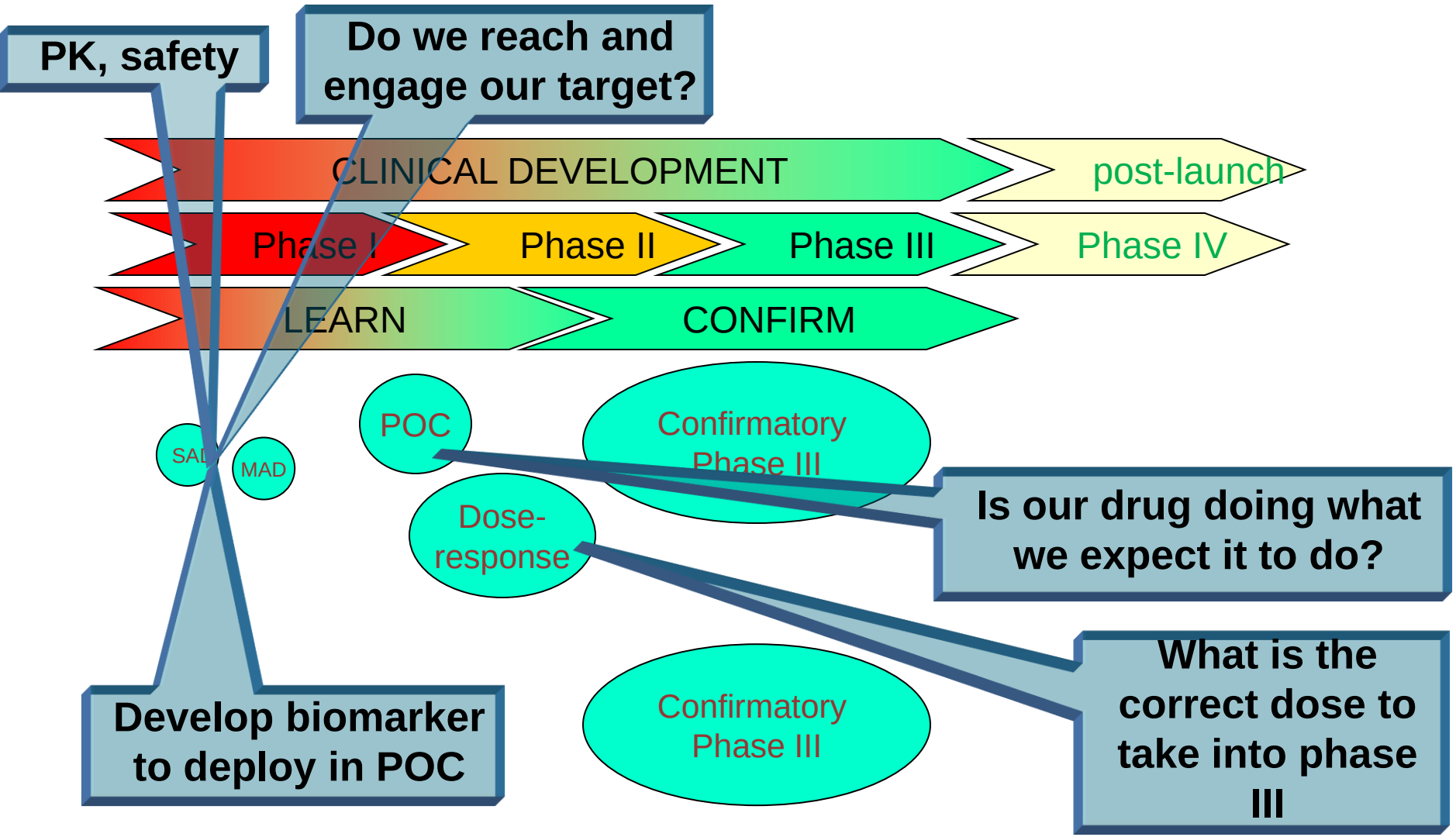


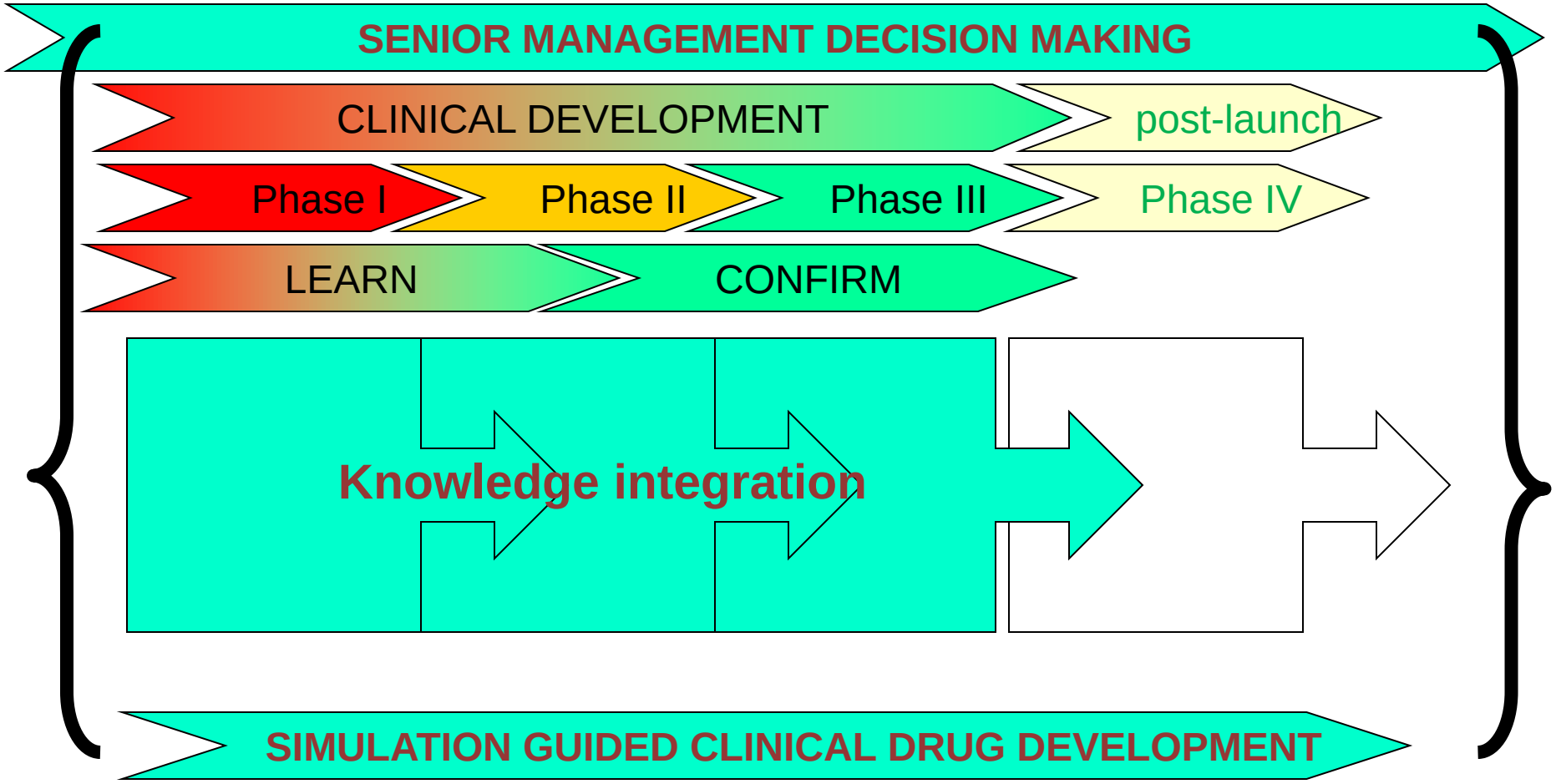
Team Objective

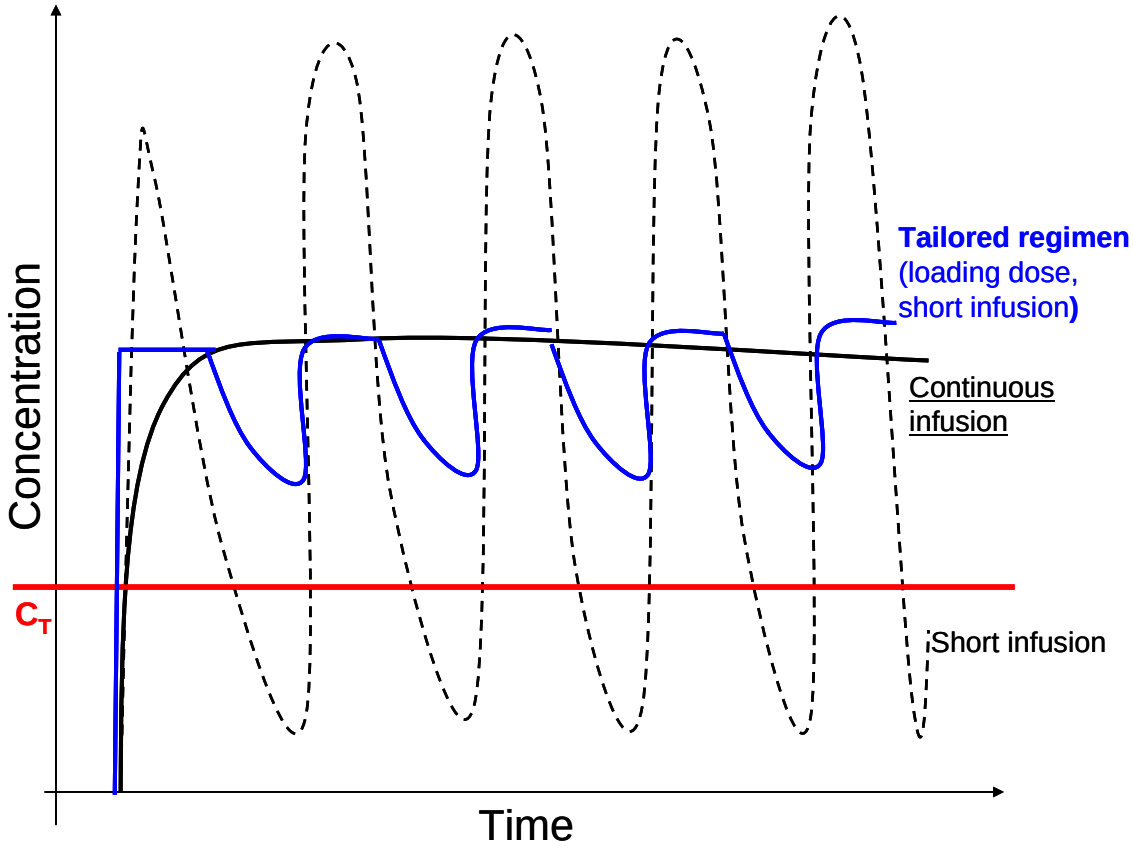
- Optimize understanding to maximize medical value
- Benefit/risk likely

Team Objective

- Optimize execution
- Benefit/risk is achieved


PK, safety
Do we reach and engage our target?
CLINICAL DEVELOPMENT
post-launch
Phase I
Phase II
Phase III
Phase IV
LEARN
CONFIRM
SAD
MAD
POC
Confirmatory Phase III
Dose-response
Is our drug doing what we expect it to do?
What is the correct dose to take into phase III
Confirmatory Phase III
Develop biomarker to deploy in POC


SENIOR MANAGEMENT DECISION MAKING
CLINICAL DEVELOPMENT
post-launch
Phase I
Phase II
Phase III
Phase IV
LEARN
CONFIRM
Knowledge integration
SIMULATION GUIDED CLINICAL DRUG DEVELOPMENT



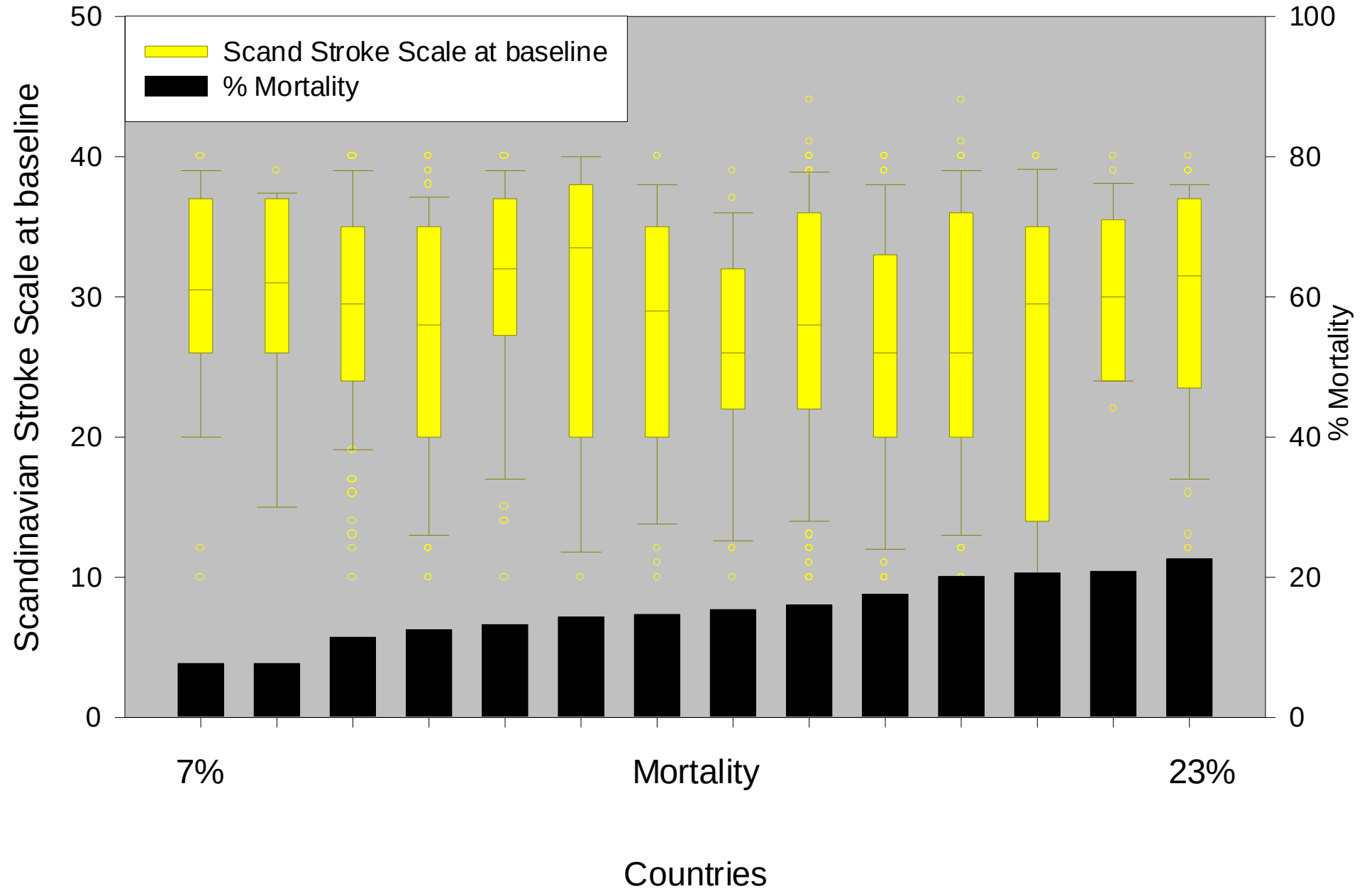
Desired PK profile to maximize Therapeutic Index:

1. Is efficacy driven by Cmax, AUC?
2. Does exposure need to be maintained over a critical threshold concentration (C_T)?
3. What is the correct “rhythm” of redosing?
4. What is the correct “duration” of treatment?

3.

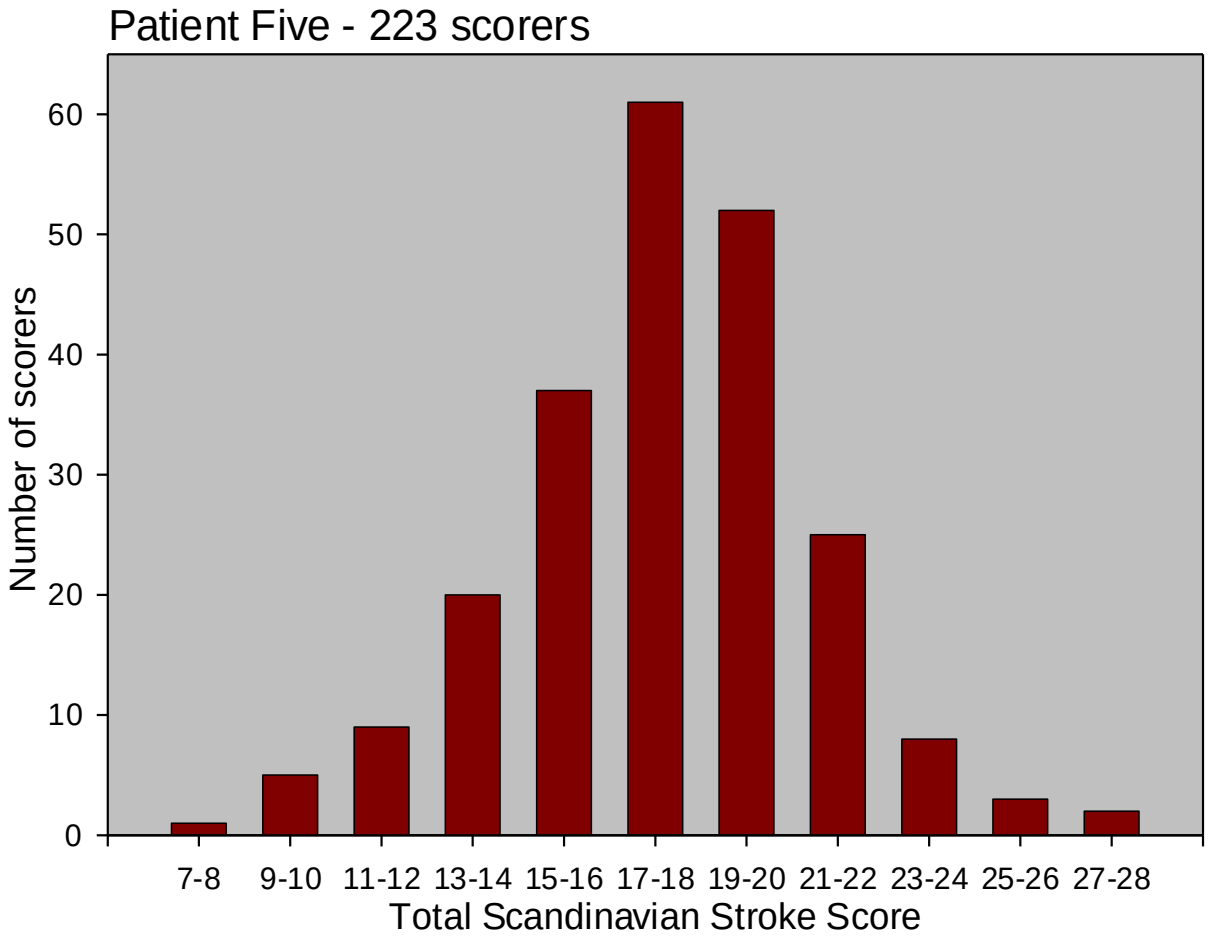
Case study: Acute stroke study

The endpoint: Mortality – “A flight across the Atlantic”

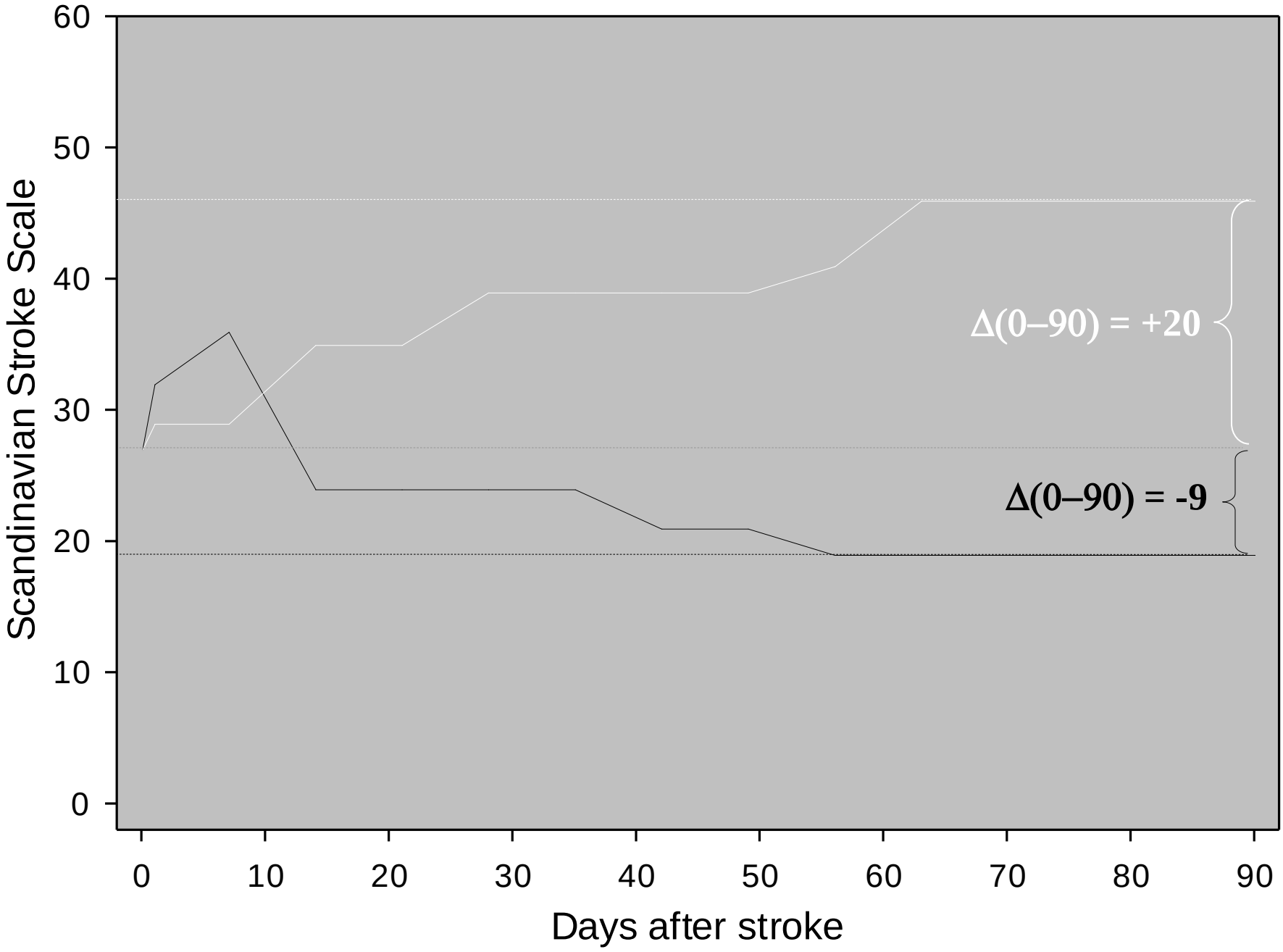


Case study: Acute stroke study
The endpoint: Neurological Stroke Scale

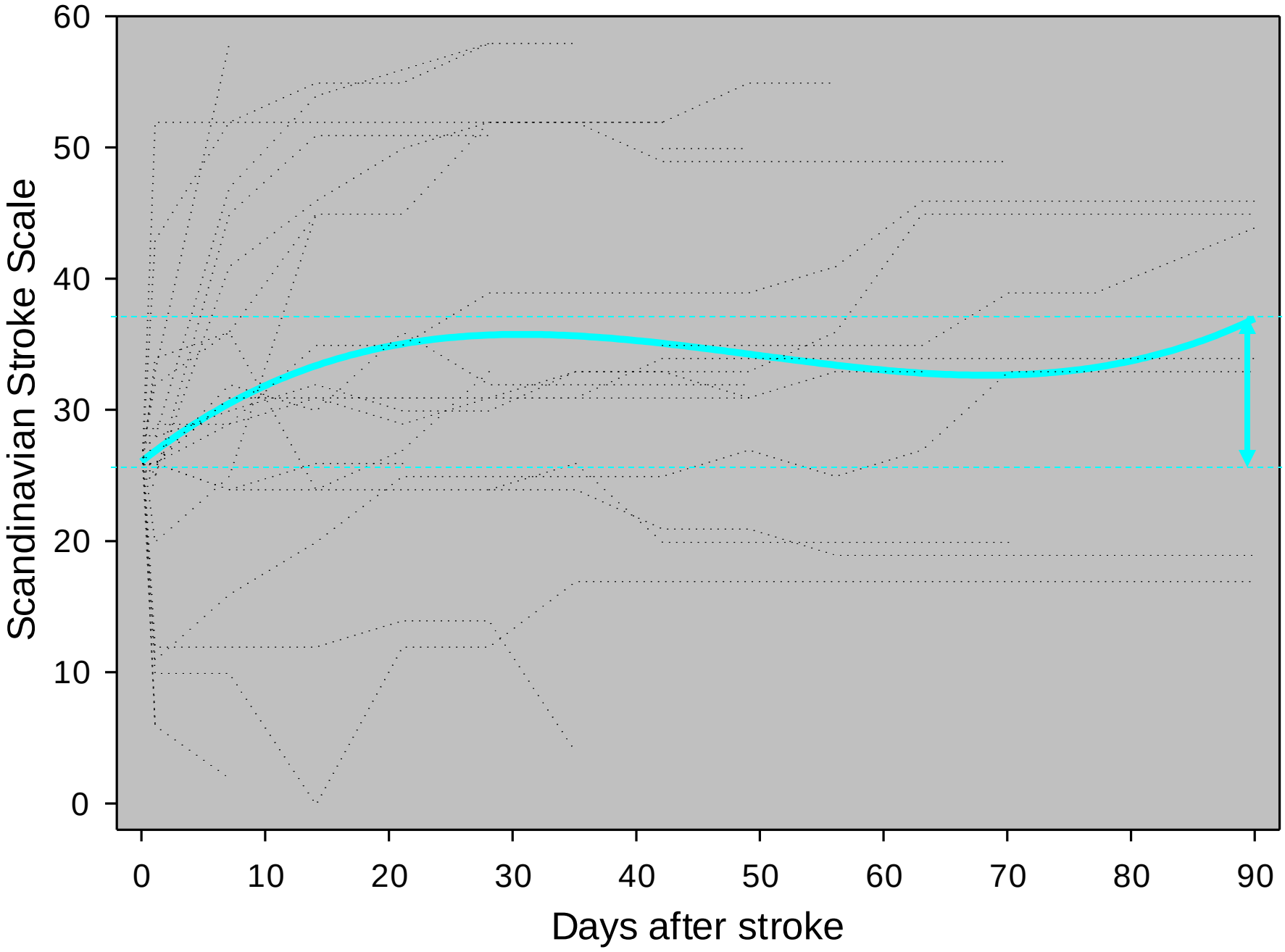
- Issues
  - Composite score
  - Sensitivity
  - Inter-rater variability



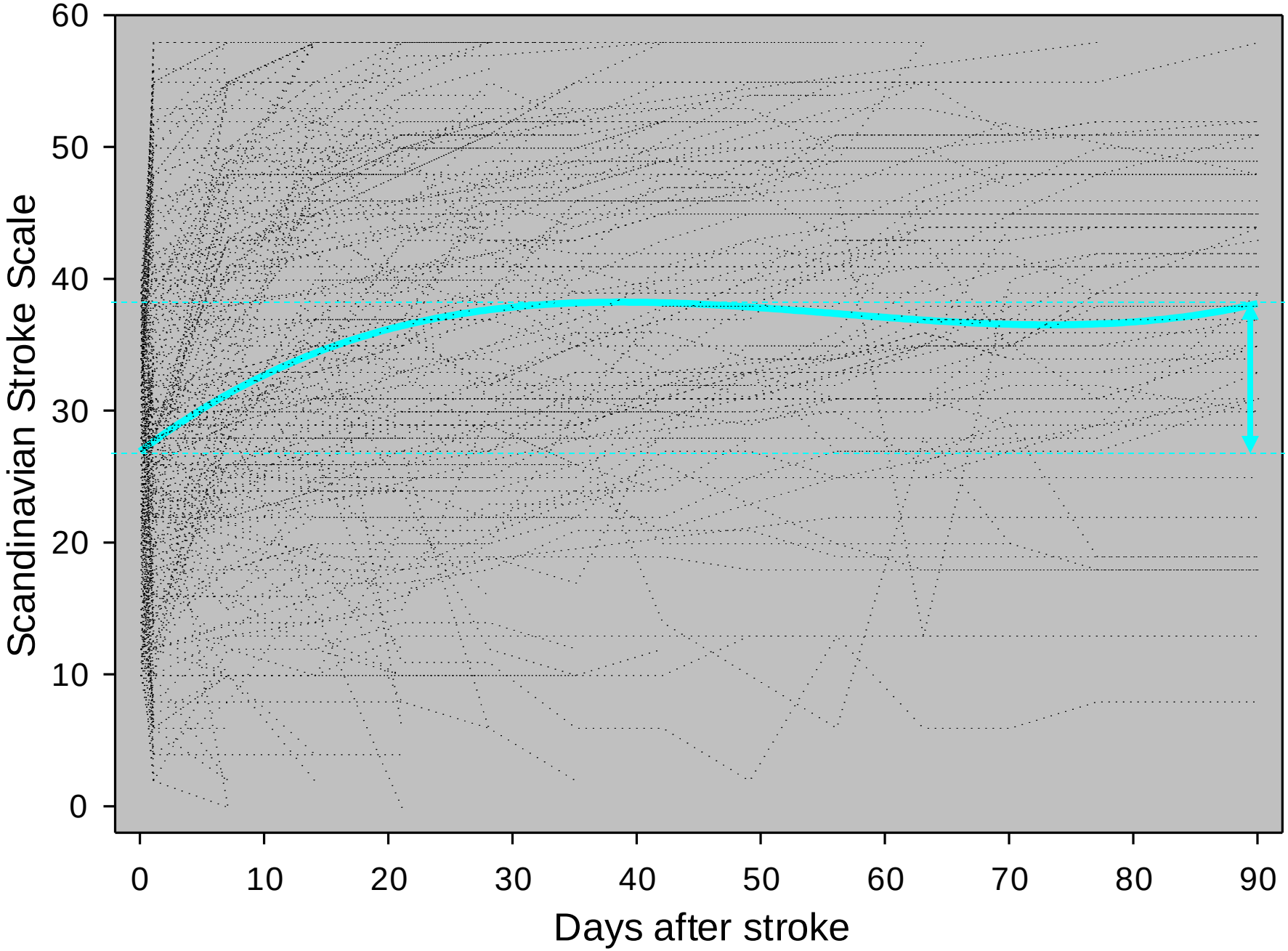
The endpoint: Acute stroke – 002 patients



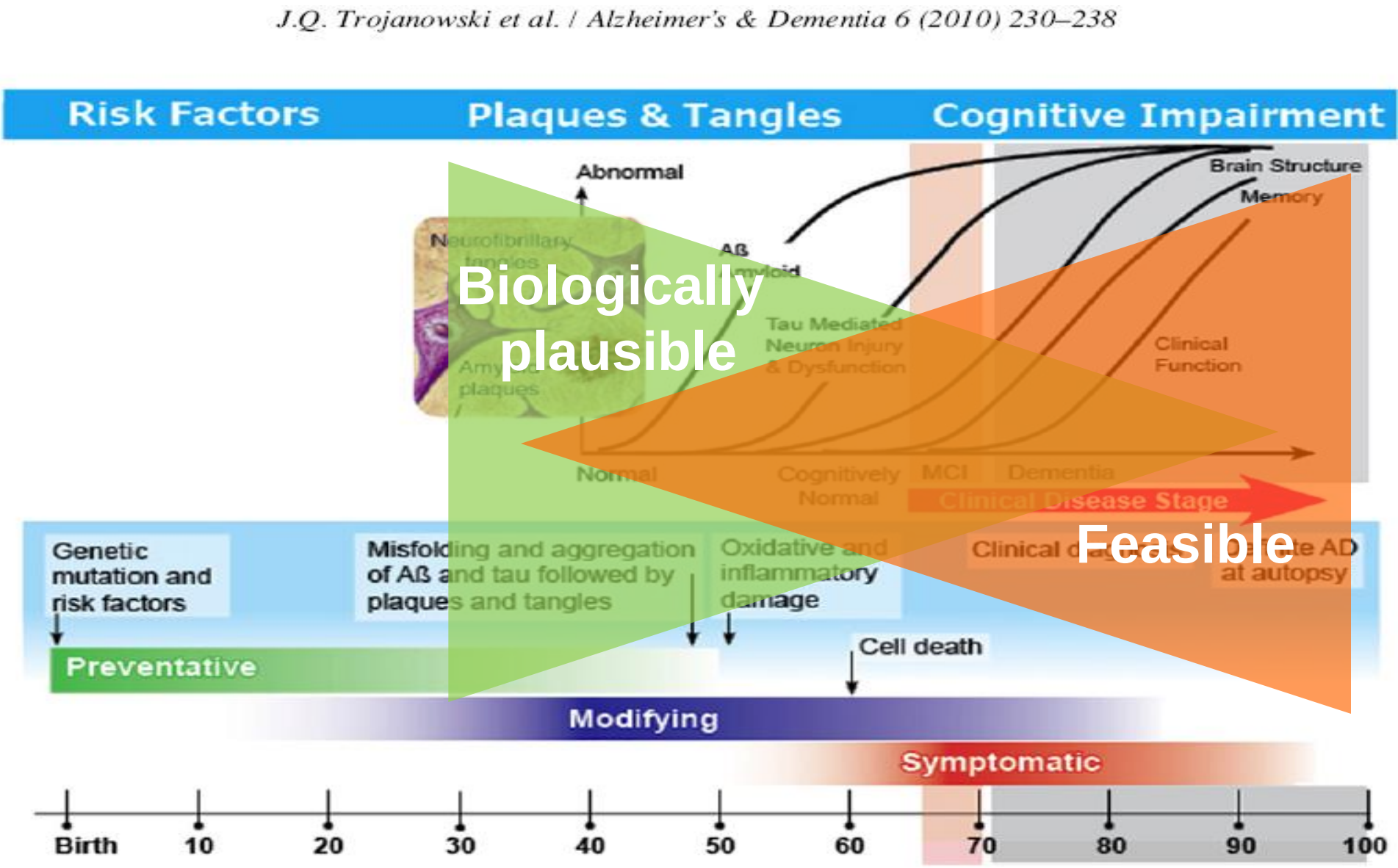
The endpoint: Acute stroke – 020 patients



The endpoint: Acute stroke – 200 patients

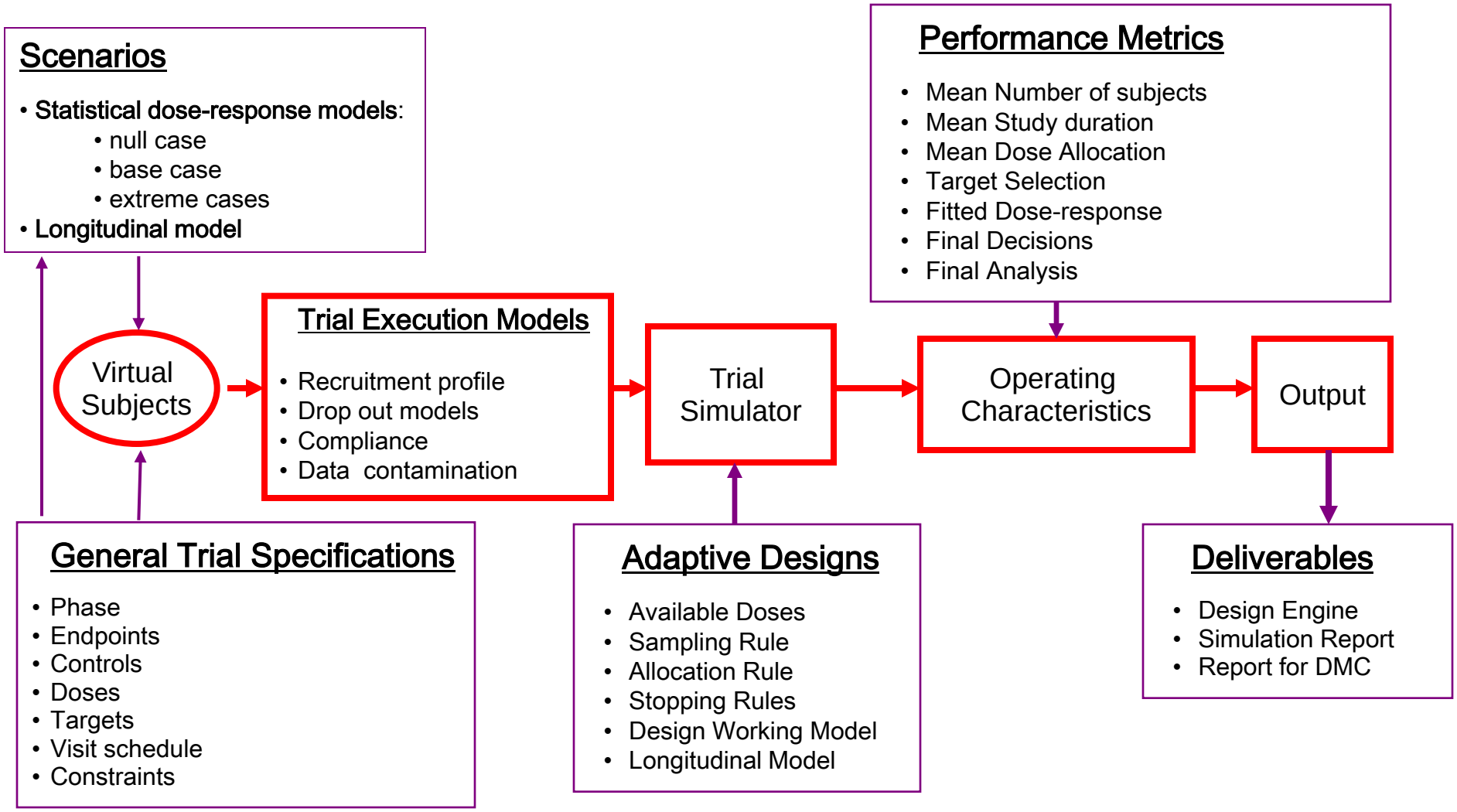


“In the name of feasibility…”

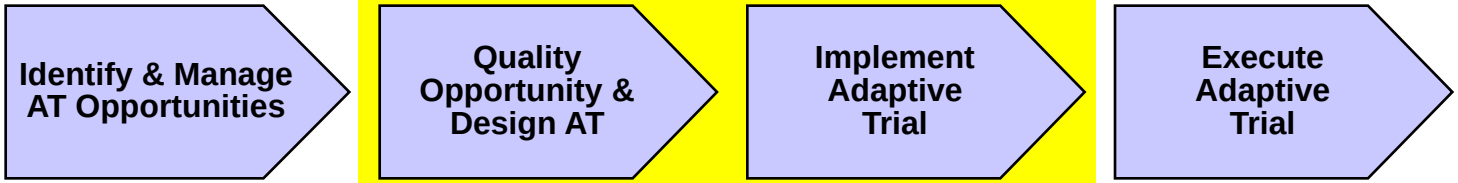


4.

Simulation guided clinical trial design



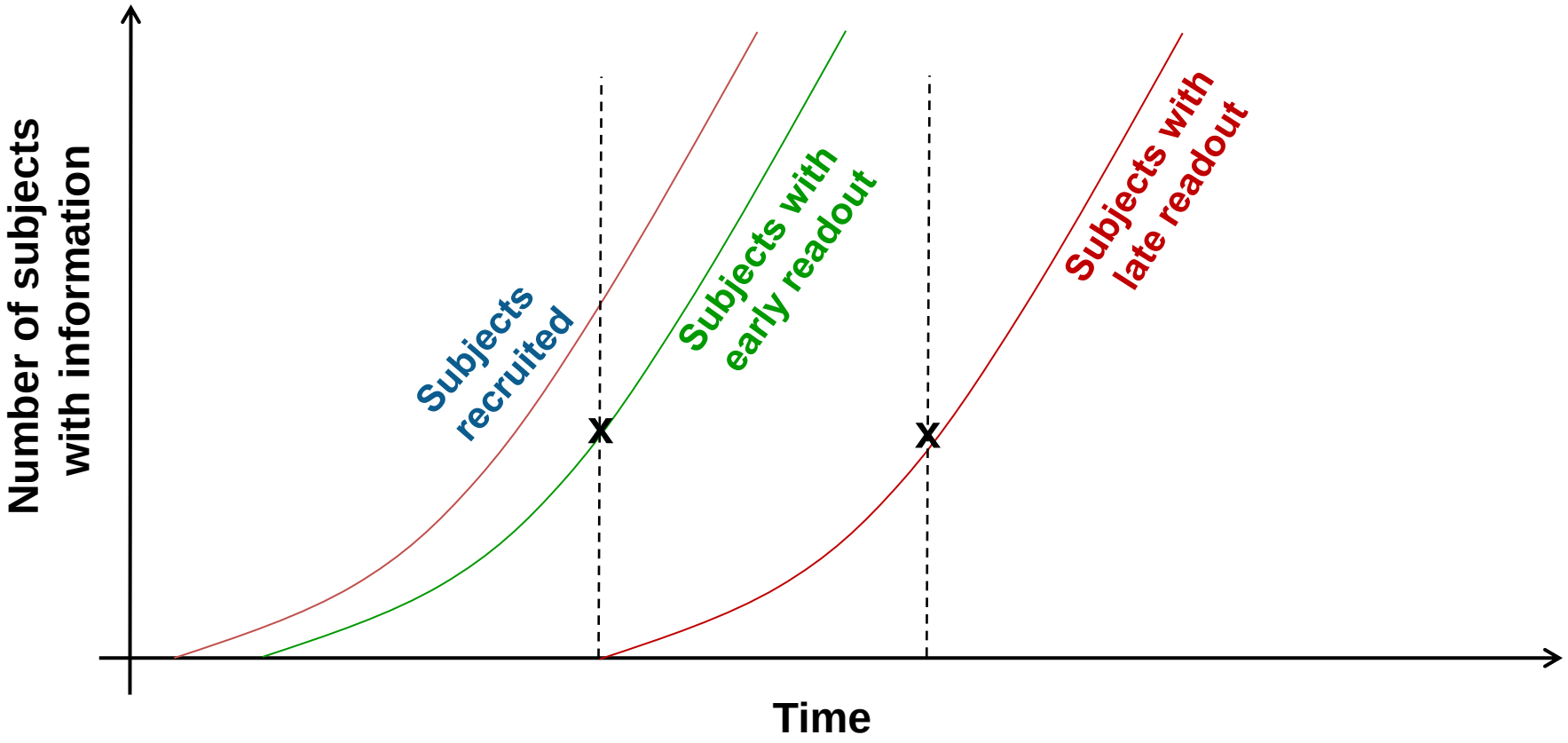
Adaptive design process

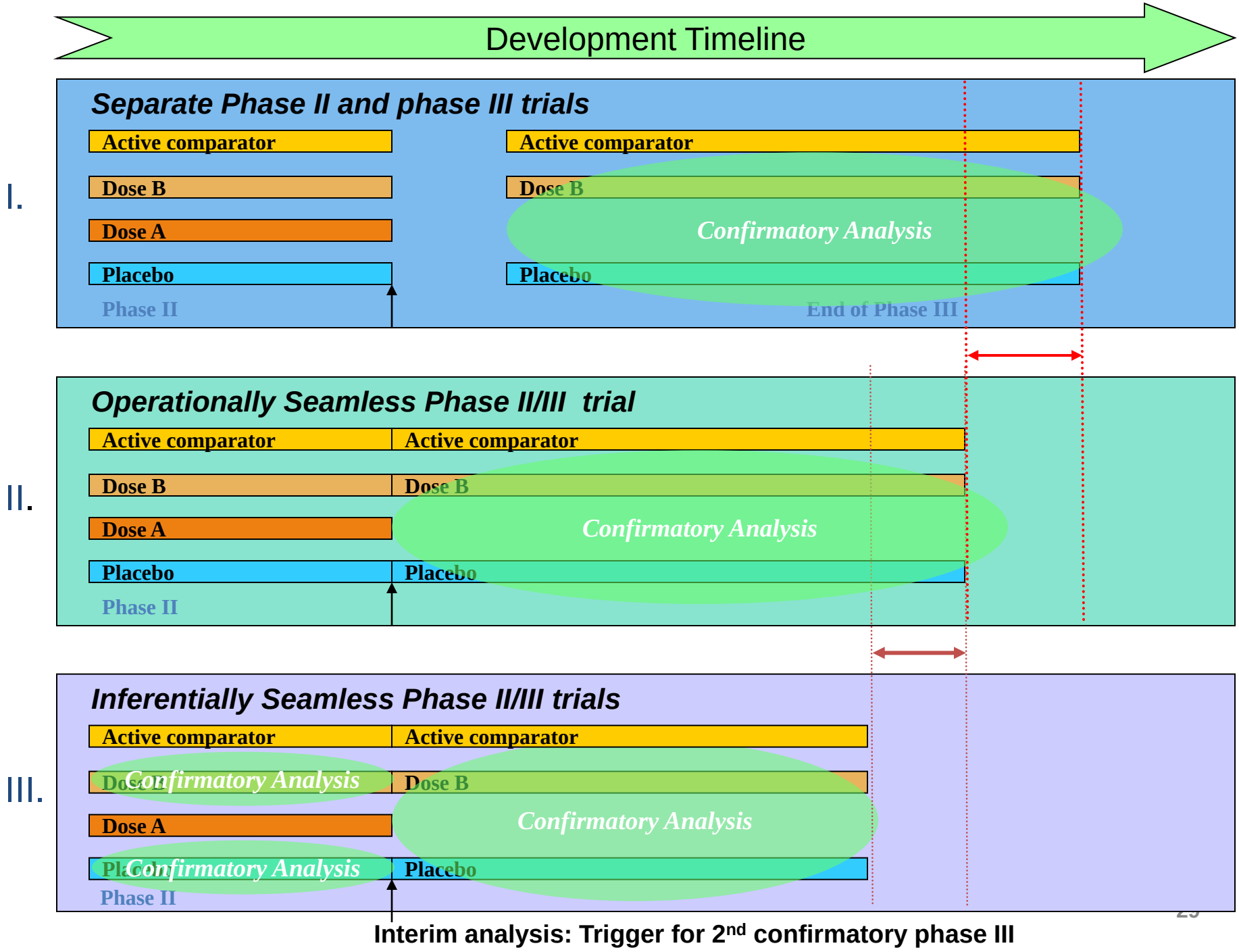


	Identify & Manage AT Opportunities	Quality Opportunity & Design AT	Implement Adaptive Trial	Execute Adaptive Trial
Activities	• Identify & prioritize opportunities • Work with project team • Track & manage opportunities	• Review clinical plan • Identify design options • Scenario analysis • Finalize protocol	• Finalize “design engine” • Charter & setup DMC • Site selection • IT setup	• Collect data • Execute engine • Hold DMC meetings • Implement adaptations
Output	• Project team interaction • Decisions on opportunities to pursue	• Scenario analysis • Simulation report • Protocol	• “Design Engine” • IT setup • DMC (charter, reports, etc.) • Sites selected	• Trial adaptations • Data collected and reported

Biomarkers and recruitment speed

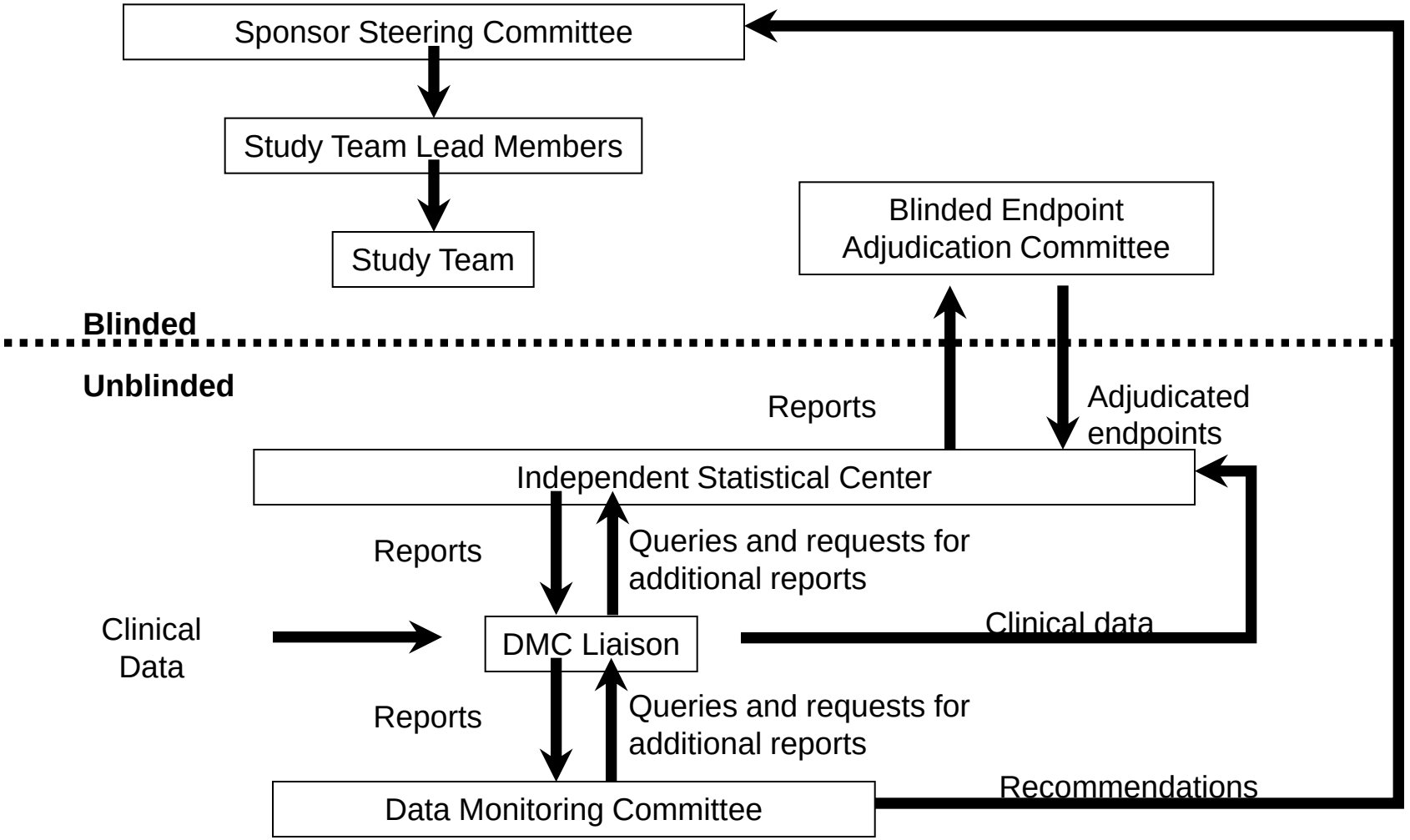
- Biomarkers as “necessary condition” with early readout
- Fit for purpose?
- MRI in Alzheimer’s Disease




Development Timeline
Separate Phase II and phase III trials
I.
Active comparator
Dose B
Dose A
Placebo
Phase II
Active comparator
Dose B
Placebo
Confirmatory Analysis
End of Phase III
Operationally Seamless Phase II/III trial
II.
Active comparator
Dose B
Dose A
Placebo
Phase II
Active comparator
Dose B
Placebo
Confirmatory Analysis
Inferentially Seamless Phase II/III trials
III.
Active comparator
Dose A
Phase II
Active comparator
Dose B
Placebo
Confirmatory Analysis
Confirmatory Analysis
Confirmatory Analysis
Interim analysis: Trigger for 2nd confirmatory phase III

Adaptive confirmatory trial

Execution - information flow, firewalls



Challenges

- Not enough time to think
  - EARLY interaction: Opportunities for adaptation?
    - Ideally pre-IND
    - 3-6 months to conduct scenario analyses and simulations
- Decision-problems/research questions not clearly defined
  - Align utilities across functions, e.g. between Commercial, Regulatory, Clinical…
- Value of model-based design poorly understood
  - There is a world out there beyond pairwise comparisons
    - In particular for dose-ranging studies in “Learn”
- Brainwashed into “Fast Recruitment”
  - Identify OPTIMAL recruitment speed given all utilities
    - Simulate execution of the trial and do sensitivity analysis on different recruitment speeds: Which one provides the highest information value per research unit invested?

5.

Discussion

- Different stages of drug development with different clinical objectives
  - Appropriate class of designs for each stage
- Their formulation
  - Dose escalation (CRM), adaptive dose-ranging (d-optimal, GADA), adaptive confirmatory designs (seamless phase II/III, group sequential)
- Challenges for implementation
- How can we walk the talk?
  - Academic research, statistical expertise within R&D, translate it into action
  - Quantitative decision making, board exam requirement for M.D.s?

* How can we increase the impact factor of experimental design in pharmaceutical R&D?

J. R. Statist. Soc. A (2005)
168, *Part* 4, *pp.* 639–656

The professionalization of the 'shoe clerk'

Andrew P. Grieve

Pfizer Global Research and Development, Sandwich, UK

[*The address of the President*, *delivered to* The Royal Statistical Society *on Wednesday, June 15th, 2005*]

Summary. The address reviews the professionalization of statisticians working in the regulated world of drug development. The need for statisticians to continue to push the boundaries of their professional environment is stressed. It is argued that to maintain the strength and influence of the profession it is neither desirable, nor necessary, to define in a statutory sense access to the profession.

Keywords: Drug development; Influence; Pharmaceutical industry; Professionalization; Regulatory guidelines

'One view of the shoe clerk's job is to please the customer well enough to earn his commission' (Bross,1974).

** Doing the right thing: Which recommendations can we make to clinical drug developers?

- Beyond simple clinical endpoints
  - Phase I study with two efficacy endpoints
  - Clinical Utility (efficacy/safety)
  - Biomarker/clinical endpoint
  - Response rate/survival rate
- So what's the utility?
  - Eierlegende Wollmichsau
  - Choice of design criterium
    (efficiency in dose-estimation vs …, which dose to take into phase III)
  - Decision theoretic approaches
  - Compromise between information and cost
  - Compute expected net gain
- Joint design for phase II/III (seamless phase II/III)
- Utility of different approaches to dose-ranging
- Minimal efficacious dose, ED95, Therapeutic Index,
- Number of doses
- Number of interim analyses

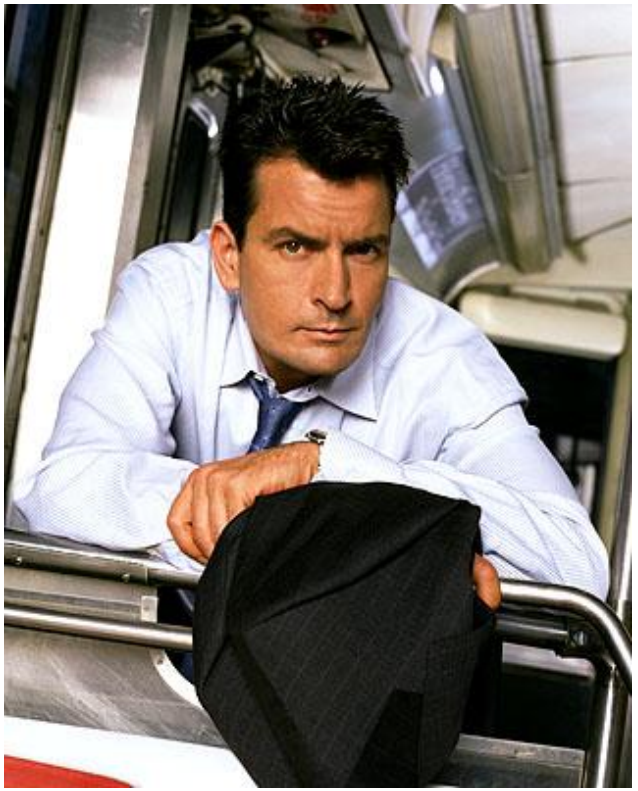
- Getting coordinated effort on big topics
  - CRM#
  - Requires statistician and computer program (3+3 doesn't)
  - Who controls, how to align across functions
- Articulate in understandable way to clinical stakeholders
- "How do you expect procedure to operate under different scenarios?" talk a language that can be understood by clinicians

- Uptake of group sequential methods
  - Advocates, champions, case studies, publications, software tools
- Economics of clinical trials as approach to get buy-in into most appropriate approach
- Request from regulatory agencies for …
- Need tool, will facilitate uptake
- ONE tool?

*** Doing the right thing:
Should we stay or should we run (another 3+3)?

- CRM,
- Dose-ranging
- Model-based designs in “Learn”
- Well understood adaptations in “Confirm”
- Use of Bayesian approaches in clinical drug development

**** Opportunity for cooperation?

- Software development
- Sharing of tools
  - Sergei's MATLAB based visualization suite,
  - Vlad's Adaptive Design Explorer,
  - Wyeth's "The Common Sense Approach" tool
  - Gernot Wassmer's ADDPLAN
  - …
- Publication of case studies in clinical journals
- Sharing of information in pre-competitive forum
  - KOL telecoms of PhRMA working group on adaptive designs
  - Val comparing NDLM based reponse adaptive designs with d-optimal approaches

***** WANTED: Dead or alive?