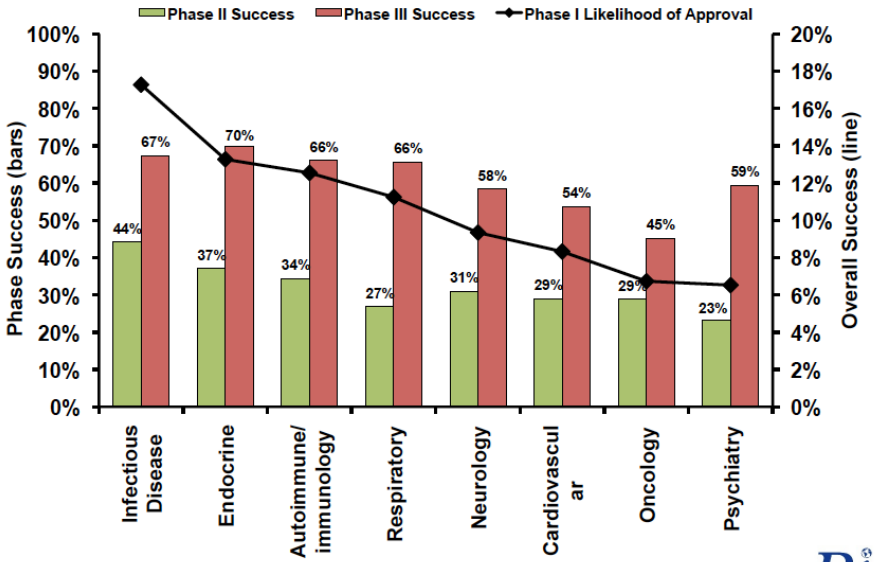
Adaptive Clinical Trials:
A Modern Approach to Drug Development

Ben Saville, Ph.D.

Senior Statistical Scientist

SUCCESS AT PHASE II AND III

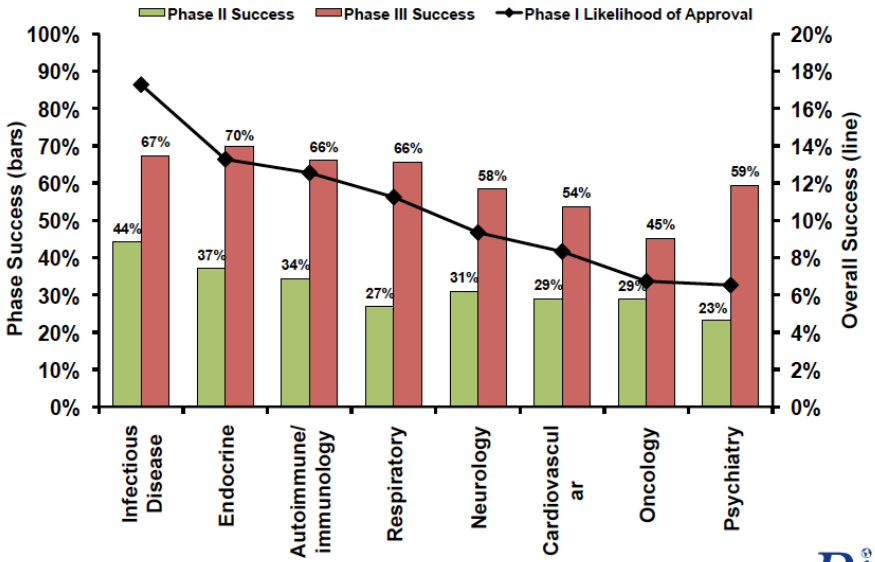


biomed tracker

Jan 2003 through Aug 2012

Bio BIOTECHNOLOGY INDUSTRY ORGANIZATION

SUCCESS AT PHASE II AND III

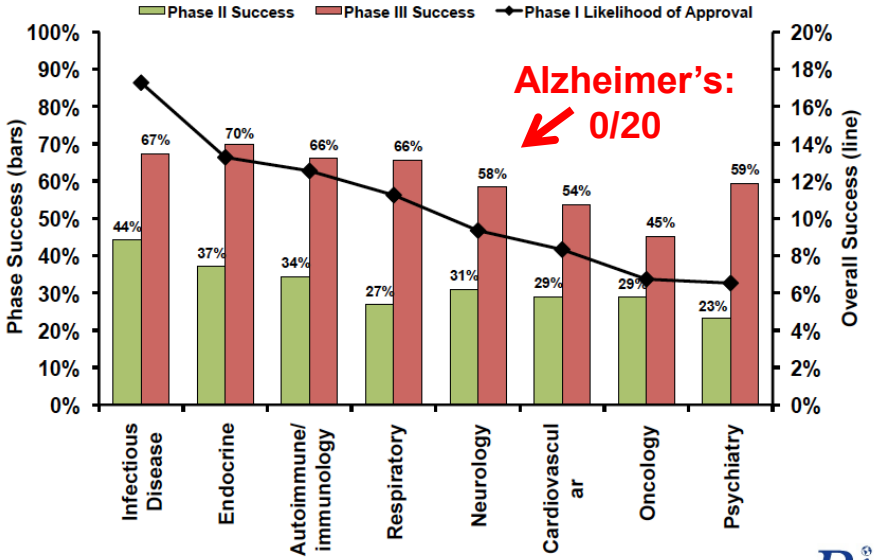


biomed tracker

Jan 2003 through Aug 2012

Bio BIOTECHNOLOGY INDUSTRY ORGANIZATION

SUCCESS AT PHASE II AND III

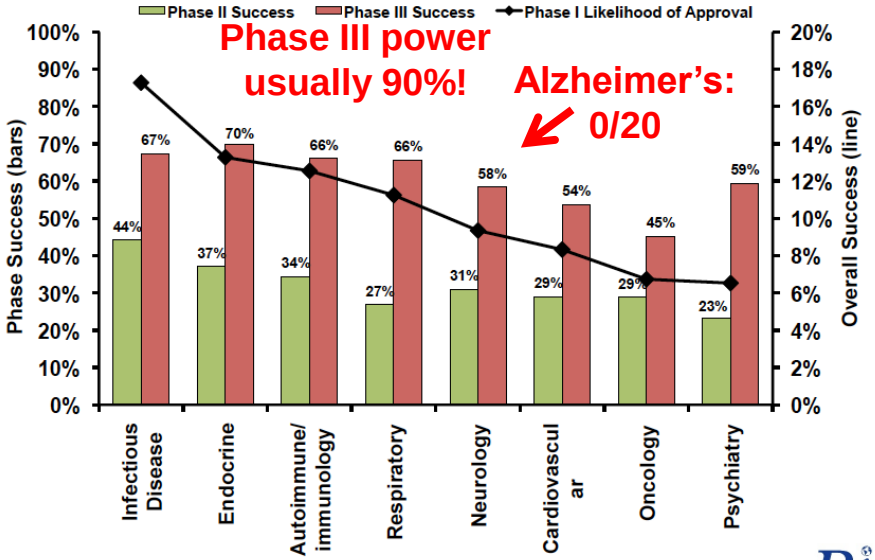


biomed tracker

Jan 2003 through Aug 2012

Bio BIOTECHNOLOGY INDUSTRY ORGANIZATION

SUCCESS AT PHASE II AND III



biomed tracker

Jan 2003 through Aug 2012

Bio BIOTECHNOLOGY INDUSTRY ORGANIZATION

Why Phase III Failures?

- Estimated cost per successful drug: $1.8 Billion
- Ineffective drug
  - Wrong endpoint in phase II
  - No randomization in phase II
  - Lottery
  - Regression to the mean
  - Silly subsetting
- Effective drug, lousy strategy
  - Underpowered
  - Wrong dose/schedule/concomitant Rx
  - Wrong population

The Brave New World of clinical cancer research: Adaptive biomarker-driven trials integrating clinical practice with clinical research☆

Donald A. Berry

Division of Quantitative Sciences, The University of Texas MD Anderson Cancer Center, Houston, TX, 2006-2010, USA

ARTICLE INFO

Article history:
Received 24 February 2015
Accepted 24 February 2015
Available online 11 March 2015

Keywords:
Biomarker-driven clinical trials
Platform trials
Basket trials
Bayesian adaptive clinical trials

ABSTRACT

Clinical trials are the final links in the chains of knowledge and for de
therapeutic advances. Unfortunately, in an important sense they a
This article describes two designs that are being explored today: platf
trials. Both are attempting to merge clinical research and clinical pr

MOLECULAR ONCOLOGY 9 (2015) 951–959

Clinical trials are the final links in the chains of knowledge and for determining the roles of therapeutic advances. Unfortunately, in an important sense they are the weakest links. … the rocketships of modern biology culminate their final stage of delivery in a wagon train.

ARTICLE INFO

Article history:
Received 24 February 2015
Accepted 24 February 2015
Available online 11 March 2015

Keywords:
Biomarker-driven clinical trials
Platform trials
Basket trials
Bayesian adaptive clinical trials

ABSTRACT

Clinical trials are the final links in the chains of knowledge and for de
therapeutic advances. Unfortunately, in an important sense they a
This article describes two designs that are being explored today: plat
trials. Both are attempting to merge clinical research and clinical pr

MOLECULAR ONCOLOGY 9 (2015) 951–959

FDA Critical Path Initiative

Many of the tools used today to predict and evaluate product safety and efficacy are badly outdated from a scientific perspective. We have not made a concerted effort to apply new scientific knowledge -- in areas such as gene expression, analytic methods, and bioinformatics -- to medical product development. There exists tremendous opportunities to create more effective tests and tools, if we focus on the hard work necessary to turn these innovations into reliable applied sciences.

U.S. Congress bill: 21st Century Cures

One pager: TITLE III – MODERNIZING CLINICAL TRIALS

- "Encouraging broader utilization of efficient, flexible trial designs … would help modernize the development and assessment of potential new treatments"

Subtitle B—Broader Application of Bayesian Statistics and Adaptive Trial Designs

Traditional "Fixed" Trial Designs

- "Fixed" Trial: Design parameters set regardless of accruing data
  - Wait until end of trial to analyze data
- Why designs are usually "fixed"
  - It's easiest to calculate type I error rates if the design parameters of the trial are all constant
  - Results obtained using "standard approaches" are widely accepted
  - Logistically simpler to execute
  - We could do the math 40 years ago
    - We still can but we can also do more sophisticated things now too

What are Adaptive Trials?

Trials in which key design parameters change during trial execution based upon *a priori* predefined rules and accumulating data from the trial to achieve goals of validity, scientific efficiency, and safety

- Planned: All possible adaptations defined *a priori*
- Well-defined: Criteria for adapting clearly explained
- Key parameters: *Not* minor inclusion or exclusion criteria, routine amendments, etc.
- Validity: Reliable statistical inference

Why Adapt?

- Reduce risk of failed/inconclusive trial
- More efficient allocation
- More accurate conclusions
- Addresses many questions in one trial
- Better treatment of patients in trials

Why Adapt?
The Prospective Postmortem

- Consider whether any adaptations might be added to *prospectively* address *potential* regrets

Why Adapt?
The Prospective Postmortem

- Consider whether any adaptations might be added to *prospectively* address *potential* regrets

- Be honest with yourself in design Phase
  - We overestimate treatment effects
  - We underestimate variability
  - Because we need to justify a doable trial

Clinical Trials as Missiles

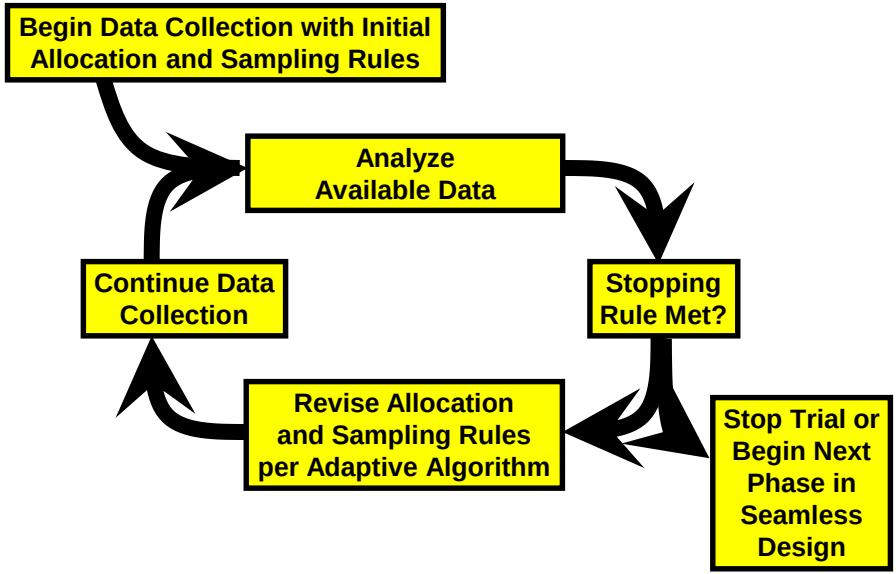
Clinical Trials as Missiles

- Fixed trial designs are like ***ballistic*** missiles
  - Acquire the best data possible a priori, do the calculations, and fire away
  - They then hope their estimates are correct and the wind doesn't change direction or speed

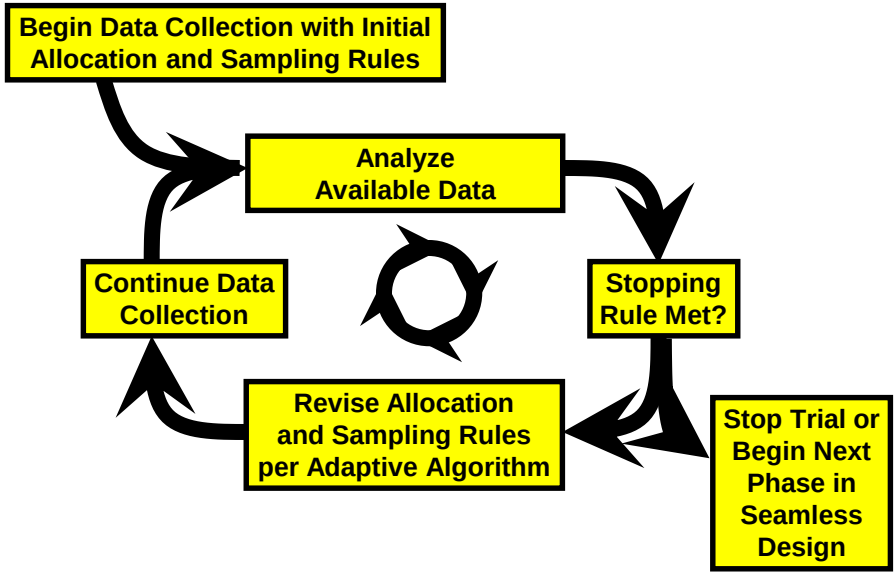
Clinical Trials as Missiles

- Adaptive trial designs are like ***guided*** missiles
  - Adaptively change course or speed depending on new information acquired
  - More likely to hit the target
  - Less likely to cause collateral damage

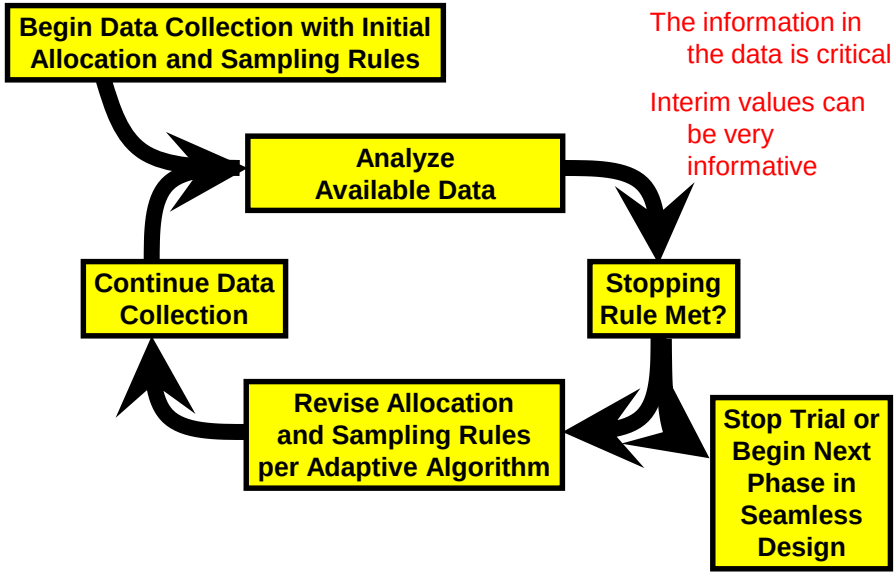
Typical Prospective Adaptive Design



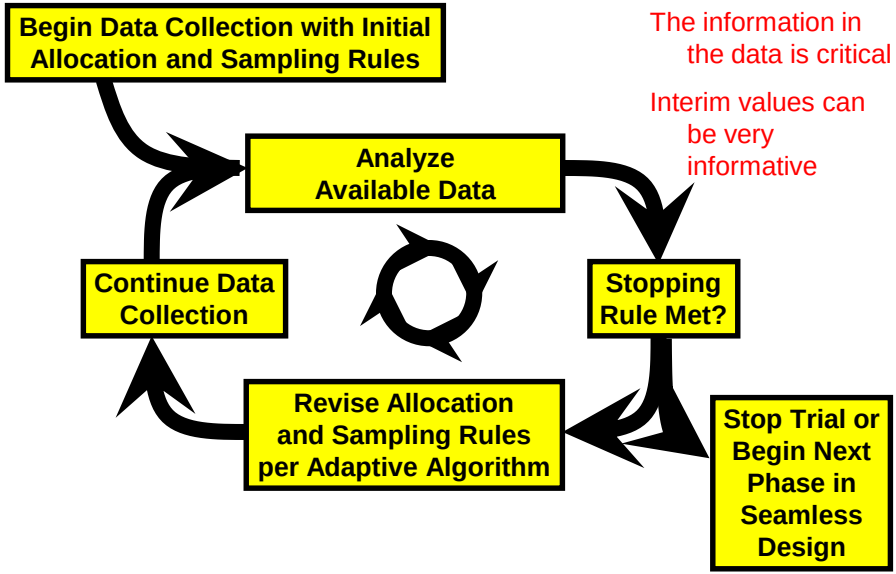
Typical Prospective Adaptive Design

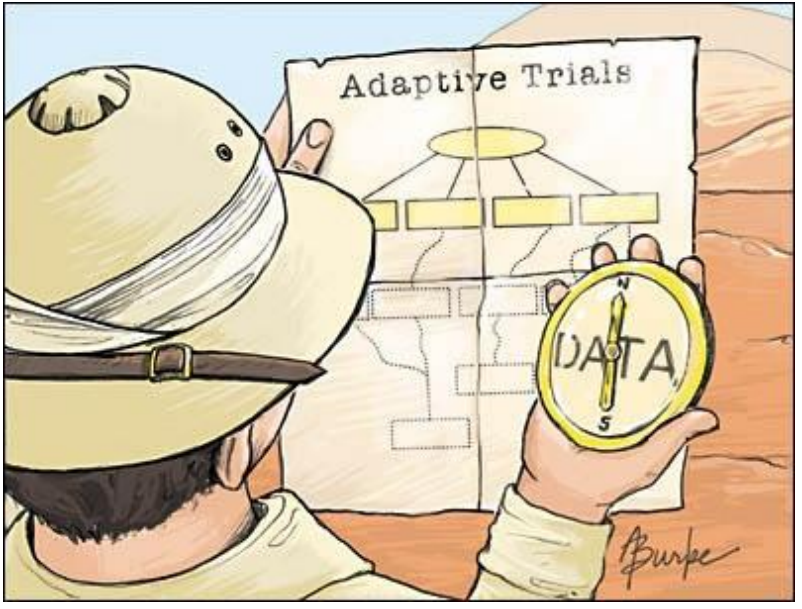


Typical Prospective Adaptive Design



Typical Prospective Adaptive Design





JAMA 2006;296:1955-1957.

Interim Analyses

- Frequent interim analyses of accruing data
- Predefined decision rules for adaptations
- Interim statistical modeling using all information
  - Partial information via longitudinal modeling
- Repeatedly ask when are primary questions answered

Common Adaptations

- Adaptive sample size
  - Stopping early for efficacy/futility
- Dose finding (& dose dropping)
- Adding treatment arms (combination therapies)
- Seamless phase 2/3
- Response adaptive randomization
- Enrichment to sub-populations
- Adaptive borrowing of information

Traditional Drug Development

- Phase I
  - tens of subjects
  - first use in humans (with or without target illness)
  - generates initial dosing and toxicity information
  - adaptive dose escalation
- Phase II
  - 100 to few hundreds of subjects with target illness
  - gain initial information on dose-response relationship (i.e., "proof of concept"), side effects
- Phase III
  - confirm superiority of new treatment
  - typically large and expensive

Phase II Challenges

- Phase II
  - a wide range of doses are possibly the "best" choice
  - consider combinations of treatments?
  - different durations, schedules of treatment?
  - different combinations may work best on patients with different histologies or previous treatments
  - *can not do a fixed trial over all possibilities*

- Traditionally we pick 2 or 3 (of many possible) doses in one population, hope we're right, & run a trial

Phase II Solutions

- Adaptive randomization
  - start looking across many doses / durations / combos
  - drop arms / lower randomization probabilities on poorly performing strategies
  - increase randomization probabilities on promising treatments
    - learning about treatments that matter
    - assigning patients to treatments most likely to help them
- Adaptive enrichment
  - Drop subgroups where no signals of efficacy

Phase III Challenges

- Often still don't really know the right dose
- Don't really know what to expect in the control arm
- Uncertainty about effect size
- *Yet traditional statistical approaches require that the trial characteristics be completely defined prior to enrolling the first phase III patient*

Phase III Solutions

- Adaptive sample size
  - Measure treatment effect & variability as we go
  - Frequent interim analyses to find appropriate N to answer question
- "Goldilocks" methodology
  - "If we stop enrolling now & track patients will we have sufficient evidence in one year?"
    - If yes stop accrual for expected success
  - "If we enroll to max N will we have fair chance of achieving goal?"
    - If no stop for futility
  - Predictive probabilities of success
    - Use observed data and amount of data yet to be collected to guide sample size

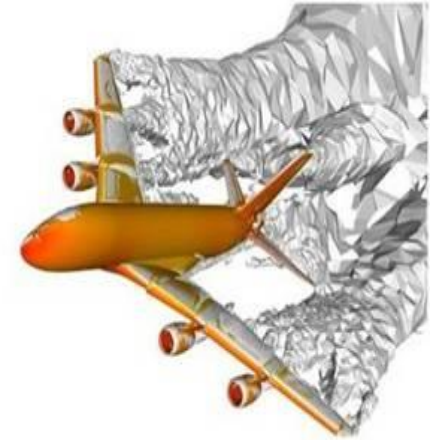
Why Adaptive in BPD?

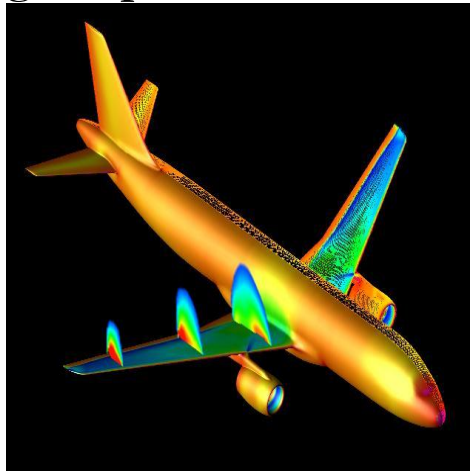
- Current strategy is not working!
- Uncertainty on multiple parameters
  - endpoint selection
  - dose selection
  - treatment effect
  - placebo response rates and/or variability
  - population (e.g. with vs. without psychotherapy, comorbidities)
- Outcomes can be collected rapidly (e.g. 12 weeks) relative to time required to accrue all participants (e.g. 2 years)

Role of Simulations

- For complex adaptive designs you cannot calculate operating characteristics (power, Type I error) with a formula
- Simulation the only way to do this…
- Incredibly valuable tool to evaluate performance, see example trials, measure everything about the trial
  - Part of the design process

Like Building Airplanes!





Simulations: complex mathematical calculation, NOT a prediction system

Limitations of Adaptation

- Infeasible if time from patient accrual to final outcomes long vs. total accrual time
- Adaptive design takes more forethought & planning
- Determining traditional Type I and II error rates more difficult
  - Rely on simulation
- People fear new
  - Most statisticians have never designed or analyzed an adaptive trial
  - Some regulatory personnel unfamiliar with
  - DMCs / IRBs may not understand
  - Clinicians may not understand

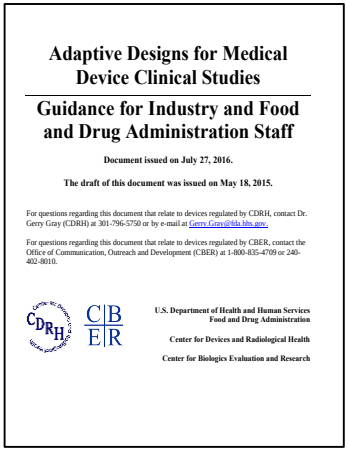
Logistical Considerations

- More work upfront, design stage is longer
- Data needs to be entered & transmitted quickly
- Data needs to be checked / validated quickly
- Events need to be adjudicated quickly
- Drug supply concerns for adaptive randomization
  - Fear of unblinding
- Need centralized randomization
  - Use web or phone systems
- Need to have many people/systems well-integrated

Who To Involve

- Sponsor
  - Project leaders
  - Statisticians
  - PK/PD
  - Clinical experts
  - Business leaders
  - Patient advocates
- Clinical site IRBs
- Data Safety Monitoring Board
- CRO who will house data
- Regulatory agencies

Regulatory Guidance



Adaptive Designs for Medical Device Clinical Studies

Guidance for Industry and Food and Drug Administration Staff

Document issued on July 27, 2016.

The draft of this document was issued on May 18, 2015.

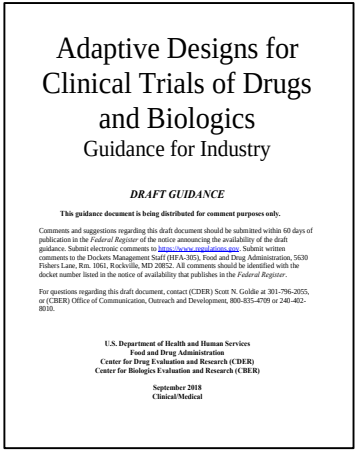
For questions regarding this document that relate to devices regulated by CDRH, contact Dr. Gerry Gray (CDRH) at 301-796-5750 or by e-mail at Gerry.Gray@fda.hhs.gov.

For questions regarding this document that relate to devices regulated by CBER, contact the Office of Communication, Outreach and Development (CBER) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research



Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

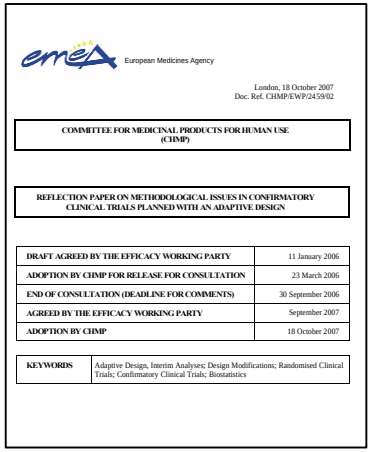
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2018
Clinical/Medical



European Medicines Agency

London, 18 October 2007
Doc. Ref. CHMP/EWP/2459/02

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN

DRAFT AGREED BY THE EFFICACY WORKING PARTY	11 January 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 March 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 September 2006
AGREED BY THE EFFICACY WORKING PARTY	September 2007
ADOPTION BY CHMP	18 October 2007

KEYWORDS	Adaptive Design, Interim Analyses; Design Modifications; Randomised Clinical Trials; Confirmatory Clinical Trials; Biostatistics

Is Now a Prime Time for Adaptive Designs in Clinical Trials?

- It's well past time
- Virtually every large pharmaceutical company, 100+ device companies, and dozens of biotech companies are using adaptive designs
- Is there a gap between perceived risk to sponsors and the real risk?
  - Risks of "fixed trial" designs? (wagon train)
  - Does industry overestimate FDA/EMA conservatism?
- Adaptive trial designs
  - Reduce risks of failed/inconclusive trials
  - The modern tool for evaluating modern science!

Some Areas of Application

- Alzheimer's Disease
- ALS
- Asthma
- Atrial Fibrillation
- Borderline Personality D
- Cancer Diagnostics
- Cancer Screening
- COVID-19
- Crohn's Disease
- Cystic Fibrosis
- Depression
- Ebola
- Heart Failure
- Ebola
- Emphysema
- HIV
- Libido
- Lymphoma
- Lung Cancer
- Lupus
- Migraines
- Multiple Sclerosis
- Obesity
- Pain
- Parkinson's
- Pandemic Flu
- Psychotic disorders
- PTSD
- Rare Ped Diseases
- Sepsis
- Spinal Cord Injury
- Spinal Implants
- Stroke
- Tinnitus
- Weight loss
- Vaccines