Adaptive Clinical Trials

From Basics to Bayesian

Alex Kaizer, PhD

June 5, 2019

ACCORDS Emerging Research Designs Conference

Outline

- What are adaptive designs?
- Adaptive design elements and examples
- Bayesian methods in adaptive trials

Adaptive Trial Designs

What are adaptive designs?

- The key to all my research woes!
- Designs where I can do whatever I want, whenever I want to (ethically) answer my research questions.
- The "good" designs that statisticians have been selfishly keeping to themselves all this time!
- "An adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design *based on accumulating data from subjects in the trial*." (FDA 2018 Adaptive Designs for Clinical Trials Guidance Document)

FDA Adaptive Elements

- Group sequential designs (i.e., interim analyses)
- Adaptations to sample size (i.e., sample size re-estimation based on interim results to preserve power)
- Adaptations to the patient population (i.e., adaptive enrichment)
- Adaptations to treatment arm selection (i.e., adding or terminating arms)
- Adaptations to patient allocation (i.e., adaptive randomization)
- Adaptations to endpoint selection
- Adaptations to multiple design features (combining multiple features above)

Sample Size Re-Estimation

Adaptations to Sample Size

Why Adapt the Sample Size?

Hypothetical Scenario:

- You design and power a study on a research topic with limited prior information (i.e., there is uncertainty in your sample size calculation assumptions)
- As the study is being conducted, the observed treatment effect is smaller than expected, *but still clinically meaningful*
- If we maintain the planned sample size, we may be underpowered to detect this difference

Image Source: Everyday Health

Sample Size Re-Estimation

- Using interim estimates we can address the prior uncertainty about the treatment effect size
- These can be blinded or unblinded, however they involve different statistical approaches and the FDA Guidance focuses primarily on the unblinded context
- FDA recommends steps should be taken to limit personnel with detailed knowledge to maintain trial integrity
- It can be challenging if the re-estimation suggests the need for a much larger sample size

Trial Example

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events

Deepak L. Bhatt, M.D., M.P.H., Gregg W. Stone, M.D., Kenneth W. Mahaffey, M.D., C. Michael Gibson, M.D., P. Gabriel Steg, M.D., Christian W. Hamm, M.D., Matthew J. Price, M.D., Sergio Leonardi, M.D., Dianne Gallup, M.S., Ezio Bramucci, M.D., Peter W. Radke, M.D., Petr Widimský, M.D., D.Sc., Frantisek Tousek, M.D., Jeffrey Tauth, M.D., Douglas Spriggs, M.D., Brent T. McLaurin, M.D., Dominick J. Angiolillo, M.D., Ph.D., Philippe Généreux, M.D., Tiepu Liu, M.D., Ph.D., Jayne Prats, Ph.D., Meredith Todd, B.Sc., Simona Skerjanec, Pharm.D., Harvey D. White, D.Sc., and Robert A. Harrington, M.D., for the CHAMPION PHOENIX Investigators*

- Study powered for composite event rates of 5.1% vs. 3.9% in study arms → 10,900 patients for 85% power and two-sided α=0.05
- Unblinded sample size re-estimation planned after 70% enrolled
- At the interim analysis, an early stopping efficacy boundary was crossed but DSMB decided to continue the trial as planned (i.e., no sample size increase)

Adapting the Patient Population

Adaptive Enrichment

Why "Enrich" the Patient Population?

Hypothetical Scenario:

- You expect the treatment effect to be greater in a certain targeted subset of the trial population: >

- Do we enroll only the targeted subpopulation?

Reasons for Population Enrichment

- Want information about *both* the targeted and non-targeted subpopulations
- Uncertain about treatment effect in non-targeted subpopulation (i.e., perhaps the treatment is as effective or less effective but still clinically meaningful)
- Can provide greater power relative to a fixed sample design without enrichment (i.e., if we restrict enrollment we have more subpopulation observations *versus* having equivalent power)

Simple Enrichment Example

1. Enroll both groups at start

2. At interim analysis, determine if you continue enrollment in the overall population or restrict future enrollment to the targeted subpopulation.

3a. Continue enrollment of both

3b. Restrict enrollment to subpop.

Seamless Designs

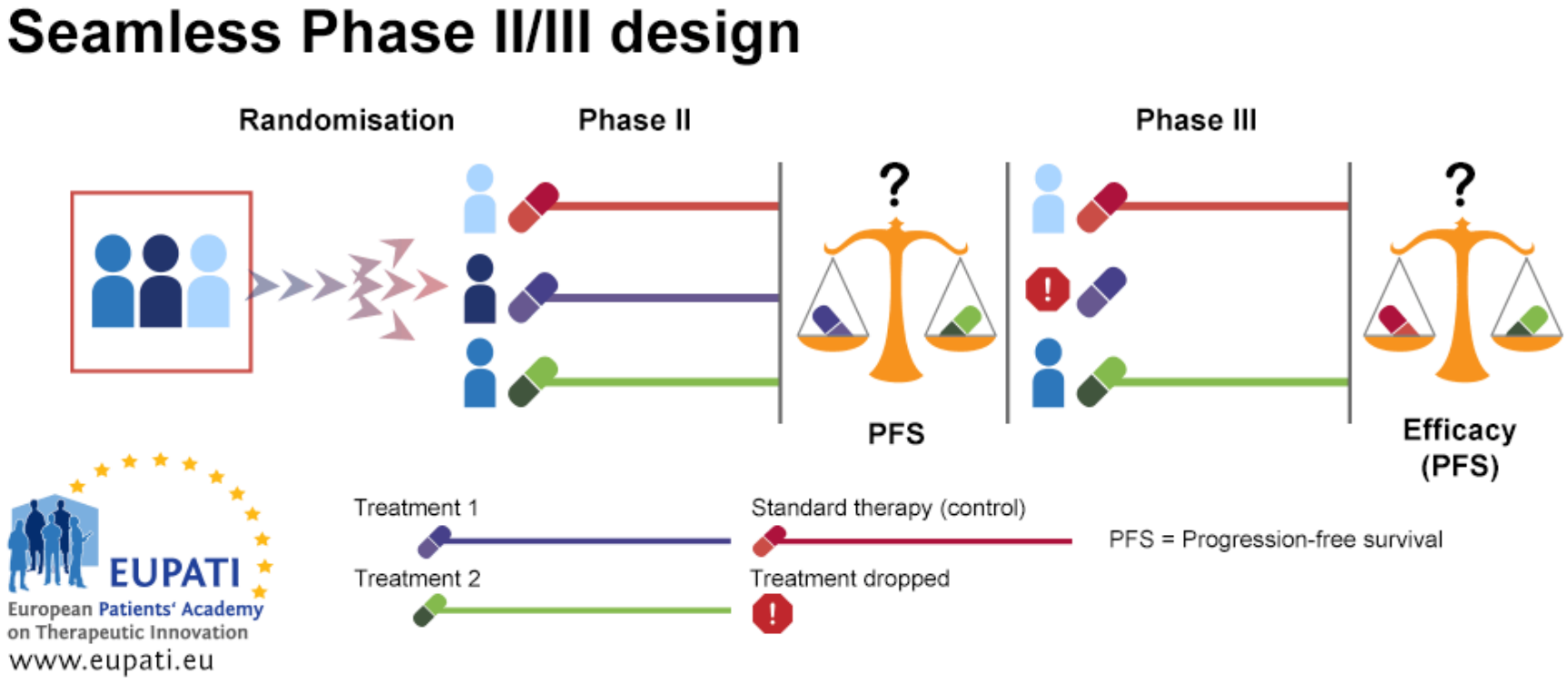
Adaptations to Treatment Arm Selection

Seamless Designs

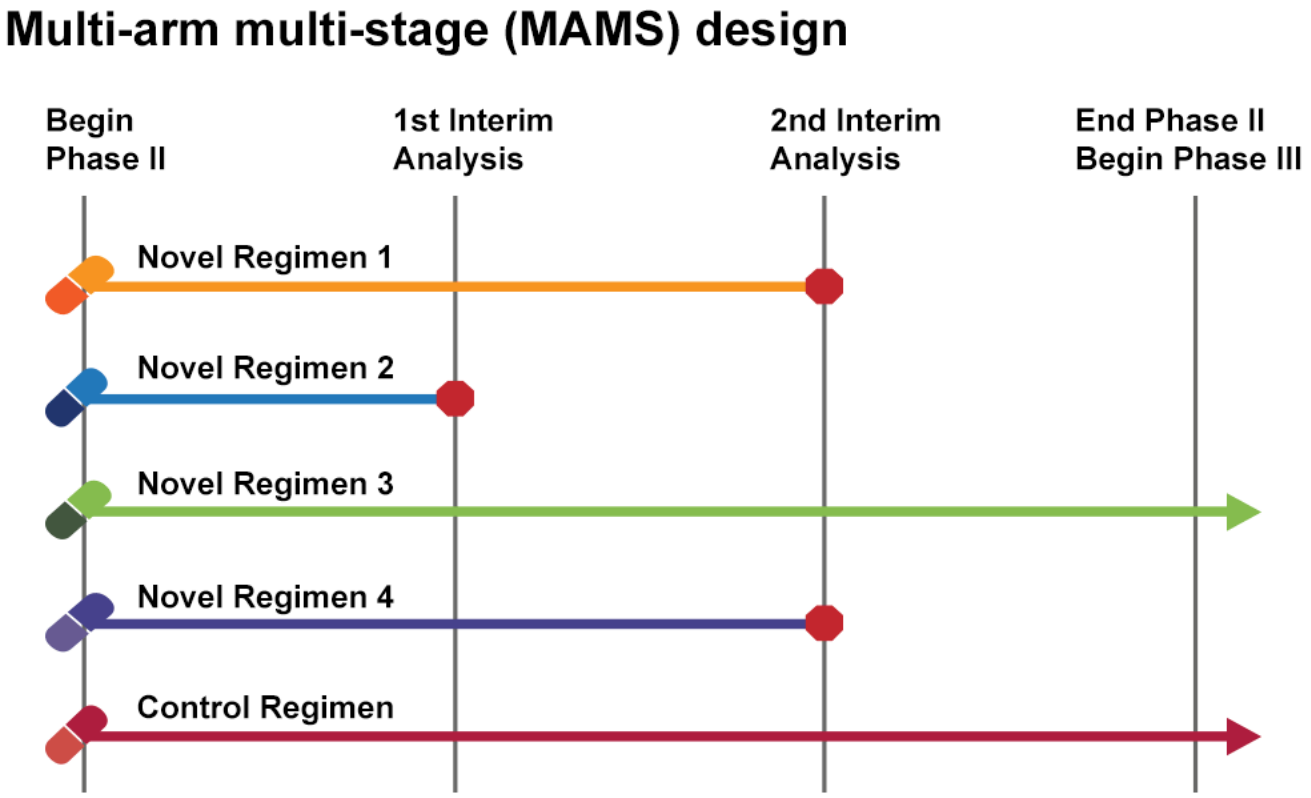
- Seamless study designs combine multiple phases of a study into one trial
  - e.g., Phase II and Phase III combined to include both treatment selection and confirmation in one trial
- Interim analyses used to determine what continues from Phase II portion of the study to Phase III
- Advantages include reducing overall study size, shorter development time, more long term safety information
- Disadvantages include logistical challenges and issues maintaining statistical properties

One Version of Seamless Phase II/III Designs

- Compare Treatment 1 and 2 after Phase II and drop least effective arm.
- Then compare efficacy after Phase III between the SOC and continued treatment using all data from Phases II and III.



Multi-Arm Multi-Stage



MAMS can drop ineffective arms early on at an interim analysis.

Promising arms seamlessly continue to a (confirmatory) Phase III trial.

One disadvantage is that you can only compare “Novel” arms to the Control arm (to maintain the type I error and power).

Adaptive Randomization

Adaptations to Patient Allocation

Baseline (Covariate) Adaptive Randomization

- The probability of the next treatment assignment is altered on the basis of the previous assignments in order to achieve better balance (i.e., biased coin, minimization procedures).
- Considerations:
  - How to implement (central entity vs. local entities)
  - Multiple treatments
  - What is considered a lack of balance
  - What covariates to use for balance

- Main advantage: opportunity to balance composition of treatment groups on several characteristics without stratification

Response/Outcome Adaptive Randomization

- Assignment probabilities are modified based on observed responses or outcomes
- The motivation is to allocate as many patients as possible to the "best" treatment arm
- Recent research has identified that outcome adaptive randomization may result in randomization to the *inferior* arm, concerns about sample size imbalance (leading to reduced power), and challenges where time effects are present

Response Adaptive Randomization Example

Zelen's 1969 Play the Winner Design (2 arm study):

1. Assign 1st participant to either arm with equal probability
2. Observe success/failure in arm
3. Depending on outcome…
    1. Observed success leads to use increasing the probability of the successful treatment being assigned for the next participant
    2. Observed failure leads to a decreased probability

Disadvantages are that sample size/power is challenging to calculate *a priori* and you need to know the previous response before randomizing the next individual (although you could update in blocks)

Master Protocol Designs

Umbrellas, Baskets, and Platforms

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

Master Protocols

- Traditionally we have conducted separate standalone studies for at most a few interventions in targeted populations, however these are becoming increasingly expensive and prohibitive
- Precision medicine and the need for flexible designs to consider multiple drugs, diseases, populations, or combinations of these are needed
- Master protocols provide a unifying framework that use one *master* protocol for a study that is designed to answer multiple questions

MP Innovation

- Woodcock and LaVange describe the many areas of innovation that can be found in master protocols

Areas of Innovation

Infrastructure
- Common screening platform for biomarker identification
- Governance
  - Steering committee
  - Adjudication committee
  - Data monitoring committee
  - Central institutional review board
- Trial networks and clinical centers
- Processes
  - Randomization
  - Data and safety capture and management
  - Quality-control oversight

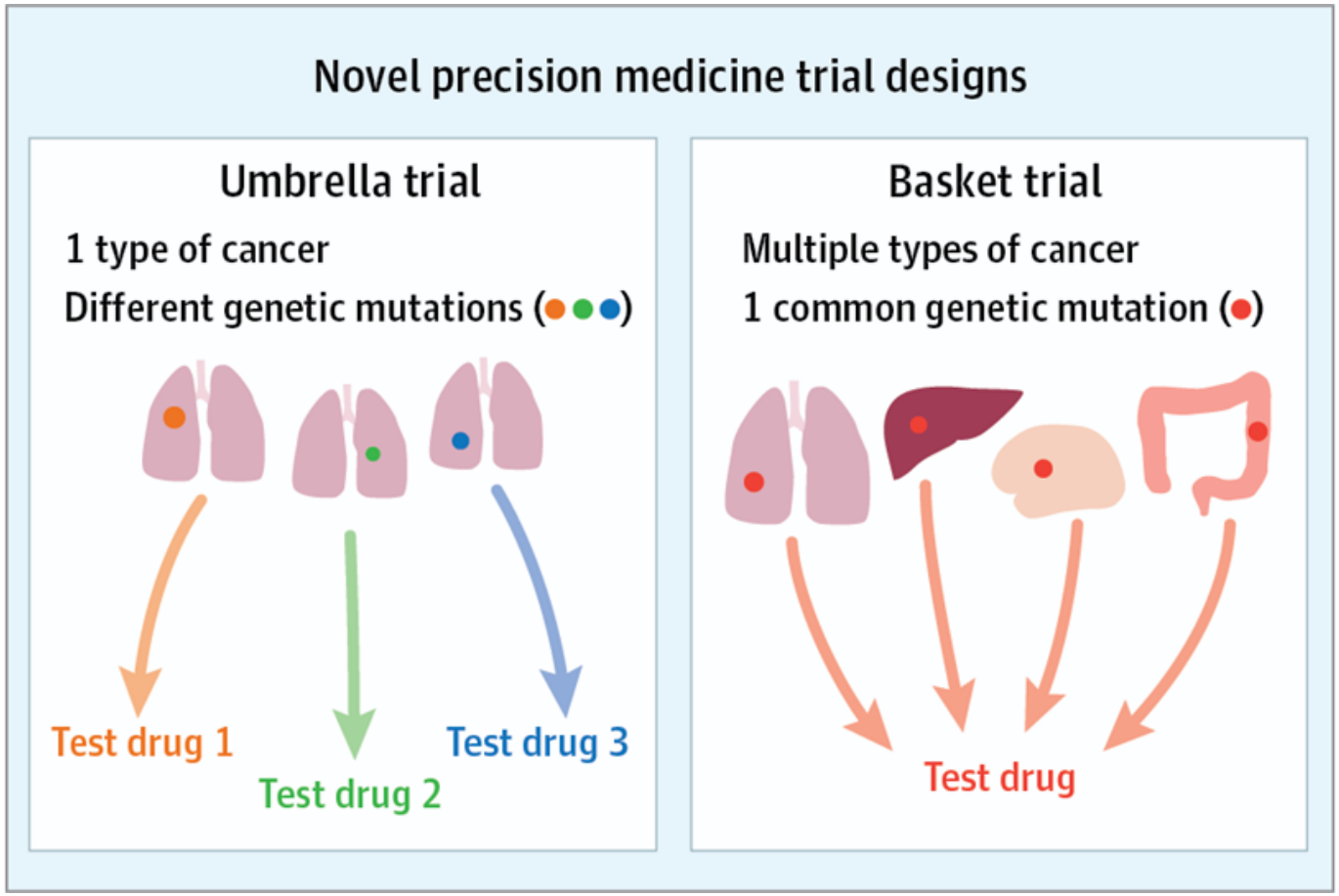
Trial Design
- Adaptive randomization and other adaptive design features
- Longitudinal modeling to determine probabilities of success or failure
- Shared control patients
- Natural-history cohort
- Biomarker qualification

General Types of Master Protocols

Table 1. Types of Master Protocols.

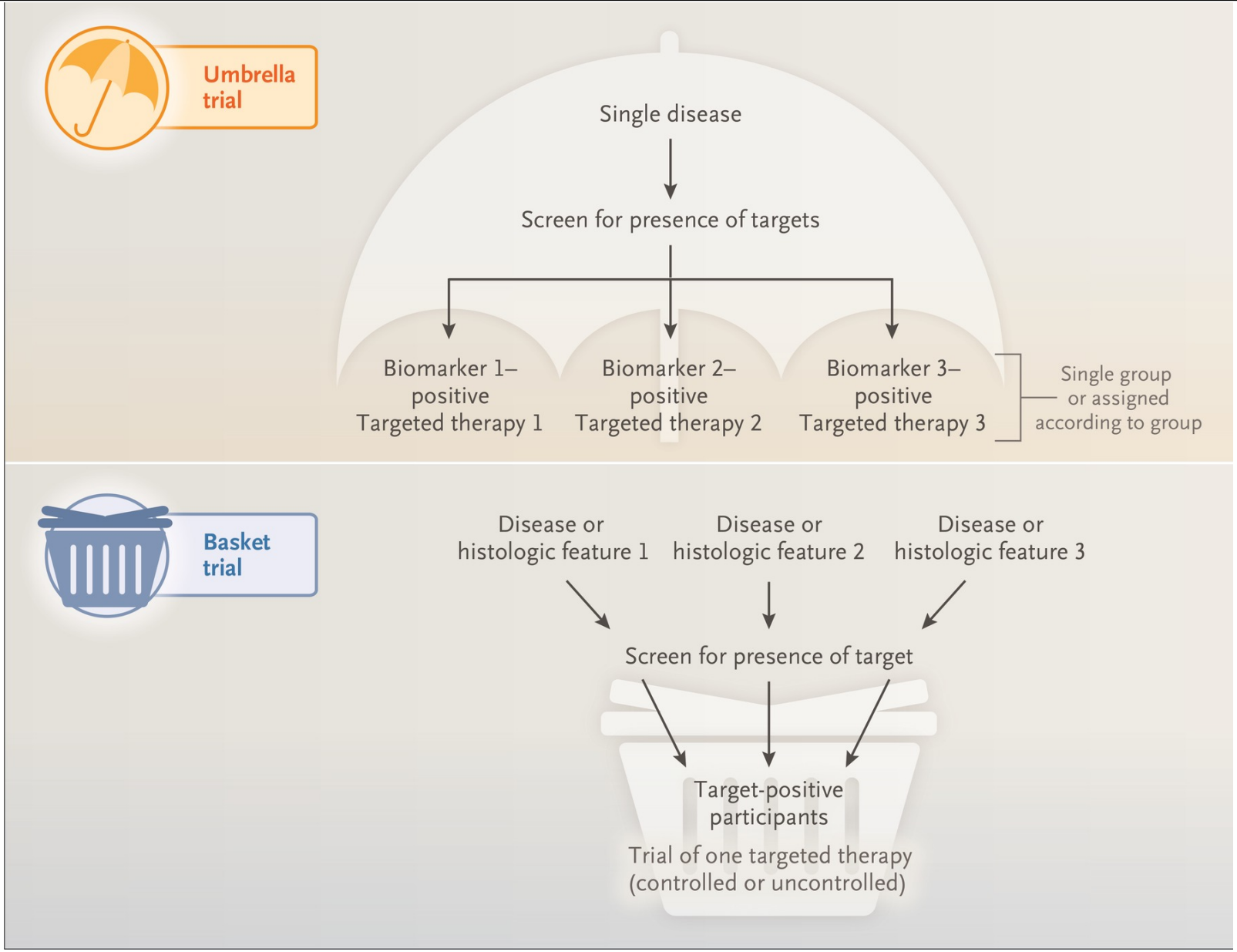
Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Umbrellas and Baskets



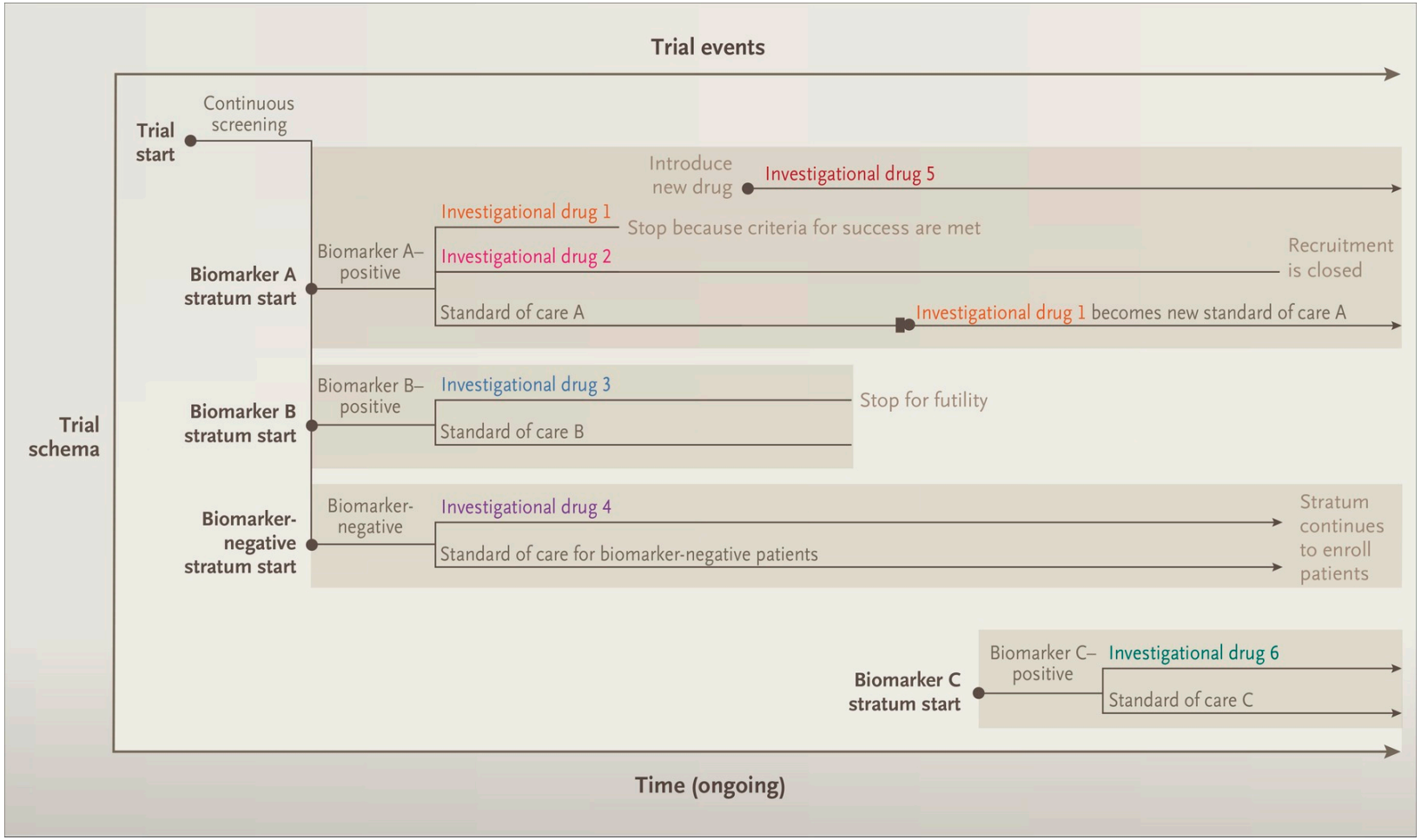
Umbrella trials identify a single (broad) disease, but then further classified by subtypes and treated accordingly

Basket trials identify a common mutation (or trait) across sites and then treat all with a common intervention



Another example figure of basket and umbrella designs (Figure 1 from Woodcock and LaVange)

Platform Trials



Platform designs can be very flexible and potentially complex (Figure 2 from Woodcock and LaVange)

Master Protocols

- Designs can be noncomparative or comparative
  - If comparative, you may have a common control group or multiple control groups depending on design
- Designs can include adaptive elements or not
- Designs can be exploratory or confirmatory
- LOTS of flexibility

Umbrella Trial Example

CANCER DISCOVERY

Research Articles

The BATTLE Trial: Personalizing Therapy for Lung Cancer

Edward S. Kim, Roy S. Herbst, Ignacio I. Wistuba, J. Jack Lee, George R. Blumenschein Jr., Anne Tsao, David J. Stewart, Marshall E. Hicks, Jeremy Erasmus Jr., Sanjay Gupta, Christine M. Alden, Suyu Liu, Ximing Tang, Fadlo R. Khuri, Hai T. Tran, Bruce E. Johnson, John V. Heymach, Li Mao, Frank Fossella, Merrill S. Kies, Vassiliki Papadimitrakopoulou, Suzanne E. Davis, Scott M. Lippman, and Waun K. Hong

DOI: 10.1158/2159-8274.CD-10-0010 Published June 2011

Abstract

The Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial represents the first completed prospective, biopsy-mandated, biomarker-based, adaptively

June 2011
Volume 1, Issue 1
Table of Contents
Table of Contents (PDF)
About the Cover
Index by Author

Umbrella Example: Study Design (BATTLE-1)

- Outcome was complete or partial response, stable disease, progression free survival, overall survival, toxicity
- Phase II, single-center, comparative trial with (response) adaptive randomization
- Four therapies (three mono and one combination)
- Study enrolled advanced NSCLC with specific mutations
- 255 adults who had at least 1 failed chemotherapy regimen

Umbrella Example cont.

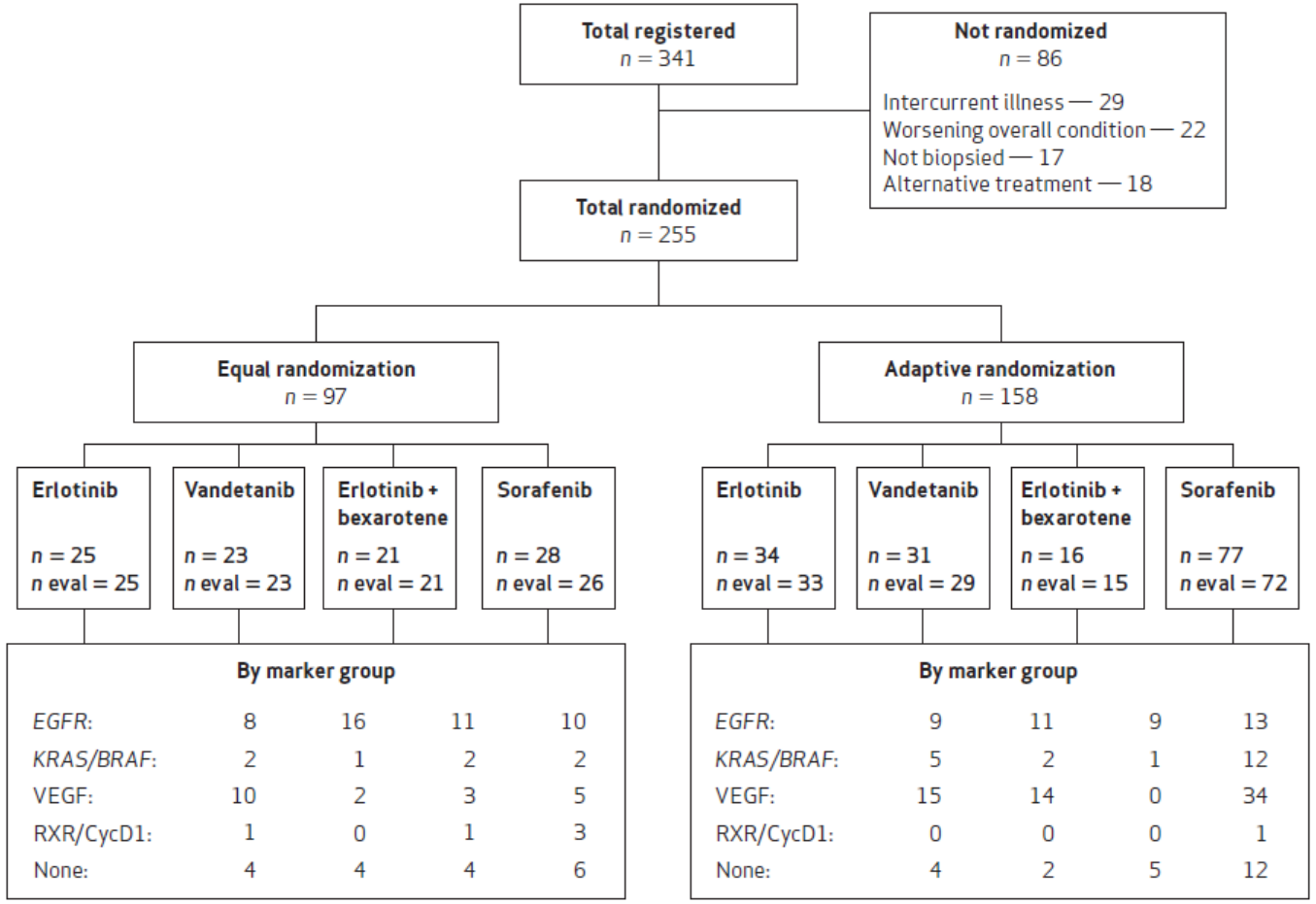
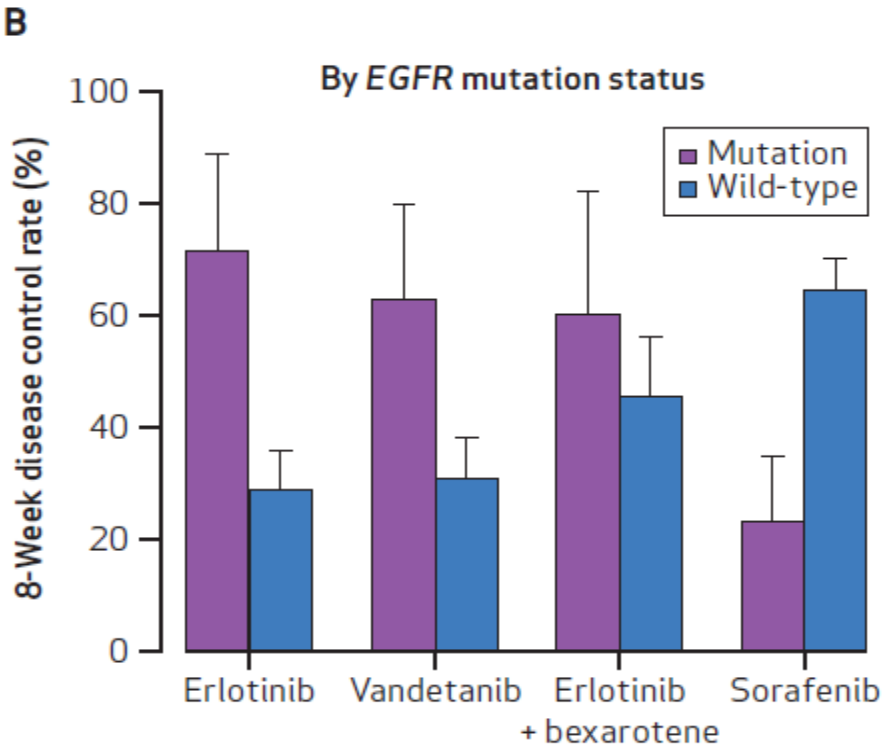
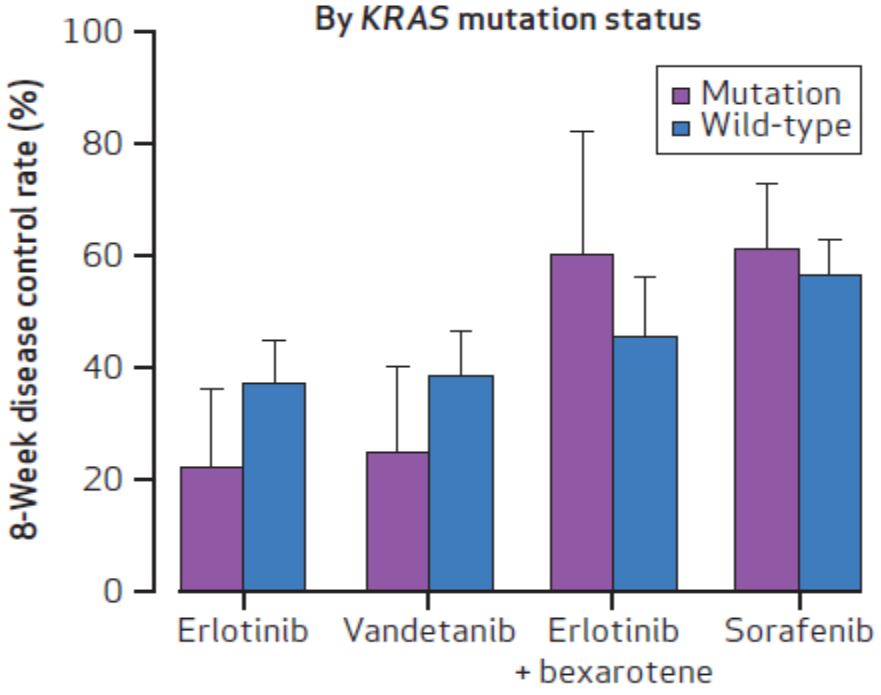


Figure 2. CONSORT diagram of the BATTLE study.

Umbrella Example: Conclusion

- Demonstrated the feasibility of the umbrella design to advance personalized treatment of NSCLC
- Different responses by mutation type and status:





Platform Trial Example

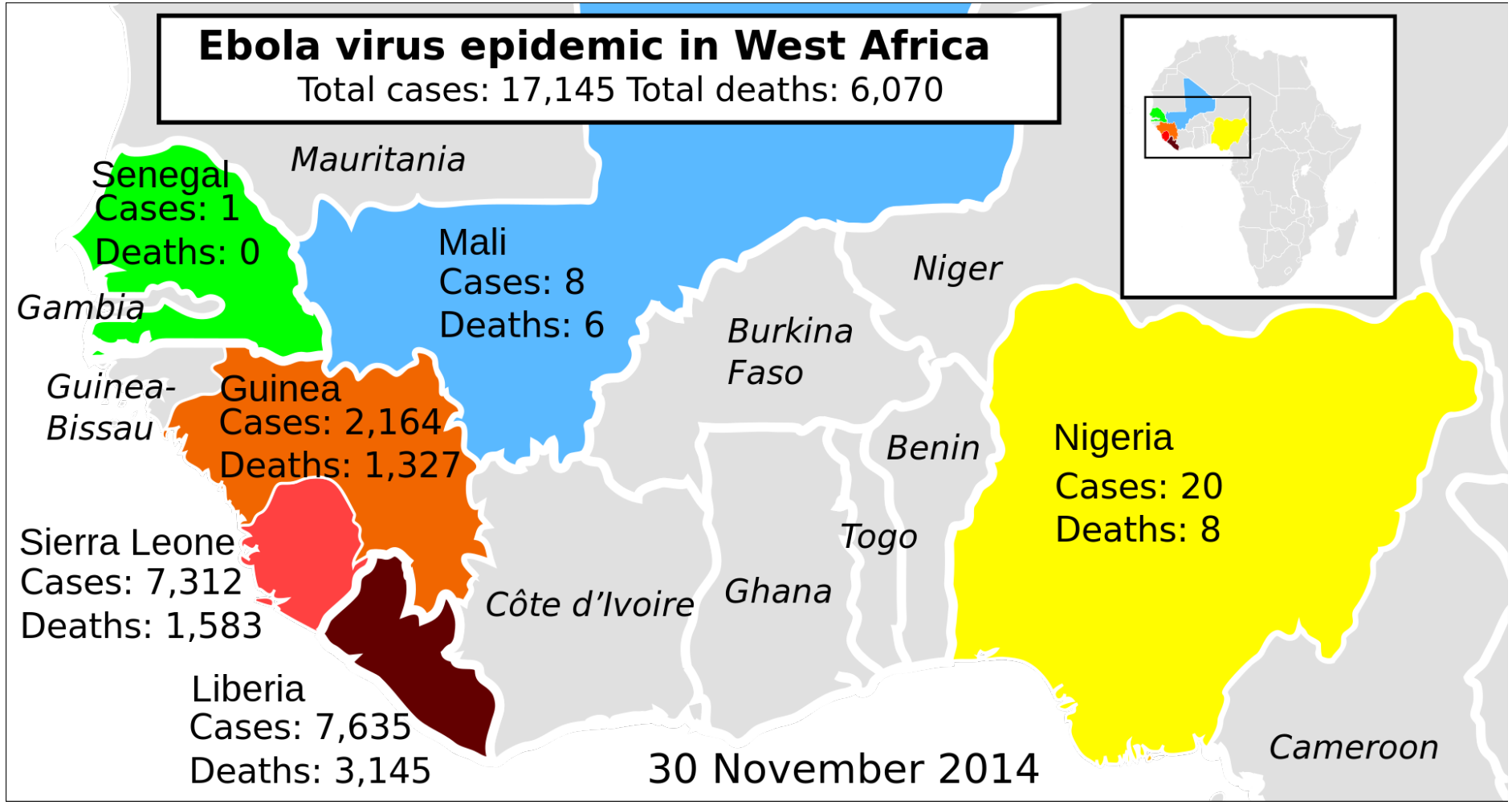
The Journal of Infectious Diseases
MAJOR ARTICLE

Design of a Randomized Controlled Trial for Ebola Virus Disease Medical Countermeasures: PREVAIL II, the Ebola MCM Study

Lori E. Dodd,[1] Michael A. Proschan,[1] Jacqueline Neuhaus,[3] Joseph S. Koopmeiners,[3] James Neaton,[3] John D. Beigel,[2] Kevin Barrett,[1] Henry Clifford Lane,[1] and Richard T. Davey Jr[1]

[1]National Institute of Allergy and Infectious Diseases, Bethesda, and [2]Leidos Biomedical Research, Frederick National Laboratory for Cancer Research, Maryland; and [3]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis

West Africa Ebola Virus Disease Outbreak

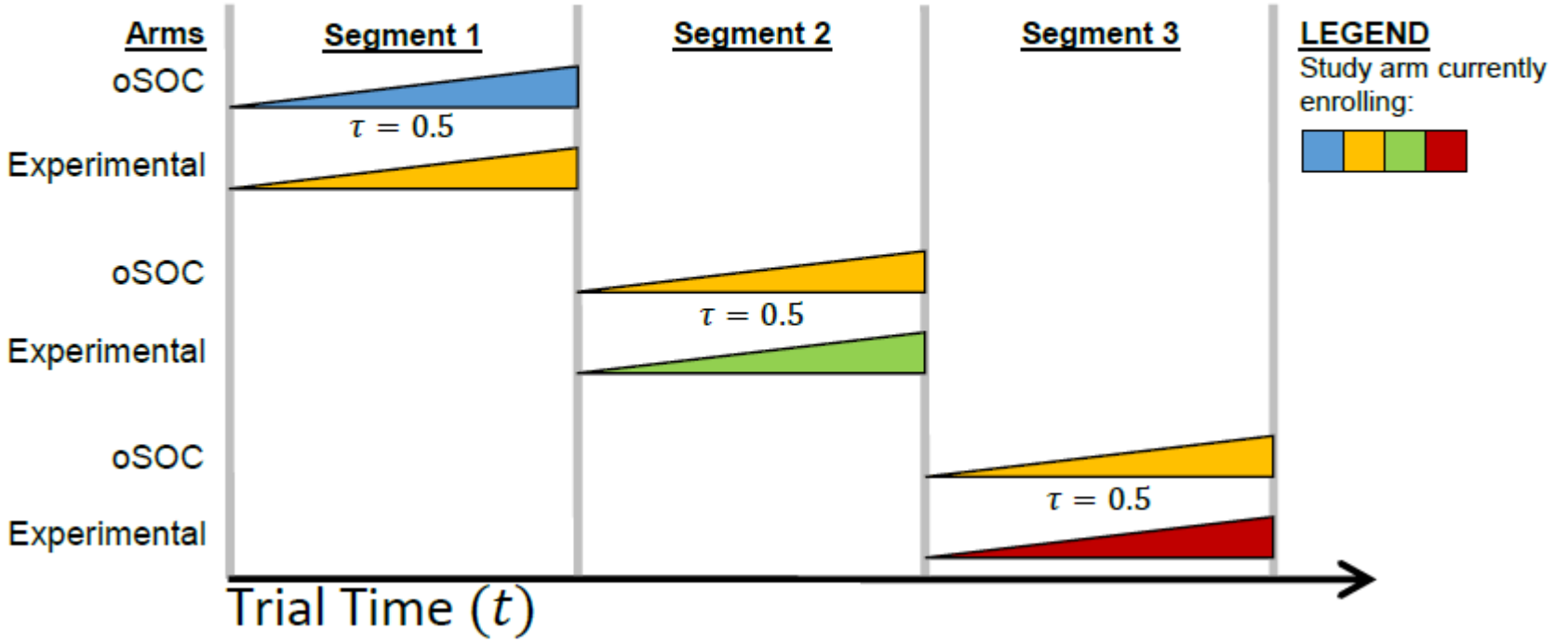


Platform Example: PREVAIL II

- No known candidate therapies or vaccines for Ebola
- Outcome was 28-day mortality
- Design sequentially considered multiple treatments within a single trial to most effectively identify beneficial therapeutics
- Used a Bayesian design with frequent interim monitoring (starting after 12 participant outcomes observed, 6 per arm)
- Used Haybittle-Peto style boundaries for interim monitoring based on the posterior probability of the experimental treatment being better than the current standard of care

PREVAIL II Example Design

I) PREVAIL II



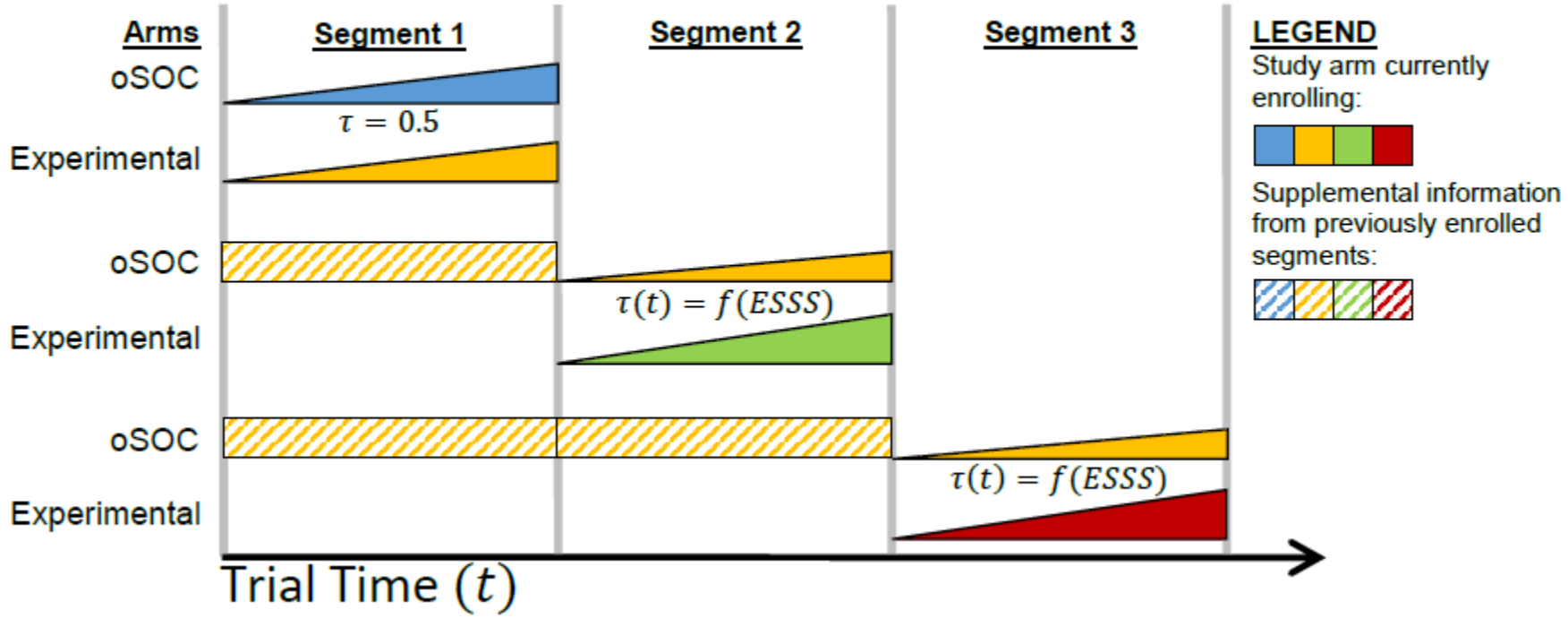
Due to concerns with time effects, only concurrent controls were used in analyses (i.e., only information within each segment).

PREVAIL II Conclusion

- Terminated early due to success of public health measures, which prevented desired enrollment of 100 per arm in first segment
- Patients in treatment arm had lower 28-day mortality rate (22% vs. 37%), but it did not meet the prespecified statistical threshold for efficacy
- Did demonstrate minimal safety concerns with the intervention

Extension to Incorporate Past Information

II) Multi-Source Adaptive Platform



Use methods to incorporate past segments when "exchangeable" (i.e., potentially use non-concurrent data)

Adaptively randomize to maintain information balance between oSOC and Experimental arms

Bayesian Methods in Adaptive Designs

A Brief Introduction

A Brief Note on Frequentist vs. Bayesian Designs

Efron's[24] comparative adjectives

	Bayes	Frequentist
• Basis	• Belief (prior)	• Behavior (method)
• Resulting Characteristic	• Principled Philosophy	• Opportunistic Methods
• _	• One distribution	• Many distributions (bootstrap?)
• Ideal Application	• Dynamic (repeated sampling)	• Static (one sample)
• Target Audience	• Individual (subjective)	• Community (objective)
• Modeling Characteristic	• Aggressive	• Defensive

“Everyone is Bayesian in the design phase” (i.e., power, type I error, effect size, etc. are usually based on prior studies or evidence)

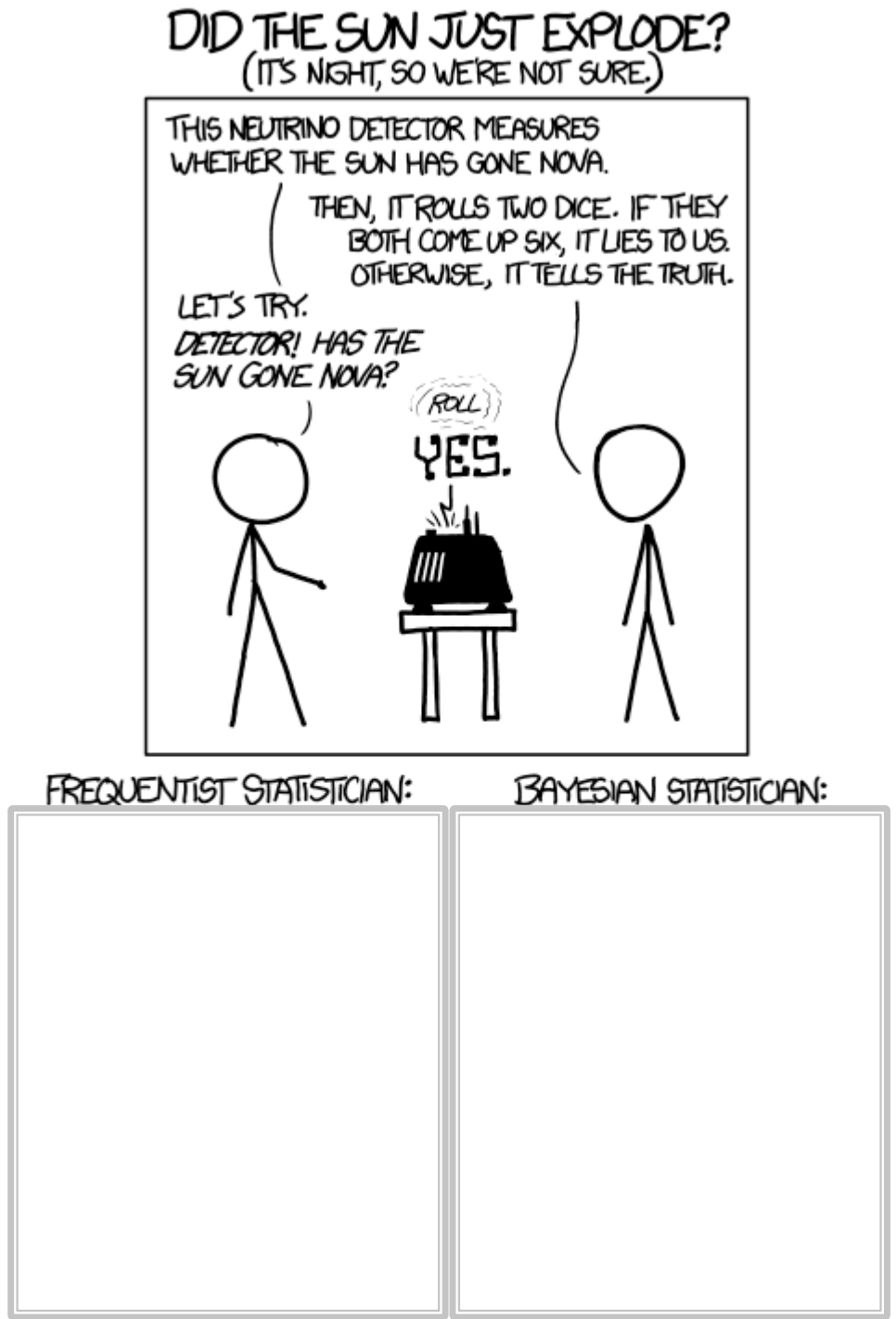
Bayesian Adaptive Design

Essentially, any designs that use Bayesian approaches for statistical reasoning and/or calculations, with some examples being:

- Use of predictive statistical modeling
- Use of assumed (prior) dose-response relationships to govern dose escalation and selection
- Borrowing information from external sources (e.g., previous trials, natural history studies, registries) via informative prior distributions
- Use of posterior probability distributions to form trial success criteria (as opposed to frequentist p-values)

Design Considerations

- The FDA requires that all trials maintain desired *frequentist* operating characteristics, including Bayesian trials:
  - Power
  - Type I error rate
- Evaluating trial operating characteristics generally involves extensive simulation studies (i.e., this is how you calculate power, the target sample size, etc.)
- Prior specification can be challenging (e.g., conjugate priors, informative priors, vague priors, etc.)



Source: xkcd.com #1132

Should I consider adaptive designs?

Advantages

- Improved flexibility
- More efficient use of resources (financial and administrative)
- Greater statistical power possible
- Ability to answer broader questions that may be refined as the trial progresses

Challenges

- Advanced analytic methods needed to avoid type I errors
- Gains in efficiency have trade-offs with other trial components
- Logistics to maintain trial conduct and integrity
- Adaptations may be limited by clinical/scientific constraints

Thank you!