

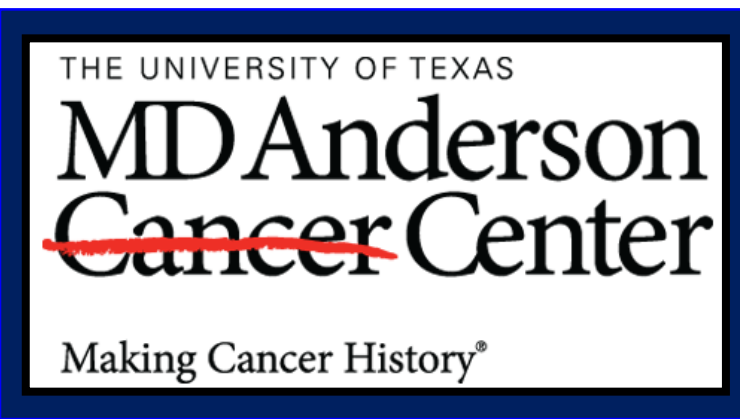
Session 2: Study Designs to Benefit Older Adults: Approaches to Early Phase Therapeutic Development:

Statistical Perspective

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Outline

- Overview of the Role of Statistics in Research
- Two Main Challenges for Finding the “Truth”
- Issues/Solutions in Drug Development & Care for Older Adults
- Statistical Considerations
 - Pragmatic trials
 - Bayesian adaptive designs
 - Platform design and adaptive enrichment
 - Bayesian hierarchical model
- Concluding Remarks

Overview of the Role of Statistics in Research

Data: *Signal + Noise*

Goal of
Data Analysis: *Extract the signal and
filter out the noise*

Statistics: *Find a needle in a
haystack*



Two Main Challenges for Finding the “Truth”

■ Bias

- Selection bias
 - Protocol eligibility criteria
- Assignment bias
 - Randomization
- Evaluation bias
 - Selection of endpoints

Older vs. Younger Adults

Single vs. Multiple Arms

OS vs. PFS; QoL; PRO

■ Variability

- Population heterogeneity
 - Define a more homogeneous group
- Measurement variability
 - Reproducible measures
- Stochastic variability
 - Increase sample size, efficient design and analysis

Generalizable

Simple & Feasible

Efficient

Key Issues and Solutions in Cancer Drug Development & Care for Older Adults

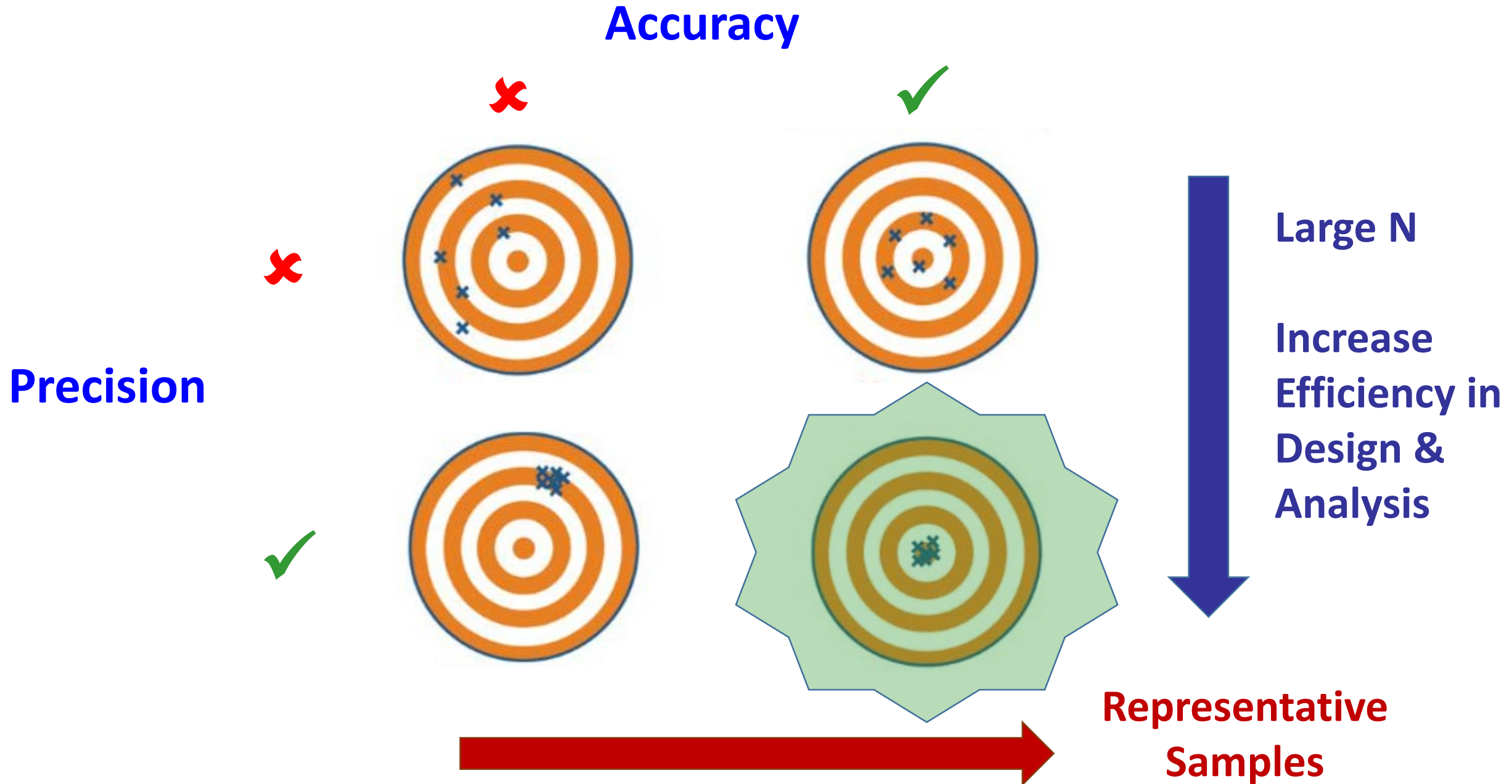
- Under-Representation of Old Adults in Trials
 - Broaden eligibility criteria
 - Relax age restrictions; Age specific inclusion/exclusion criteria
 - Pragmatic trials
 - Easy to enroll and conduct; Results are more generalizable
- Endpoints – What matter?
 - Grade II versus Grade III/IV toxicities
 - Progression-free survival vs. Overall survival?
 - Quality of life (QoL), Patient Report Outcomes (PRO)
- Age or Frailty?
 - Lower dose for patients with higher frailty; Dose-toxicity/ Dose-efficacy relationship
 - Competing risks associated with age/frailty

Burdett et al. Competing Risks in Older Patients With Cancer: A Systematic Review of Geriatric Oncology Trials, JNCI 2018

Dale and Mohile. Lessons Learned from Arti—Collaborating to Improve Care: the Past, Present, and Future of the Cancer and Aging Research Group. J Am Geriatr Soc, 2019

Sedrak et al. Older Adult Participation in Cancer Clinical Trials: A Systematic Review of Barriers and Interventions, CA Cancer J Clin 2021

Accurate and Precise Inference



Randomized Controlled Trial vs. Pragmatic Trial

	Randomized Controlled Trial	Pragmatic Trial
Condition	Ideal	Real World
Setting	Controlled	Clinical Practice
Comparator	Placebo	Standard of Care
Eligibility	Restrictive	Broad
Accrual	Hard	Easy
Treatment	Fixed / Protocol Specified	Flexible / Patient Oriented
Endpoints	Rigorously Assessed	Easily Assessed
Focus	Response, PFS, OS	QoL, PRO
Generalizability	Less	More

Adaptive Trial Design Shiny Applications

(30+ online programs freely available)



**INTEGRATED PLATFORM
FOR DESIGNING
CLINICAL TRIALS**

RESEARCH EDUCATION INNOVATION

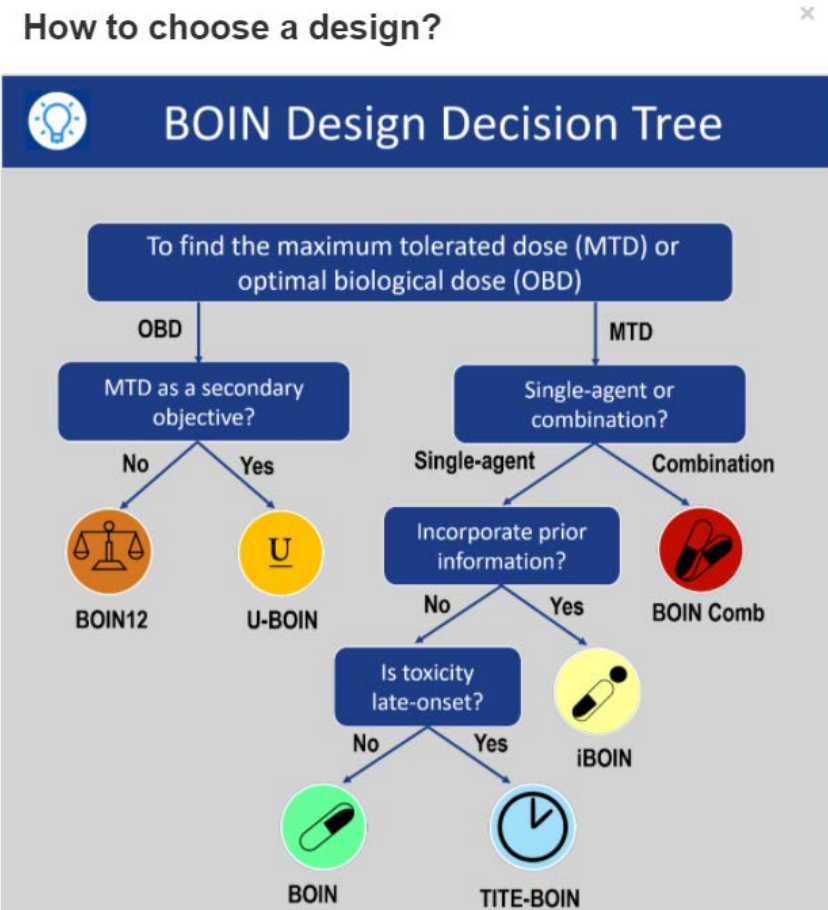
BASKET & PLATFORM

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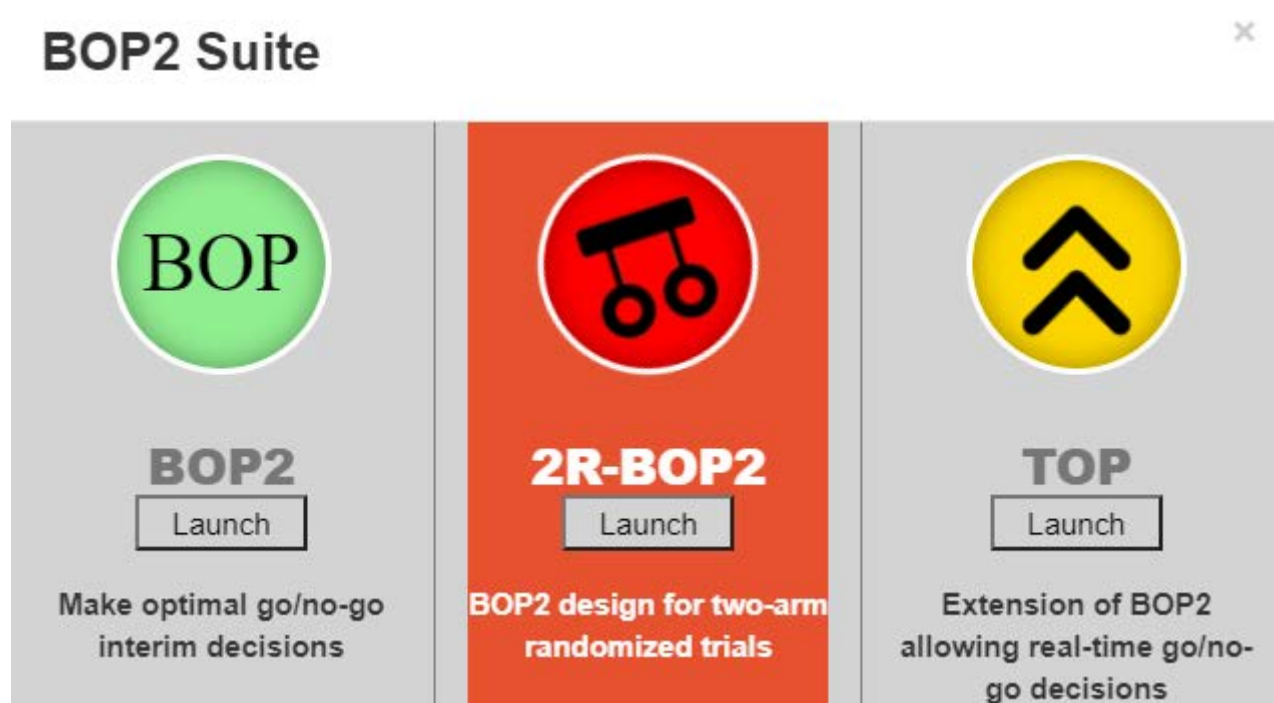
<https://trialdesign.org>

Bayesian Adaptive. Model-Assisted Designs for Phase I/II Trials

Bayesian Optimal Interval (BOIN) Designs



Bayesian Optimal Phase 2 (BOP2) Designs



Berry SM, Carlin BP, Lee JJ, and Mueller P. Bayesian Adaptive Methods for Clinical Trials. CRC Press: Boca Raton, FL, 2010.

Yuan Y, Lee JJ and Hilsenbeck SG. Model-Assisted Designs for Early Phase Clinical Trials: Simplicity Meets Superiority. JCO PO 2019

Platform Design with Adaptive Enrichment in Randomized Phase II Trials

- Start with one control and multiple experimental arms or **age subgroups**
- Continuous toxicity monitoring
 - Drop subgroups when excessive toxicity is found
- Apply equal randomization (ER) or adaptive randomization (AR)
 - Adaptive enrichment via AR
- Calculate the predictive probability or posterior probability of each subgroup being better than the control
 - Sufficiently low: Drop the subgroup
 - Sufficiently high: Graduate the subgroup
 - Otherwise, continue patient enrollment until reach N_{max}
- A perpetual, drug screening platform
 - Write a protocol with the “backbone” infrastructure
 - Add new treatments whenever needed
 - Amend the protocol by adding subgroups

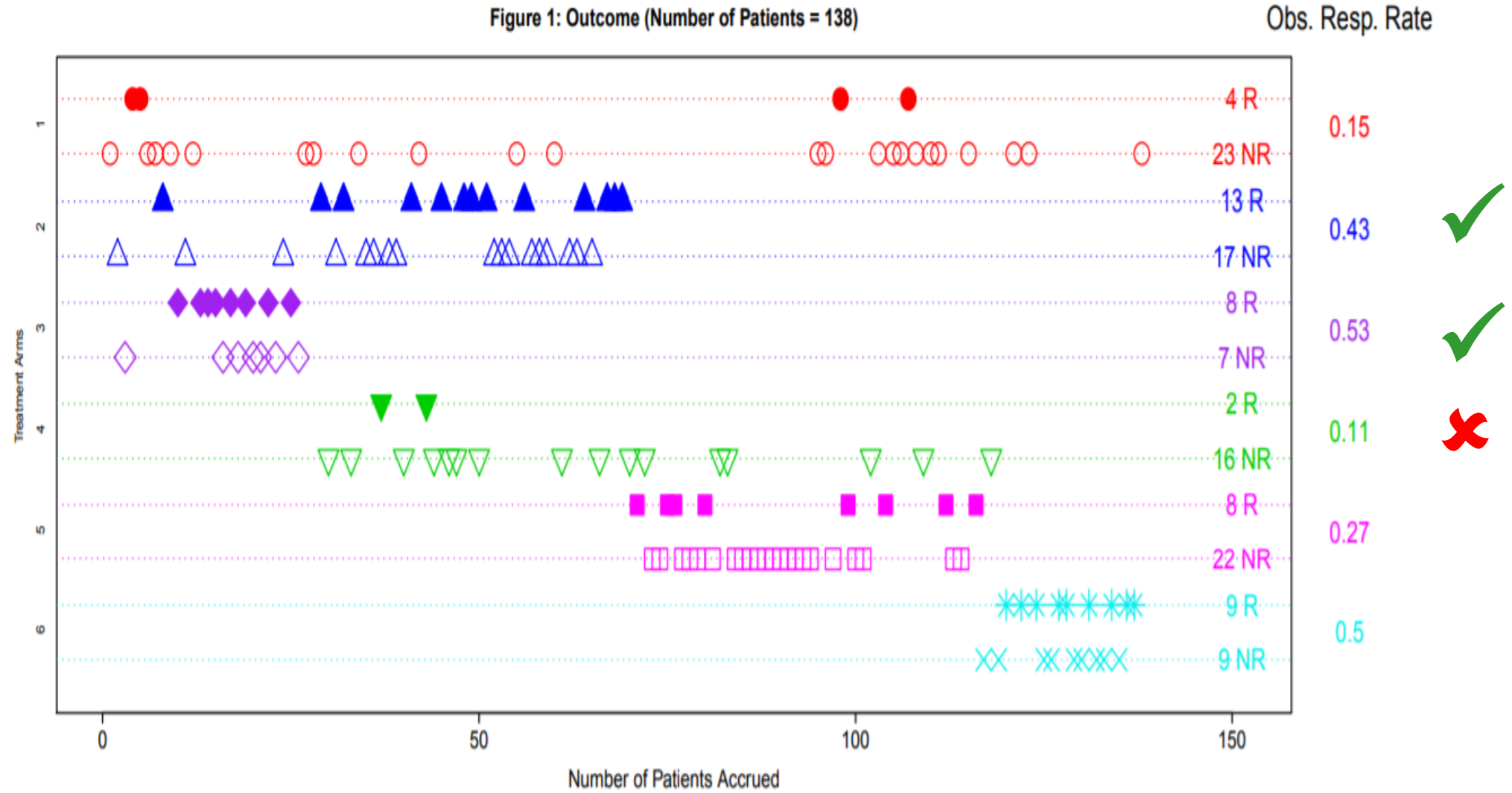
Hobbs BP, Chen N, Lee JJ. Controlled multi-arm platform design using predictive probability. Stat Methods Med Res 27(1):65-78, 2018

Zhu H, Piao J, Lee JJ, Hu F, Zhang L. Response adaptive randomization procedures in seamless phase II/III clinical trials. J Biopharm Stat 30(1):3-17, 2019

Platform Trial with AR, Response Rate: $\theta_1=0.2, \theta_2=0.3, \theta_3=0.4, \theta_4=0.2, \theta_5=0.3, \theta_6=0.4$



Figure 1: Outcome (Number of Patients = 138)



Bayesian Hierarchical Model for Synthesizing Information

- Clinical Trials often have subgroups
 - Different histology subtypes or age subgroups
- How do we analyze data?
 - Treat each subgroup separately
 - Do not use information efficiently
 - Combine all subgroups into one group
 - Not all groups are the same
- Bayesian hierarchical model can borrowing information across subgroups
 - More borrowing when subgroups are more alike and less borrowing when subgroups are more different. (nice!)
- Bayesian hierarchical model can synthesize trial data and real world evidence

Chen, N. and Lee, J. J. Bayesian hierarchical classification and information sharing for clinical trials with subgroups and binary outcomes, *Biometrical Journal* 2019.

Chen and Lee, Bayesian cluster hierarchical model for subgroup borrowing in the design and analysis of basket trials with binary endpoints, *Statistical Methods in Medical Research* 2020

Borrowing Across Subgroups

Parameters for BHM

Hyper Prior for overall mean, μ_0 :

μ_0 τ_0

Hyper Prior for precision of μ , τ_0 :

Γ_a Γ_b

Prior distribution for p_i : Beta(a_0, b_0)

a_0 b_0

Credible Interval $(1 - \alpha) \times 100\%$: α

WinBUGS Settings

Burnin Iter

Sample Information

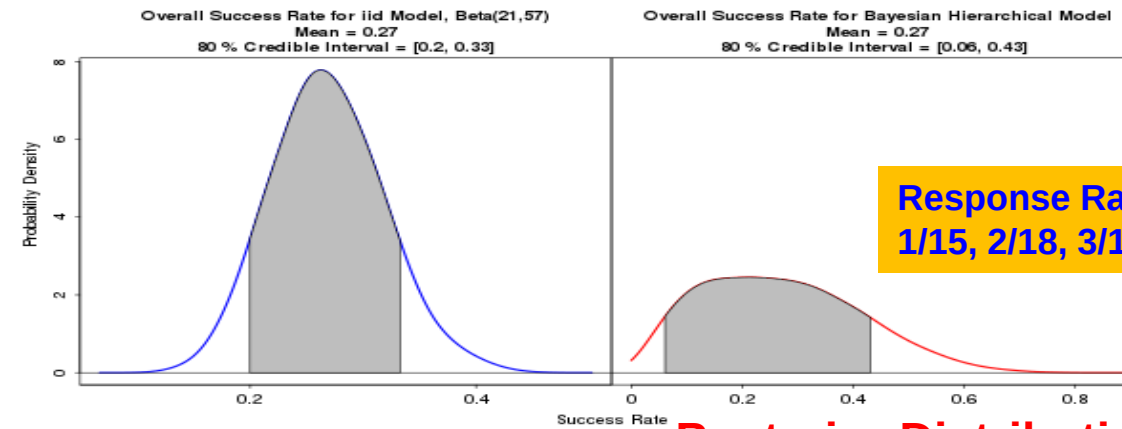
Number of Groups

Number of Success for Each Group (separate by a comma)

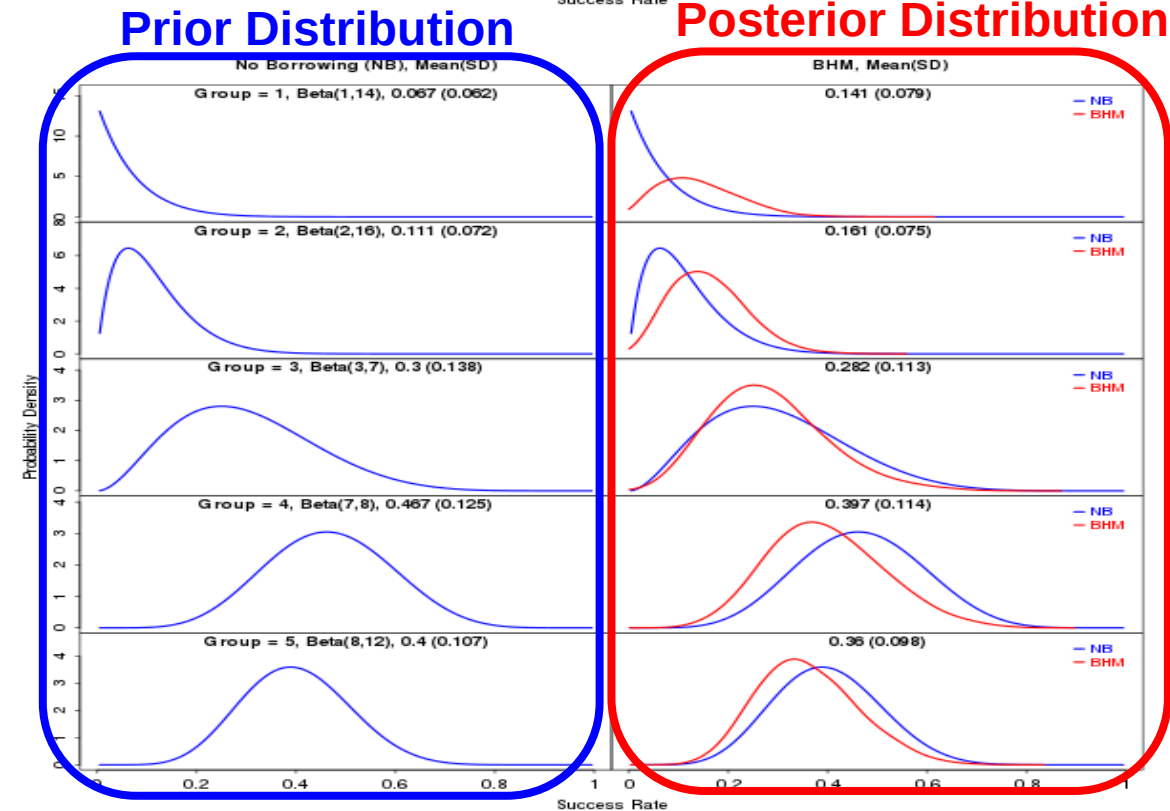
Sample Size for Each Group (separate by a comma)

BHM - Binomial Data

Support Document



Response Rates in 5 Age Subgroups:
1/15, 2/18, 3/10, 7/15, 8/20



Age

≥ 80

60-79

40-59

20-39

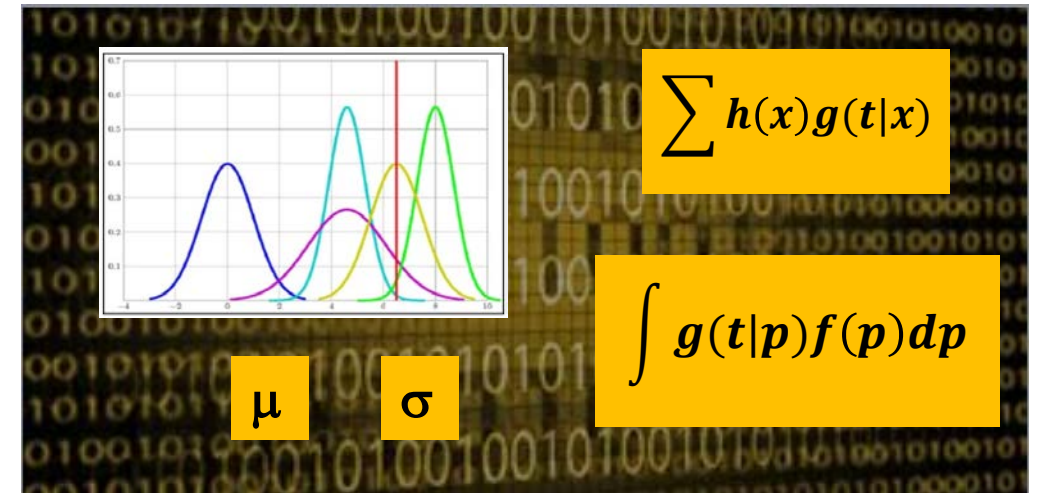
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Concluding Remarks

- Statistics can help in extracting signals from the data
 - Avoid bias
 - Reduce variability / Increase efficiency
- Simplify the trial design and conduct
- Apply novel statistical methods
- Statistics can help in cancer drug development & care for older adults

Data Acquisition, Analysis, and Interpretation

- Data is a “gold mine”
- Acquire more high-quality data
- Apply novel statistical design/analysis
- Make generalizable inference
- Turn “gold mine” into “pure gold”



Work closely with statisticians from beginning to end in every project.

Team Work!



***Clinical
Trialists***

***Patients
Advocates***

***Scientists
Statisticians***