The Role of Simulations for Bayesian Analyses, Adaptive Designs, and Regulatory Approval

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April 21, 2015

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Outline

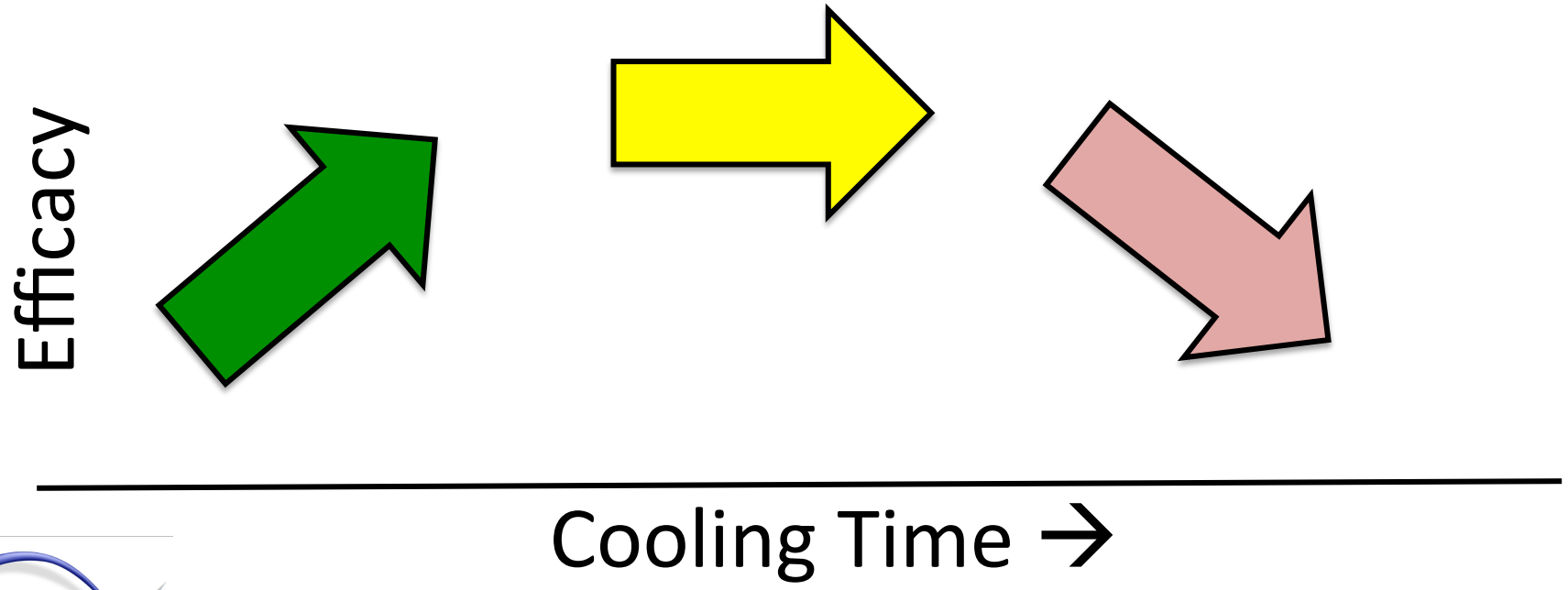
- The Need? What's Next?
  - Modeling
  - Adaptive Designs
- What Are Simulations
- Role of Simulations
- Regulatory Role

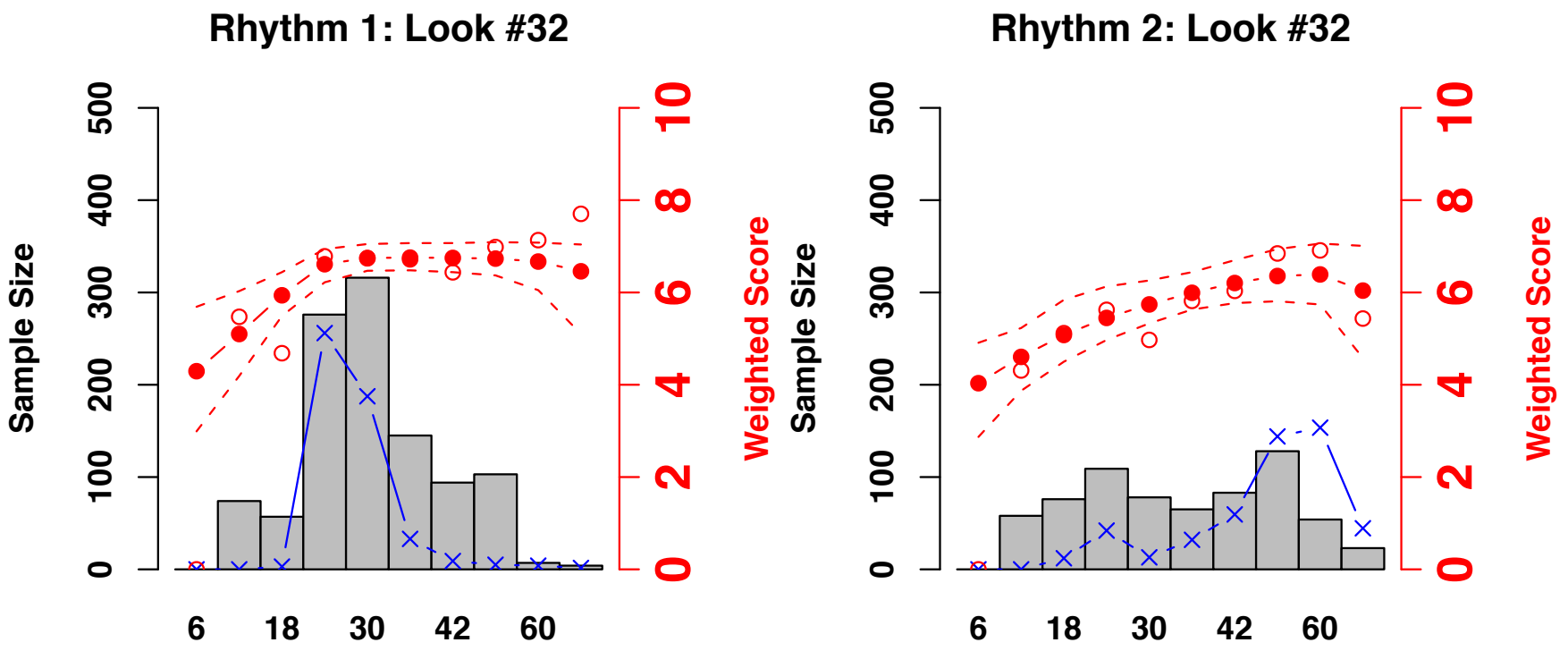
ICECAP

- ICECAP – Hypothermia after post cardiac arrest coma
  - Background
    - Two small surface cooling trials demonstrated efficacy (different durations and endovascular cooling more frequently used)
    - Medically accepted that this works
    - No FDA approval
  - Goals
    - To identify optimum cooling duration
    - What types of subject (rhythm types) vs. duration
  - Fixed Design:
    - 400 On 12, 24, 48 hours cooling

The Duration-Response

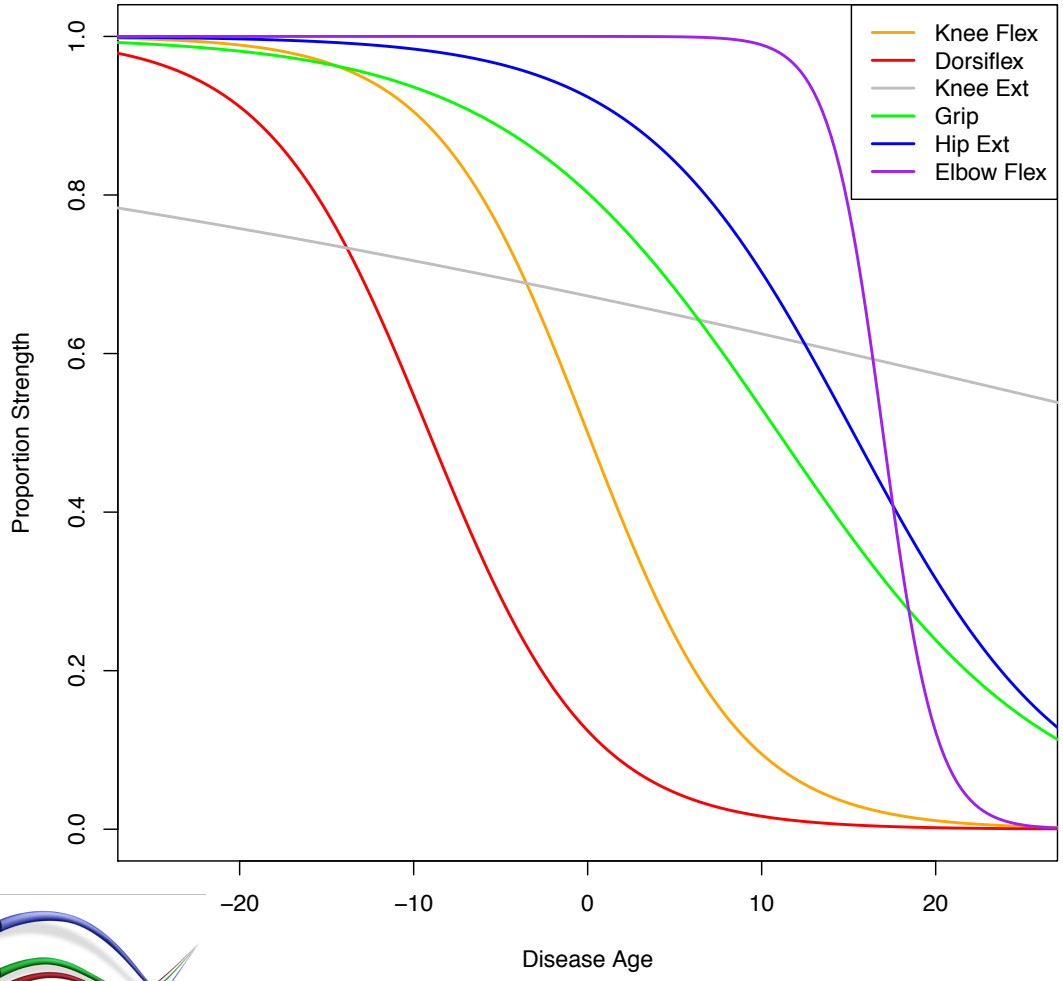
- The biology is that certain shapes are “not possible/believable”
- The model:





- A Bayesian parametric model that restricts the shape to be "Inverted-U"
- Allows 10 durations instead of 3
- Demonstration of a significant increase by cooling

Disease Progression Modeling



- GNE Myopathy
- Muscle-wasting disease
- Progresses from bottom up
- Joint model of muscle decline

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Disease Progression Modeling

$$\mu_i = \begin{cases} \text{logit}^{(-1)}[\theta_{m(i)} + \beta_{m(i)}(t_i - \alpha_{s(i)})] * M_{s(i),m(i)} & t < I \\ \text{logit}^{(-1)}[\theta_{m(i)} + \exp(\gamma)\beta_{m(i)}(t_i - \alpha_{s(i)})] * M_{s(i),m(i)} & t \geq I \end{cases}$$

- A joint model for 6-muscle progression
- Single parameter captures treatment effect
- Small sample sizes, asymptotics troubling
- Full Bayesian model available

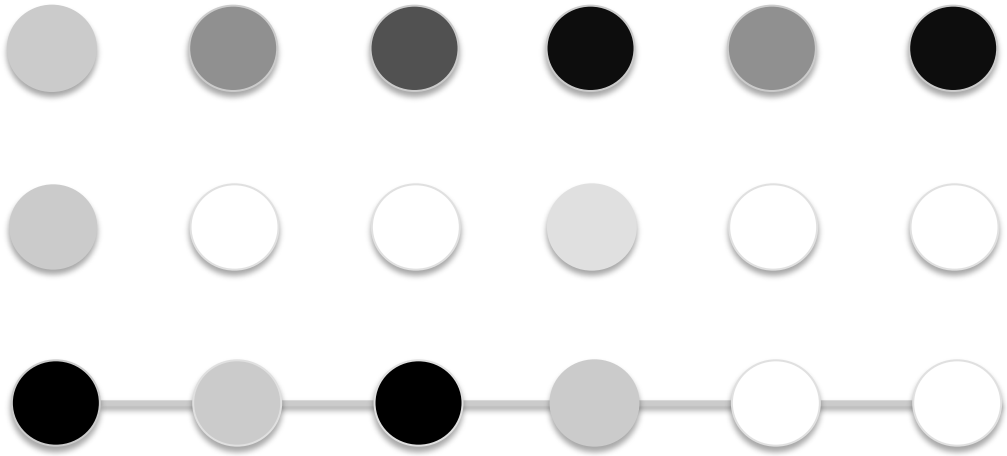
Personalized Medicine

- A “basket” trial on multiple subgroups, say 6 disease subclassifications
- A Bayesian hierarchical (cluster model) is a very natural and powerful way to analyze the results of each basket – can be type I error very protective

Example 1:

Example 2:

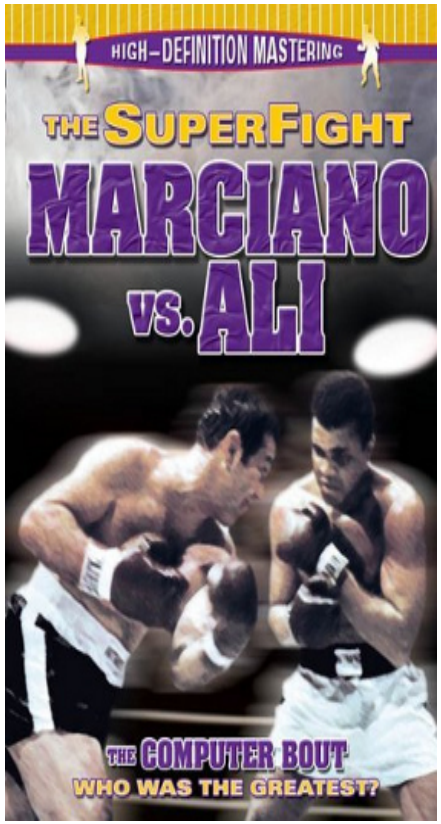
Example 3:



Innovative Designs

- An EBOLA trial that uses 4 treatments and all 2-way combinations vs. SOC
- Response adaptive randomization to all possible regimens – weekly
- Possibly drop/add new treatments
- Very effective trial: treats patients better, much faster to effective therapies
- Platform trials in oncology, infectious disease, alzheimers, ICU treatments, auto immune diseases, and more!

What are Simulations?



Madden NFL 25 Simulations: Who will win it all?

By Adam Rank
NFL Media writer
Published: Sept. 6, 2013 at 10:39 p.m. Updated: Sept. 18, 2013 at 01:42 p.m. 999+ Likes | 999+ Comments

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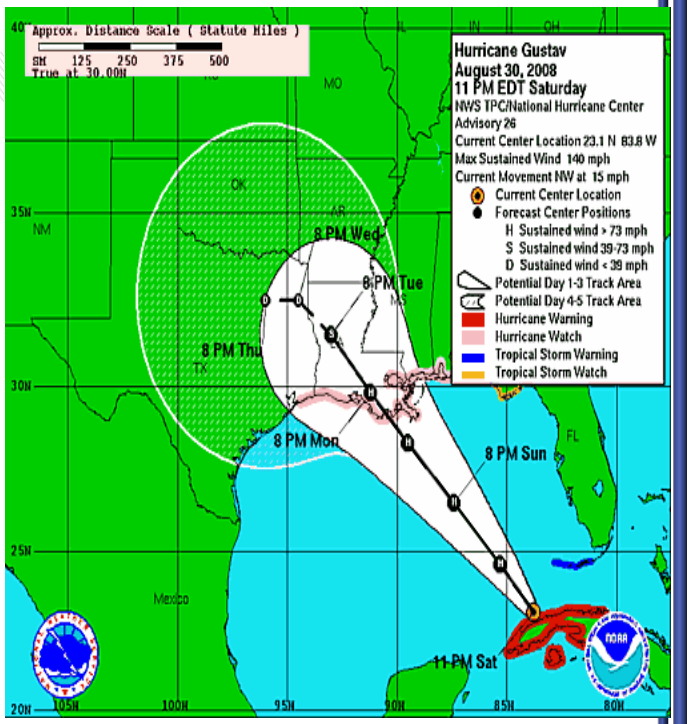
EA Sports

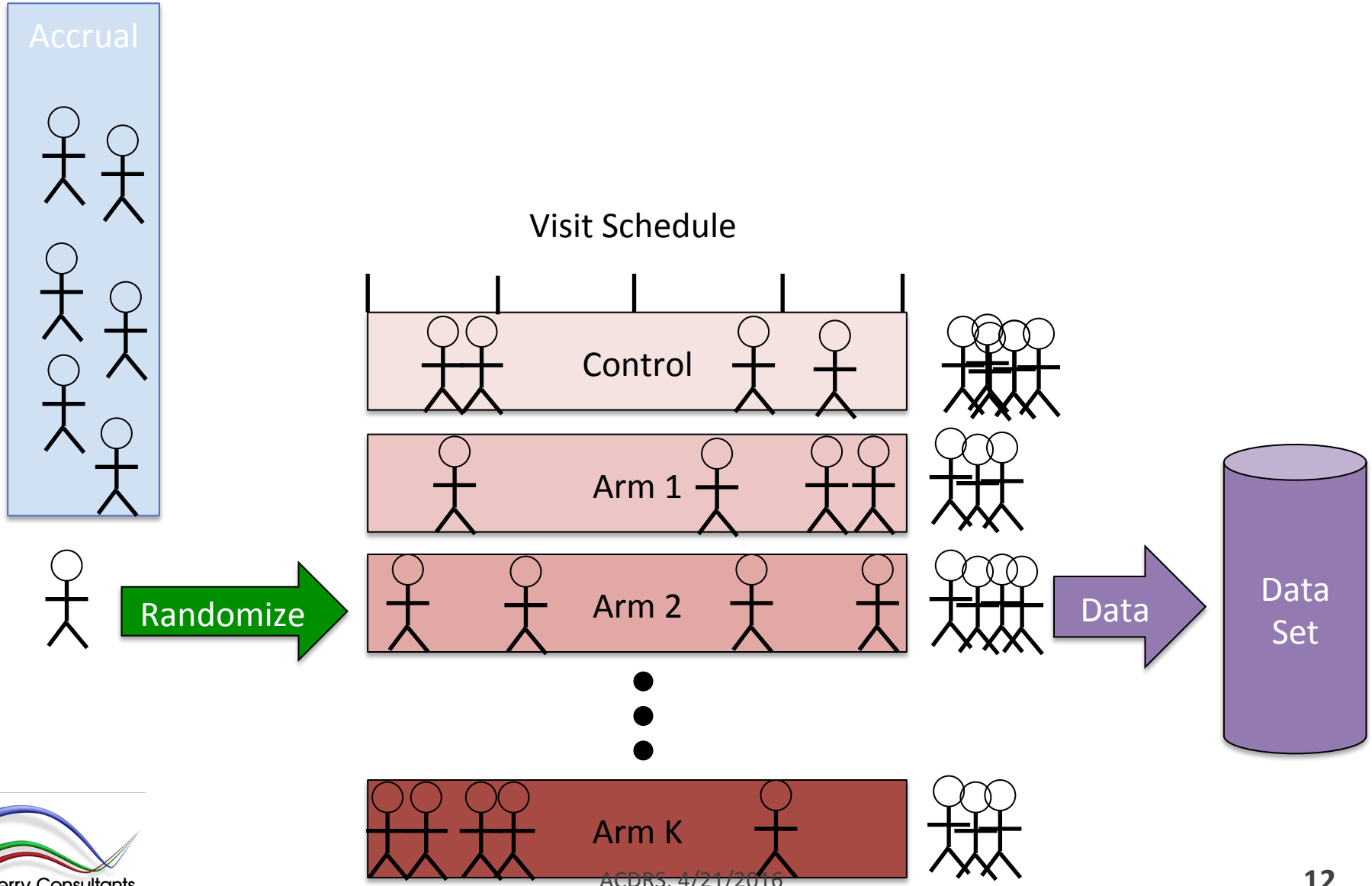


We are inundated with "simulations" being used as *predictions*

Role of Simulations

- This is common for PK/PD scientists – *predict* what will happen in humans
- This is not how simulations are used in creating *in silico designs*
- The "simulation" evaluation is nothing more than numerical integration
- Can it be the source of evaluation of a design/ Bayesian analysis?

Clinical Trial Simulation



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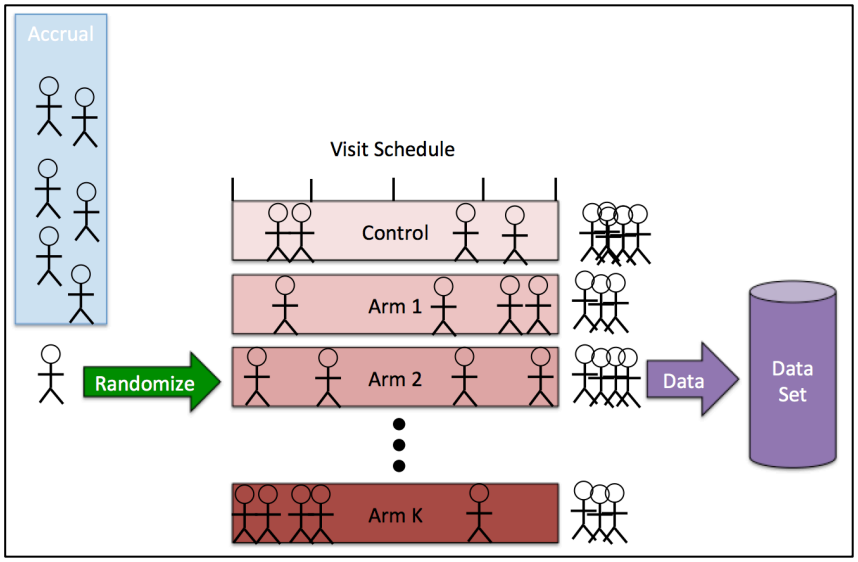
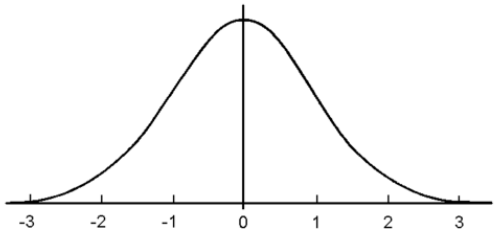
Frequentist Approach



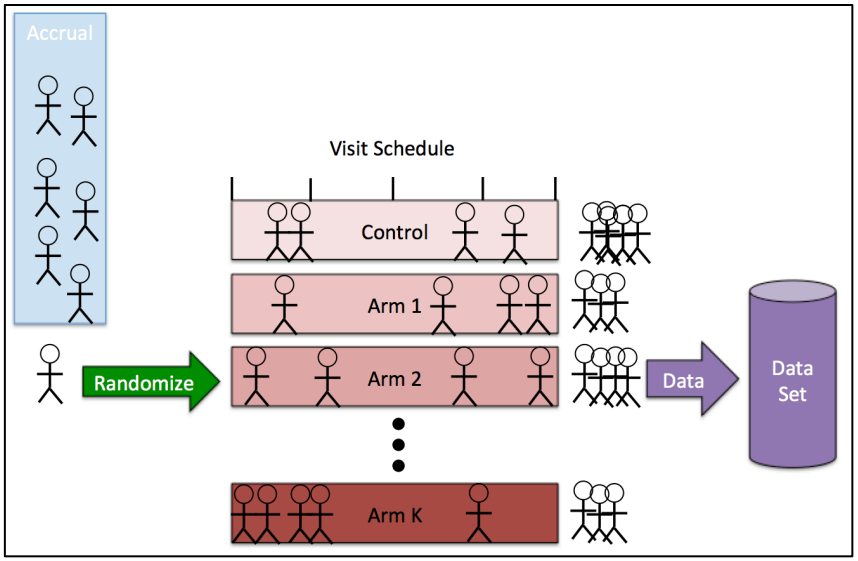
The "theoretical" distribution of T(x) from repeated experiments

$$T(x) \sim$$



- The "model" must be simple enough to get theoretical result
- The design must be simple to get closed form long-run distribution

Bayesian Approach

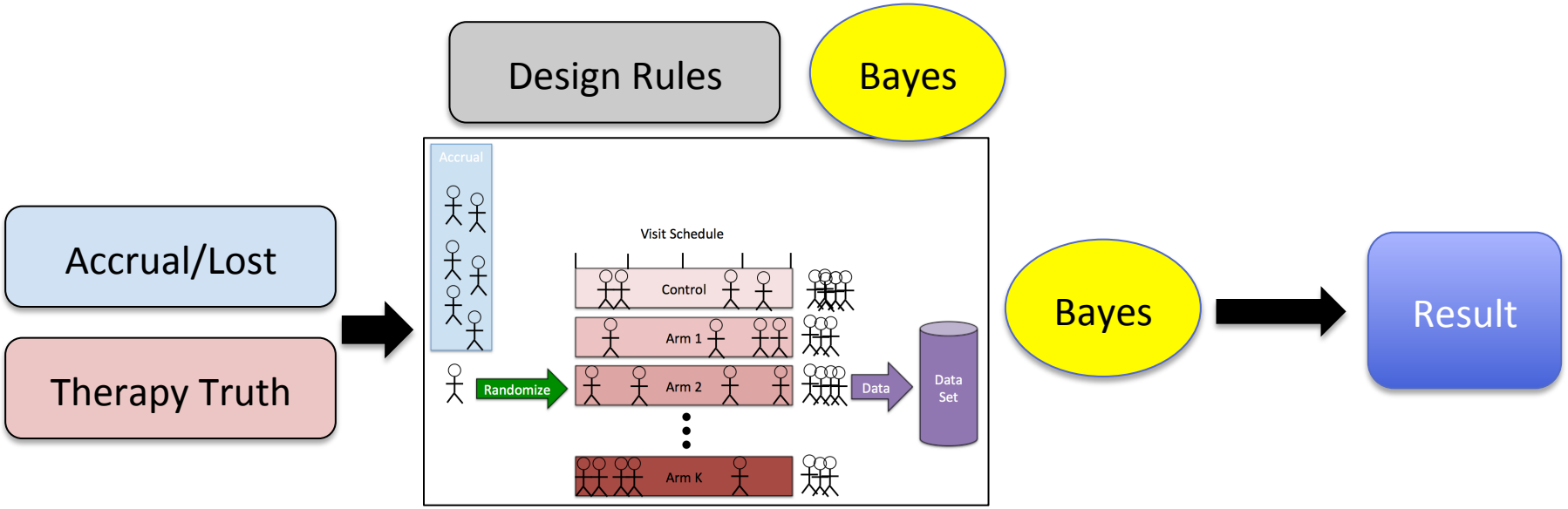


$$f(\theta \mid x)$$

Pr(Superiority)=Y

- Model can be appropriately complex
- Design can be appropriately flexible

Simulation of Bayesian Approach



- Repeated to measure the *exact* long-term behavior of any quantity of interest
- Numerical Integration

Regulatory Role

- A flexible design and/or Bayesian analysis is submitted
  - Completely prespecified (design + success)
  - Model fully defined
    - What if procedures
- Simulations conducted; submitted
- Null space fully explored/covered
- Post-simulation plan

Conclusions

- The ability to demonstrate long-run characteristics by numerical integration:
  - Opens up the analysis to innovative, needed, Bayesian analyses
  - Opens up to innovative, needed, flexible trial designs
- Improves trial designs, analyses, information, and drug development – which of course improves regulatory decision making