An Introduction to Flexible Adaptive Designs

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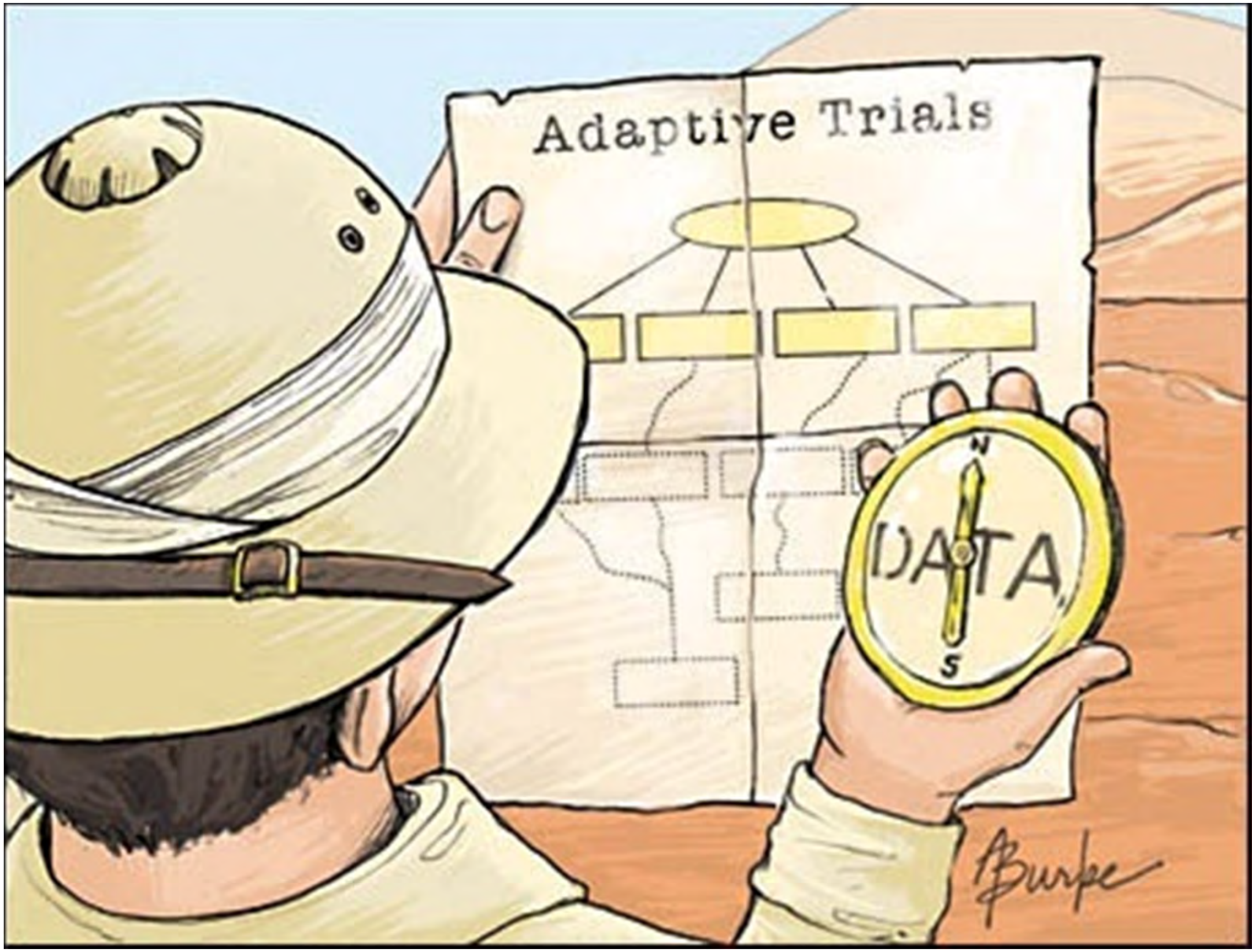
Characteristics of Adaptive Design

- Clarity of goals
  - E.g., proof of concept vs. identification of dose to carry forward vs. confirmation of benefit
  - A statistically significant *p* value is not a goal
- Frequent “looks” at the data and data-driven modification of the trial
- Adaptive “by design”
- Extensive use of simulation to adjust characteristics of trial design

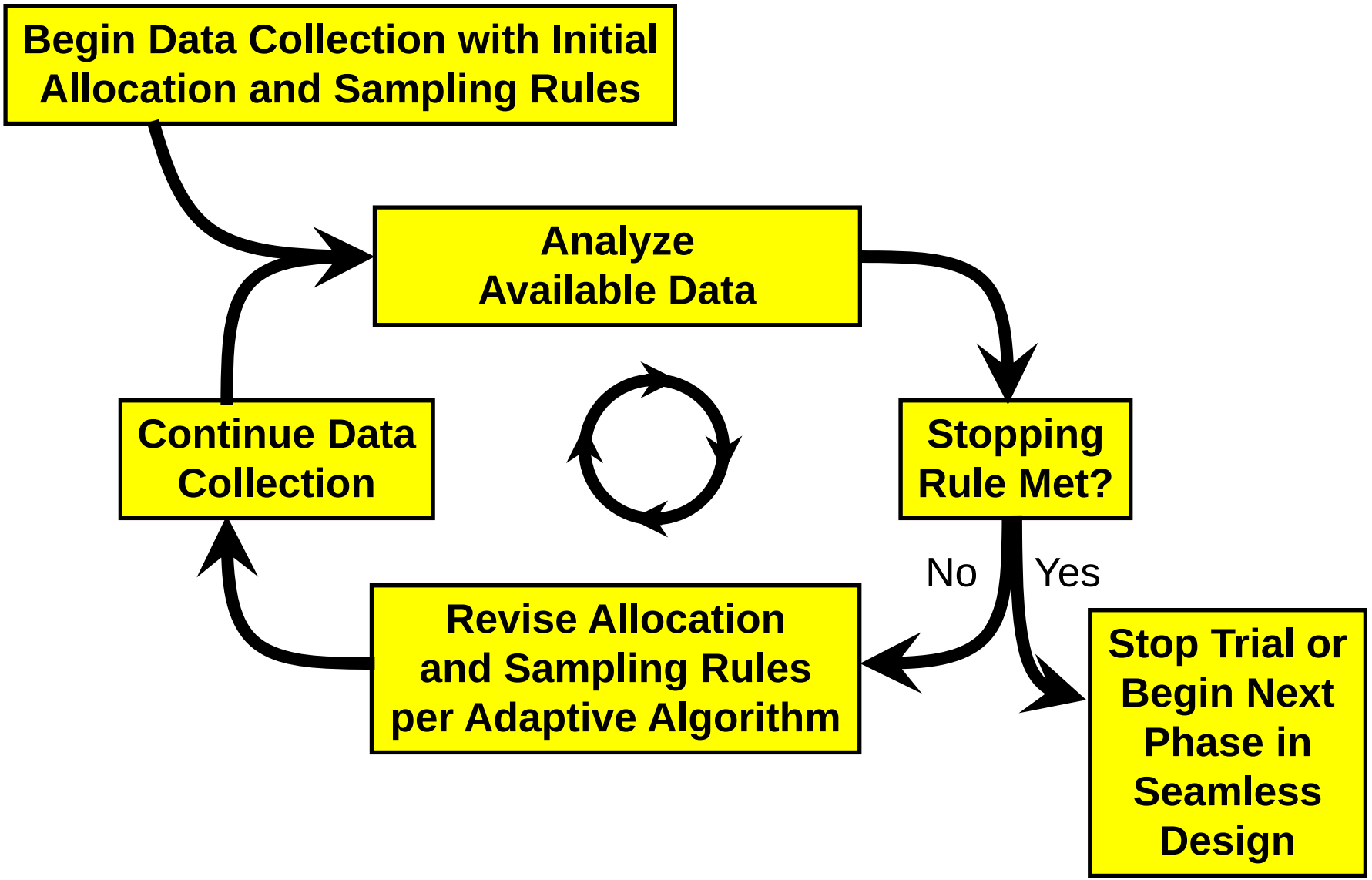
Adaptation: Definition

- Making planned, well-defined changes in key clinical trial design parameters, during trial execution based on data from that trial, to achieve goals of validity, scientific efficiency, and safety
  - Planned: Possible adaptations defined *a priori*
  - Well-defined: Criteria for adapting defined
  - Key parameters: *Not* minor inclusion or exclusion criteria, routine amendments, etc.
  - Validity: Reliable statistical inference



JAMA 2006;296:1955-1957.

The Adaptive Process



Why Do Adaptive Clinical Trials?

- To avoid getting the wrong answer!
  - Drawing an incorrect qualitative conclusion
- To avoid taking too long to draw the right conclusion
  - Time, human subjects, and resources

Avoiding Anticipated Regret

- A substantial fraction of all confirmatory trials fail despite promising “learn phase” results
- Investigators can anticipate the design decisions they would wish to “take over” after the trial fails
- Areas of “anticipated regret” are promising targets for adaptations

Historical Context

- Historically, obtaining results that were “reliable and valid” required fixed study designs
- Allowed the determination of theoretical error rates
- Fundamental characteristic of the “culture” of biostatistics and clinical trial methodology

Why are Study Designs Fixed?

- It's easiest to calculate type I error rates if the design parameters of the trial are all constant
- There are some other reasons:
  - Results obtained using "Standard approaches" are generally considered valid
  - Logistically simpler to execute
  - Fixed designs are less sensitive to "drift" in the characteristics of subjects over time

When is Adaptation Most Valuable?

- Outcomes or biomarkers available rapidly relative to time required for entire trial
- Substantial morbidity, risks, costs
- Large uncertainty regarding relative efficacy, adverse event rates, etc.
- Logistically practical
- Able to secure buy-in of stakeholders

Why Not Adapt?

- Determining traditional type I and type II error rates is more difficult
  - Usually need to use simulation via custom programming or specialized software
- Statistical training issues
  - Most statisticians have never designed or analyzed an adaptive trial
- Logistical Issues
  - Data availability
  - Centralized randomization
  - Drug supply

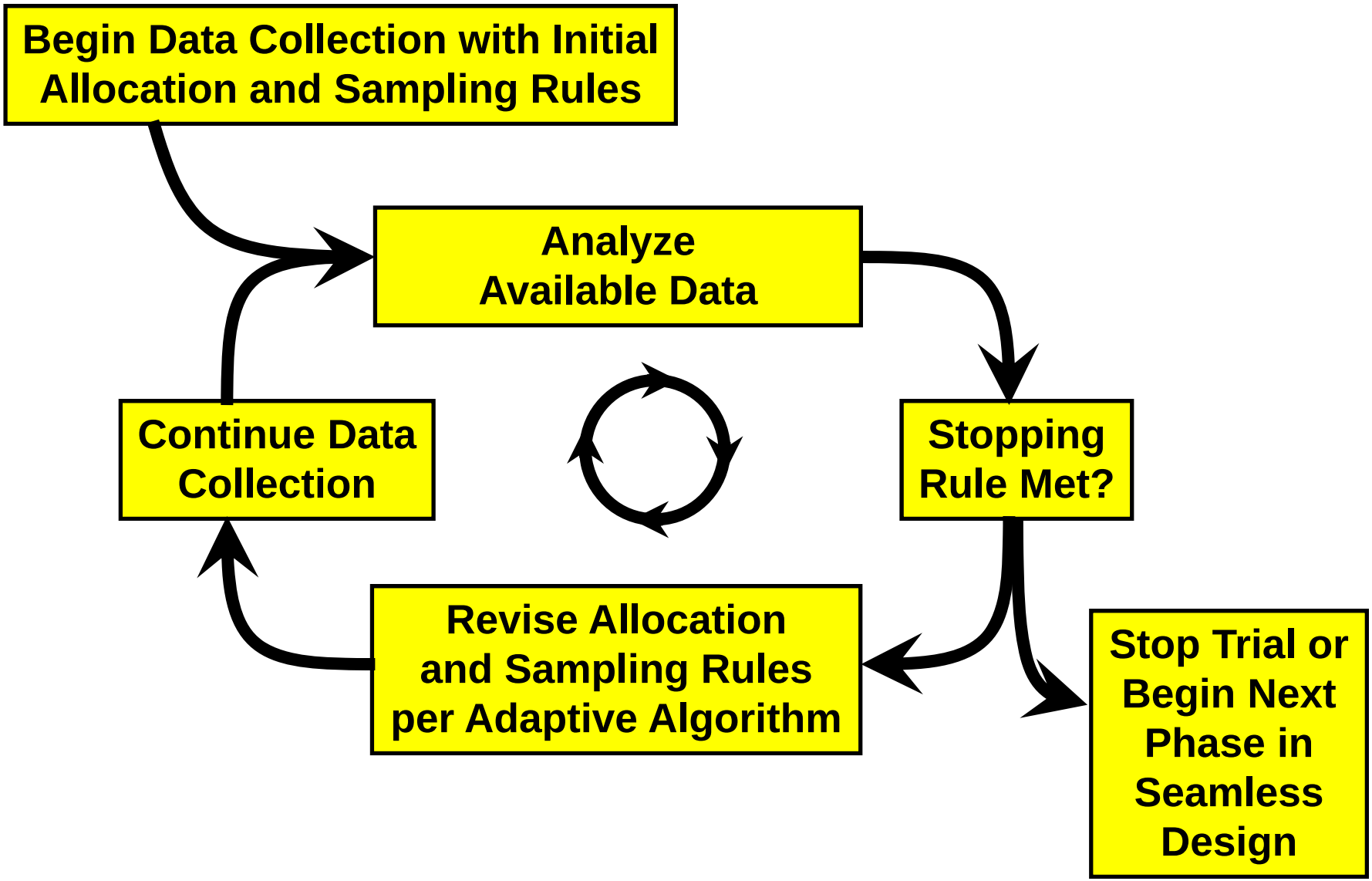
Traditional vs. Flexible Methods

Component	Traditional	Flexible
Interim Analyses	Limited (1 to 2)	Frequent
Randomization	Fixed (1:1, 2:1)	Variable
Number of Arms	Limited (2 to 3)	Few to Many
Use of Incomplete Data	Imputation at Final Analysis	Imputation at All Stages
Philosophy	Frequentist	Bayesian or Frequentist
Control of Error Rates	Via Theoretical Calculation	Via Extensive Simulation

Some (Bayesian) Adaptive Strategies

- Frequent interim analyses
- Explicit longitudinal modeling of the relationship between proximate endpoints and the primary endpoint of the trial
- Response-adaptive randomization to efficiently address one or more trial goals
- Explicit decision rules based on predictive probabilities at each interim analysis
- Dose-response modeling
- Enrichment designs
- Extensive simulations of trial performance

The Adaptive Process




HIRAM S. DUDSON
1930 - 1993
Member,
Placebo Group
D. Reilly

L-Carnitine and Sepsis

- Clinical setting
  - Adult patients with severe sepsis or shock
  - Phase II, dose-finding trial of L-carnitine to improve end organ function and survival
- Goals
  - Identify most promising dose
  - Determine if L-carnitine should be evaluated in a confirmatory, phase III trial
  - Enroll more patients to doses most likely to be beneficial, based on accumulating information

L-Carnitine and Sepsis

- More Background
  - L-carnitine is believed to work through reducing multi-organ system failure
  - Multi-organ system failure quantified by SOFA score
  - Baseline SOFA is key predictor of mortality
  - Reduction in SOFA over 48 hours is desired proximate treatment effect
  - Reduction in 28-day mortality would be registration endpoint

Adaptive Trial Structure

- Outcome measures
  - Proximate: Δ SOFA score
  - Definitive: Survival to 28 days
- Structure of trial
  - 4 arms (0 g, 6 g, 12 g, and 18 g) with dose-response model
  - Maximum sample size of 250 subjects
  - Interim analyses at 40 subjects, then every 12
  - Subjects randomized according to probability that the dose results in the best (negative) Δ SOFA
  - May be stopped early for futility or success, based on probability that best dose improves SOFA and would be successful in phase III

Simulation Strategy

- Outcome measures
  - Proximate: Δ SOFA score
  - Definitive: Survival to 28 days
- To create simulated subjects, one must assume
  - A particular dose-response curve for Δ SOFA score
  - A particular relationship between Δ SOFA score and the odds of 28-day survival
- We used data from an observational study to determine an empirical relationship between Δ SOFA score and the odds of 28-day survival

Operating Characteristics of Proposed Trial Design: Results of Monte Carlo Simulations						
	No Effect (Null)		**Mild Effect**		**Strong Effect**	
Assumed Treatment Effects for Simulations						
	ΔSOFA	Mortality	ΔSOFA	Mortality	ΔSOFA	Mortality
Outcome: Control	0	40%	0	40%	0	40%
Outcome: 6 g	0	40%	0	40%	-1	34%
Outcome: 12 g	0	40%	-1	34%	-2	28%
Outcome: 18 g	0	40%	-2	28%	-4	19%

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Trial Performance						
Probability of Positive Trial	0.043 (type I error)		0.911 (power)		0.999	
Probability of Stopping Early	For futility: 0.431 For success: 0.023		For futility: 0.001 For success: 0.679		For futility: 0.000 For success: 0.981	
Average Req'd Sample Size	198.0		172.4		119.5	
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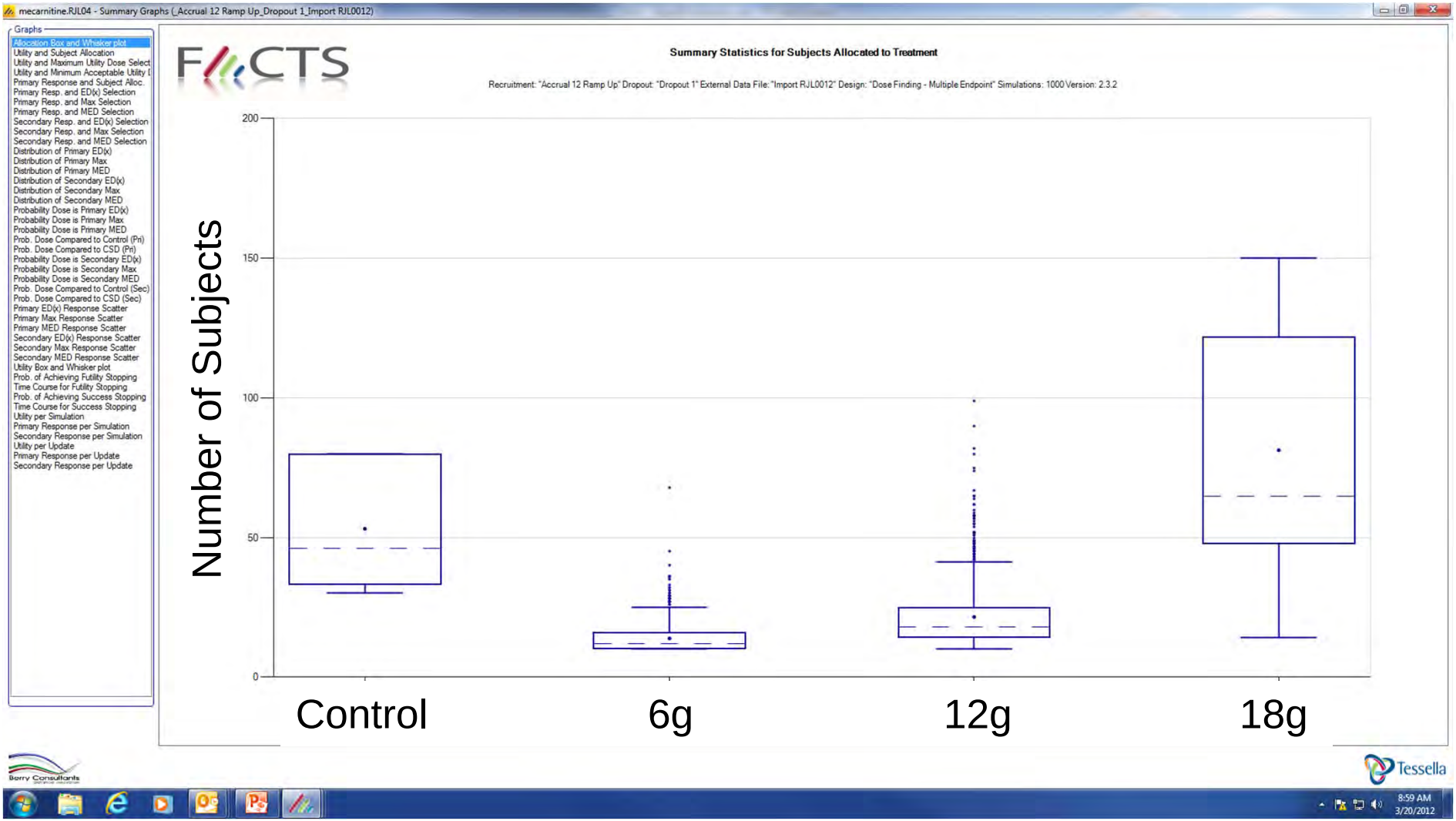
Average Allocation of Subjects Between Treatment Arms – n per arm (%)						
Control	62.7 (32%)		54.1 (31%)		36.5 (31%)	
6 g	47.0 (24%)		13.8 (8%)		10.5 (9%)	
12 g	38.7 (20%)		21.5 (12%)		12.5 (10%)	
18 g	49.6 (25%)		83.0 (48%)		60.0 (50%)	

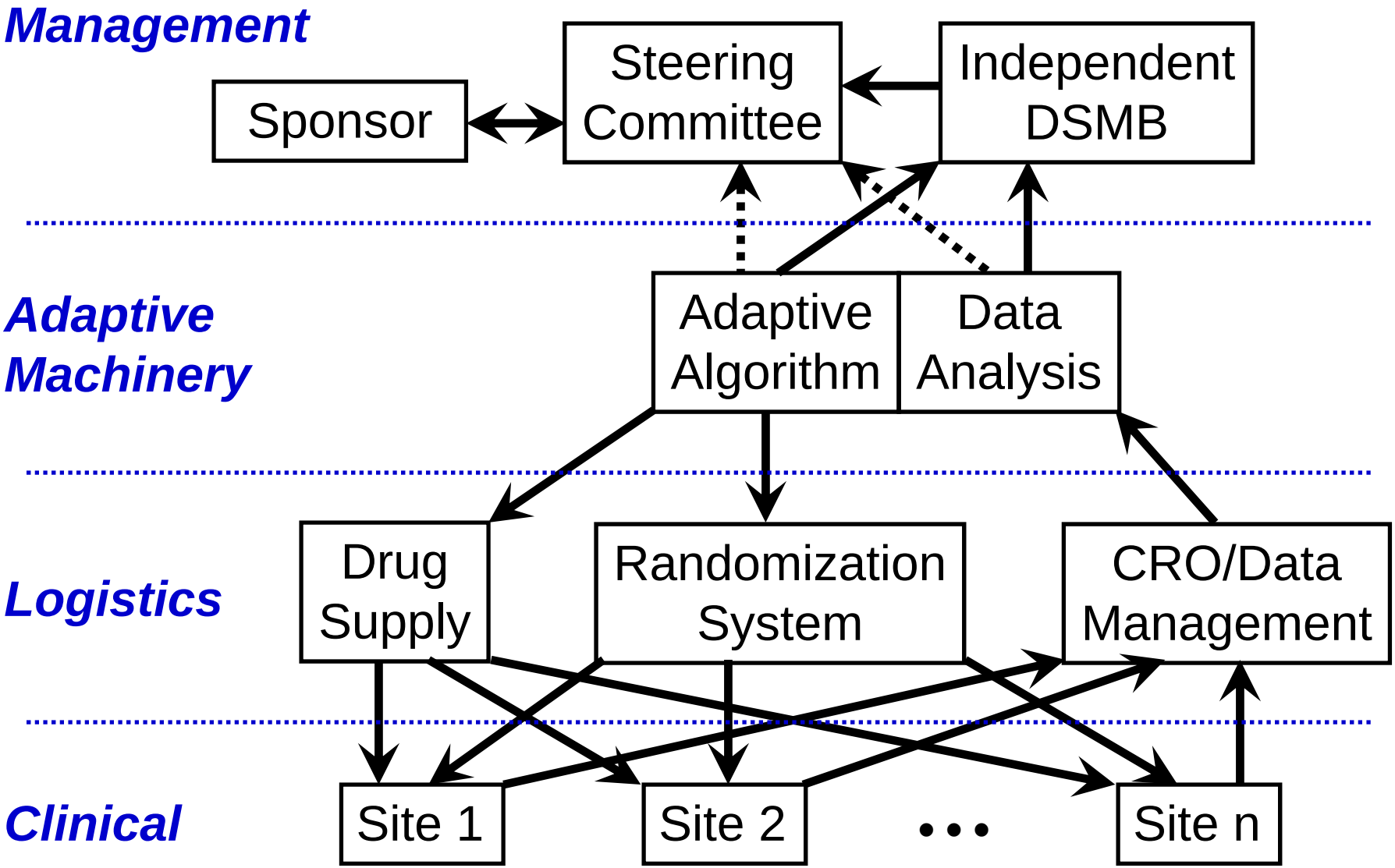
Characteristics with Mild Effect



Trial Status

- Funded by US National Institutes of Health/National Institute of General Medical Sciences (R01GM103799)
- Led by Alan E. Jones, MD at the University of Mississippi, Department of Emergency Medicine
- Currently beginning trial implementation

Components of an Adaptive Trial



IRB Review

- IRBs review/approve the full protocol, including the planned adaptations
- No new review when adaptations made
  - IRBs may request to be informed (e.g., new sample size, dropping of a surgical arm)
- Amendments are different
  - Not preplanned
- Irony
  - Little changes (e.g., amendments) may require IRB review
  - Big changes (adaptations) are defined by design and only reviewed/approved once

Data and Safety Monitoring Boards

- What's different in an adaptive trial?
  - Requires expertise to assess whether the planned adaptations continue to be safe and appropriate
  - May increase need to include sponsor personnel
- What's unchanged in an adaptive trial?
  - The DSMB ensures completion of the trial *as planned, including the adaptation*
  - It is the trial that's adaptive, not the DSMB

Conclusions

- Not all trials need (or should have) adaptive designs
- When used appropriately, adaptive designs may:
  - Improve efficiency and reduce cost
  - Maximize the information obtained
  - Minimize risk to subjects and sponsor
- Design decisions should be based on objective performance rather than habit
- An adaptive design will not save a poorly planned trial or ineffective treatment