Innovative Approaches to Study Planning and Design: Power, Simulation and Adaptation

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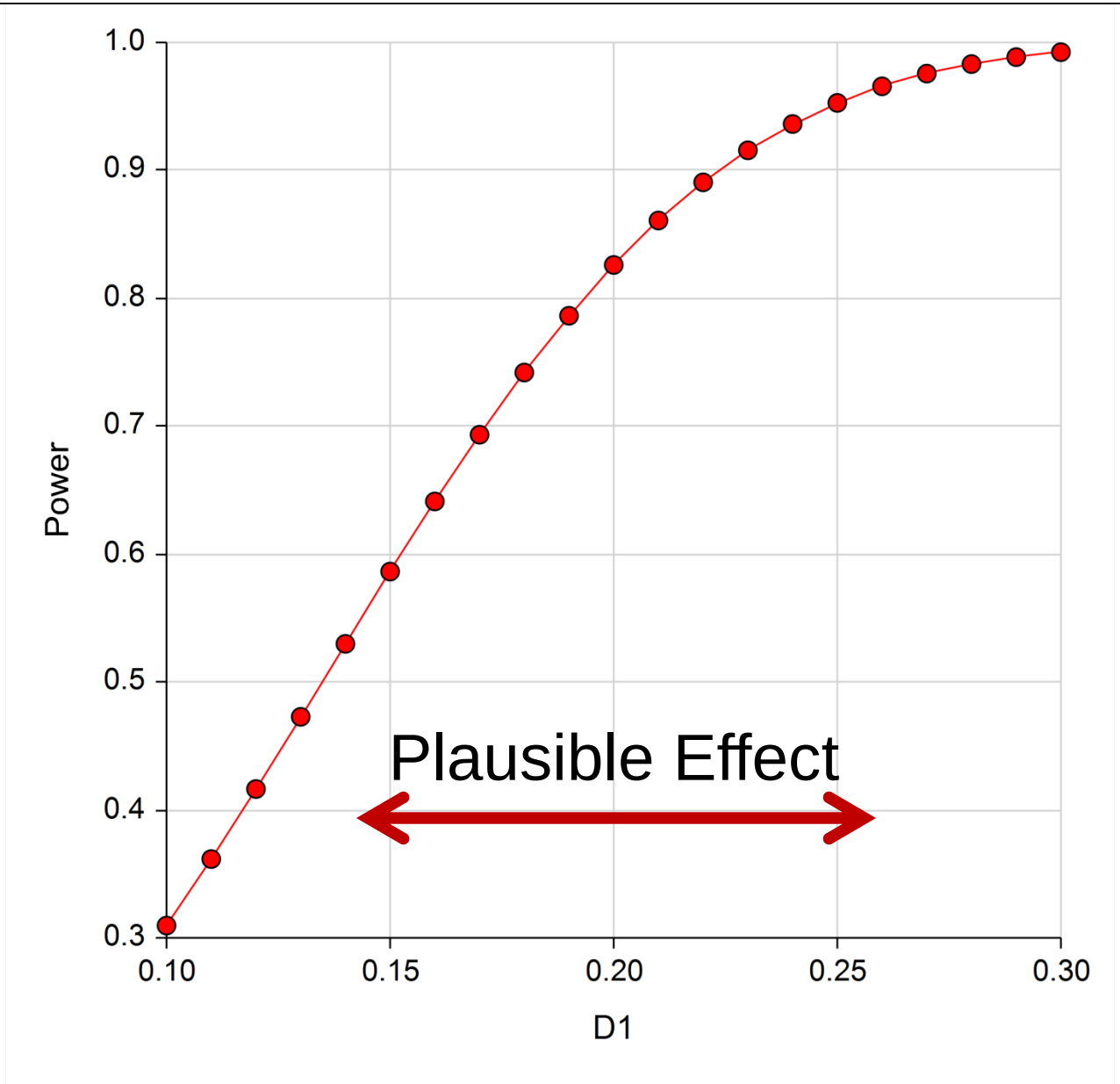
- Octapharma AG

Example

- Consider a clinical trial intended to determine which of two treatment strategies is better
  - Best guess success rate with treatment A: 40%
  - Best guess success rate with treatment B: 60%
- PASS software: power = 0.83 with 100/group
- What is the probability that the trial will be successful with that sample size?

Example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Plausible Effect

“Straw Man” Example

- What if the control treatment has a higher or lower success rate?
- What if there is substantial heterogeneity of treatment effect?
- What if there is a substantial secular trend in the underlying success rate?
- What if a new treatment becomes common place, or even a new standard of care?
- What if the clinical setting is, in fact, much more complex (treatments, populations, outcomes)?

PCORI and Trial Simulation

- Simulation is extremely useful in understanding the strengths, limitations, and vulnerabilities of many clinical trial designs
- Existing capacity for and experience with trial simulation is quite limited in most academic medical centers and research networks
- Goal is to encourage and support increased use of simulation, where it is most likely to be valuable, in a manner that increases capacity

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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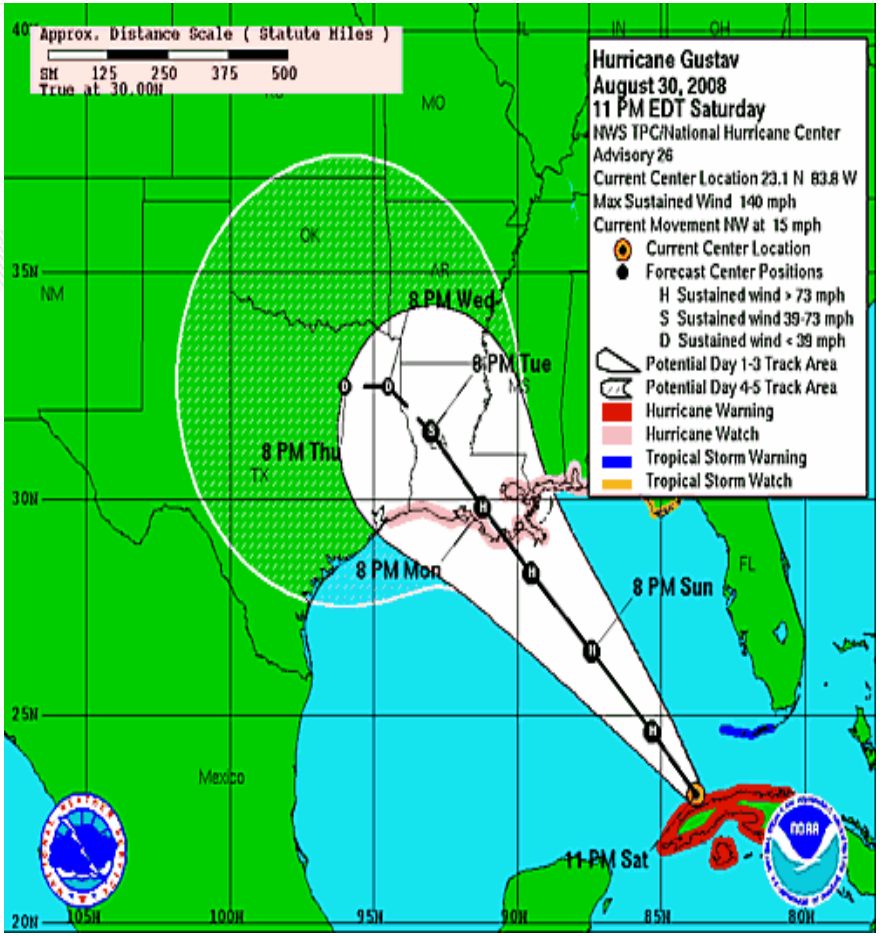
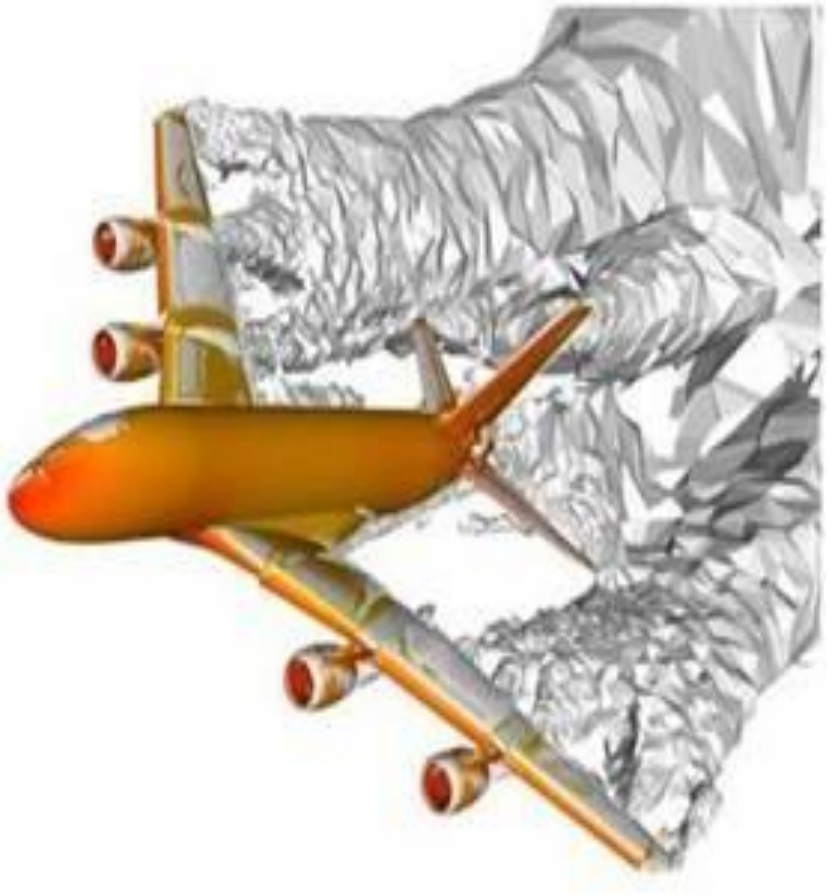
EA Sports

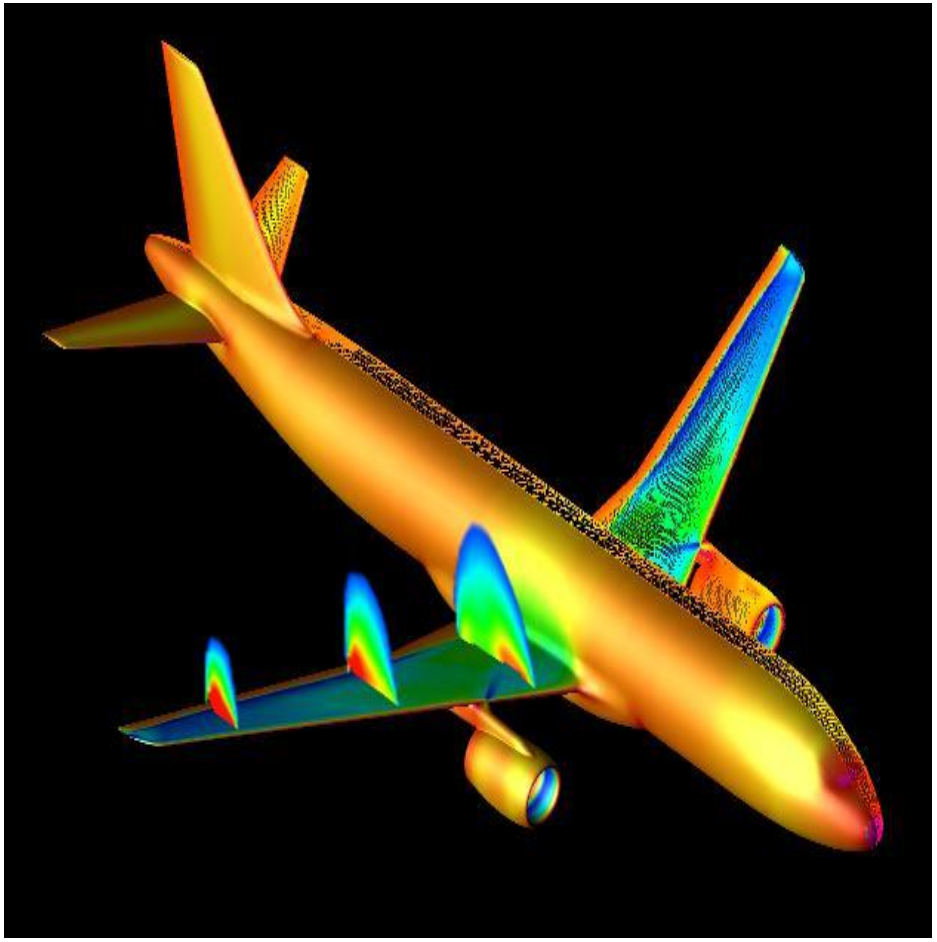


What are Simulations?

- We are inundated with “simulations” being used as *predictions*
- 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*

Building Airplanes?

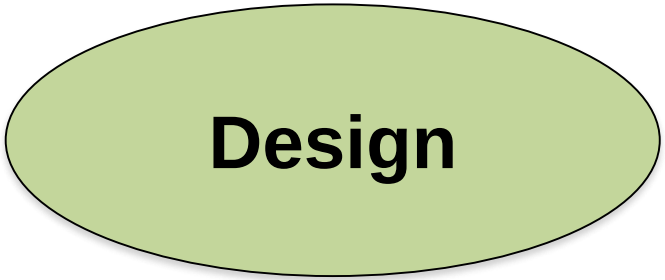




Computer Simulation Design

- We simulate the behavior of a design in order to find its performance on various metrics
- In this way it is a complex mathematical calculation as opposed to a prediction system
- This is *numerical integration*
- Allows fully vetting the design as an instrument to learn about treatment strategies
- Ability to calculate virtually any performance characteristic

In Silico Design



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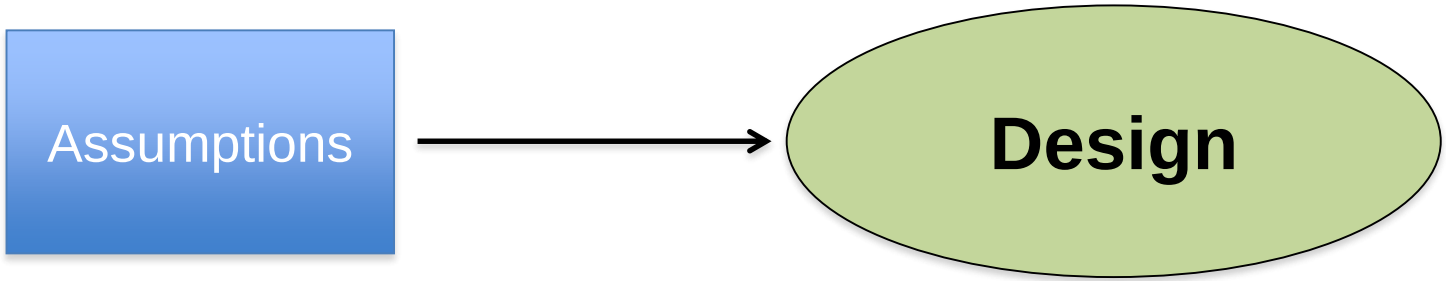

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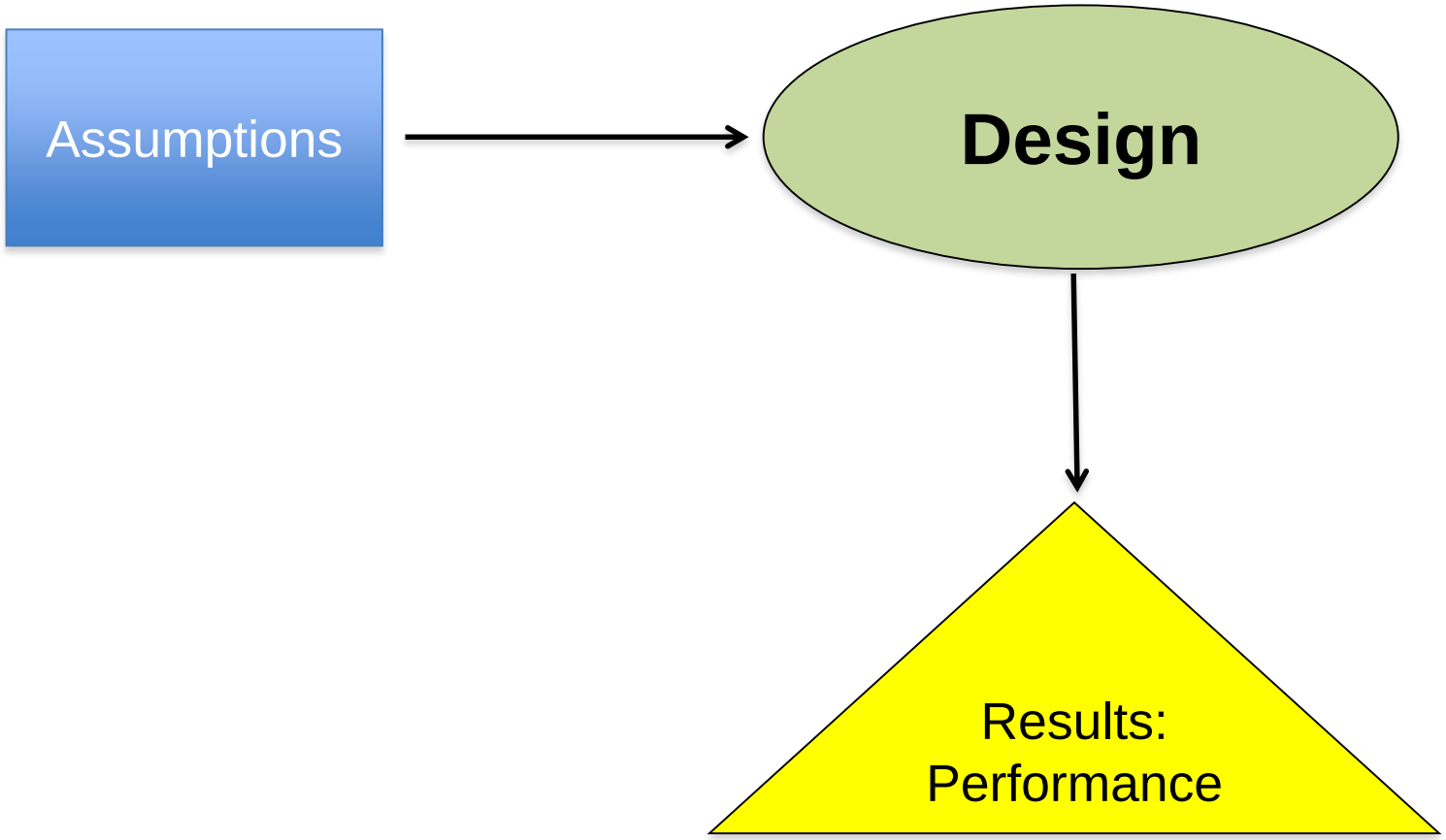

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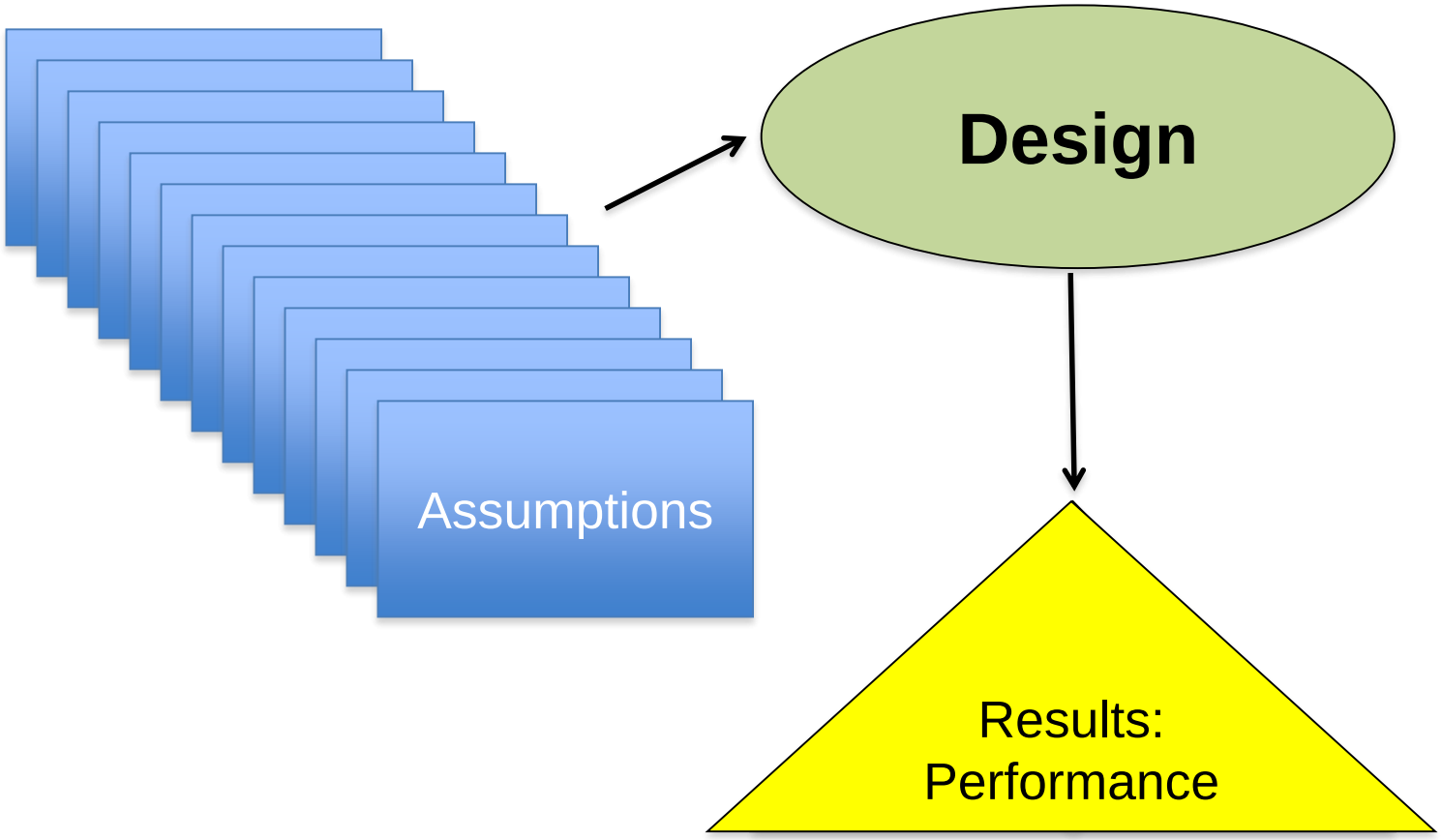

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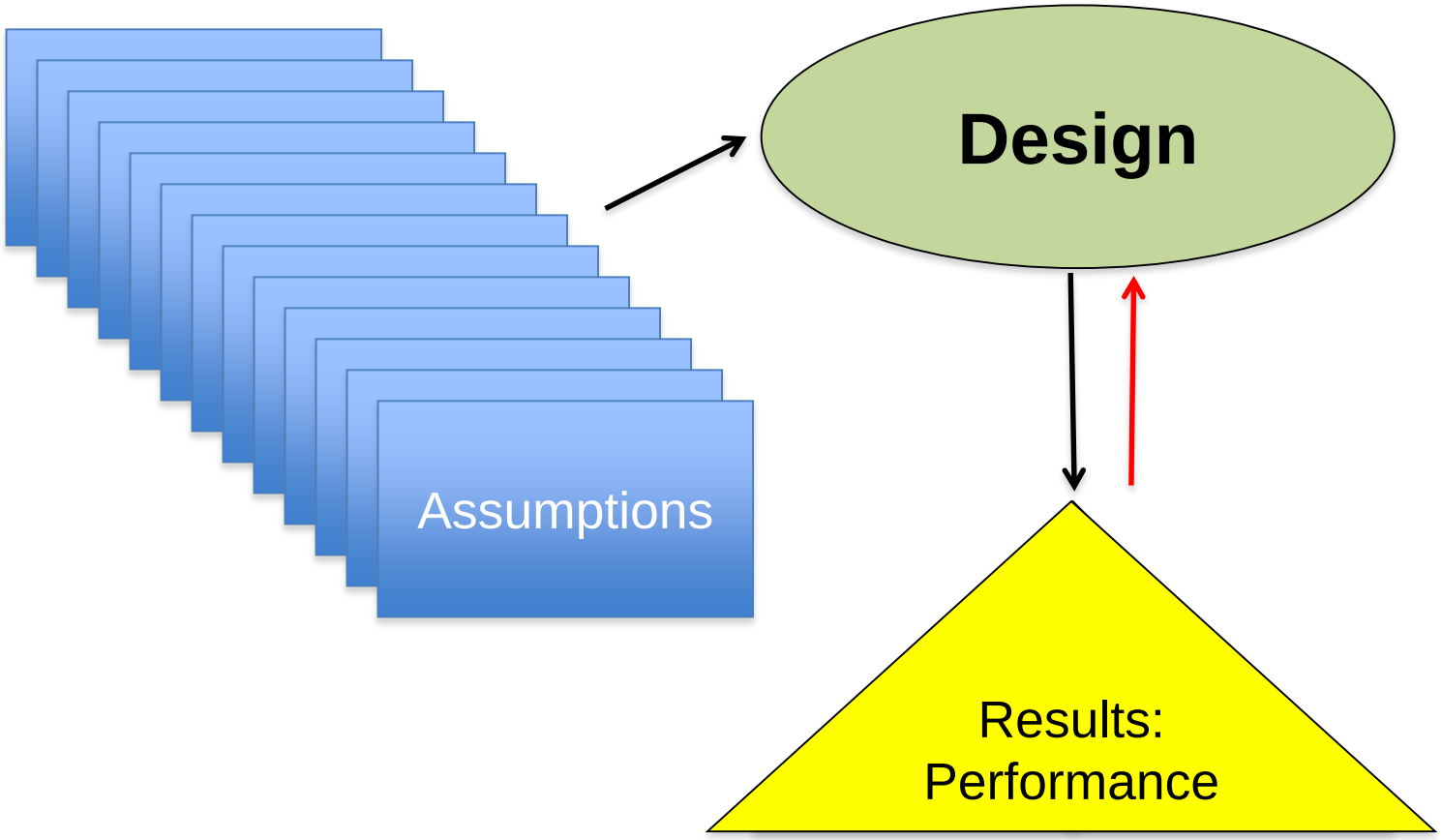
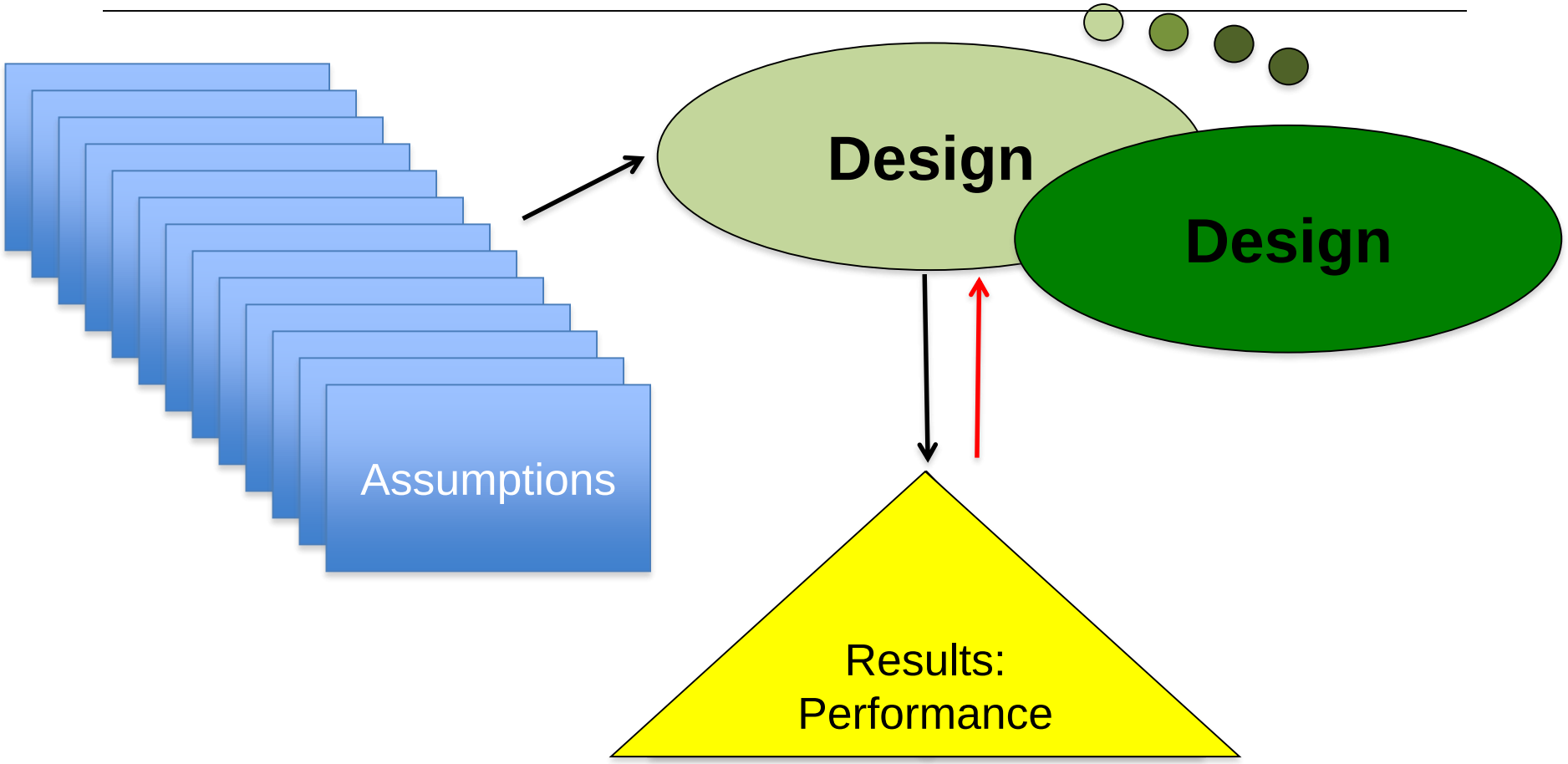


In Silico Design



Exploration & Iteration

- Can compare different designs – or features and measure directly how well it works
- Can vary the possible truths for sensitivity
- Measuring the design's characteristics – not directly trying to *predict outcome*
- Very common that "flight simulating" a design leads to new design – adaptive designs
- We also get to consider how the results will be interpreted and inform clinical practice

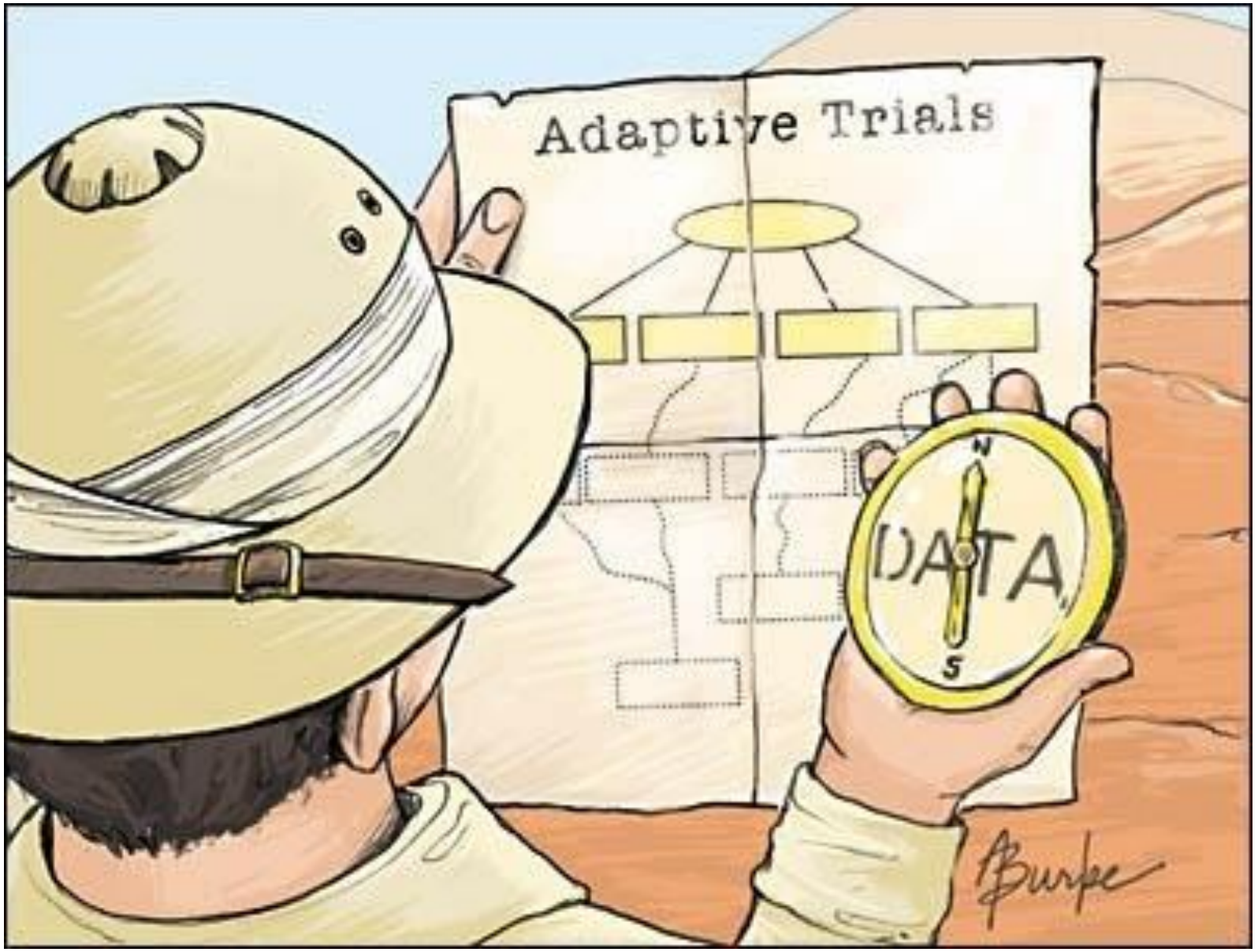
Adaptive Design

Motivation for Adaptive Trials

- When designing a trial there is substantial uncertainty regarding how best to treat subjects in the experimental arm (e.g., uncertainty in optimal dose, best duration, target population)
- This creates uncertainty in the optimal trial design
- Traditionally, all key trial parameters must be defined and held constant during execution
- This leads to increased risk of negative or failed trials, even if a treatment is inherently effective

Motivation for Adaptive Trials

- Once patients are enrolled and their outcomes known, information accumulates that reduces uncertainty regarding optimal treatment approaches
- Adaptive clinical trials are designed to take advantage of this accumulating information, by allowing modification to key trial parameters in response to accumulating information and according to predefined rules

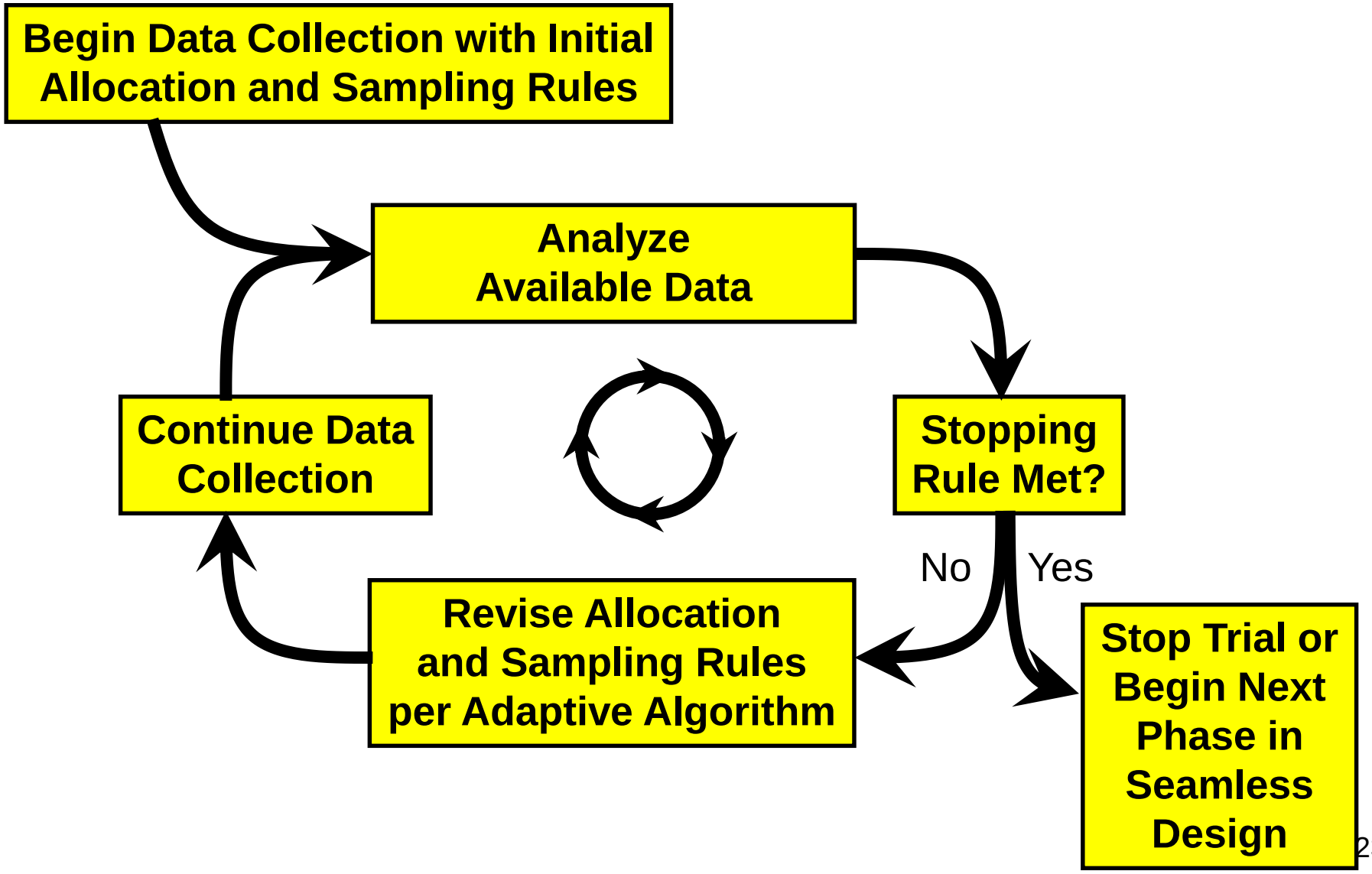


JAMA 2006;296:1955-1957.

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

The Adaptive Process



Why Do Adaptive Clinical Trials?

- Usual Reasons
  - To avoid getting the wrong answer!
  - To avoid taking too long to draw the right conclusion
- In the setting of PCOR
  - To learn about effectiveness, and apply what we learn, simultaneously
  - To continually improve patient outcomes

Selected Adaptive Strategies

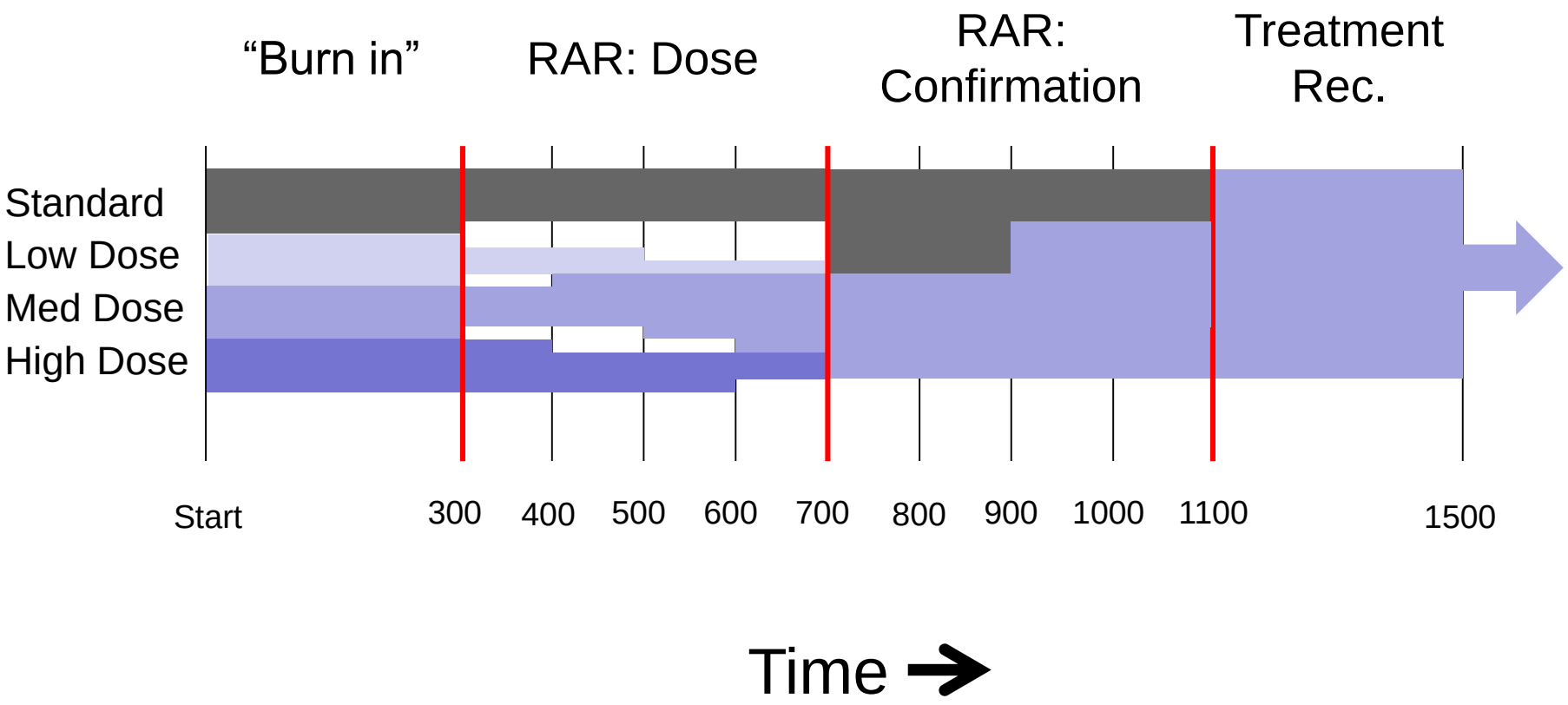
- Frequent interim analyses
- Response-adaptive randomization to efficiently address one or more trial goals
- Explicit decision rules based on Bayesian predictive probabilities at each interim analysis
- Enrichment designs
- Longitudinal modelling
- Extensive simulations of trial performance


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

Response-adaptive Randomization

- **Response-adaptive randomization** to improve important trial characteristics
- May be used to address one or more of:
  - To improve subject outcomes by preferentially randomizing patients to the better performing arm
  - To improve the efficiency of estimation by preferentially assigning patients to doses in a manner that increases statistical efficiency
  - To improve the efficiency in addressing multiple hypotheses by randomizing patients in a way that emphasizes sequential goals
  - Includes arm dropping

Example Learning Strategy



Adaptive Clinical Trials

A Partial Remedy for the Therapeutic Misconception?

William J. Meurer, MD, MS
Roger J. Lewis, MD, PhD
Donald A. Berry, PhD

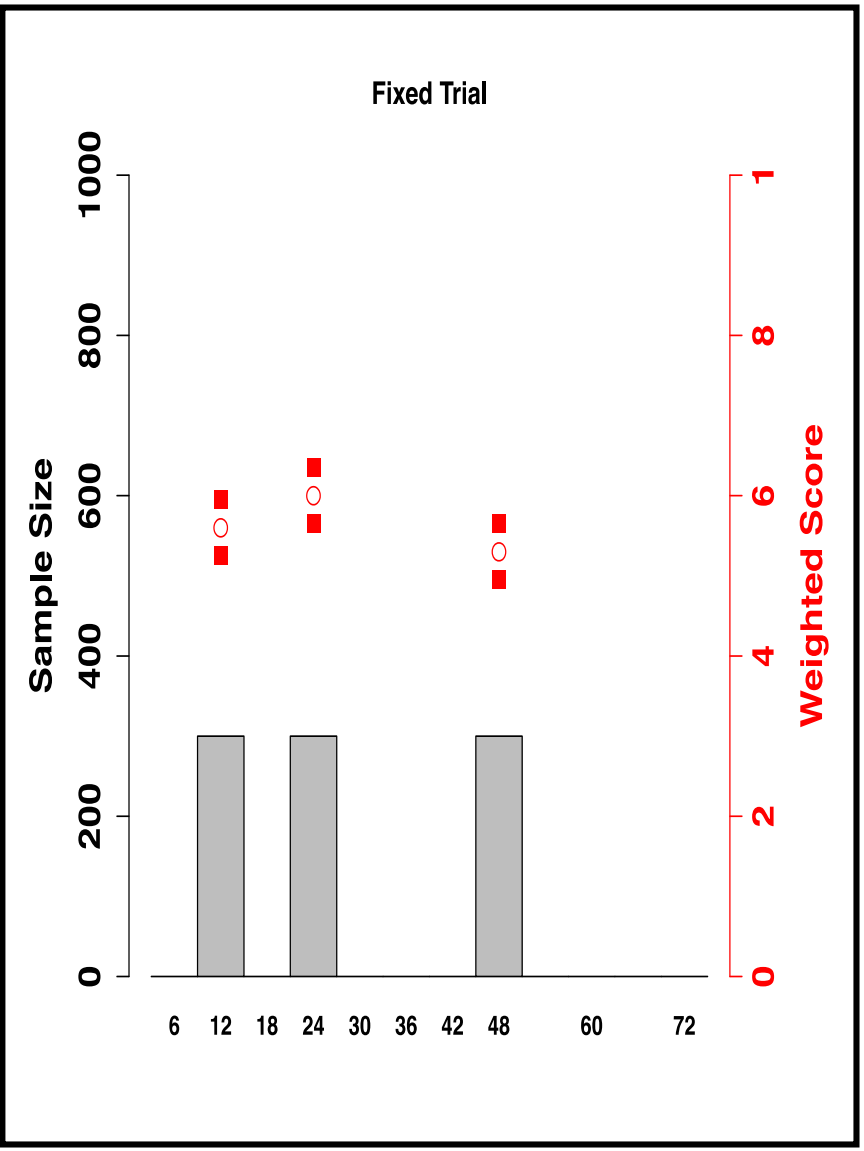
THERE IS A COMMON "THERAPEUTIC MISCONCEPTION" among patients considering participation in clinical trials.[1] Some trial participants and family members believe that the goal of a clinical trial is to improve their outcomes—a misperception often reinforced by media advertising of clinical research.[2] Clinical trials have primarily scientific aims and rarely attempt to collectively improve the outcomes of their participants. The overarching goal of most clinical trials is to evaluate the effect of a treatment on disease outcomes.[3] Comparisons are usually

Although knowledge regarding the relative effectiveness of the treatments involved accumulates over the course of a clinical trial, beginning with a state of equipoise and having high confidence near the end, fixed assignment ensures that this information is ignored. The result is that a fixed proportion of patients will receive potentially inferior therapy—whichever therapy that turns out to be—assuming there are differences in efficacy of the treatments in the trial. The primary scientific goal of a clinical trial should not be compromised, but interim information available in a trial could be used to improve the outcomes of trial participants, especially those who enroll later in the trial. Using accumulating information can increase the probability, but not guarantee, that future trial participants are assigned to the study group with a better expected outcome

ICECAP

- ICECAP – Hypothermia for coma after cardiac arrest coma
  - Background
    - Two small surface cooling trials demonstrated efficacy
    - Medically accepted that this works
    - No FDA approval
  - Goals
    - To identify optimum cooling duration
    - Gain additional insight into efficacy (functional form of duration response model)
    - What types of subject (rhythm types) vs. duration
  - Fixed Design:
    - 400 On 12, 24, 48 hours cooling

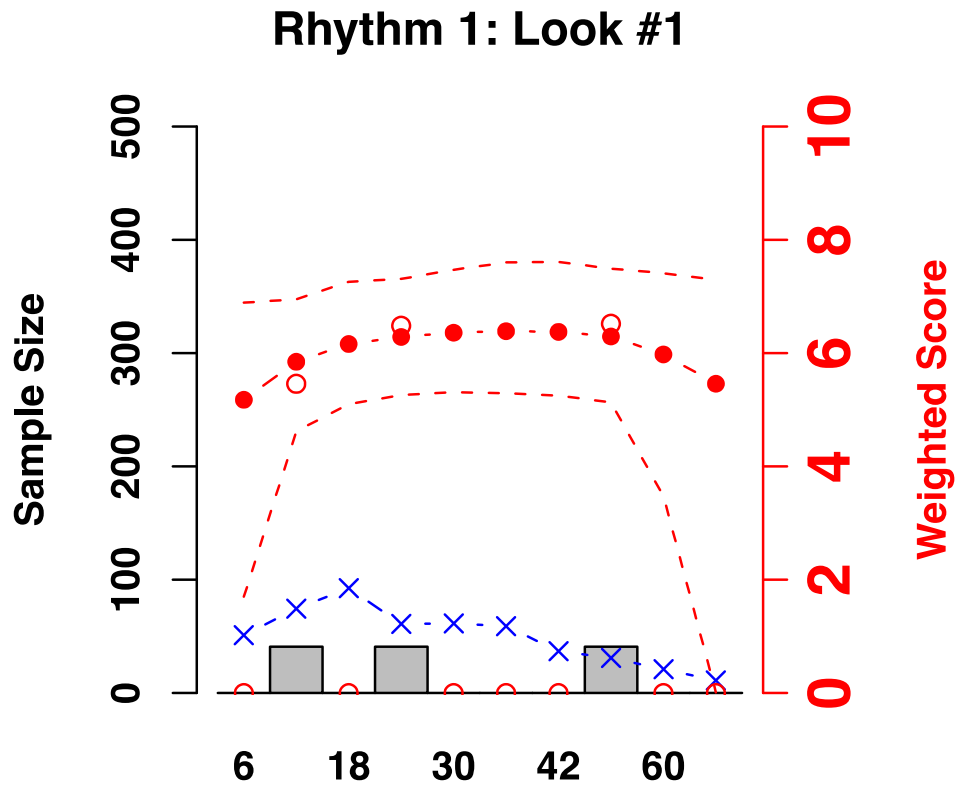
Building Complex Trial



- For most simulated trials great “regret”
- Ideal result here?
  - Flat then negative?
  - Sloping up, 24 best, then slopes down?
  - 36 optimal?
  - Flat?

ICECAP

- 10 durations of cooling
  - 6, **12**, 18, **24**, 30, 36, 42, **48**, 60, 72
- RAR over durations
  - 2 subgroups (shockable, non-shockable)
- Final analysis of positive duration-response
- Optimal Duration?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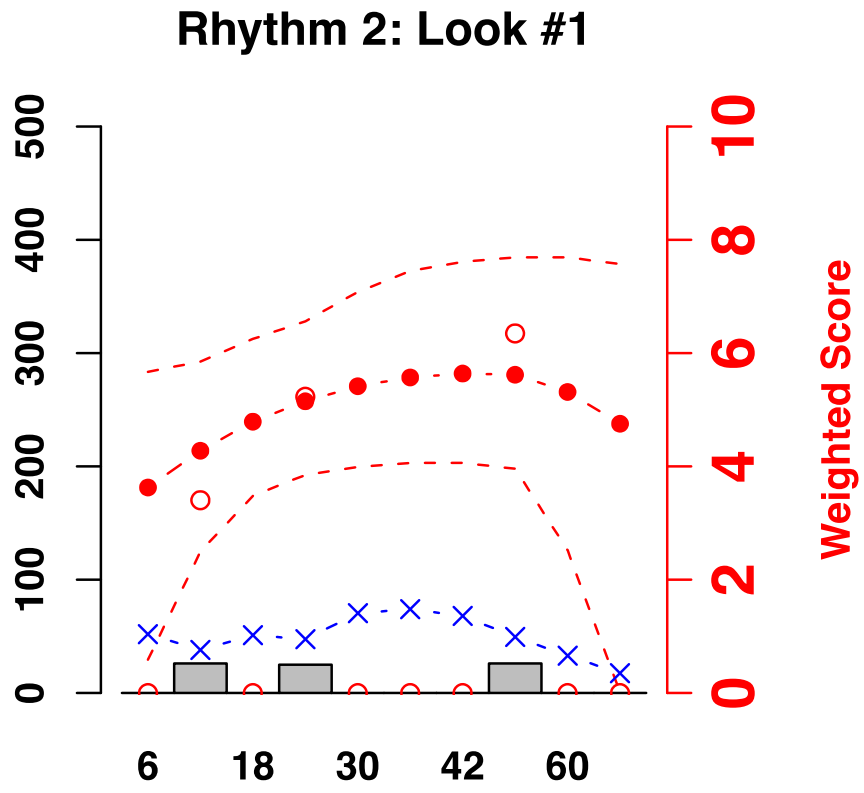
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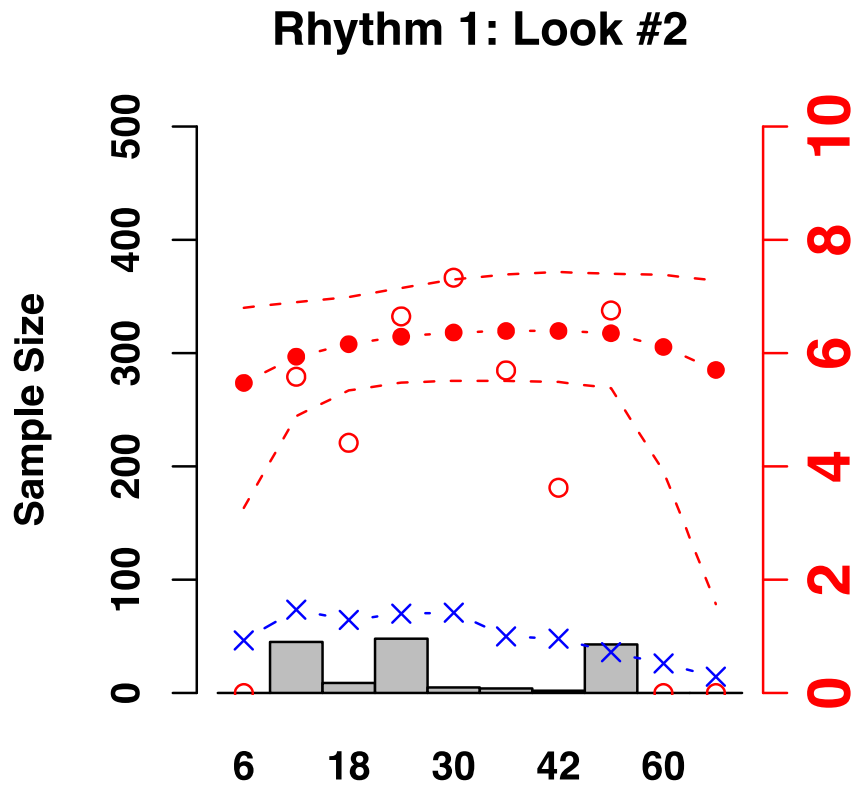
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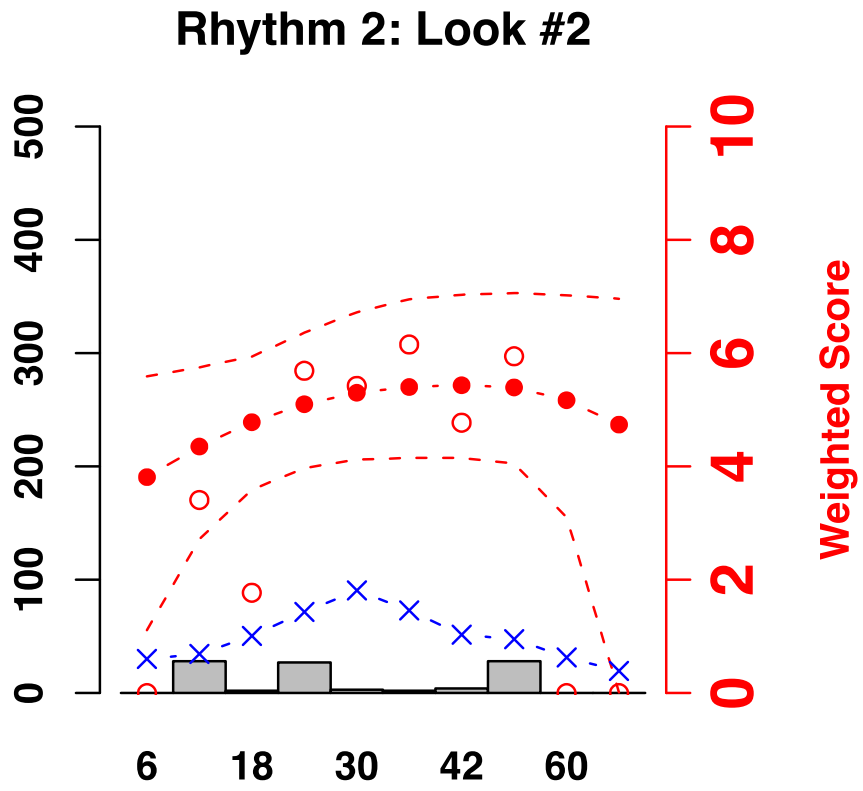
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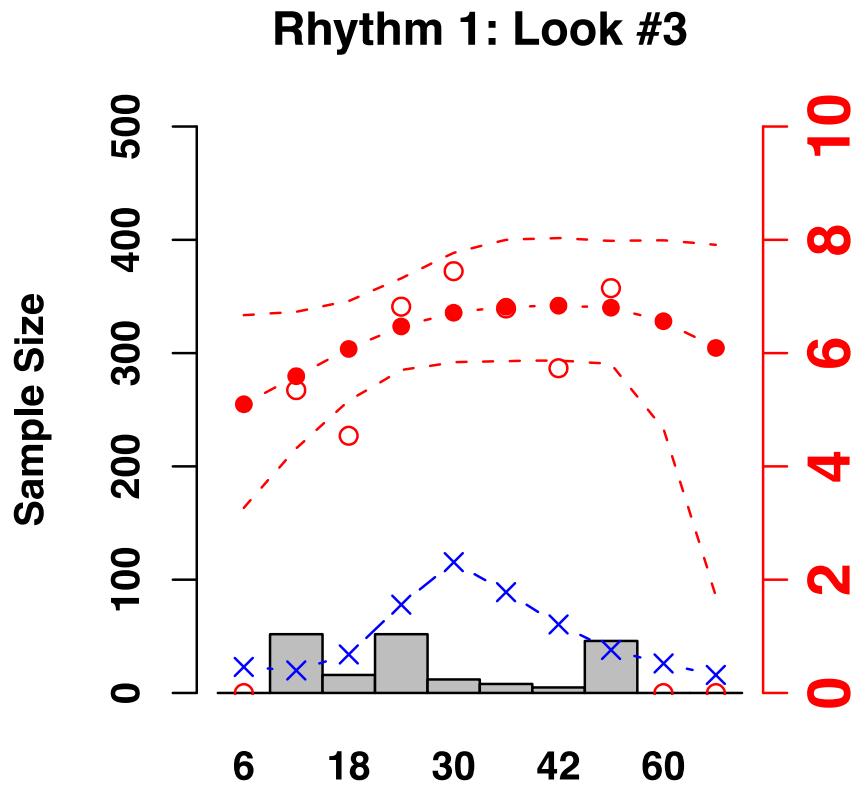
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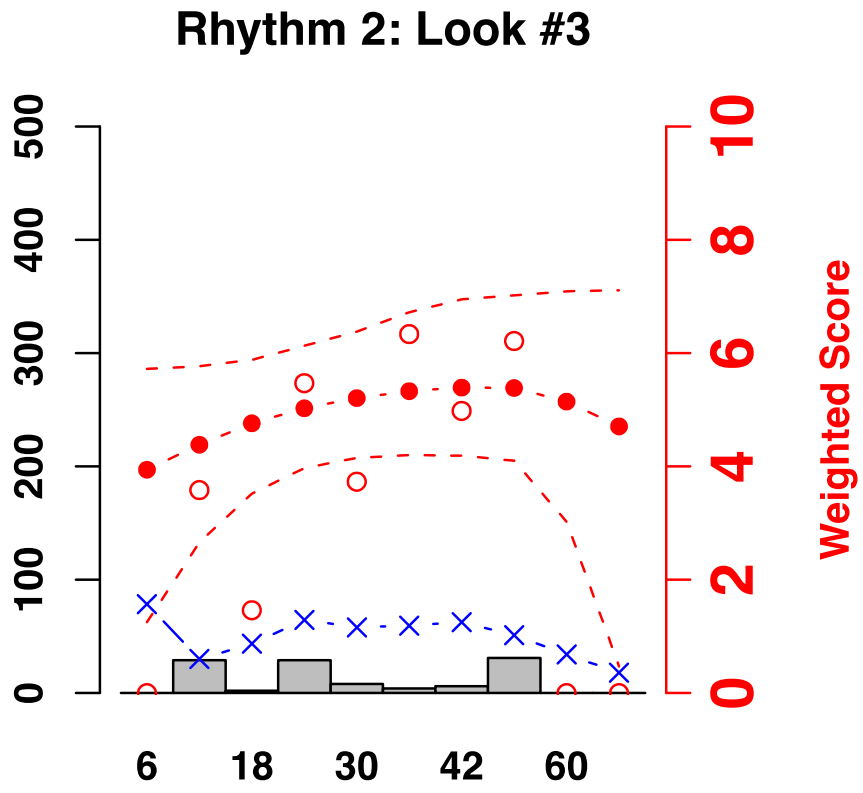
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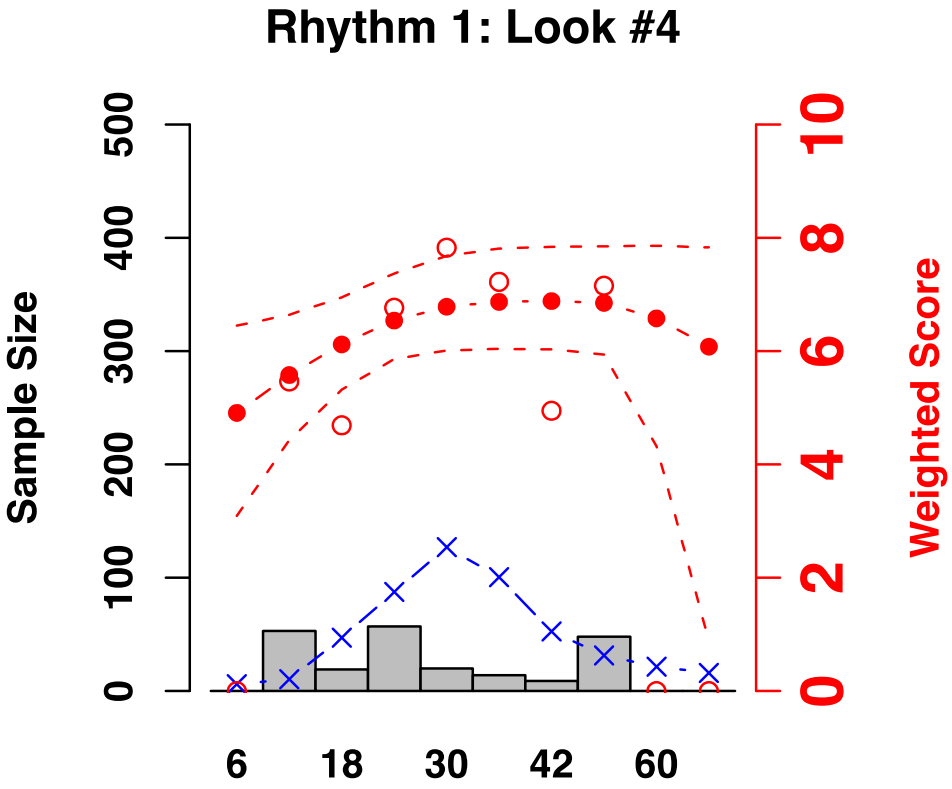
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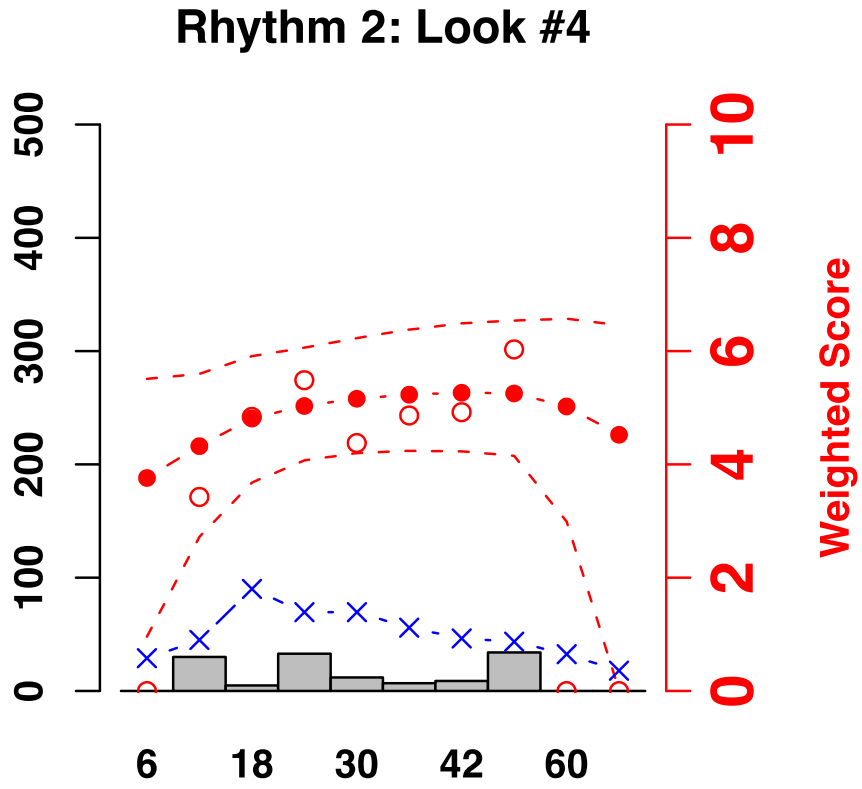
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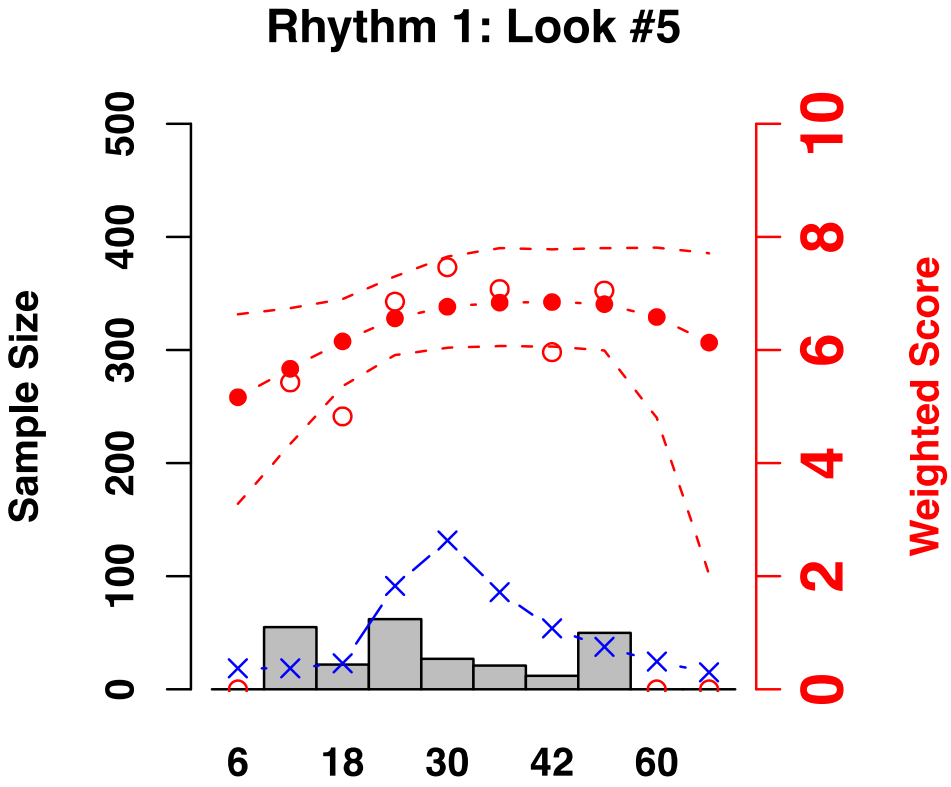
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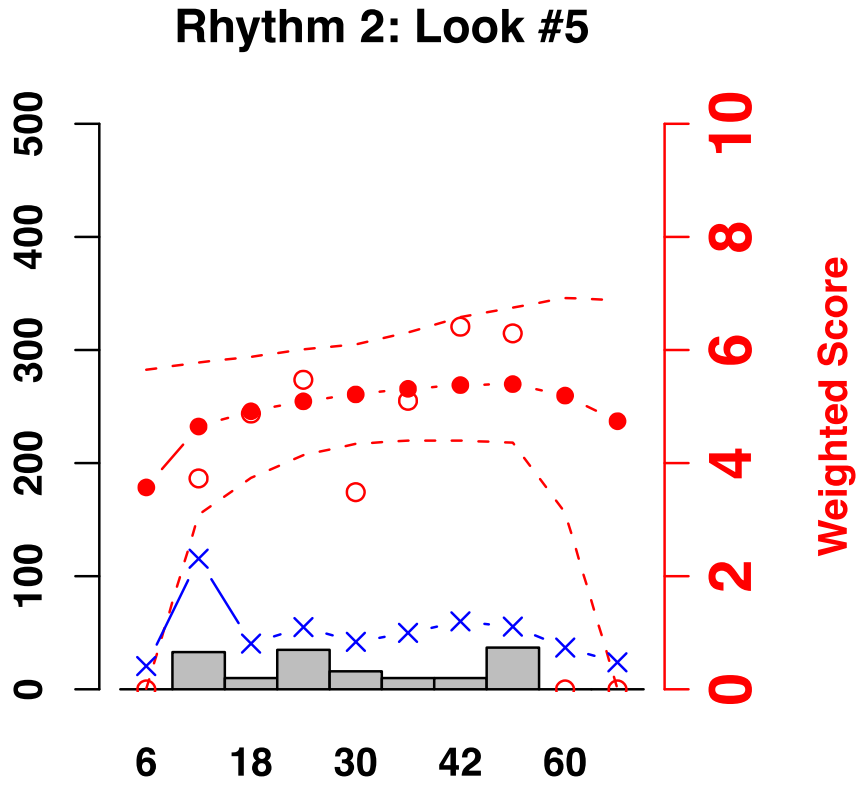
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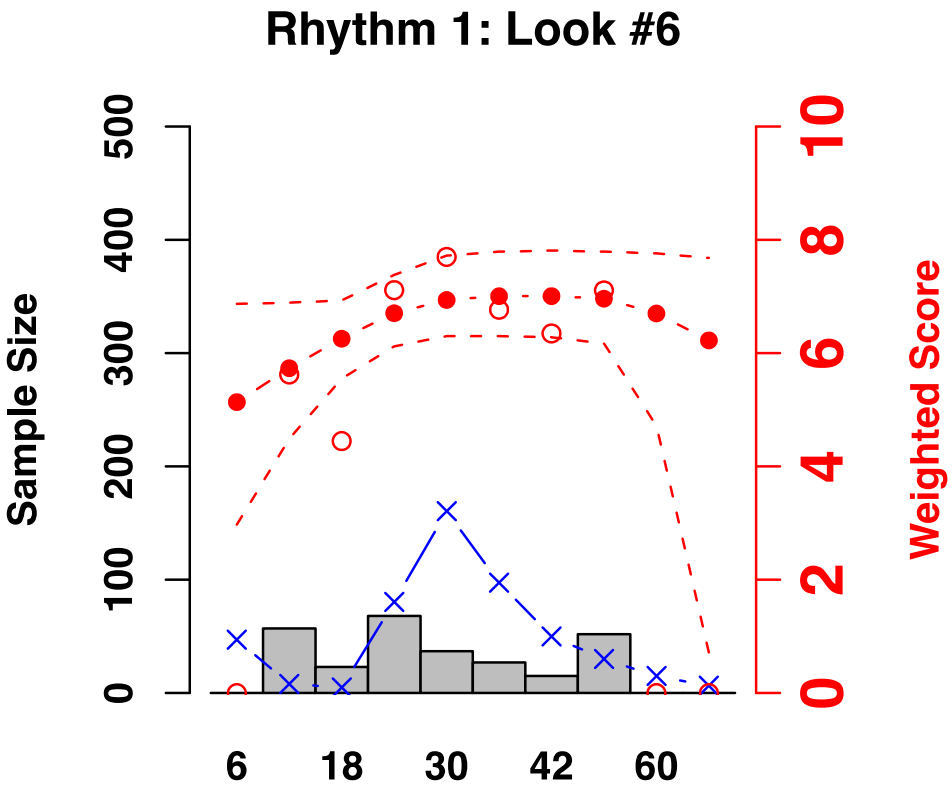
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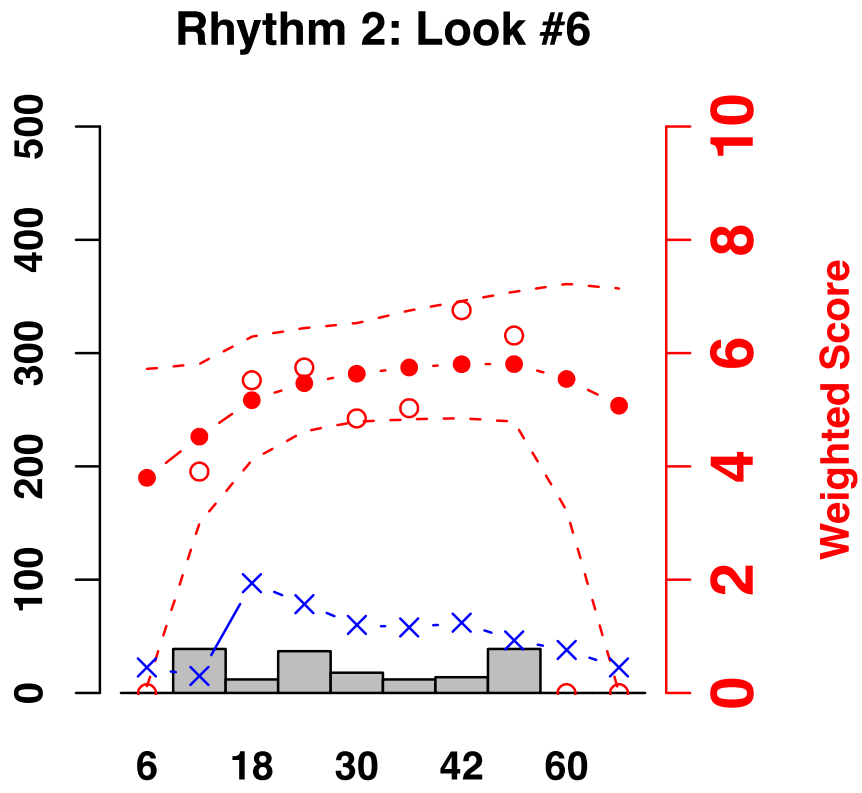
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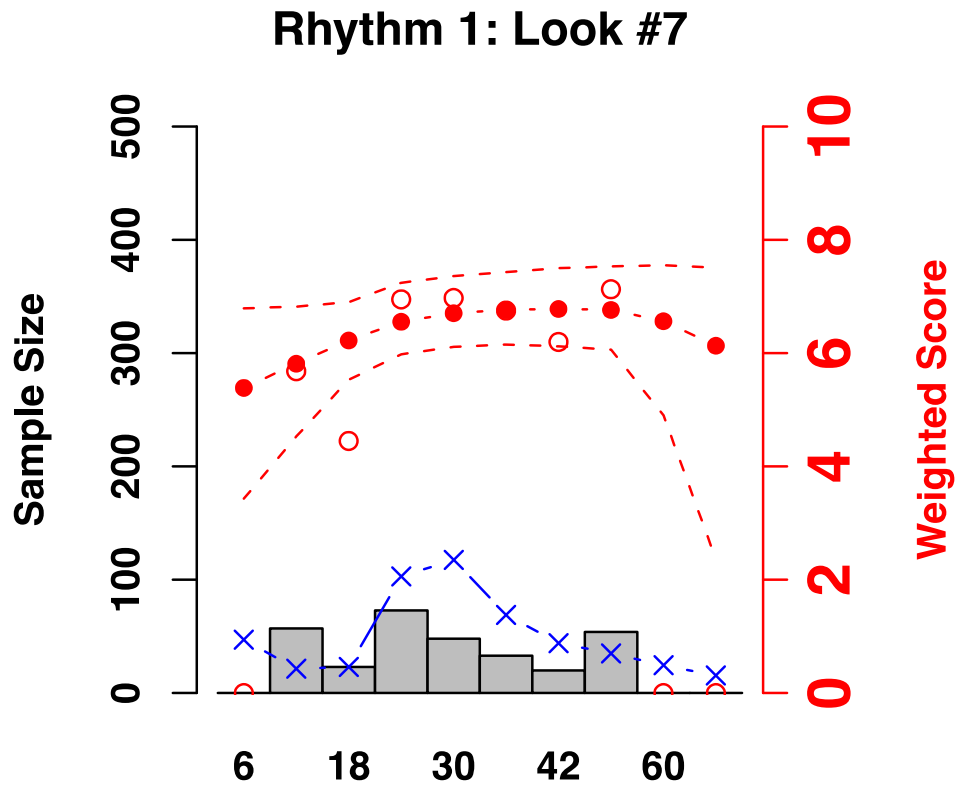
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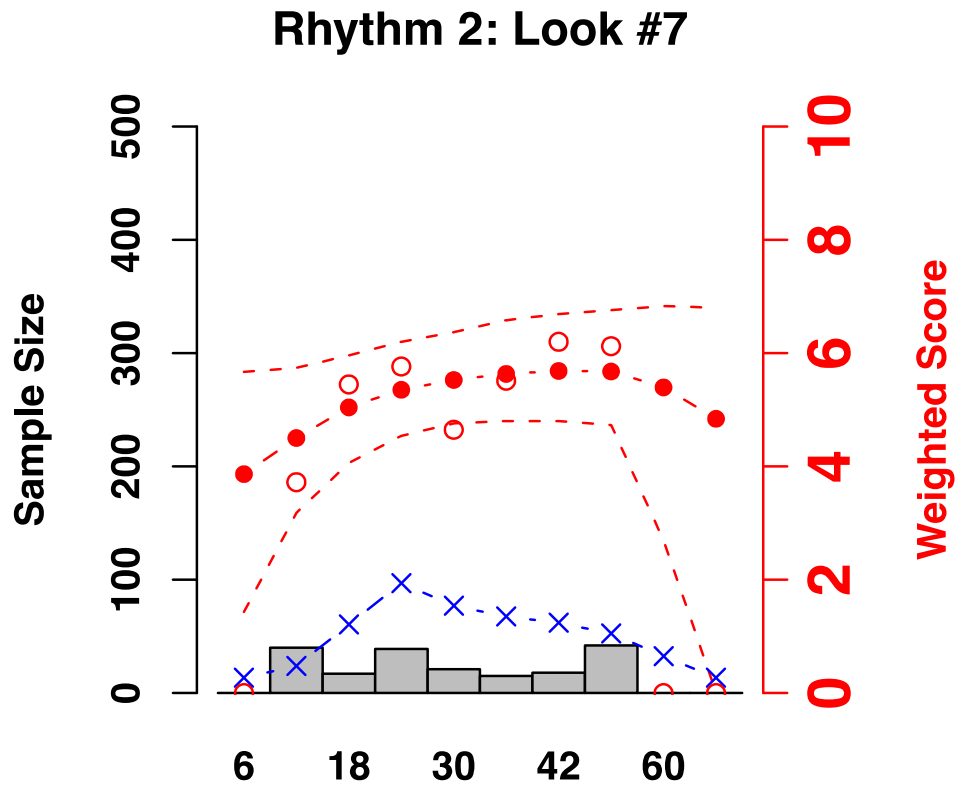
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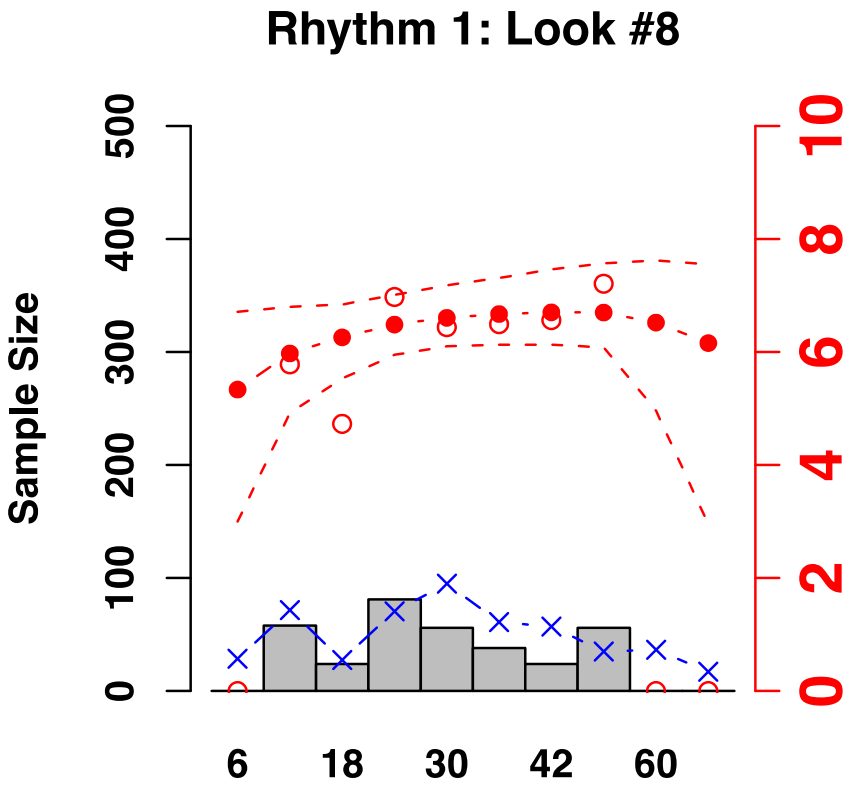
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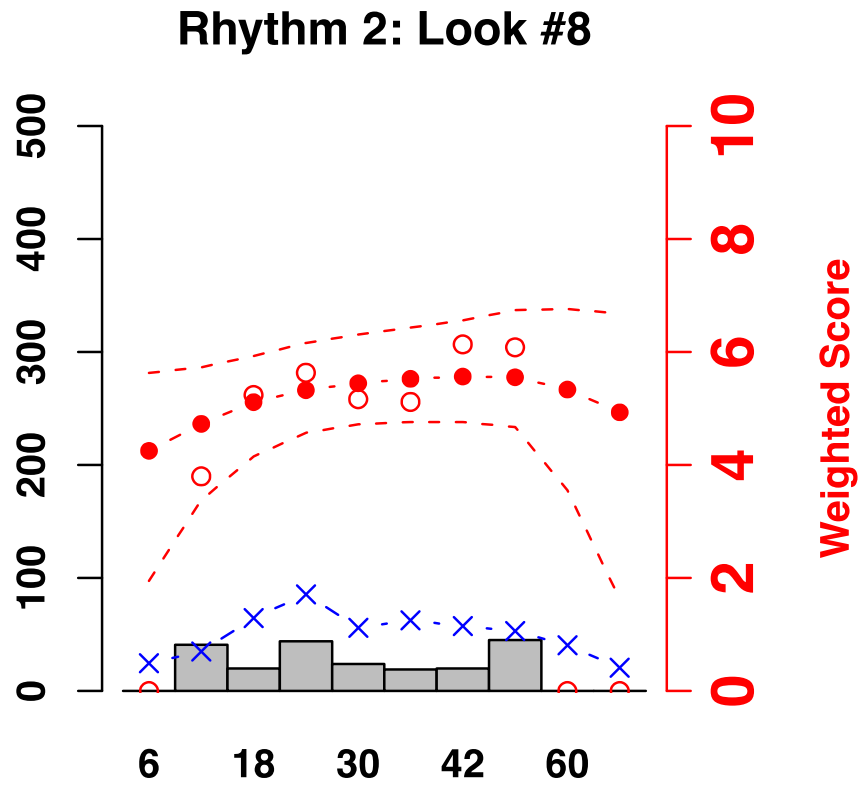
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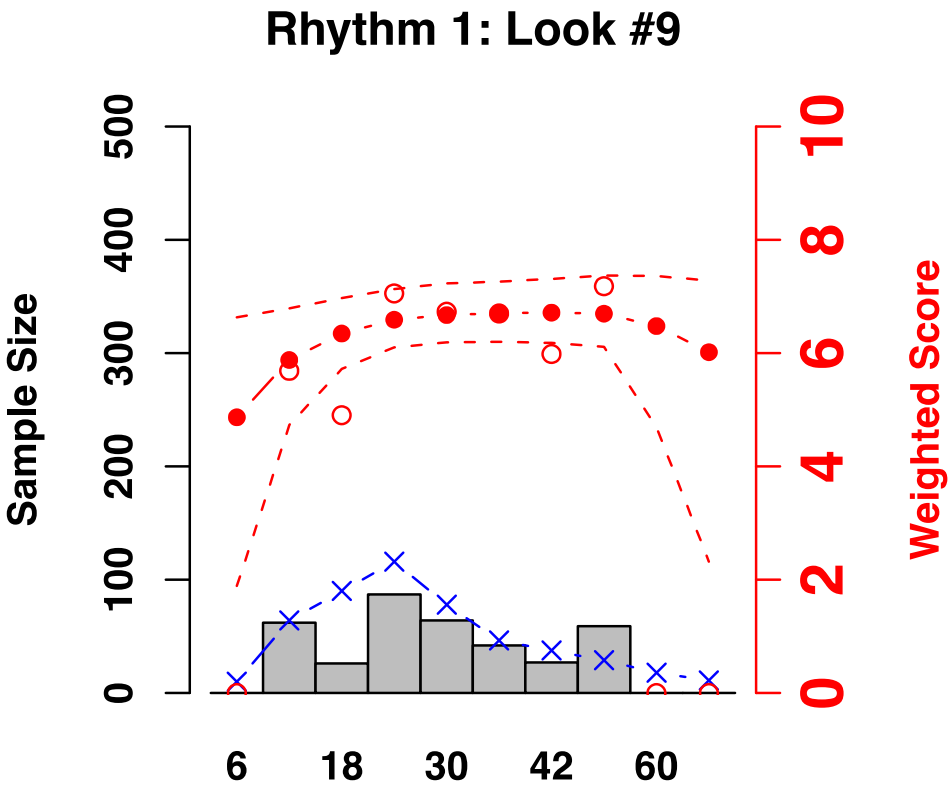
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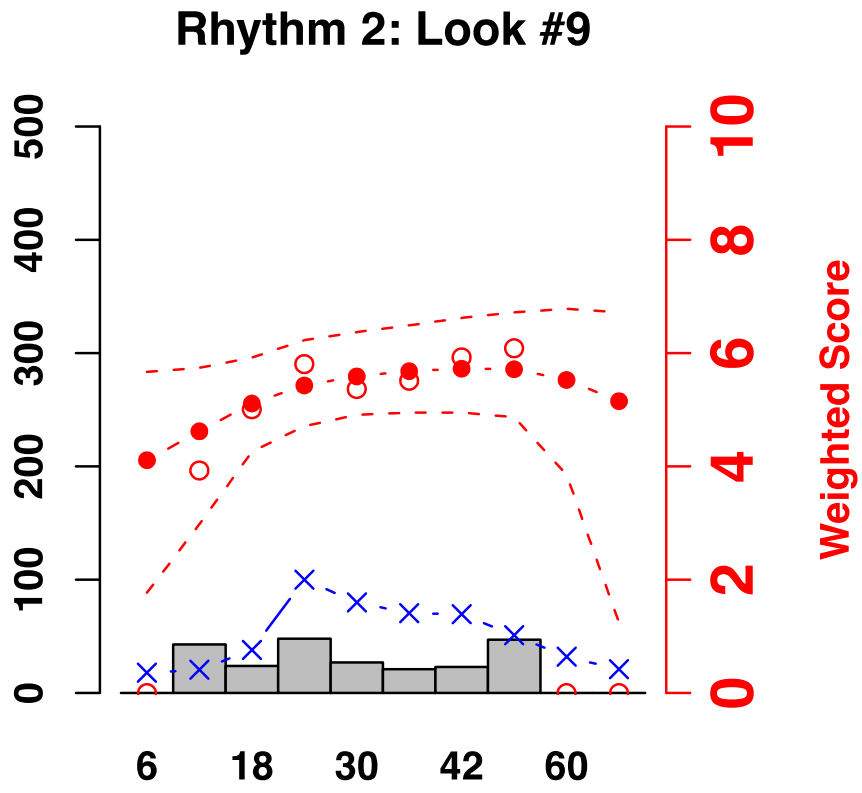
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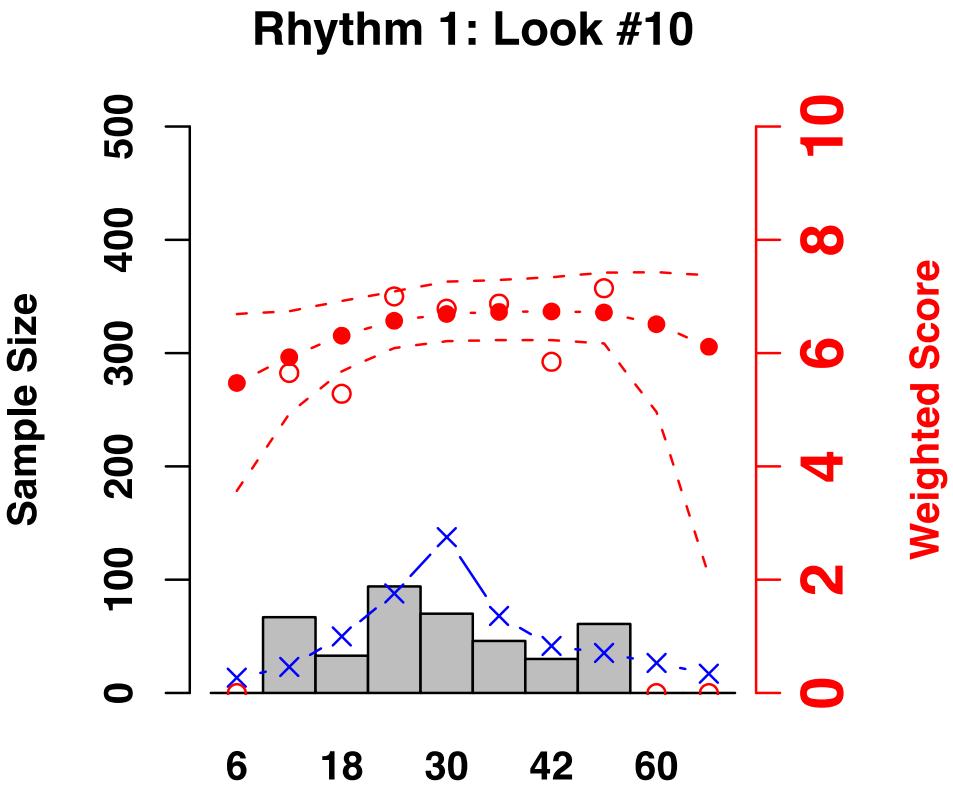
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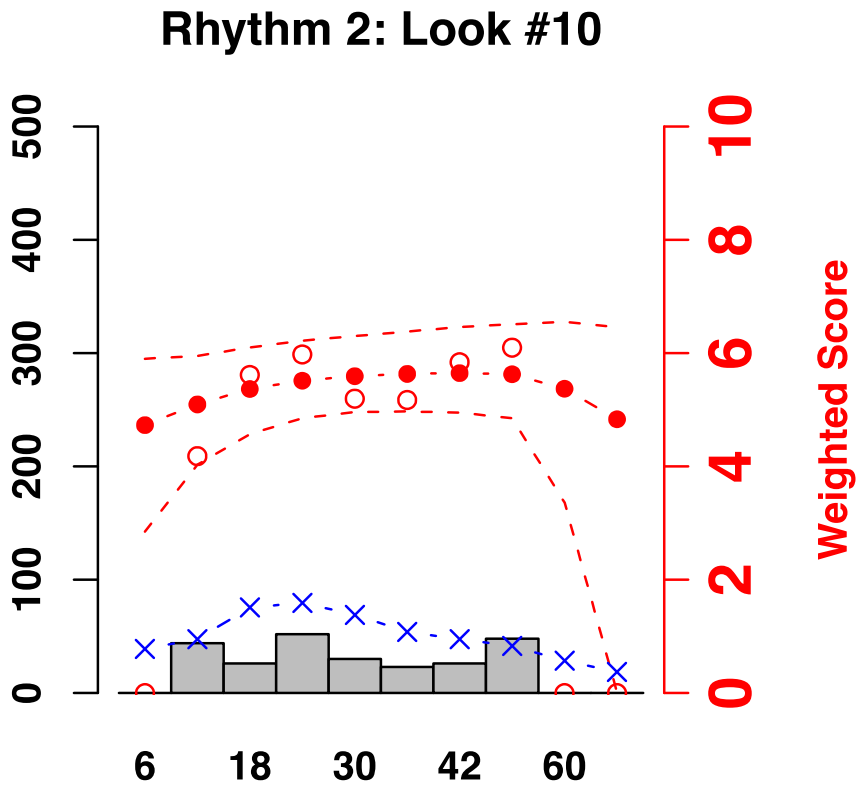
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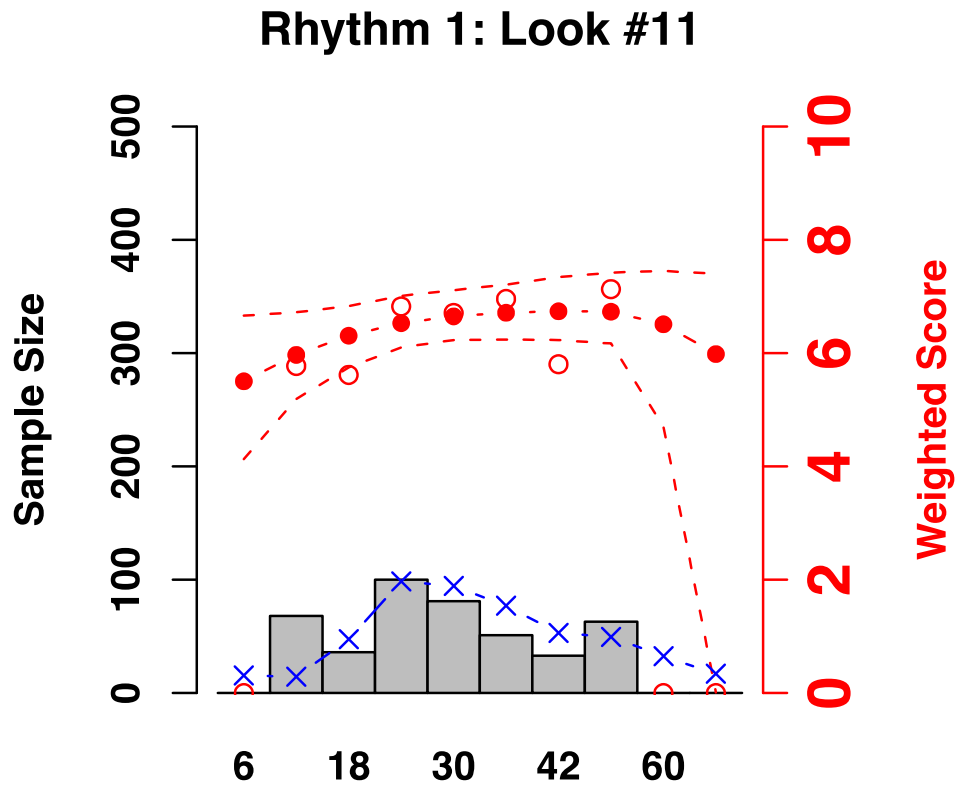
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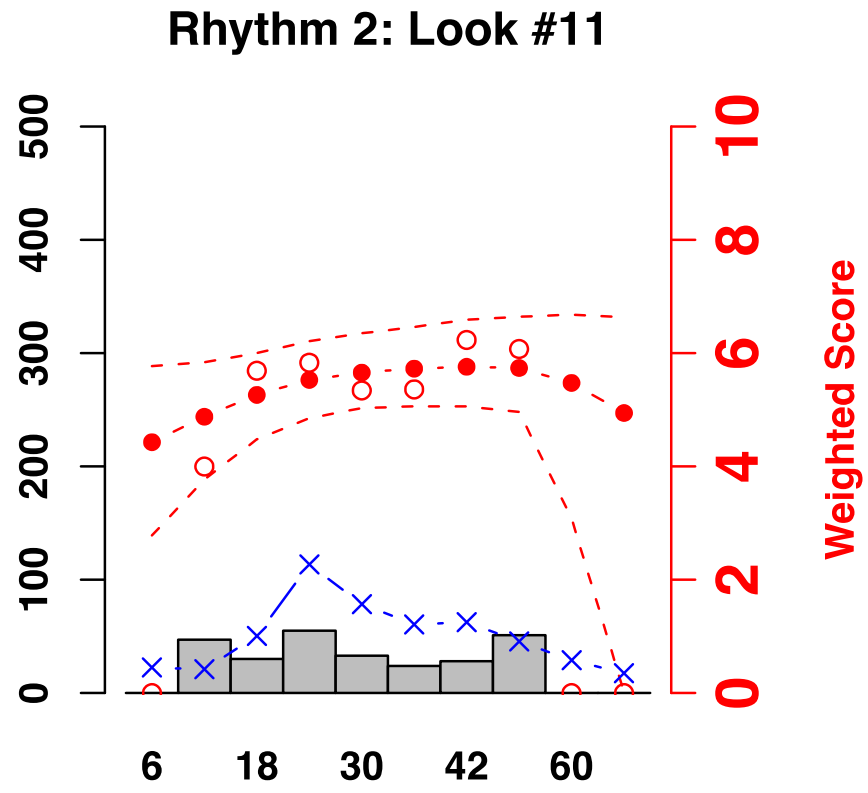
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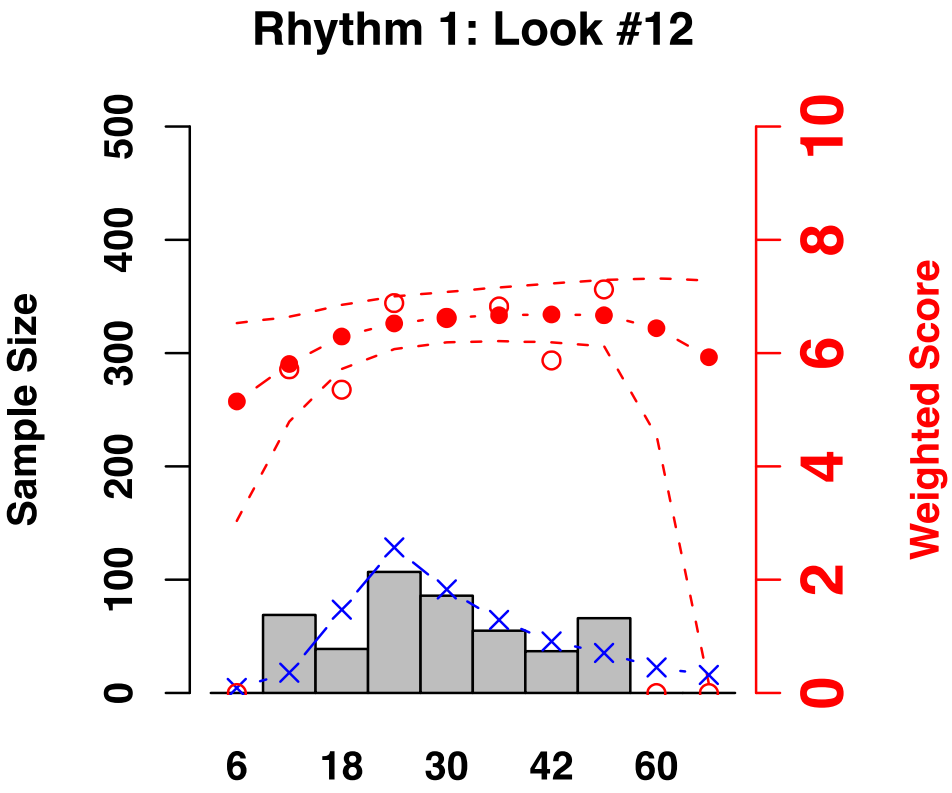
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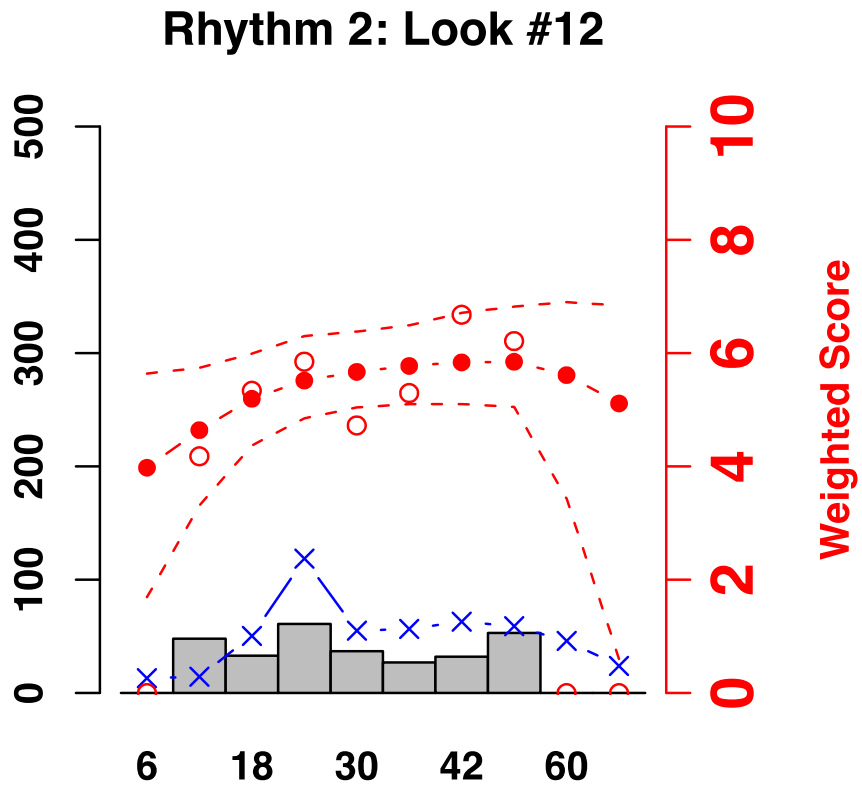
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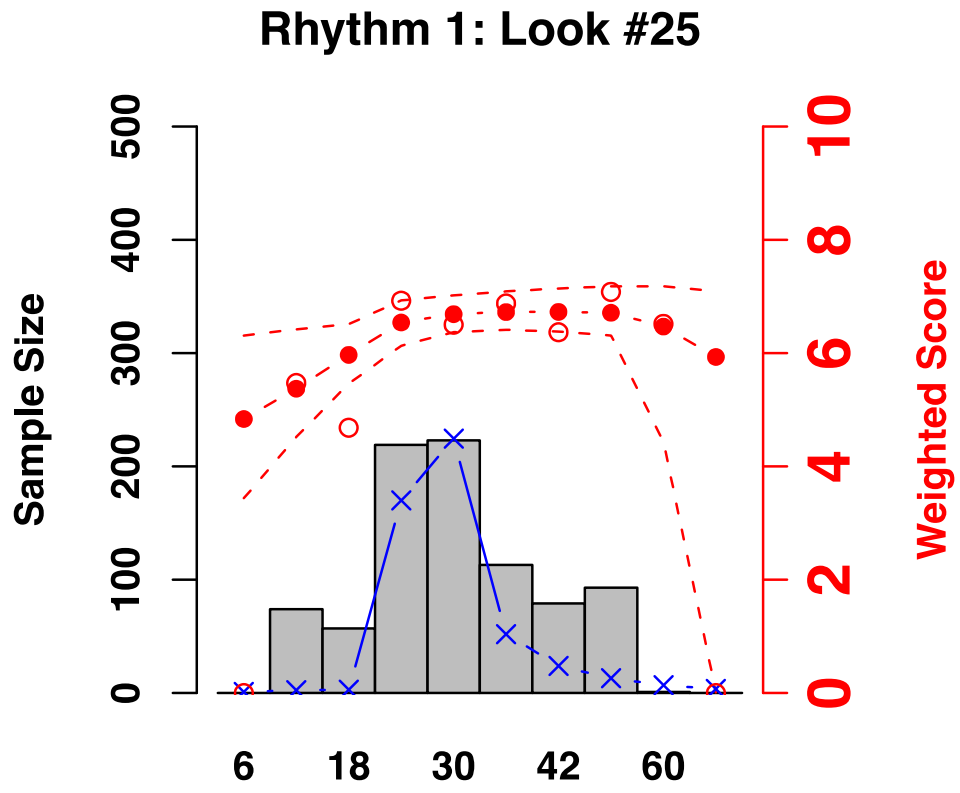
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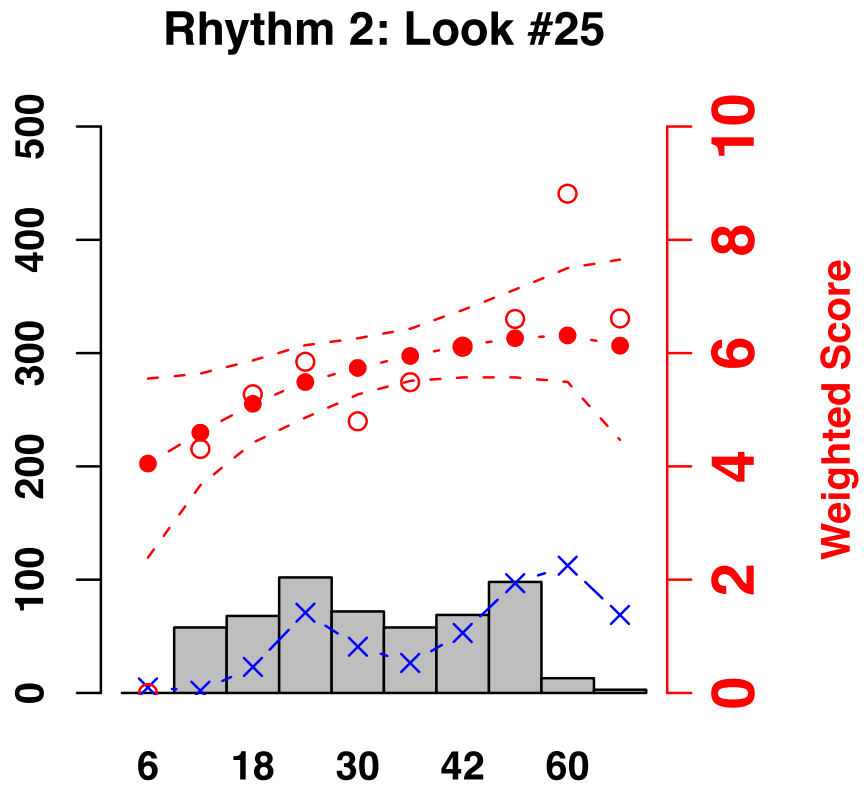
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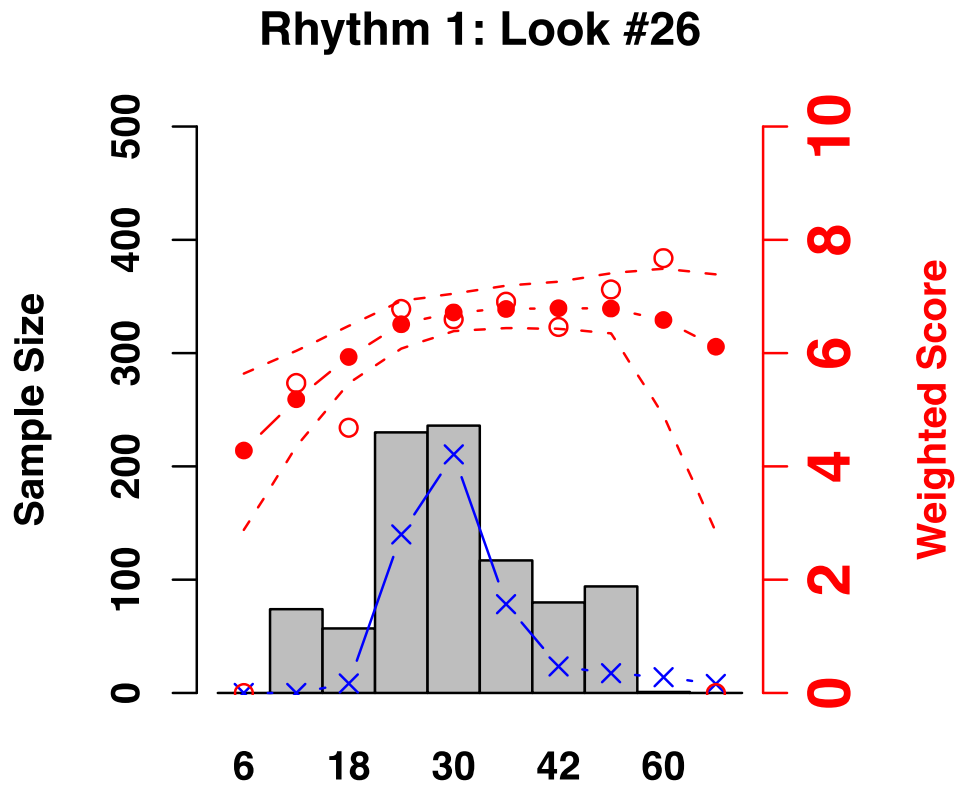
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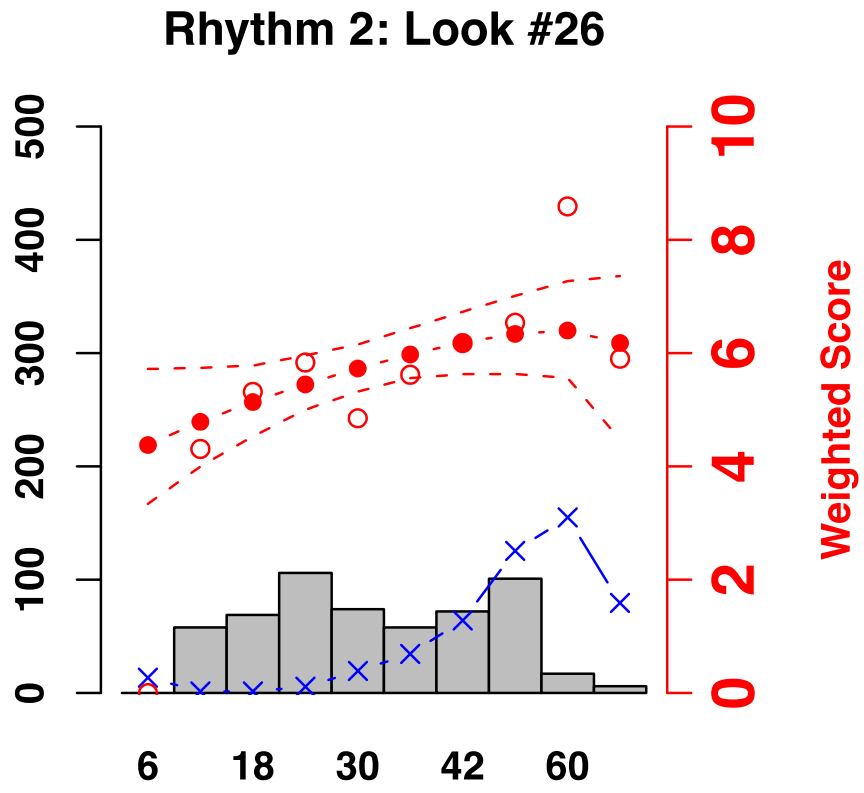
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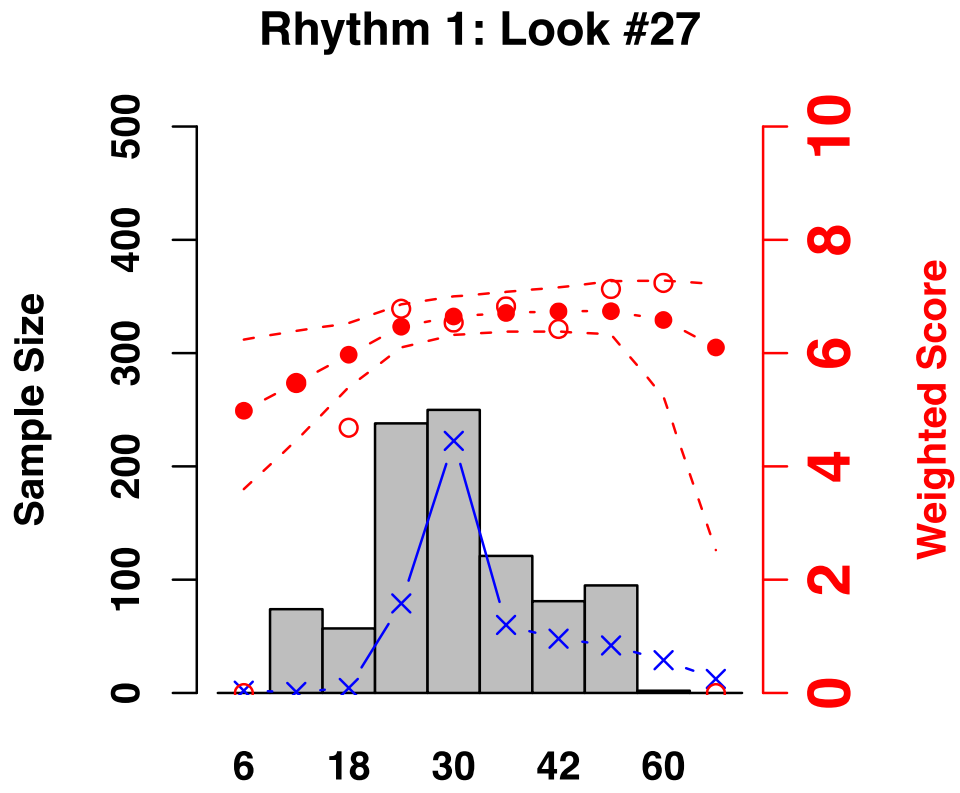
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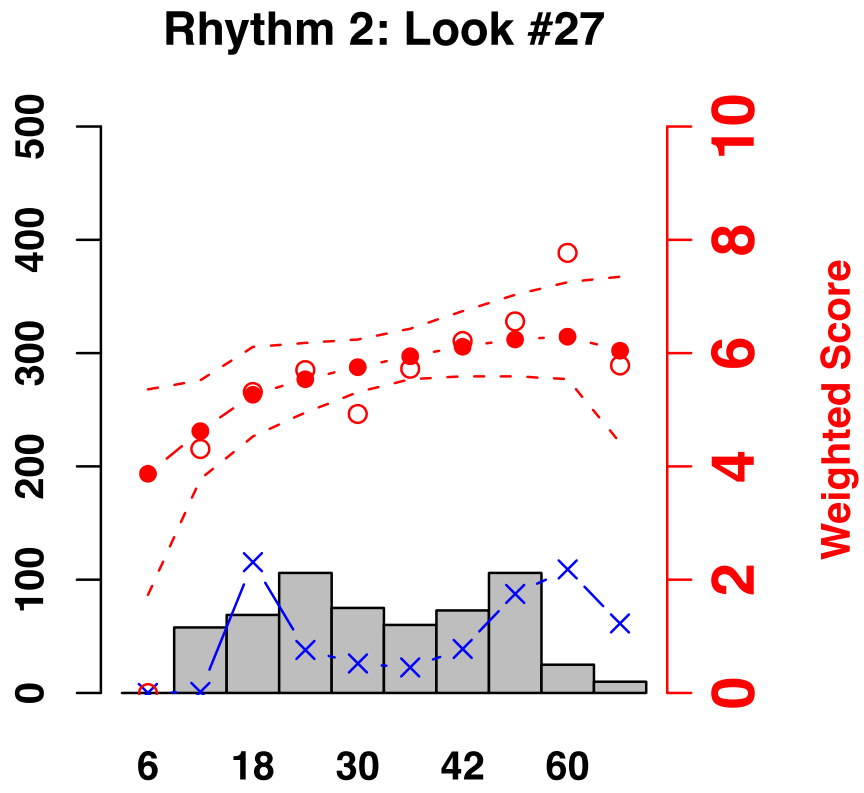
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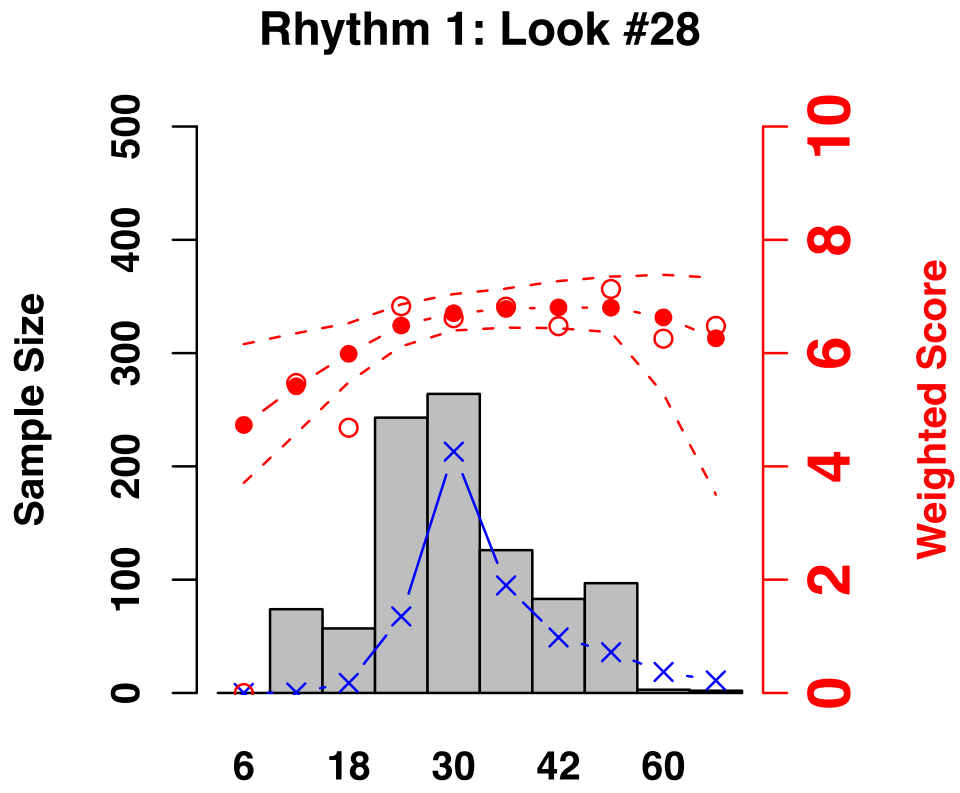
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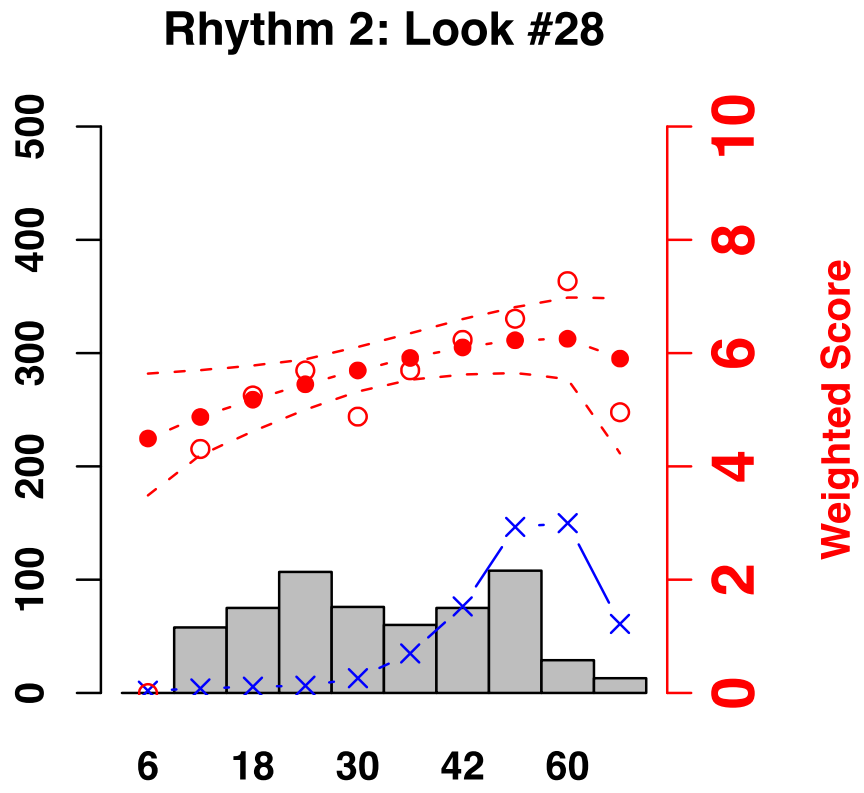
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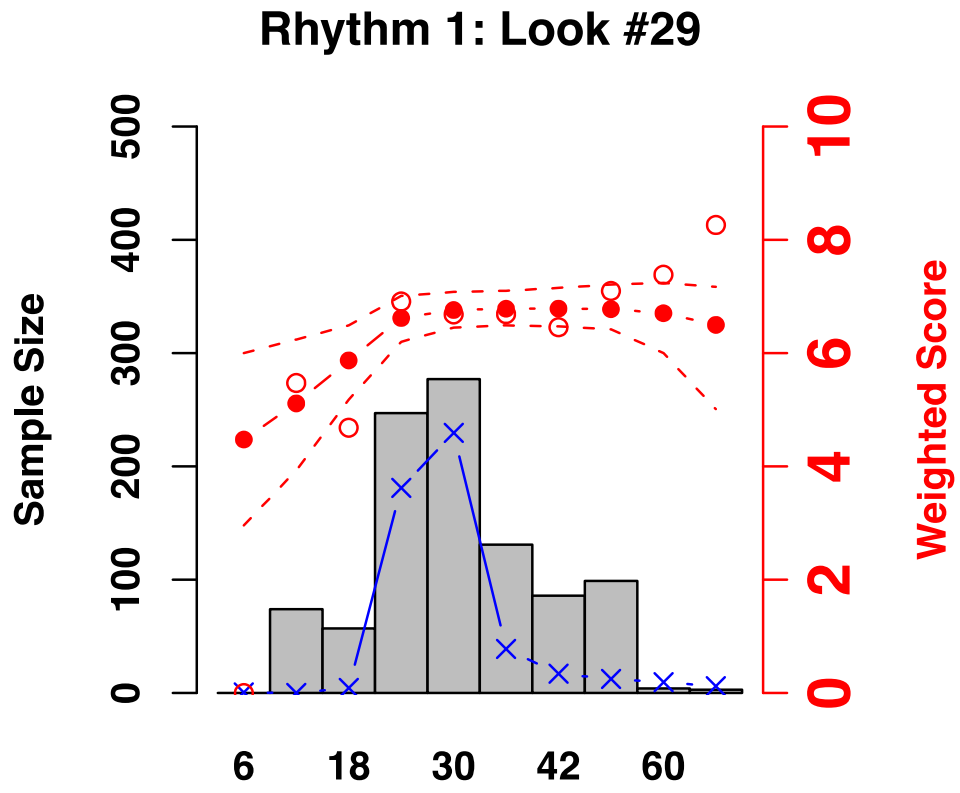
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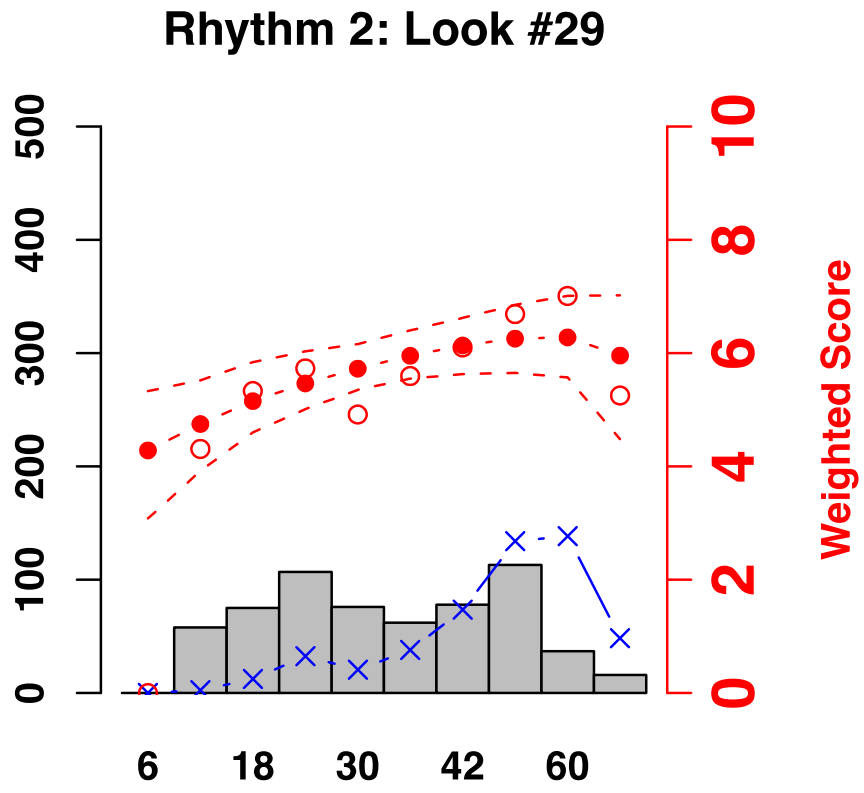
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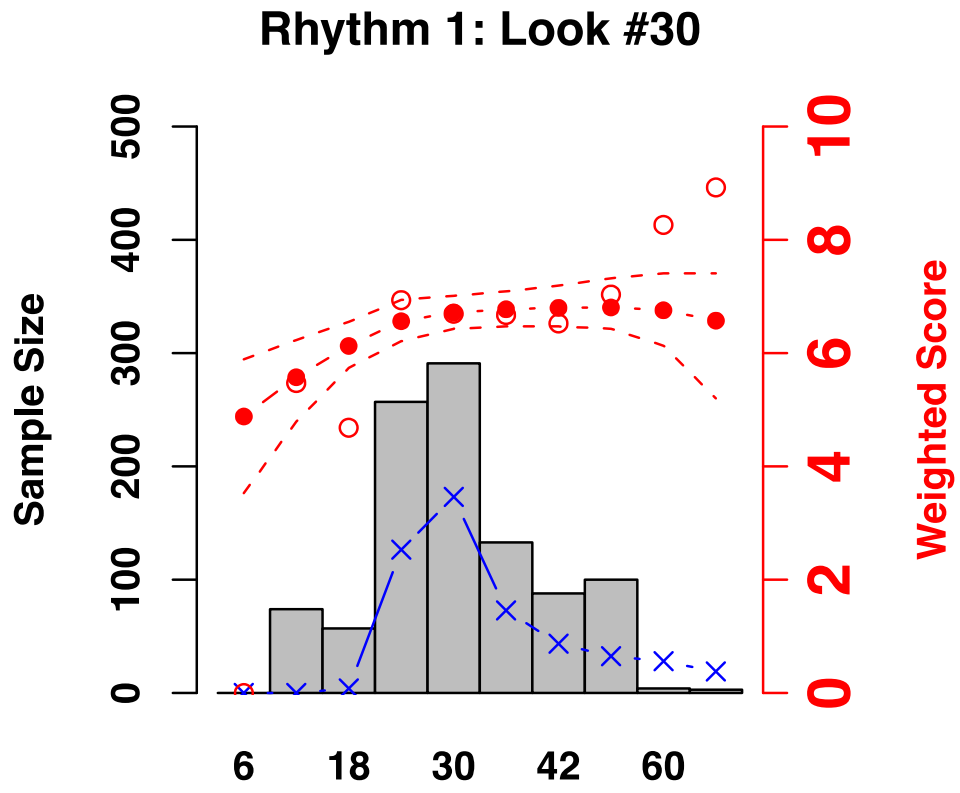
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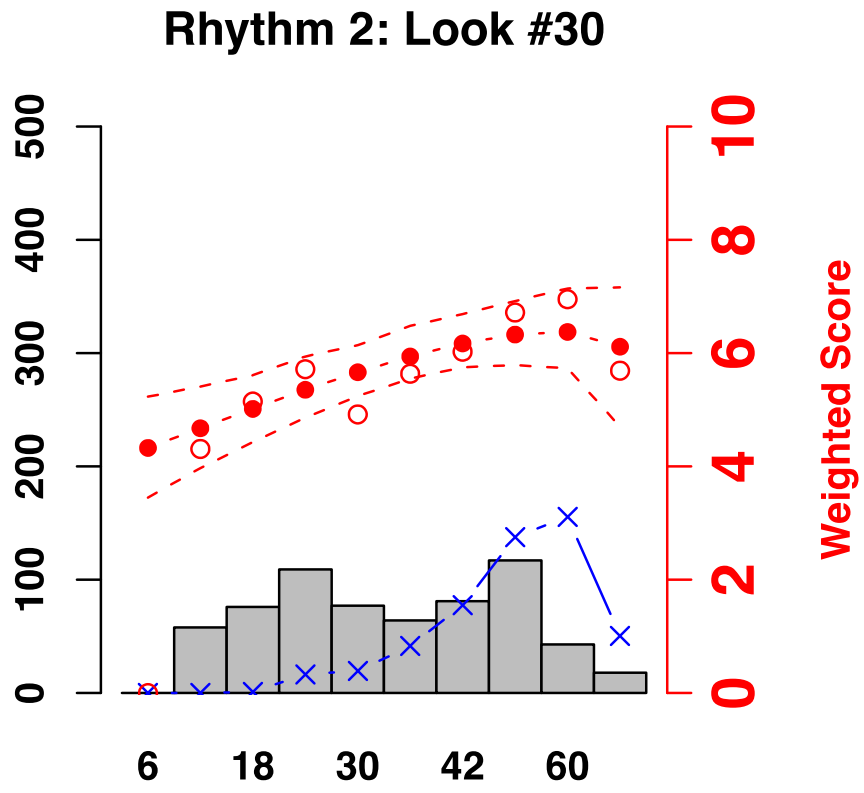
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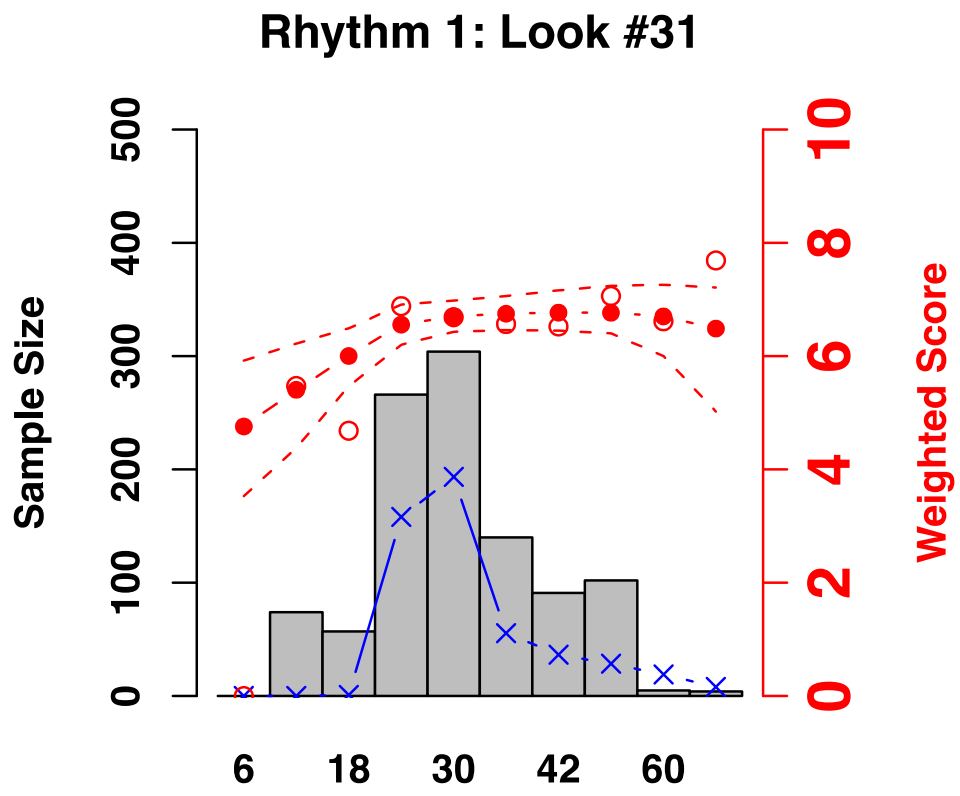
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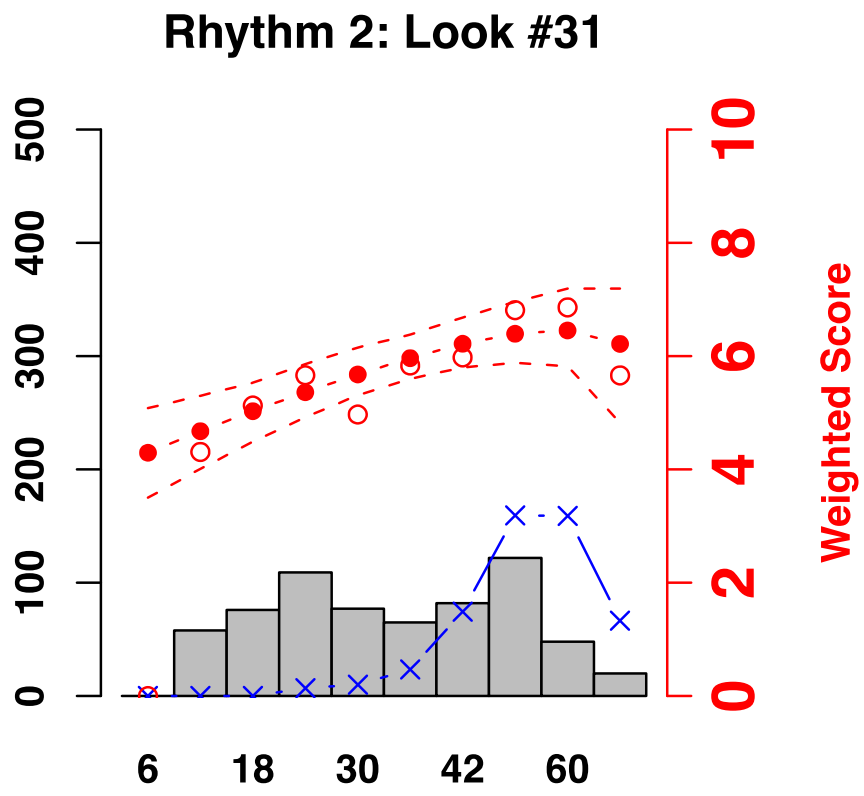
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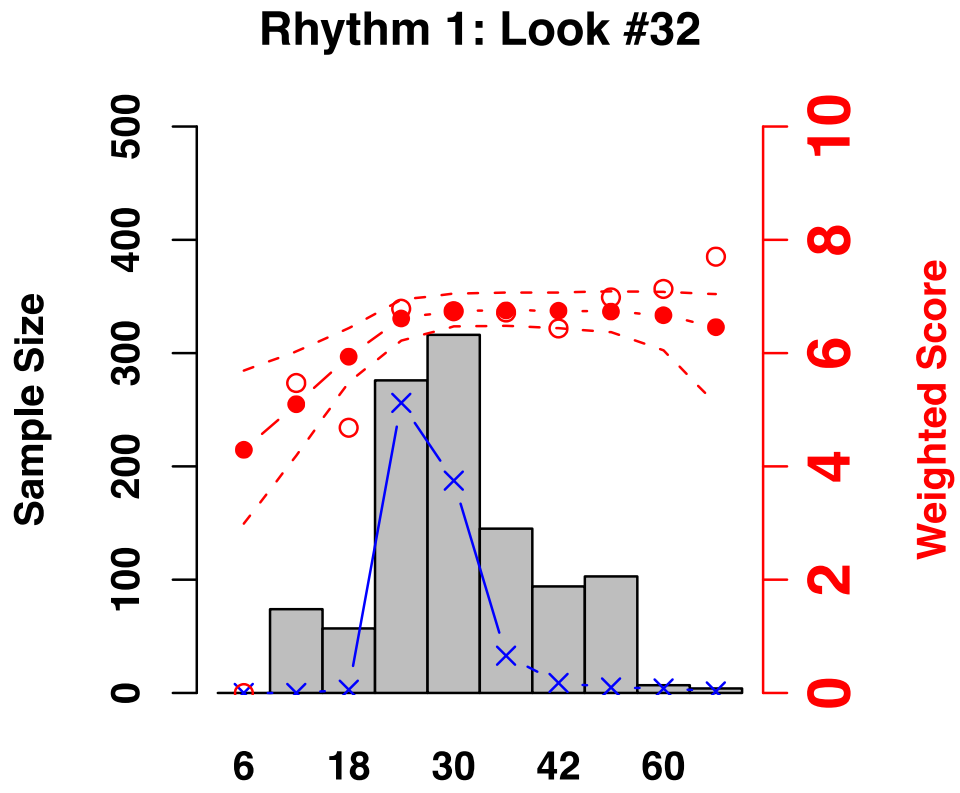
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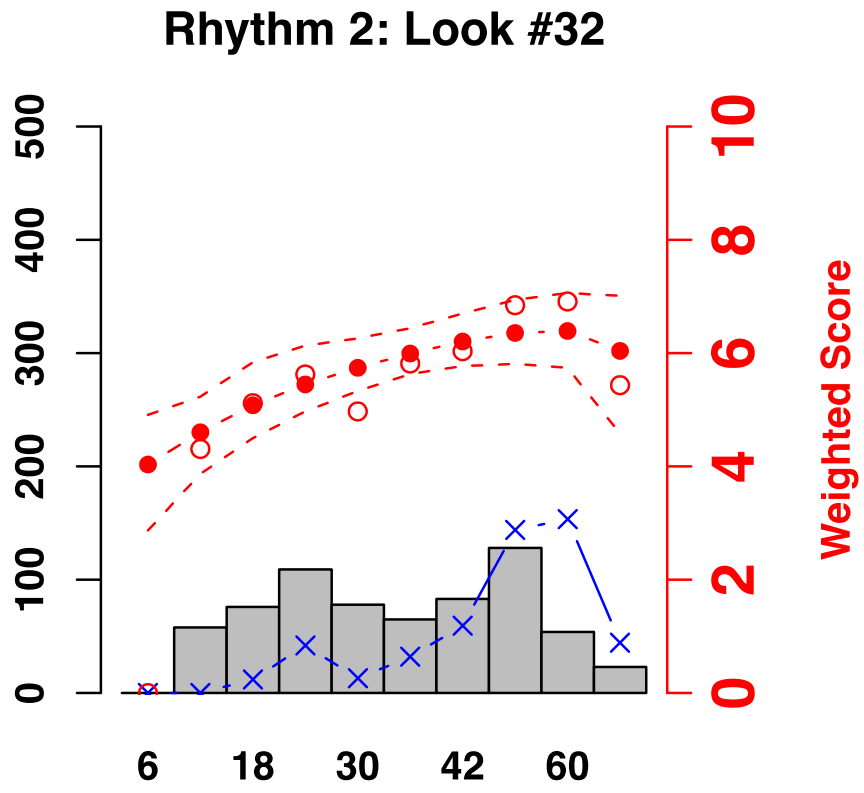
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Weighted Score
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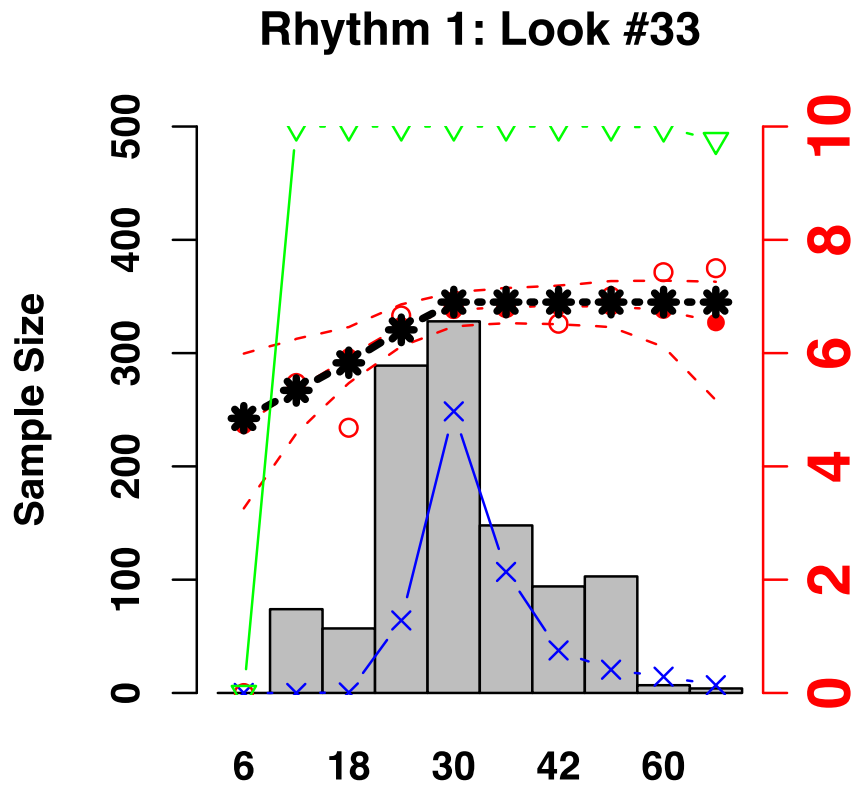
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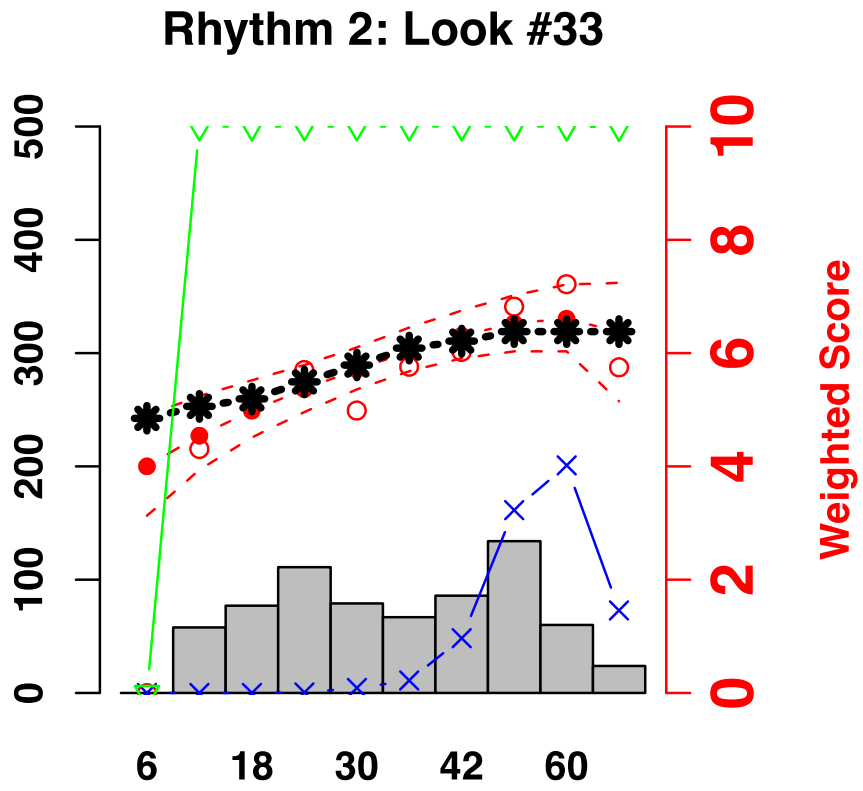
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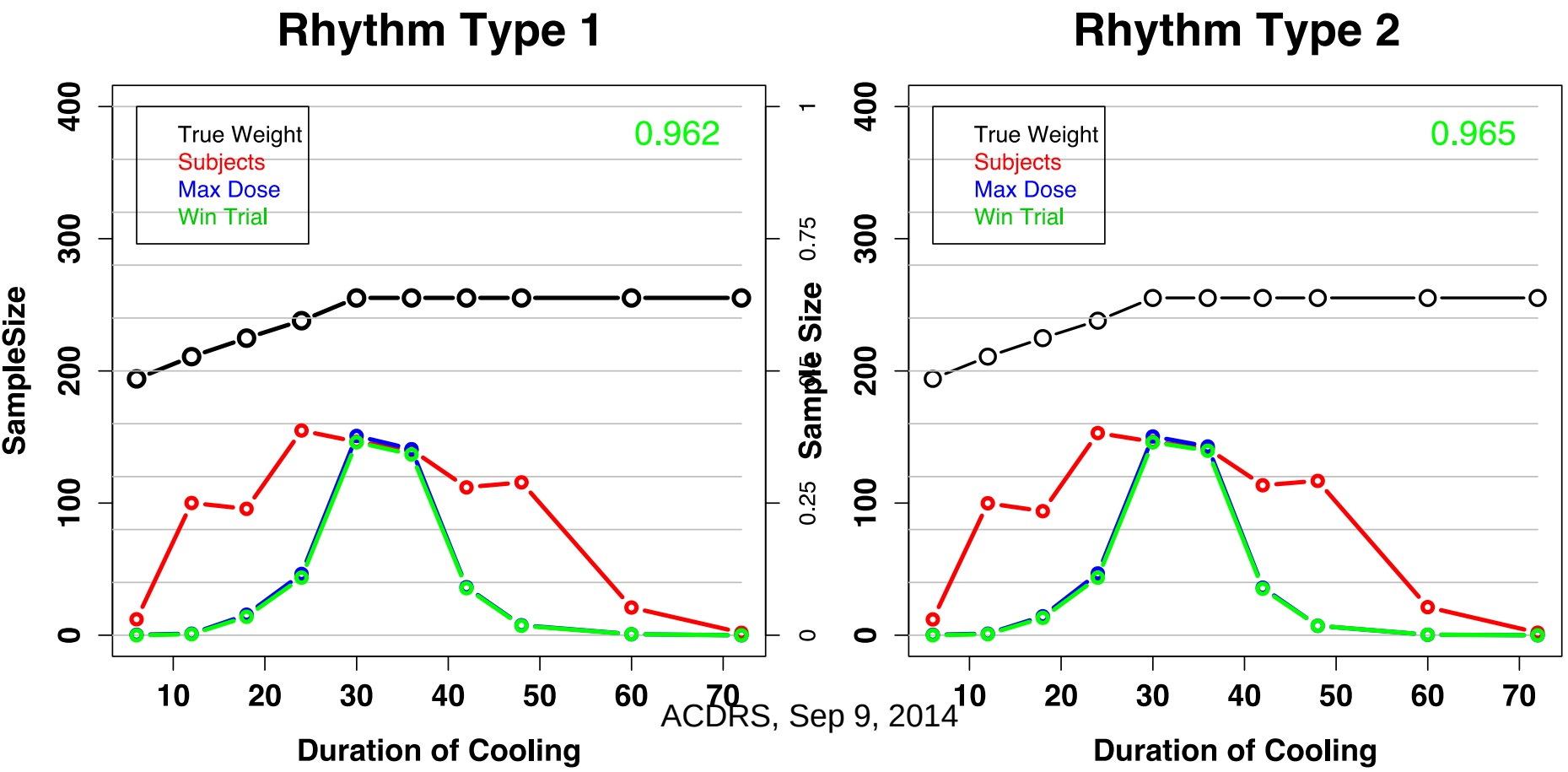
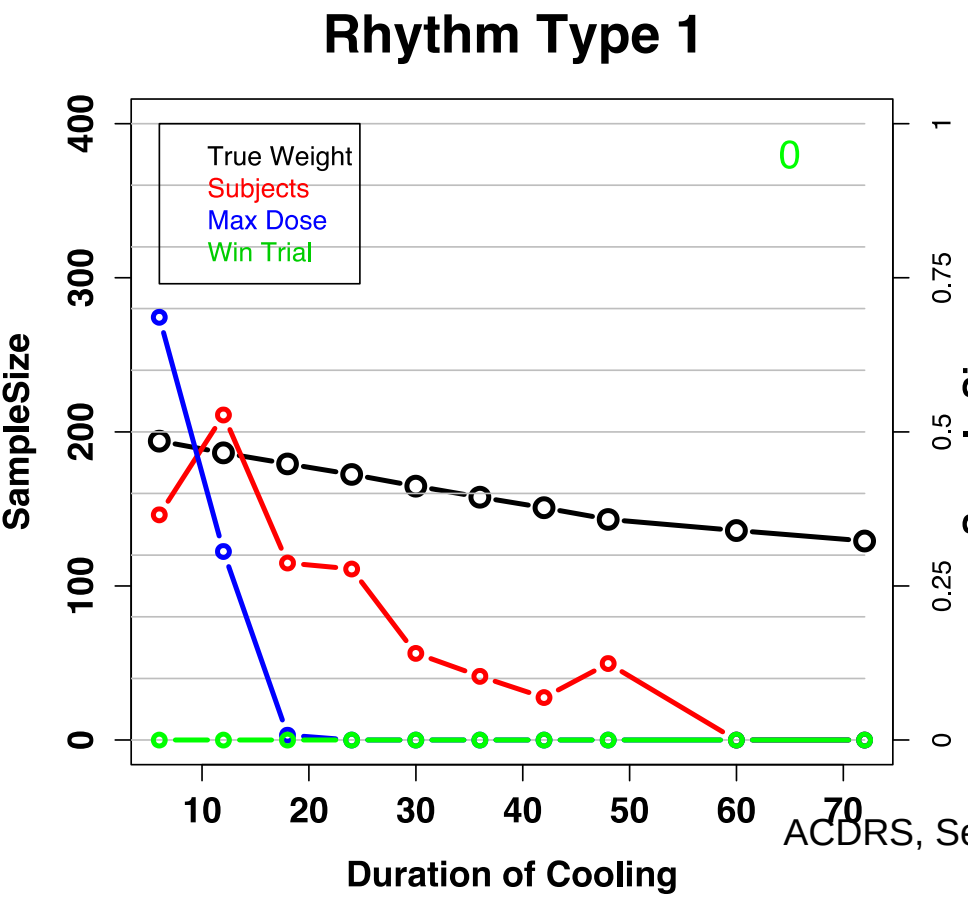
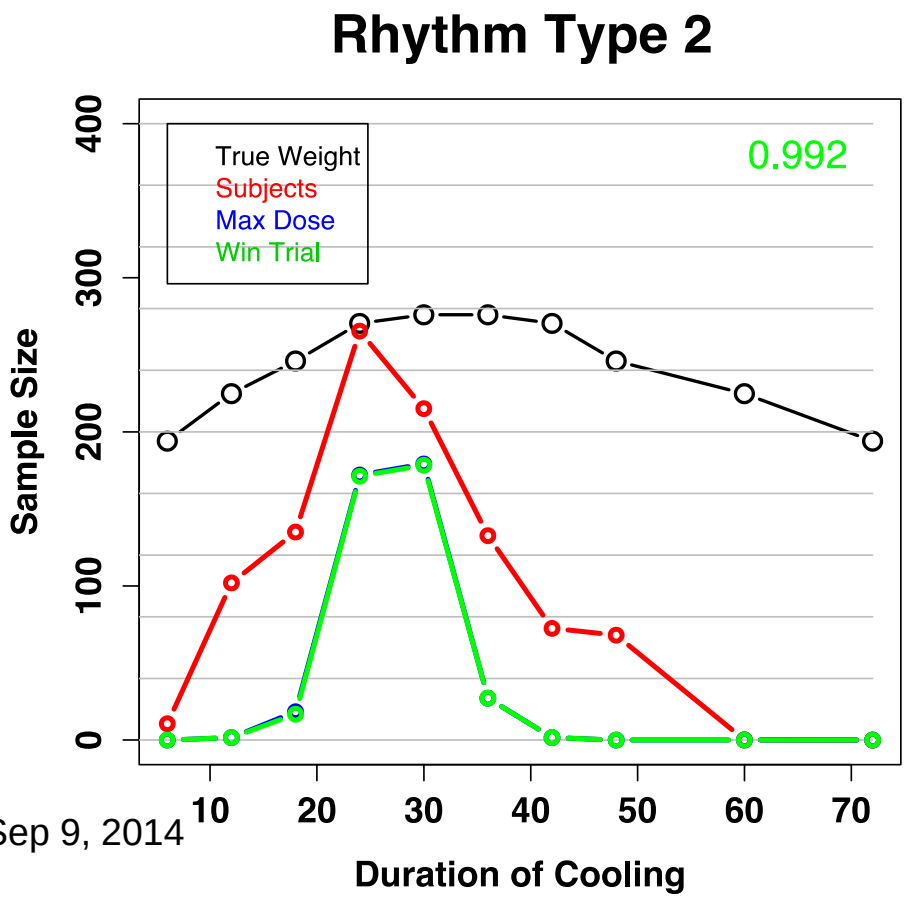
Operating Characteristics



Operating Characteristics





Platform Trials

Platform Trial

- An experimental infrastructure to evaluate multiple treatments, often for a group of diseases, and intended to function continually and be productive beyond the evaluation of any individual treatment
  - Designed around a group of related diseases rather than a single treatment
  - Dynamic list of available treatments, assigned with response-adaptive randomization
  - Preferred treatments may depend on health system, patient, or disease-level characteristics

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

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Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

Jason T. Connor, PhD
Berry Consultants LLC, Austin, Texas; and University of Central Florida College of Medicine, Orlando.

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Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California; and Berry Consultants LLC, Austin, Texas.

The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population, one drug, one disease" strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants for stroke.[2] Effective treatments for such diseases will likely require combining treatments to affect multiple targets in complex cellular pathways and, perhaps, tailoring treatments to subgroups defined by genetic, proteomic, metabolomic, or other markers.[3]

There has been increasing interest in efficient trial strategies designed to evaluate multiple treatments and combinations of treatments, in heterogeneous patient

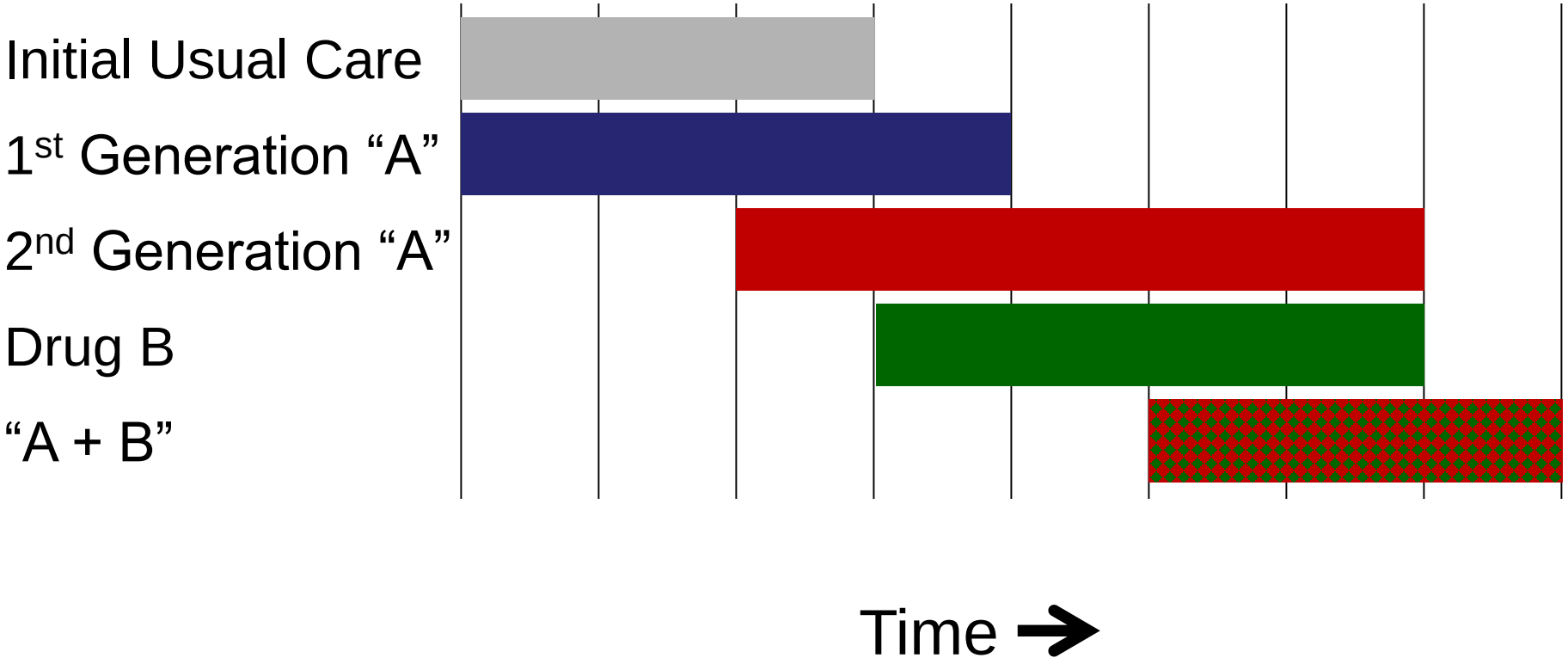
benefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

What Is a Platform Trial?

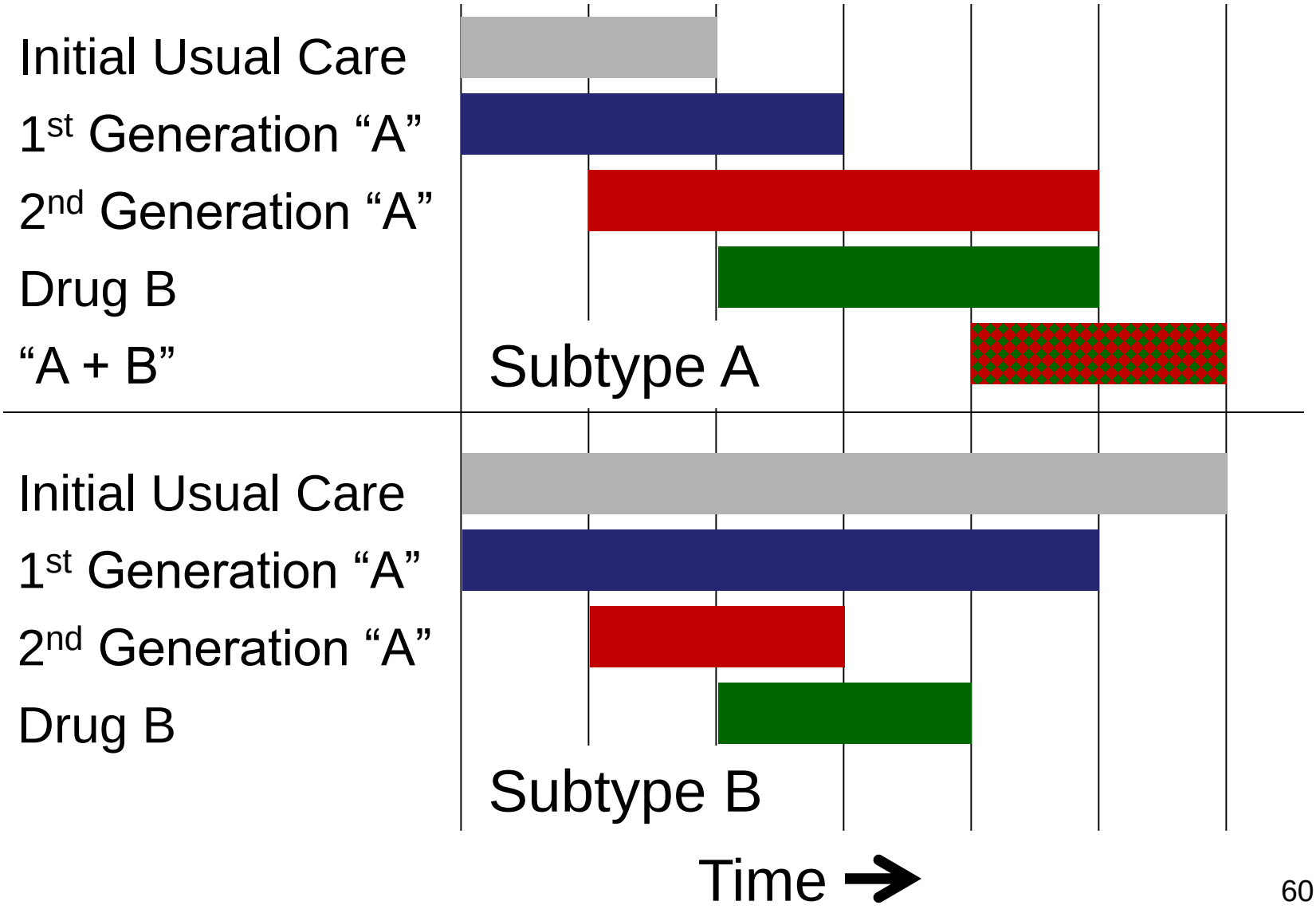
A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy. A platform trial is often intended to continue beyond the evaluation of the initial treatments and to investigate treatment combinations, to quantify differences in treatment effects in subgroups, and to treat patients as effectively as possible within the trial. Although some of the statistical tools used in platform trials are frequently used in other settings and some less so, it is the integrated application of multiple tools that allows a platform trial to address its multiple goals. The **Table** summarizes the general differences between a traditional clinical trial and a platform trial

JAMA. Published online March 23, 2015. doi:10.1001/jama.2015.2316

Platform Trial



Platform Trial



“Random” versus “Randomized”

- There is tremendous enthusiasm for analyzing large observational datasets to determine best treatment
  - Unrecognized confounding that likely varies in highly complex ways
  - Convenience versus reality?
  - False conclusions from very large studies are particularly dangerous (precise versus valid)
  - Goal is to replace random treatment with randomized treatment to support learning

Example

The PREPARE Consortium

- **P**latform fo**R** **E**uropean **P**reparedness **A**gainst (**R**e)emerging **E**pidemics
  - 25 million euro FP7 strategic award
- Work Package #5 – 'PREPARE CAP'
  - An adaptive trial platform to determine best care for severe acute respiratory failure of presumed infectious origin
    - Endemic - severe CAP
    - Epidemic – severe respiratory viral illness (e.g., H1N1)

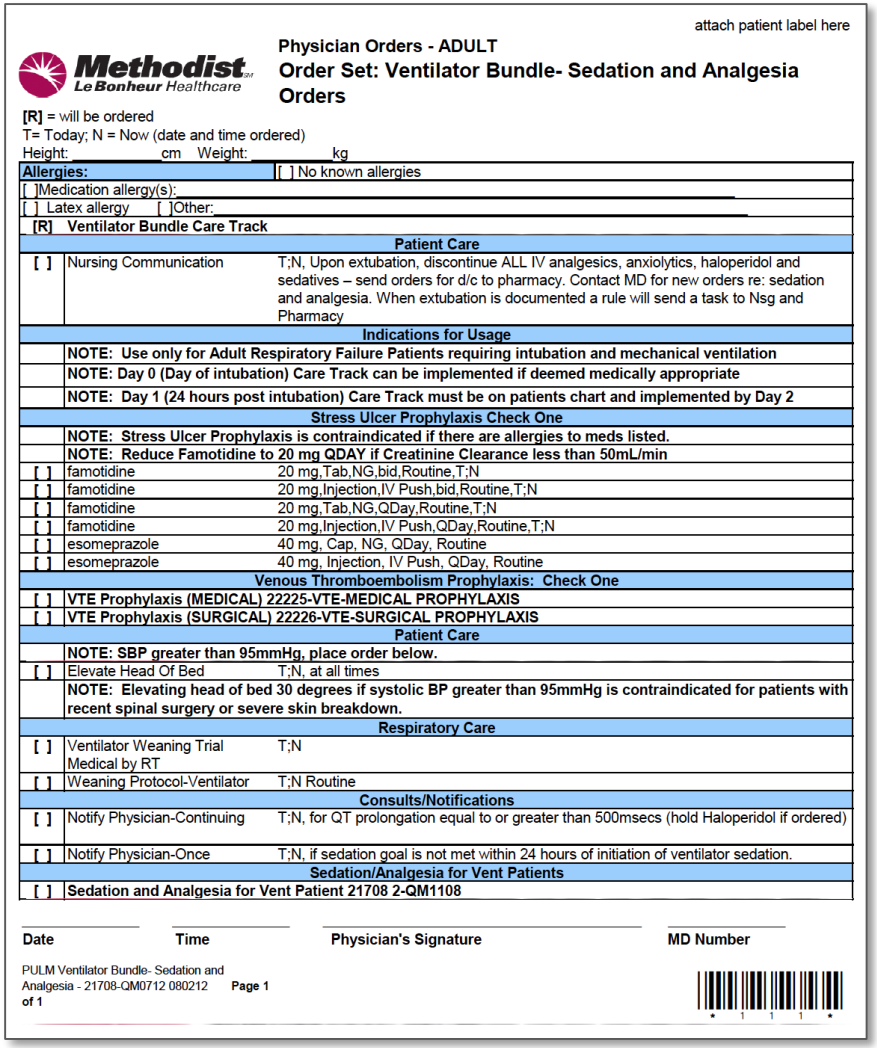
PREPARE is funded by the European Commission under grant number 602525

Scope of PREPARE CAP

- Simultaneously considers
  - Anti-infective strategies (i.e., antibiotic choice)
  - Host response modulation (i.e., steroids)
  - Organ support strategies (i.e., mechanical ventilation)
- Design stratifies by different subgroups
  - Shock or not
  - Severe vs. moderate hypoxemia
- With five “yes/no” strata (treatments and subgroups) there are $2^5 = 32$ “cells”
- Additional complexity
  - Add or drop factors by region, country, patient sub-group, and season (e.g., “influenza flu season”)

Embedding the Trial into Routine Care

- For EVERY patient who presents with severe CAP, clinical team calls IVRS for the patient's unique order set



attach patient label here

Methodist Le Bonheur Healthcare

Physician Orders - ADULT

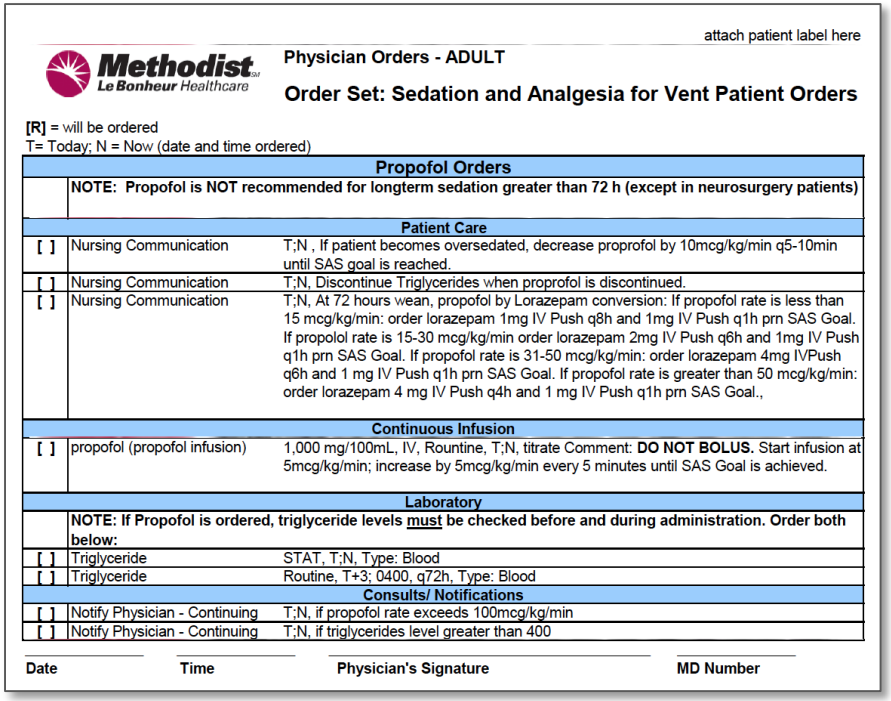
Order Set: Ventilator Bundle- Sedation and Analgesia Orders

[R] = will be ordered
T= Today; N = Now (date and time ordered)
Height: _____cm Weight: _____kg

Allergies:		[ ] No known allergies
[ ]Medication allergy(s):		
[ ] Latex allergy	[ ]Other:	
[R] Ventilator Bundle Care Track		
	Patient Care	
[ ]	Nursing Communication	T;N, Upon extubation, discontinue ALL IV analgesics, anxiolytics, haloperidol and sedatives – send orders for d/c to pharmacy. Contact MD for new orders re: sedation and analgesia. When extubation is documented a rule will send a task to Nsg and Pharmacy
	Indications for Usage	
	NOTE: Use only for Adult Respiratory Failure Patients requiring intubation and mechanical ventilation	
	NOTE: Day 0 (Day of intubation) Care Track can be implemented if deemed medically appropriate	
	NOTE: Day 1 (24 hours post intubation) Care Track must be on patients chart and implemented by Day 2	
	Stress Ulcer Prophylaxis Check One	
	NOTE: Stress Ulcer Prophylaxis is contraindicated if there are allergies to meds listed.	
	NOTE: Reduce Famotidine to 20 mg QDAY if Creatinine Clearance less than 50mL/min	
[ ]	famotidine	20 mg,Tab,NG,bid,Routine,T;N
[ ]	famotidine	20 mg,Injection,IV Push,bid,Routine,T;N
[ ]	famotidine	20 mg,Tab,NG,QDay,Routine,T;N
[ ]	famotidine	20 mg,Injection,IV Push,QDay,Routine,T;N
[ ]	esomeprazole	40 mg, Cap, NG, QDay, Routine
[ ]	esomeprazole	40 mg, Injection, IV Push, QDay, Routine
	Venous Thromboembolism Prophylaxis: Check One	
[ ]	**VTE Prophylaxis (MEDICAL) 22225-VTE-MEDICAL PROPHYLAXIS**	
[ ]	**VTE Prophylaxis (SURGICAL) 22226-VTE-SURGICAL PROPHYLAXIS**	
	Patient Care	
	NOTE: SBP greater than 95mmHg, place order below.	
[ ]	Elevate Head Of Bed	T;N, at all times
	NOTE: Elevating head of bed 30 degrees if systolic BP greater than 95mmHg is contraindicated for patients with recent spinal surgery or severe skin breakdown.	
	Respiratory Care	
[ ]	Ventilator Weaning Trial Medical by RT	T;N
[ ]	Weaning Protocol-Ventilator	T;N Routine
	Consults/Notifications	
[ ]	Notify Physician-Continuing	T;N, for QT prolongation equal to or greater than 500msecs (hold Haloperidol if ordered)
[ ]	Notify Physician-Once	T;N, if sedation goal is not met within 24 hours of initiation of ventilator sedation.
	Sedation/Analgesia for Vent Patients	
[ ]	**Sedation and Analgesia for Vent Patient 21708 2-QM1108**	

Date **Time** **Physician's Signature** **MD Number**

PULM Ventilator Bundle- Sedation and Analgesia - 21708-QM0712 080212 **Page 1 of 1**



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Methodist Le Bonheur Healthcare

Physician Orders - ADULT

Order Set: Sedation and Analgesia for Vent Patient Orders

[R] = will be ordered
T= Today; N = Now (date and time ordered)

	Propofol Orders	
	NOTE: Propofol is NOT recommended for longterm sedation greater than 72 h (except in neurosurgery patients)	
	Patient Care	
[ ]	Nursing Communication	T;N , If patient becomes oversedated, decrease proprofol by 10mcg/kg/min q5-10min until SAS goal is reached.
[ ]	Nursing Communication	T;N, Discontinue Triglycerides when proprofol is discontinued.
[ ]	Nursing Communication	T;N, At 72 hours wean, propofol by Lorazepam conversion: If propofol rate is less than 15 mcg/kg/min: order lorazepam 1mg IV Push q8h and 1mg IV Push q1h prn SAS Goal. If propolol rate is 15-30 mcg/kg/min order lorazepam 2mg IV Push q6h and 1mg IV Push q1h prn SAS Goal. If propofol rate is 31-50 mcg/kg/min: order lorazepam 4mg IVPush q6h and 1 mg IV Push q1h prn SAS Goal. If propofol rate is greater than 50 mcg/kg/min: order lorazepam 4 mg IV Push q4h and 1 mg IV Push q1h prn SAS Goal.,
	Continuous Infusion	
[ ]	propofol (propofol infusion)	1,000 mg/100mL, IV, Rountine, T;N, titrate Comment: **DO NOT BOLUS.** Start infusion at 5mcg/kg/min; increase by 5mcg/kg/min every 5 minutes until SAS Goal is achieved.
	Laboratory	
	NOTE: If Propofol is ordered, triglyceride levels must be checked before and during administration. Order both below:	
[ ]	Triglyceride	STAT, T;N, Type: Blood
[ ]	Triglyceride	Routine, T+3; 0400, q72h, Type: Blood
	Consults/ Notifications	
[ ]	Notify Physician - Continuing	T;N, if propofol rate exceeds 100mcg/kg/min
[ ]	Notify Physician - Continuing	T;N, if triglycerides level greater than 400

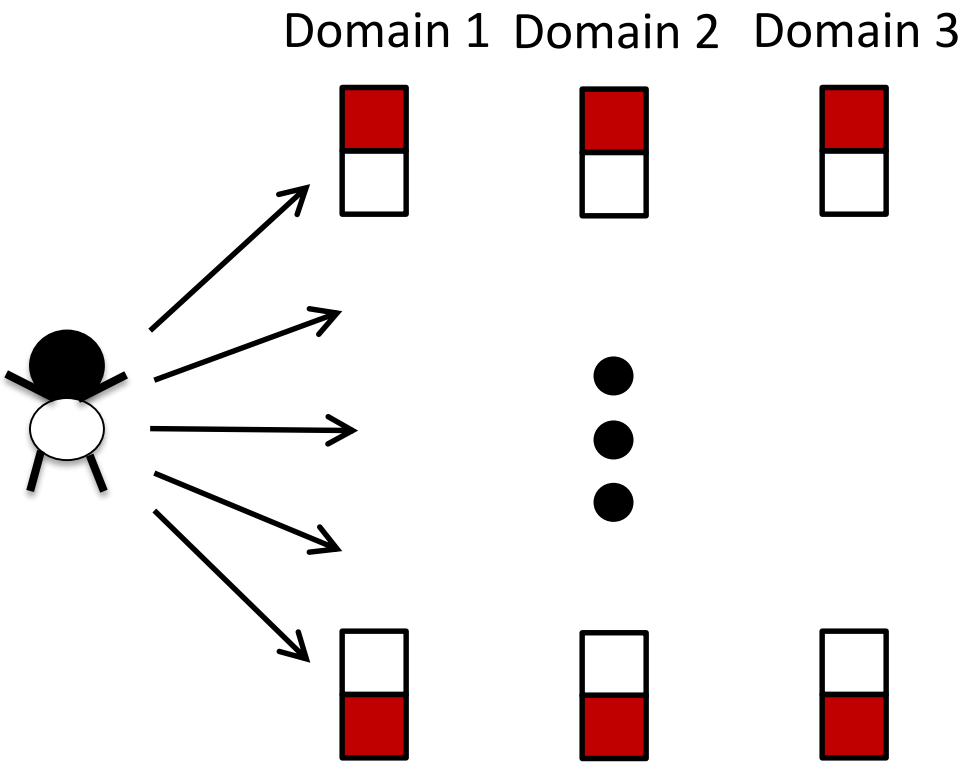
Date **Time** **Physician's Signature** **MD Number**

Starting Conditions/Burn In

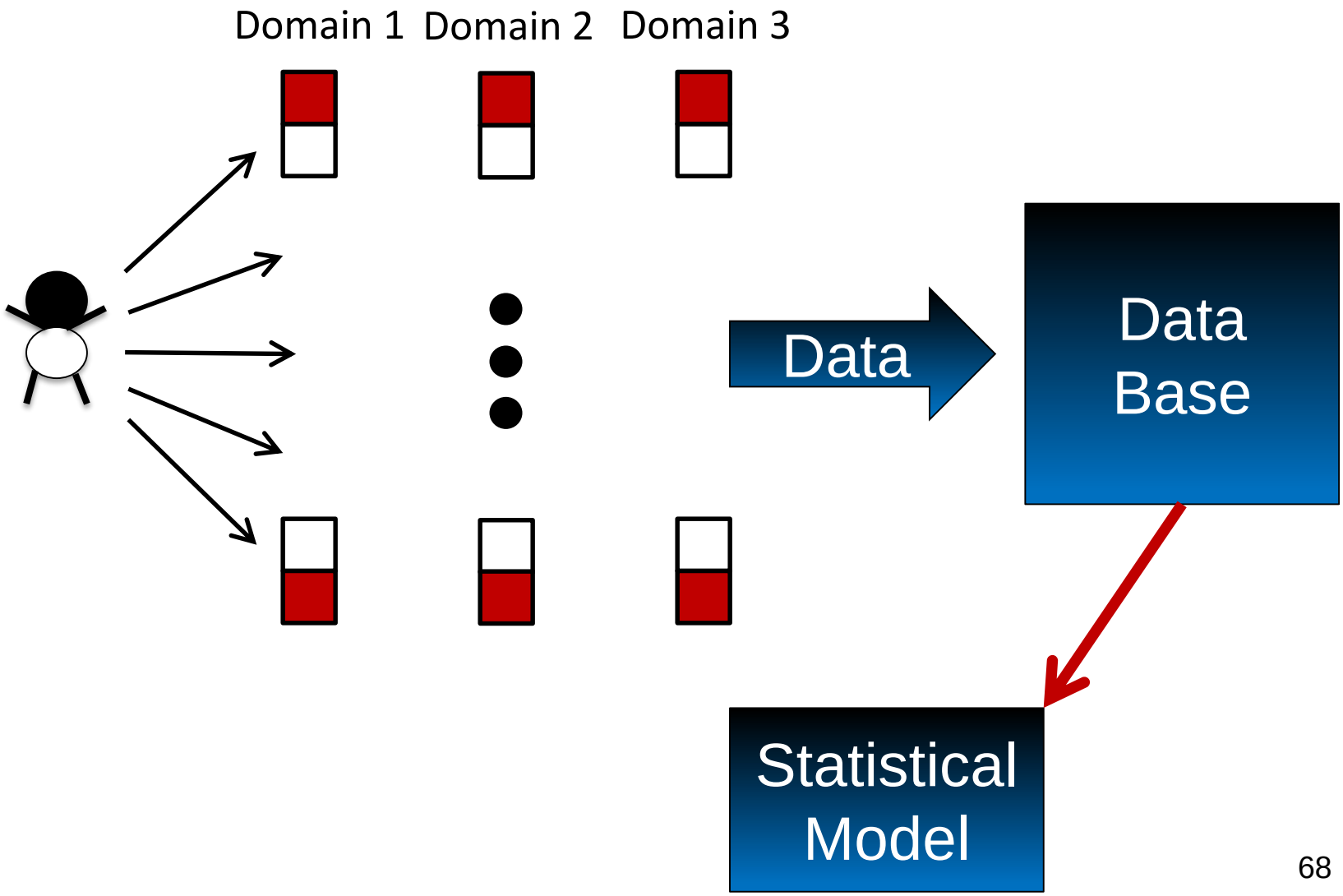
Regimen	Anti-infective	Immunomodulation	Ventilation strategy
#1	Quinolone	Hydrocortisone	6cc/kg
#2	Quinolone	Hydrocortisone	4cc/kg
#3	Quinolone	None	6cc/kg
#4	Quinolone	None	4cc/kg
#5	Combination Rx	Hydrocortisone	6cc/kg
#6	Combination Rx	Hydrocortisone	4cc/kg
#7	Combination Rx	None	6cc/kg
#8	Combination Rx	None	4cc/kg

- Equal randomization for first 200 patients (burn-in)
- RAR driven by a full factor statistical model
  - Factor for each single factor
  - Interactions of two factors
  - 3-way interactions
  - Priors expecting low interactions, allows for learning

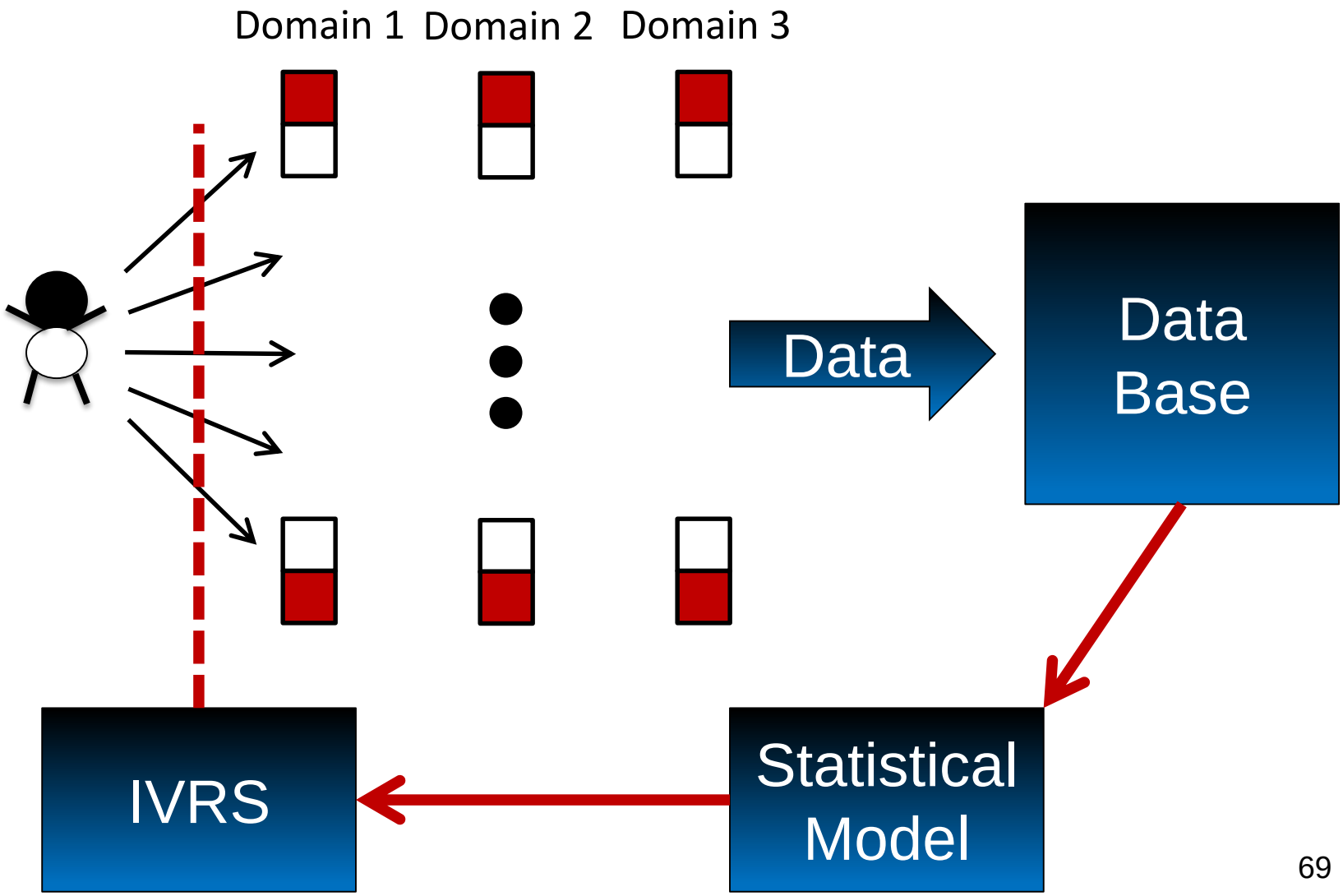
Trial Schematic



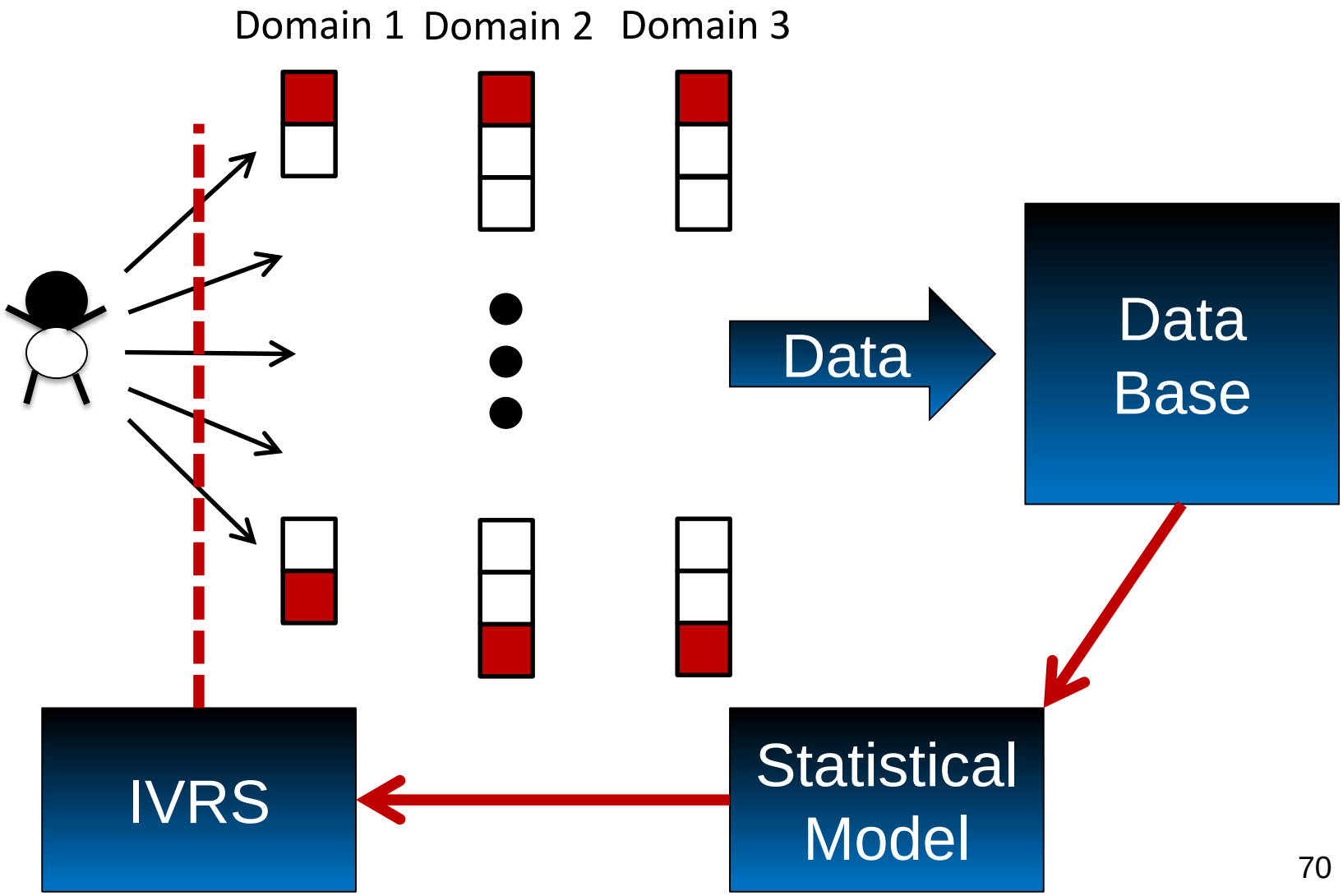
Trial Schematic



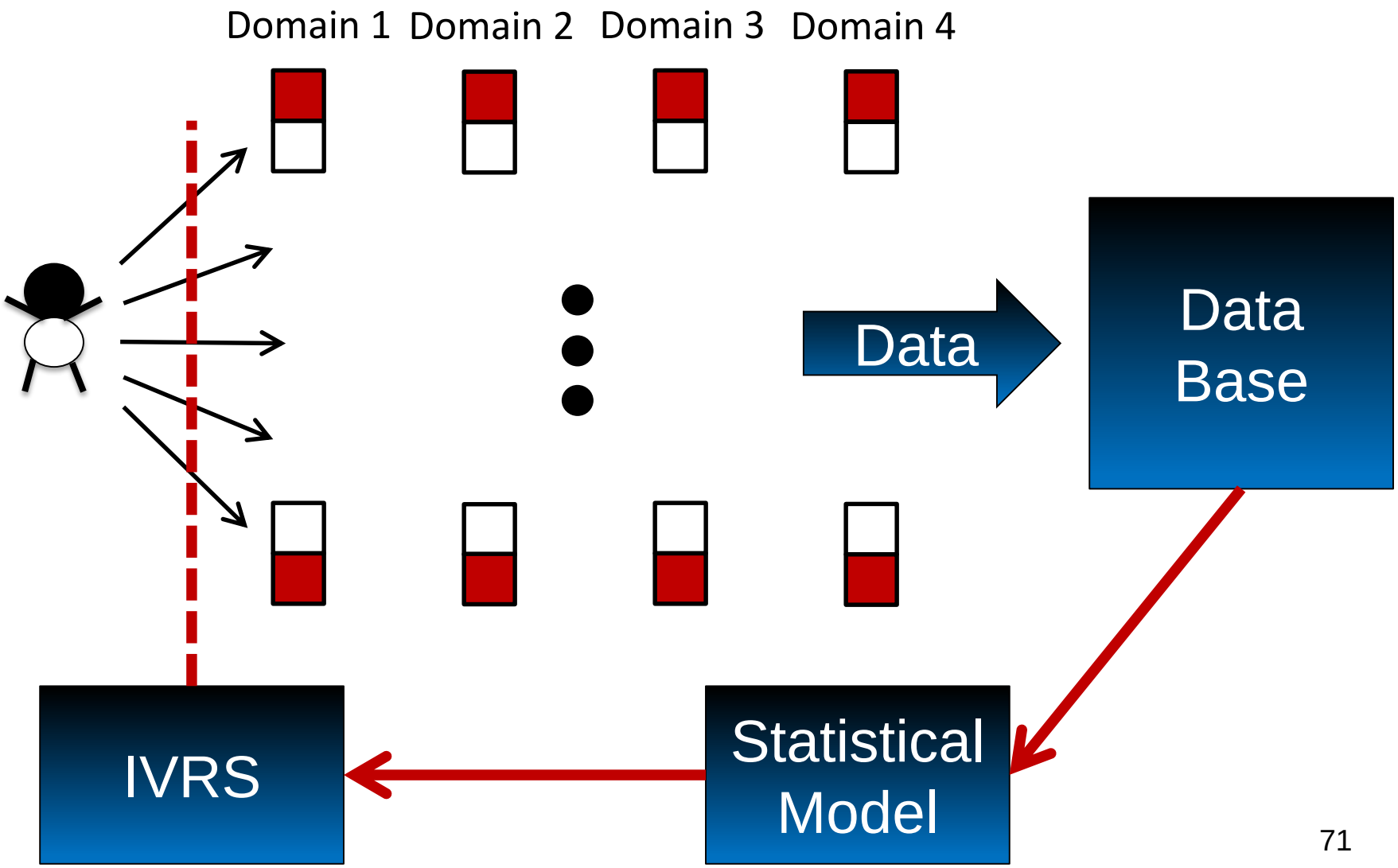
Trial Schematic



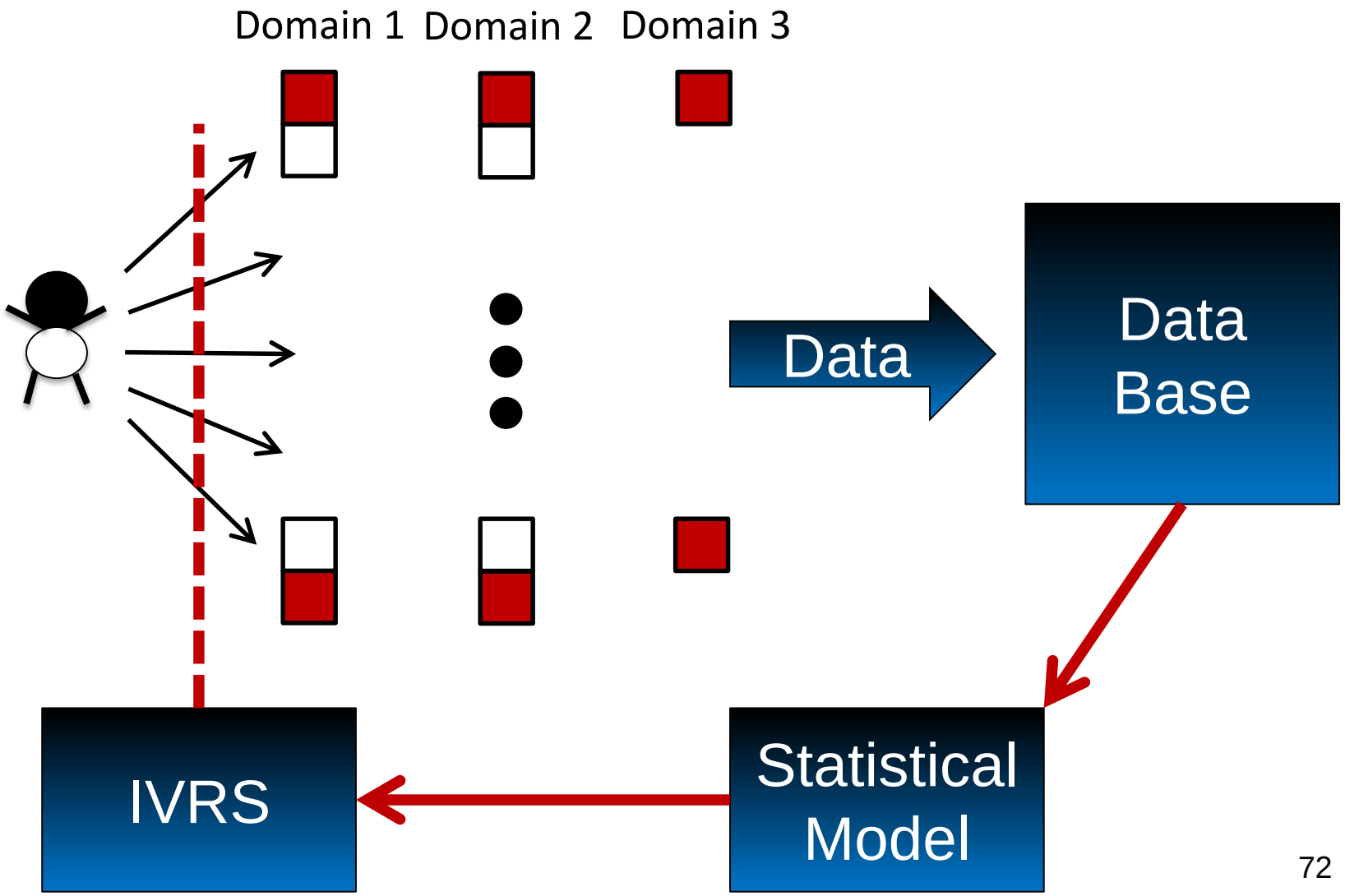
Trial Schematic: Adding Factors



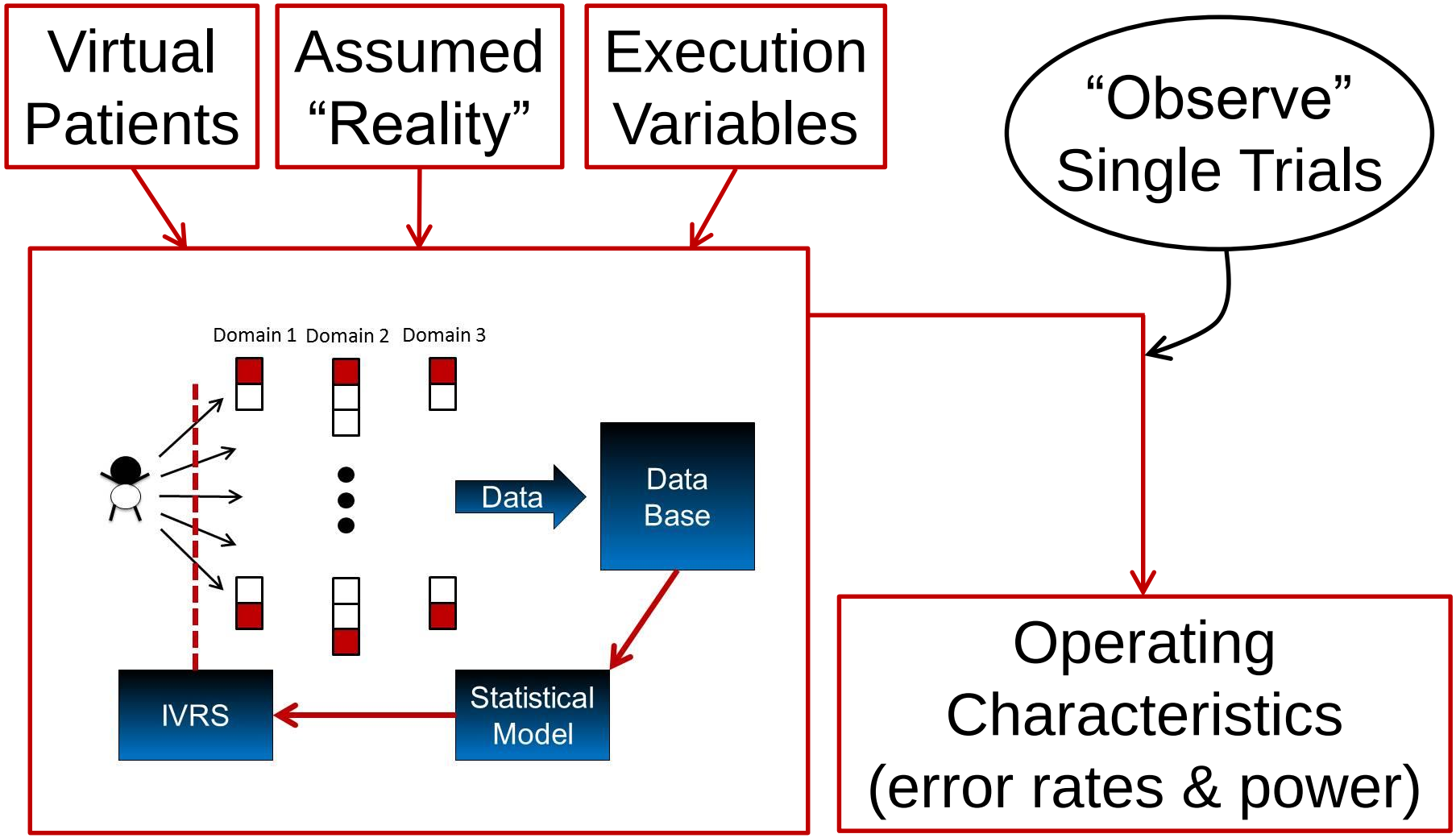
Trial Schematic: Adding a Domain



Trial Schematic: Selecting a Factor



Trial Simulation



Simulated Trial Performance

Truth

Simulated Trial Performance

Truth

Conclusions

- Clinical trial simulation can be used to evaluate, improve, and better understand proposed clinical trial designs
- Adaptive trial designs can be used to create a seamless process in which new evidence about effectiveness is immediately used to improve patient care
- A platform trial can extend this process beyond a single treatment or few treatments