Bayesian Adaptive Designs for Clinical Trials

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MASTER PROTOCOLS
PLATFORM TRIALS

Master Protocols

Woodcock & Lavange, NEJM 2017

- High-quality evidence is what we use to guide medical practice. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered.
- A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure. Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions.

Woodcock & Lavange, NEJM 2017

- Master protocols may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions, each targeting a particular biomarker-defined population or disease subtype. Included under this broad definition of a master protocol are three distinct entities: umbrella, basket, and platform trials (Table 1 and Figs. 1 and 2). All constitute a collection of trials or substudies that share key design components and operational aspects to achieve better coordination than can be achieved in single trials designed and conducted independently.

Master Protocols

- May or may not compare treatment across groups
  - One structure, but each TX vs. common control
  - Reported as multiple trials (e.g. 1 per intervention)
  - Sites have one set of rules, execute like 1 trial
- Intensive pretrial discussion among sponsors
  - data use, publication rights, and the timing of regulatory submission
- Matchmaker
  - Therapies to targeted subpopulations

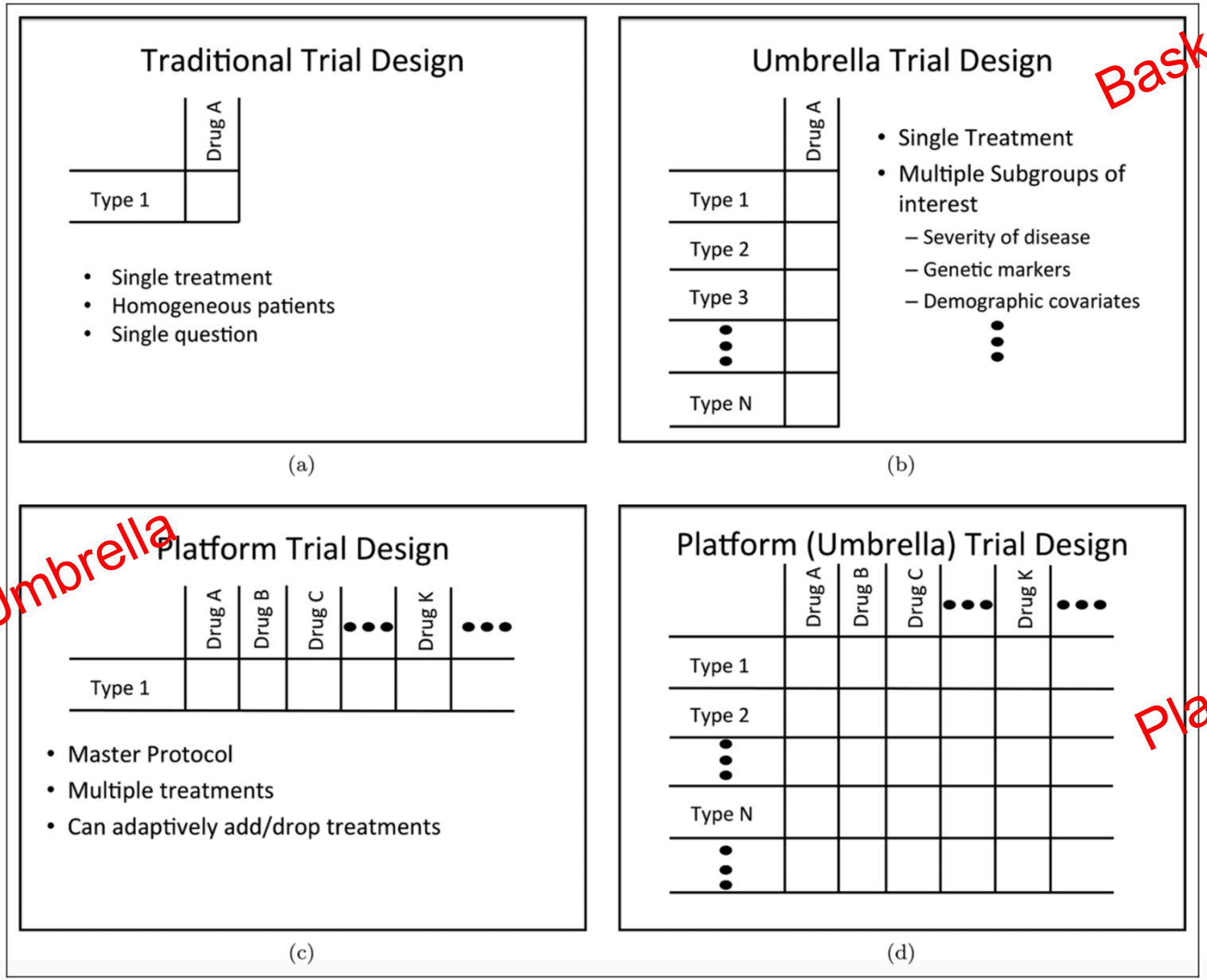
Master Protocols

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

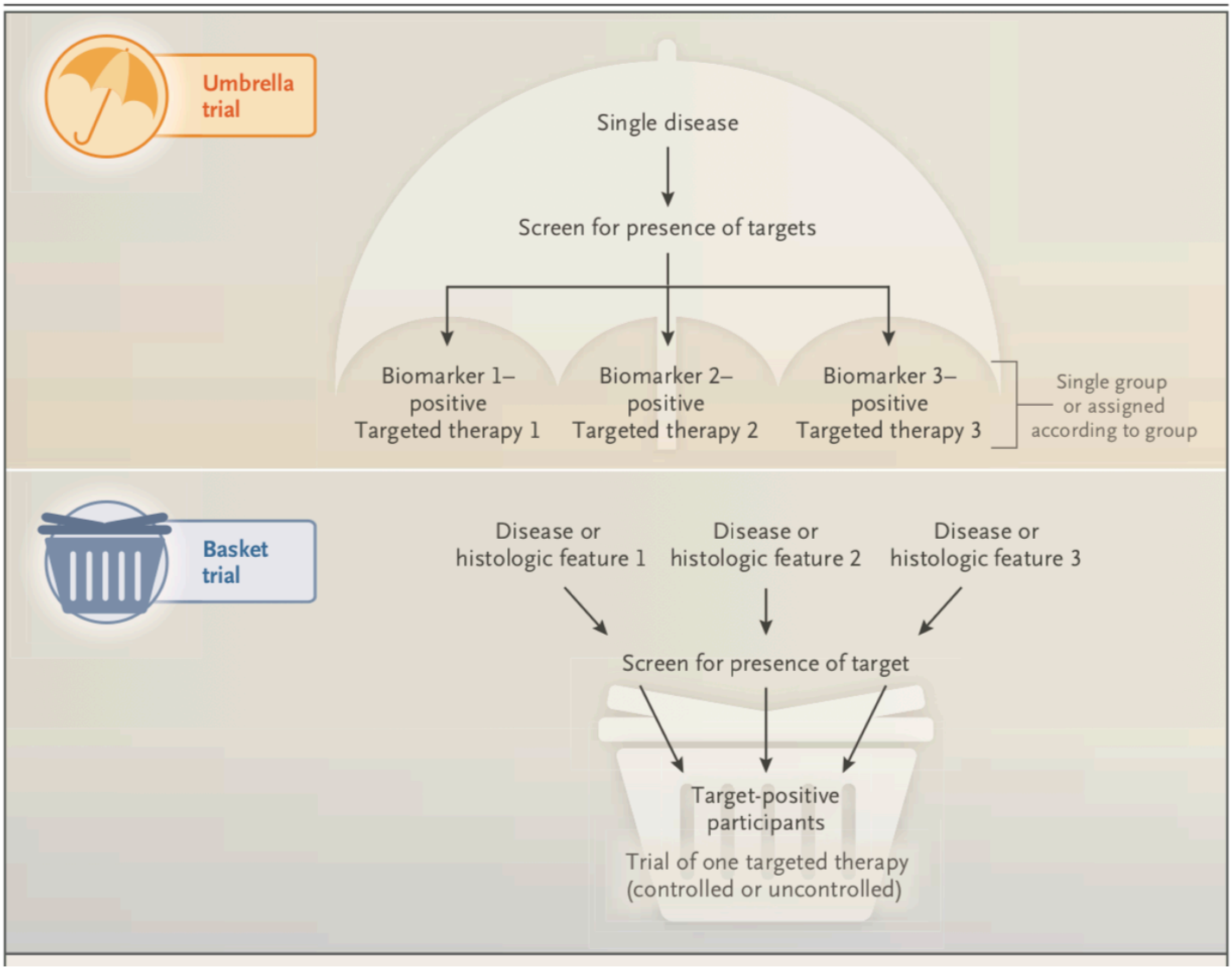
NEJM 377, 1, p63, Table 1

Master Protocols



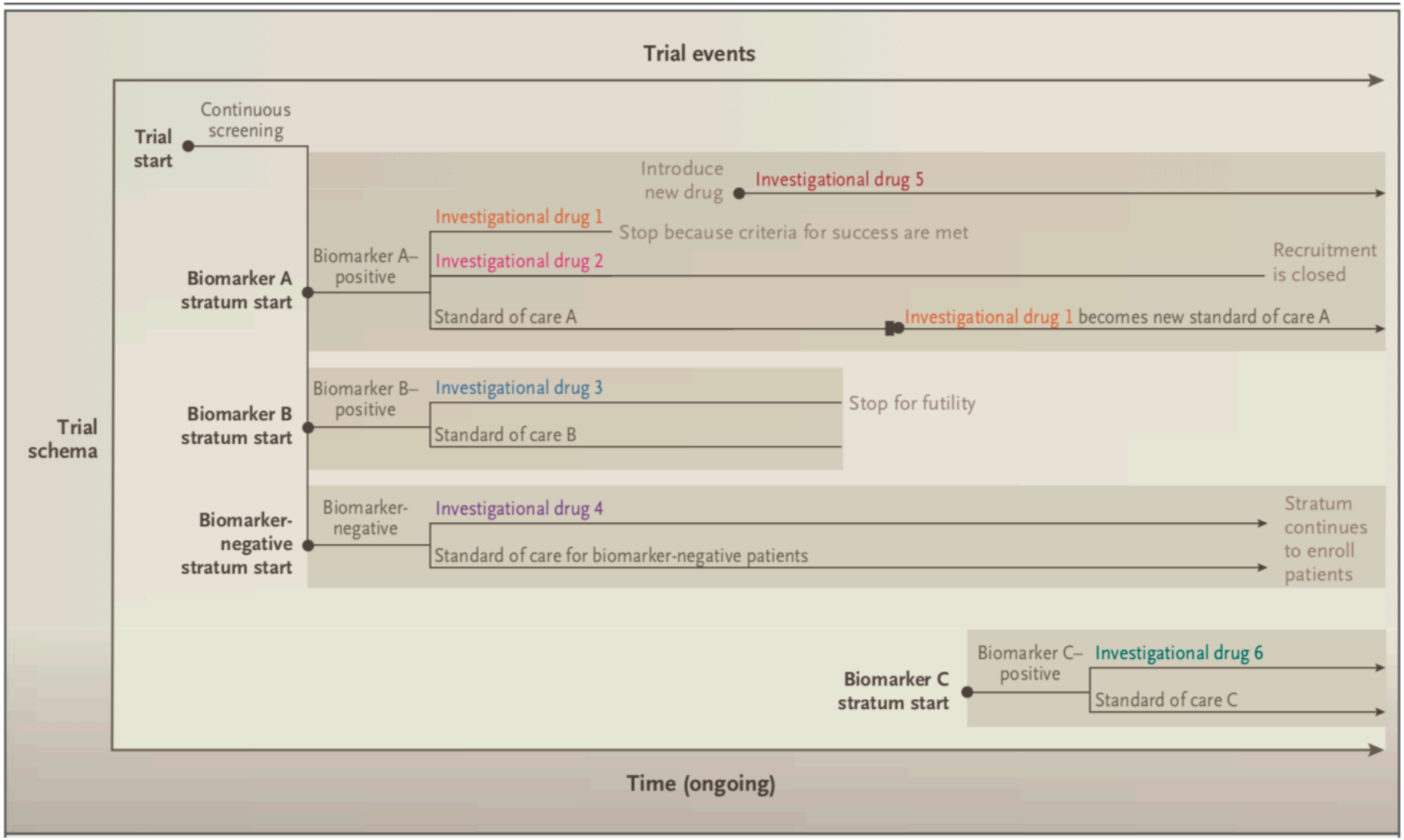
Graphic fromSaville & Berry, Clinical Trials, 2016
Red labels match Woodcock & Lavange defintions

Master Protocols



NEJM 377, 1, p63, Figure 1

Master Protocols



NEJM 377, 1, p63, Figure 2

Master Protocols

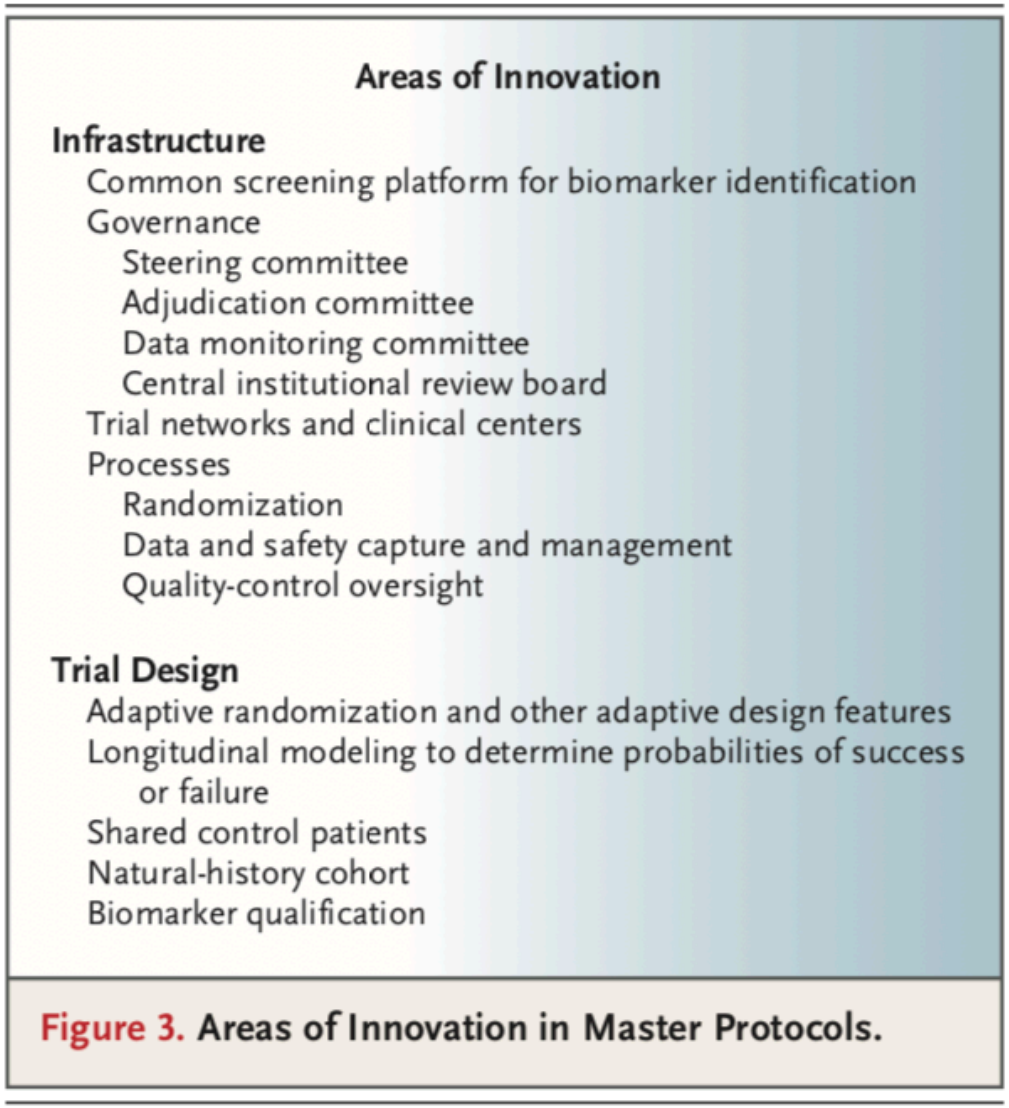


Figure 3. Areas of Innovation in Master Protocols.

NEJM 377, 1, p63, Figure 3

- Master protocols come in different sizes and shapes but share many commonalities.
- Increased planning efforts and coordination to satisfy the objectives of different stakeholders.
- Maximum information is obtained from the research effort
- Infrastructure required for imple-mentation increases data quality and trial efficiencies, as compared with those in stand-alone trials.
- Can last many years, even decades, with innovations from the laboratory translating quickly to clinical evaluation.

Platform Trials

Asking the Right Question

- Current Clinical Trials

  Is Drug A Effective and Safe?

  More precisely

  What is the probability of the observed data assuming the treatment is no good?

Asking the Right Question

- Current Clinical Trials
  - Is this drug effective and safe compared to a placebo?
  - Is this drug effective & safe compared to the SOC
- Correction Question
  - What is the best treatment for this Patient?
  - What is the best treatment for this type of patient?

Traditional Trial Design

- Single treatment vs. Control
- Homogenous patient population
- 1 or 2 questions per 1 trial
- Start with assuming a particular control group effect and a particular (usually optimistic) treatment group effect
- Assume ‘average’ effect relevant to all patients
- Calculate a sample size as if we know the true effect

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
  - Disease focused not treatment focused
  - 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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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

From: **The Platform Trial: An Efficient Strategy for Evaluating Multiple Treatments**

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

Table. General Characteristics of Traditional and Platform Trials[a]

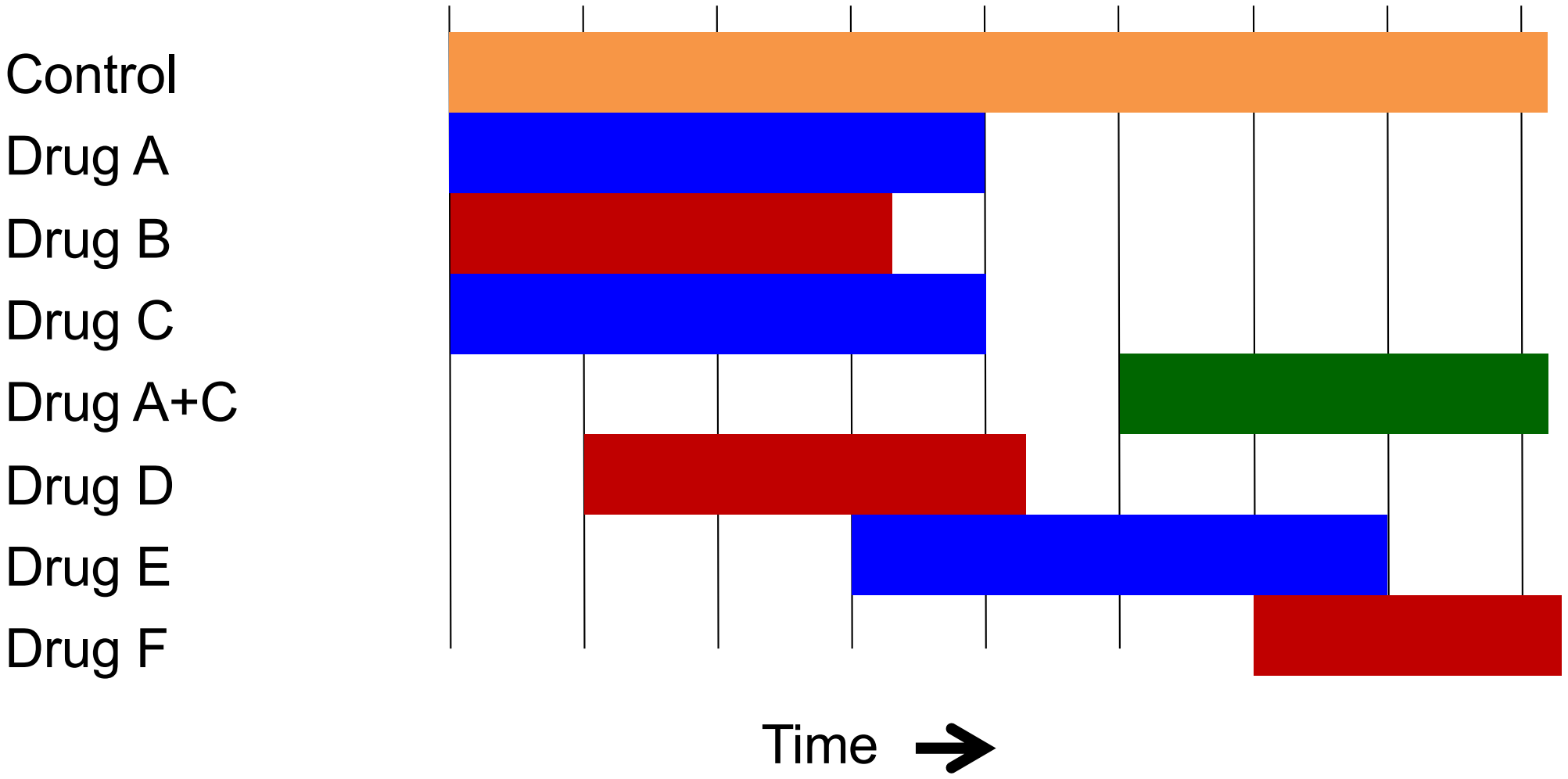
Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

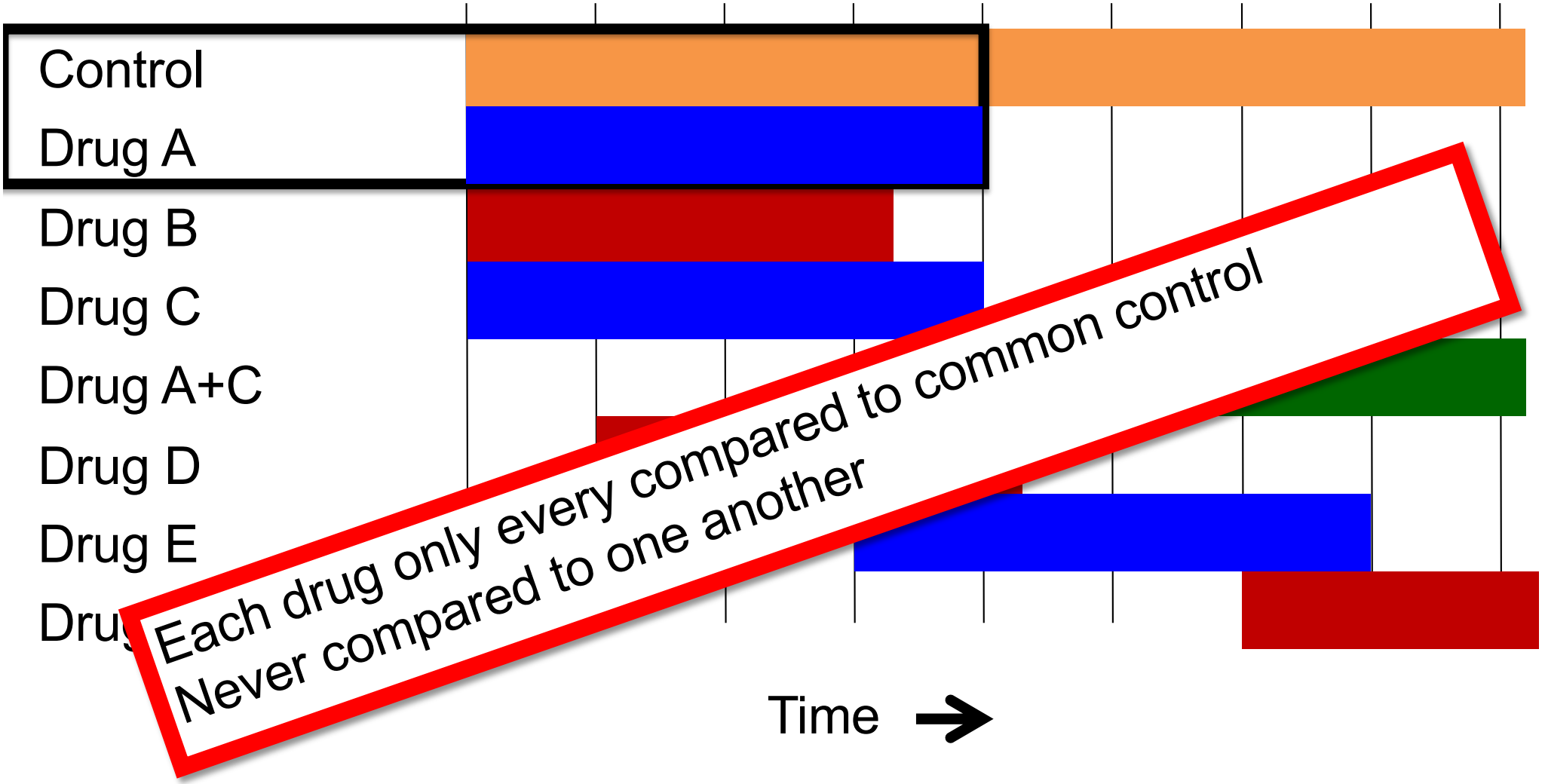
Table Title:

General Characteristics of Traditional and Platform Trials[a]

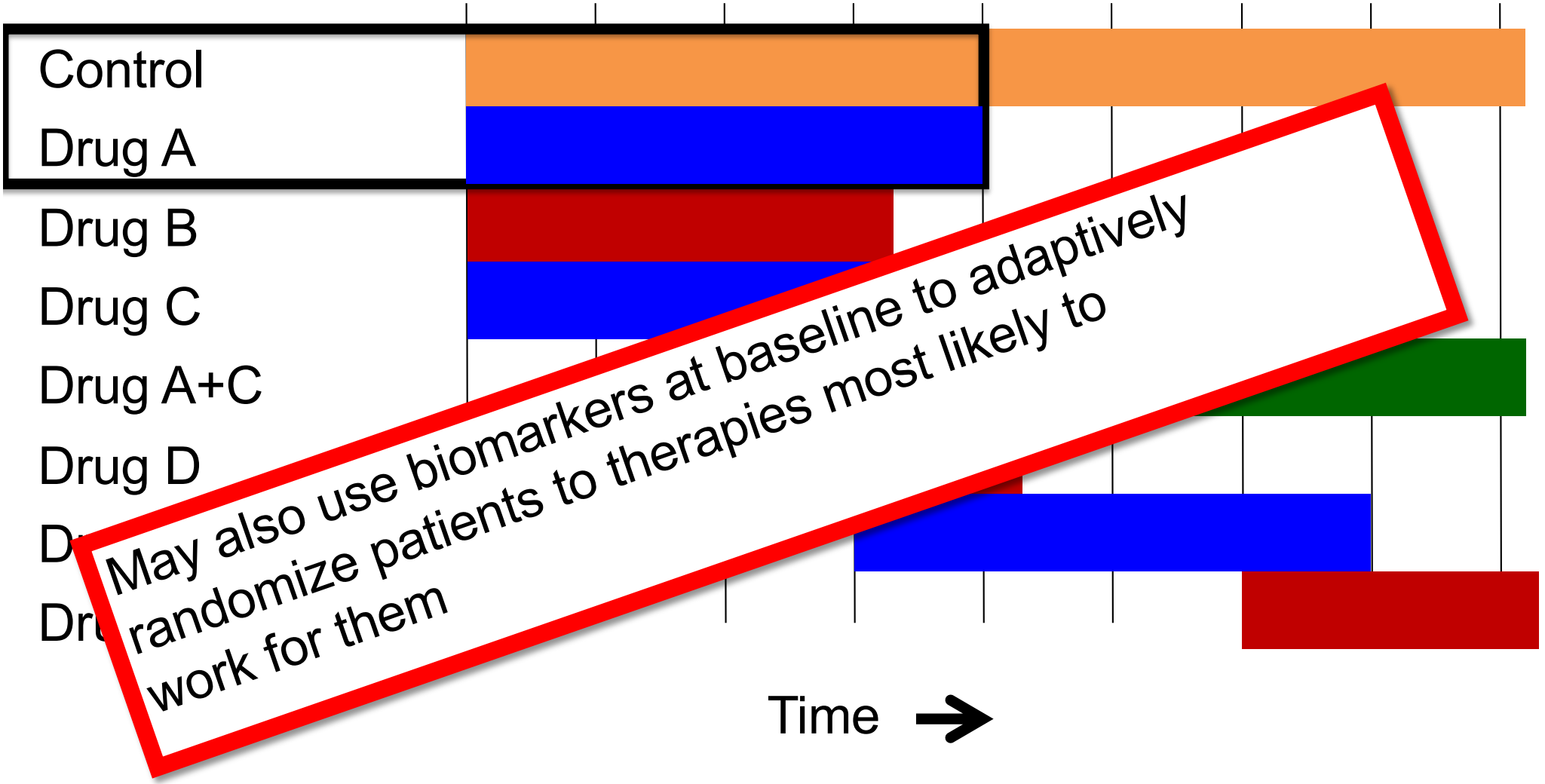
Platform Trial



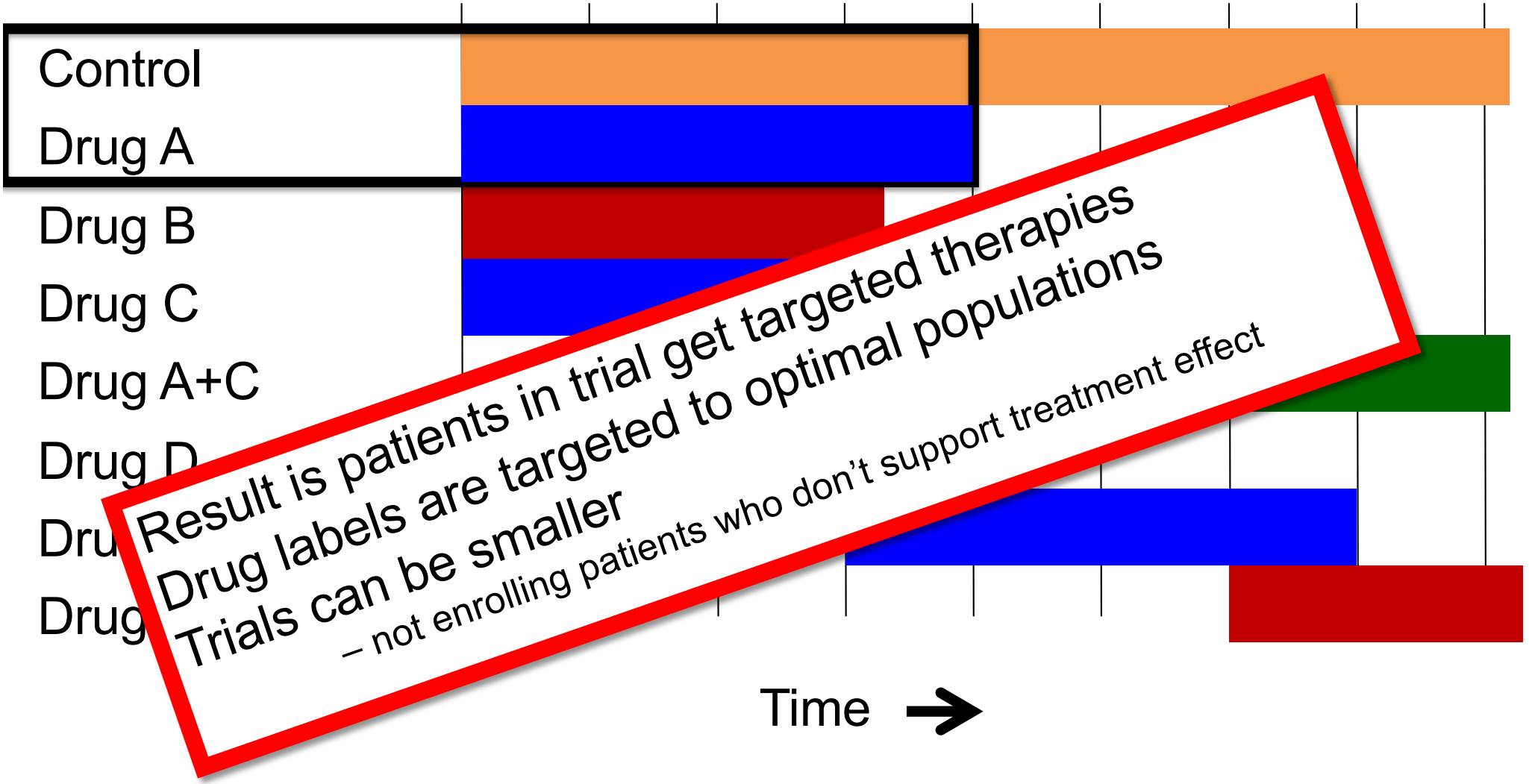
Platform Trial



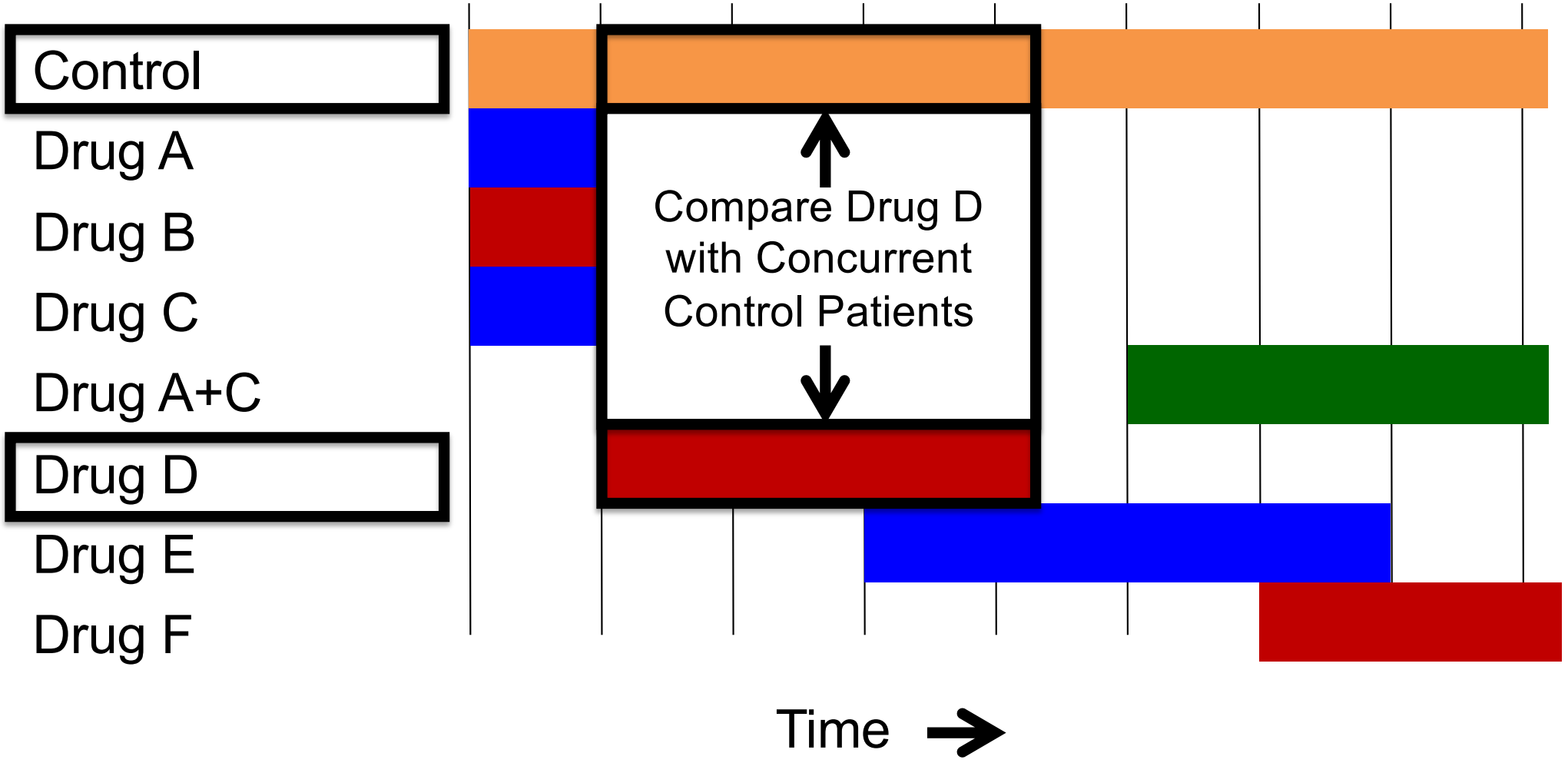
Platform Trial



Platform Trial

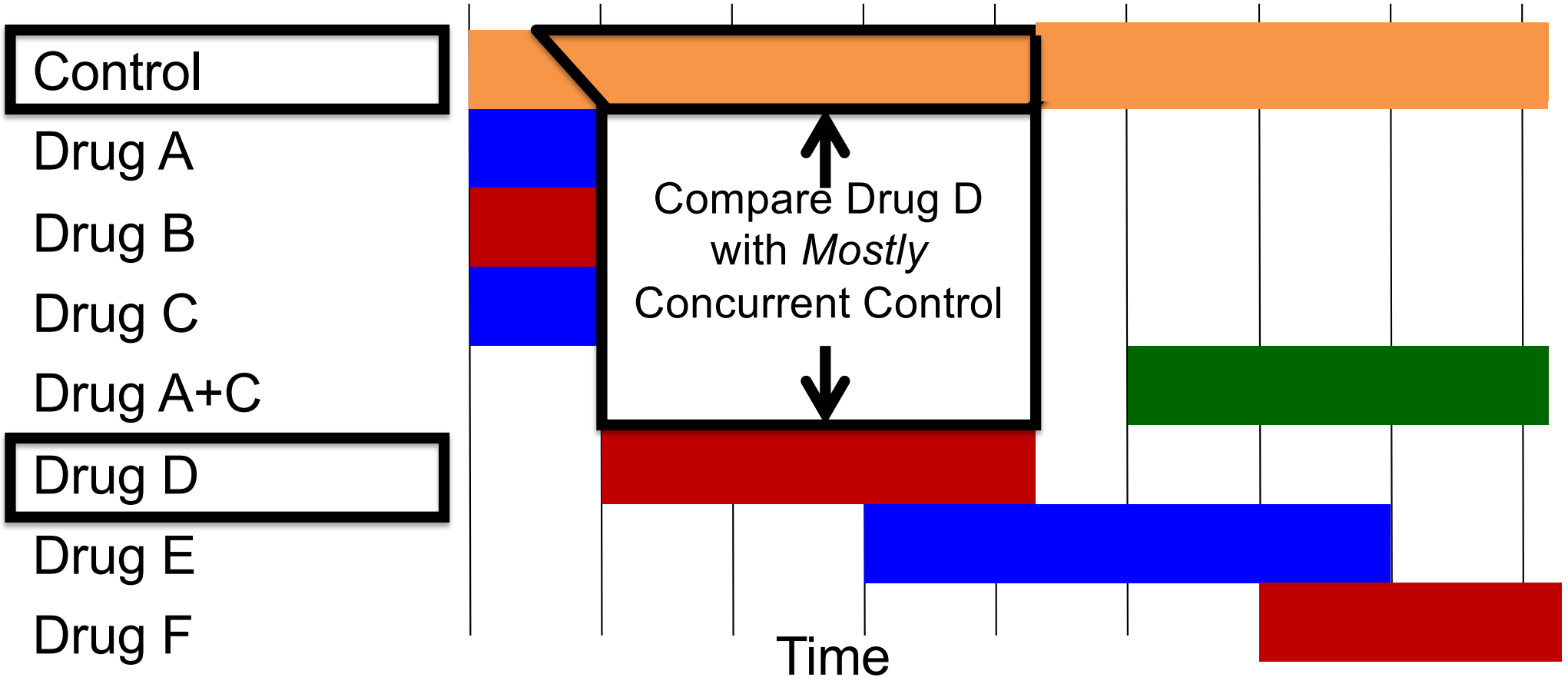


Platform Trial



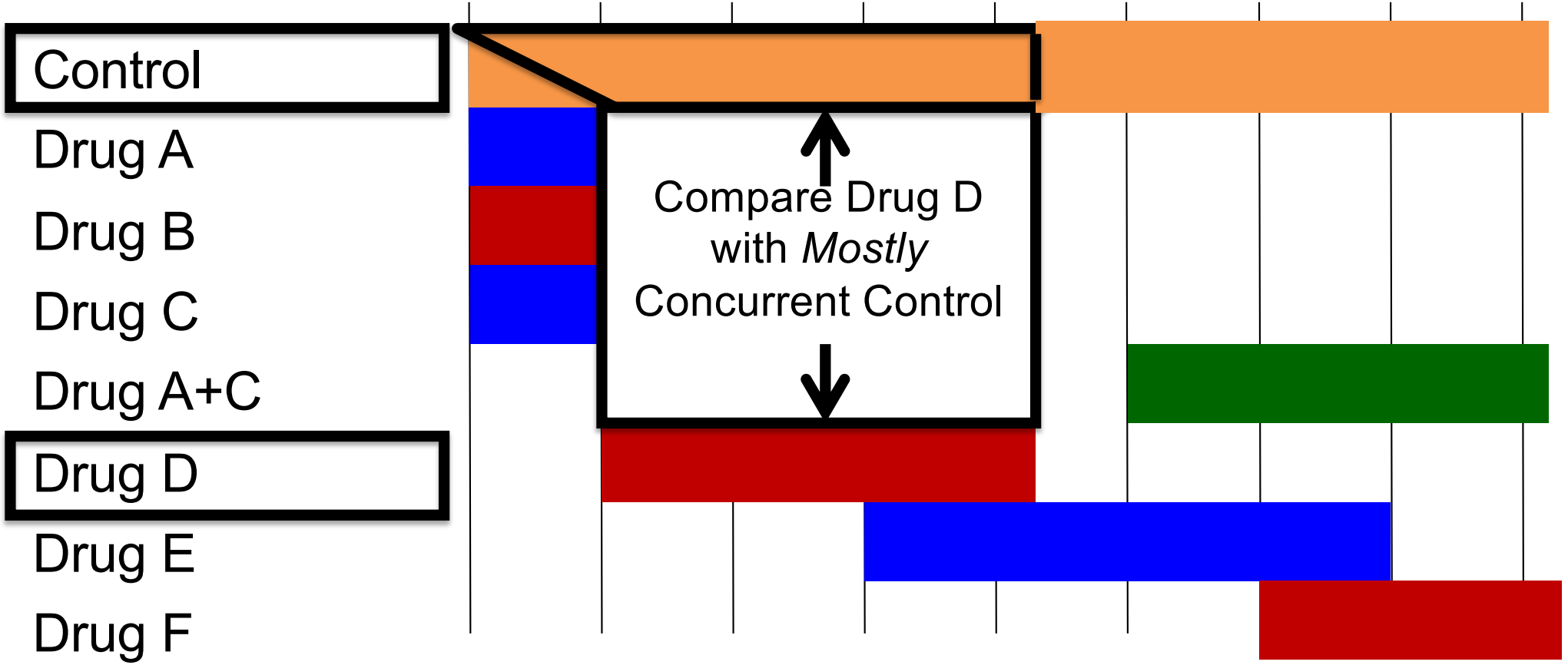
Time Machine

Model how controls change over time, if similar, then use some controls outside concurrent window



Time Machine

If controls change little over time, then use more weight from non-concurrent controls, increases power & efficiency



Platform Trials are Happening

- Infection diseases
  - Gates Foundation sponsored Ebola design
  - PREPARE: European Consortium for Disease Preparedness (Pandemic flu & CAP)
- Cancer
  - I-SPY2 in Breast Cancer
  - GBM AGILE in Glioblastoma multiforme
  - LUNG-MAP in Lung Cancer
- Alzheimer's
  - EPAD: European Prevention of Alzheimer's Dementia
  - DIAN: Dominantly Inherited Alzheimer's Network

Characteristics of Modern Platform Trials	Cancer Trials							
	I-SPY 2	MICAT	BATTLE	LUNG-MAP	UK MATRIX	GBM-AGILE	Alzheimer's	Ebola
Screen markers for all pts	✔	✔	✔	✔	✔	✔	—	—
Master protocol	✔	✔	✔	✔	✔	✔	✔	✔
Many regimens	✔	✔	✔	✔	✔	✔	✔	✔
Combination therapies	✔	✔	✔			✔	✔	✔
Sequential therapies		✔				✔		
Assembly line	✔	✔			✔	✔	✔	✔
Learn off-target effects	✔	✔	✔			✔	—	—
Pair regimens/biomarkers	✔	✔	✔			✔	—	—
Common control arm	✔	✔				✔	✔	✔
Adaptive randomization	✔	✔	✔			✔	✔	✔
Adaptive sample size	✔	✔				✔	✔	✔
Early "curable" disease	✔					✔	✔	✔
Registration endpoint	✔					✔	✔	✔
Seamless phases						✔		
Longitudinal modeling	✔	✔				✔	✔	
Bayesian	✔	✔	✔			✔	✔	✔

Article

CLINICAL TRIALS

Clinical Trials
1–9

DOI: 10.1177/1740774515626362
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Efficiencies of platform clinical trials: A vision of the future

Benjamin R Saville[1,2] and Scott M Berry[1,3]

Abstract

Background: A "platform trial" is a clinical trial with a single master protocol in which multiple treatments are evaluated simultaneously. Adaptive platform designs offer flexible features such as dropping treatments for futility, declaring one or more treatments superior, or adding new treatments to be tested during the course of a trial.

Methods: A simulation study explores the efficiencies of various platform trial designs relative to a traditional two-arm strategy.

Results: Platform trials can find beneficial treatments with fewer patients, fewer patient failures, less time, and with greater probability of success than a traditional two-arm strategy.

Conclusion: In an era of personalized medicine, platform trials provide the innovation needed to efficiently evaluate modern treatments.

Keywords

Platform trial, master protocol, multi-arm, adaptive, Bayesian, clinical trial design

CLINICAL TRIALS

Clinical Trials
1–9

DOI: 10.1177/1740774515621721
ctj.sagepub.com
SAGE

A response adaptive randomization platform trial for efficient evaluation of Ebola virus treatments: A model for pandemic response

Scott M Berry[1,2], Elizabeth A Petzold[3], Peter Dull[4], Nathan M Thielman[5], Coleen K Cunningham[6], G Ralph Corey[5], Micah T McClain[6], David L Hoover[7], James Russell[8], J McLeod Griffiss[7] and Christopher W Woods[3,5,6]

Abstract

The outbreak of Ebola virus disease in West Africa is the largest ever recorded. Numerous treatment alternatives for Ebola have been considered, including widely available repurposed drugs, but initiation of enrollment into clinical trials has been limited. The proposed trial is an adaptive platform design. Multiple agents and combinations will be investigated simultaneously. Additionally, new agents may enter the trial as they become available, and failing agents may be removed. In order to accommodate the many possible agents and combinations, a critical feature of this design is the use of response adaptive randomization to assign treatment regimens. As the trial progresses, the randomization ratio evolves to favor the arms that are performing better, making the design also suitable for all-cause pandemic preparedness planning. The study was approved by US and Sierra Leone ethics committees, and reviewed by the US Food and Drug Administration. Additionally, data management, drug supply lines, and local sites were prepared. However, in response to the declining epidemic seen in February 2015, the trial was not initiated. Sierra Leone remains ready to rapidly activate the protocol as an emergency response trial in the event of a resurgence of Ebola. (ClinicalTrials.gov Identifier: NCT02380625.) In summary, we have designed a single controlled trial capable of efficiently identifying highly effective or failing regimens among a rapidly evolving list of proposed therapeutic alternatives for Ebola virus disease and to treat the patients within the trial effectively based on accruing data. Provision of these regimens, if found safe and effective, would have a major impact on future epidemics by providing effective treatment options.

EBOLA

Thanks to: Scott Berry,

Elizabeth Petzold,

Chris Woods, David Hoover

The Problem: Ebola Treatment Trial

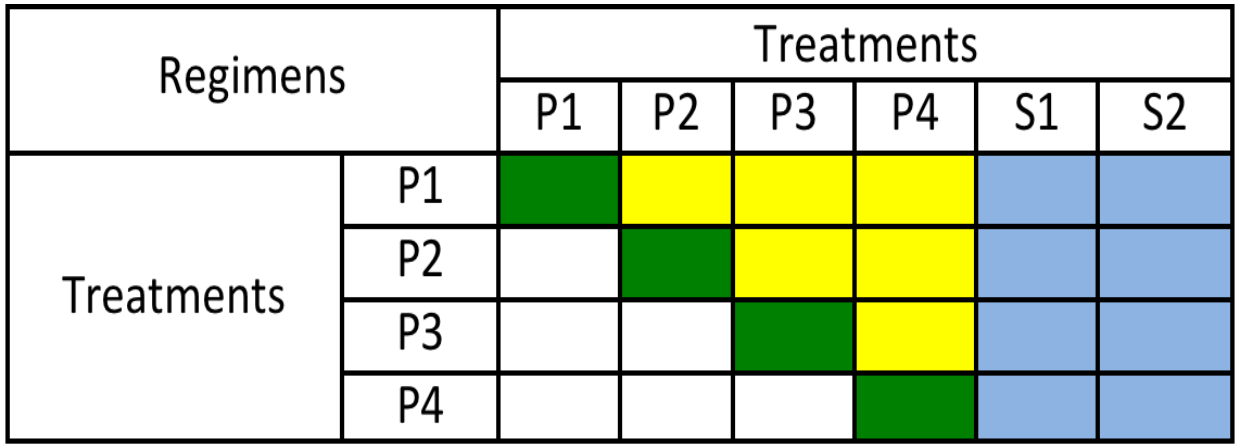
- Acknowledge universe of possible treatments
  - Will evolve over time
  - Recognition that combinations may play an important role
- Uncertainty over role of standard of care
- Our Goal: To determine best treatment for treating ebola
  - Not a trial to determine if a single drug X works

EV-003 Adaptive Platform Design

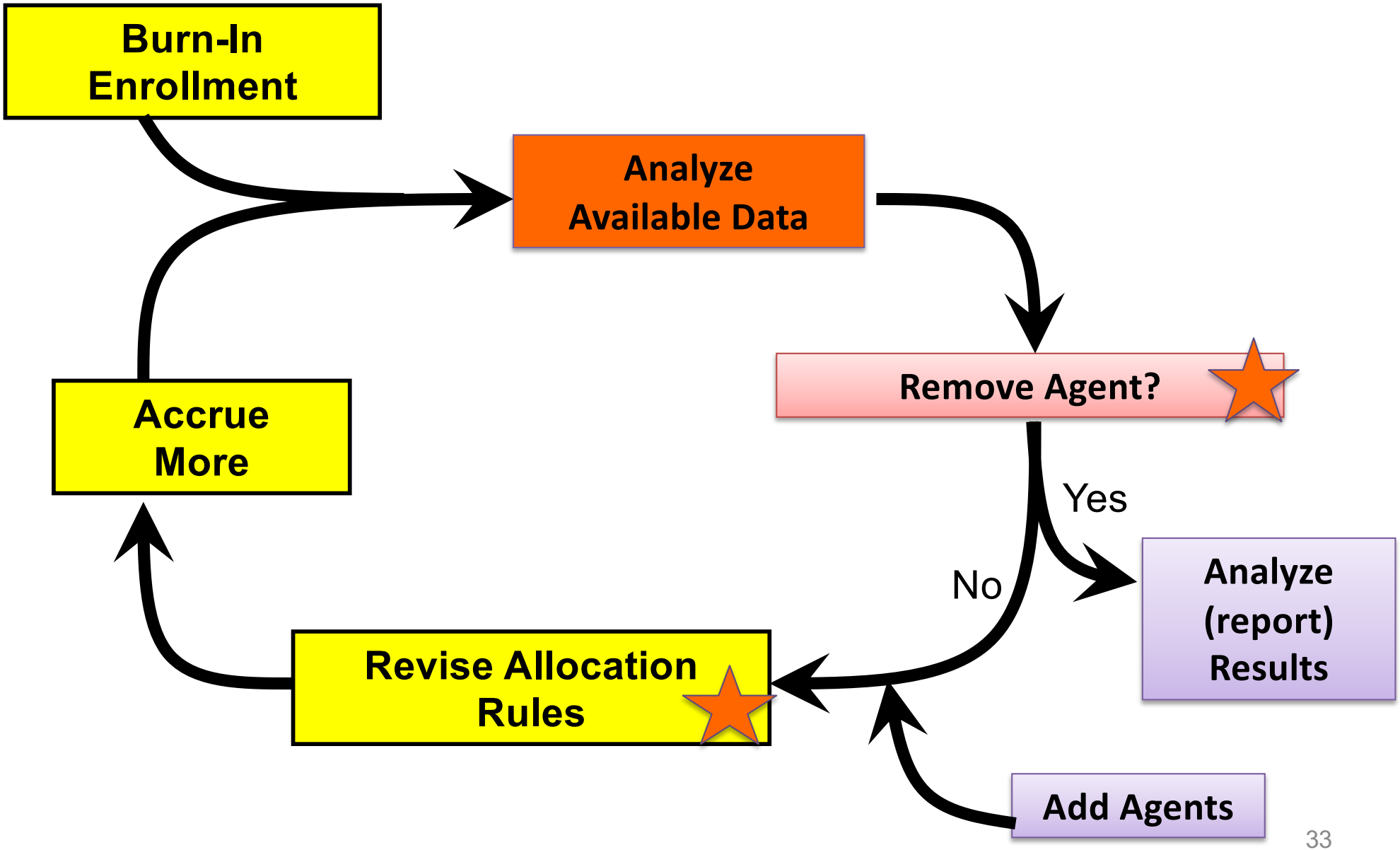
- Reviewed and approved by:
  - Duke University IRB
  - University of Sierra Leone ethics committee
- *Master Protocol* dictates trial behavior, each treatment included as an appendix
- Multiple Agents
  - Primary & Secondary agents
  - Combination + Single agents
- Response Adaptive Randomization (RAR)
  - Run by a single algorithm
  - Assigns treatment regimens that are performing better using collection of primary endpoint data
- Protocol is built so trial arms evolve (part of the protocol!), trial is **perpetual**
- Endpoint is 14-day mortality

Primary/Secondary Agents

- All arms receive optimized standard of care (SOC)
- Primary and Secondary agents
  - Primary: Expected capability to work as single agent (e.g. anti-viral efficacy)
  - Secondary: Expected to work with other agents (not given alone)



Adaptive Platform Design



Design Details

- Endpoint: Death (Dichotomous, events are bad)
- Start with burn-in period to all 10 regimens
  - Equal randomization to 10 arms
  - 30 subjects / 3 per arm
- After burn-in
  - Response adaptive randomization
  - Proportional to probability regimen is optimal
    - Adjusted for information
  - Continue perpetually (committee can change vote)

Starting Structure

Burn-In Enrollment

- Allocate 50% of subjects to single-agent arms
- Allocate 50% to combination arms
- If a SOC arm is to be included, it gets a minimum of 20% allocation

Decision Criteria (In/Out)

Analyze (report) Results

- If there is a less than 0.01 probability an agent is part of the optimal regimen
  - Candidate for futility
- If the probability an agent is in the optimal regimen is greater than 0.95
  - Report to the steering committee for public dissemination
- If a regimen has at least a 0.95 probability of being superior to SOC Alone then SOC Alone is reported for removal

Revise Allocation Rules

Allocation Rules

- If a SOC it gets minimum of 20%...
- Randomize to regimens with probability proportional to:

$$r_{ij} \sim \frac{\Pr\left(\pi_{ij} = \max\left(\pi\right)\right)}{n_{ij}+1}$$

Statistical Model

Analyze Available Data

$$\log\left(\frac{p}{1-p}\right) = \alpha + \sum_{X=1}^{M}[X] + \sum_{X=1}^{M}\sum_{Y=X+1}^{M}[X,Y] + \lambda_{TIME}$$

- Priors:

$$[X] \sim N(0,1^2) \qquad [X,Y] \sim N(0,0.2^2)$$

Statistical Model

Analyze Available Data

$$\log\left(\frac{p}{1-p}\right) = \alpha + \sum_{X=1}^{M}[X] + \sum_{X=1}^{M}\sum_{Y=X+1}^{M}[X,Y] + \lambda_{TIME}$$

- Priors:

$$[X] \sim N(0,1^2) \qquad [X,Y] \sim N(0,0.2^2)$$

N(0,1) has 95% CI from about 1/7 to 7.

Statistical Model

Analyze Available Data

$$\log\left(\frac{p}{1-p}\right) = \alpha + \sum_{X=1}^{M}[X] + \sum_{X=1}^{M}\sum_{Y=X+1}^{M}[X,Y] + \lambda_{TIME}$$

- Priors:

$$[X] \sim N(0,1^2) \qquad [X,Y] \sim N(0,0.2^2)$$

$N(0,0.2^2)$ has 95% CI from about 2/3 to 3/2.

Statistical Model

Analyze Available Data

$$\log\left(\frac{p}{1-p}\right) = \alpha + \sum_{X=1}^{M}[X] + \sum_{X=1}^{M}\sum_{Y=X+1}^{M}[X,Y] + \lambda_{TIME}$$

- Priors:

$$[X] \sim N\left(0,1^2\right) \qquad [X,Y] \sim N\left(0,0.2^2\right)$$

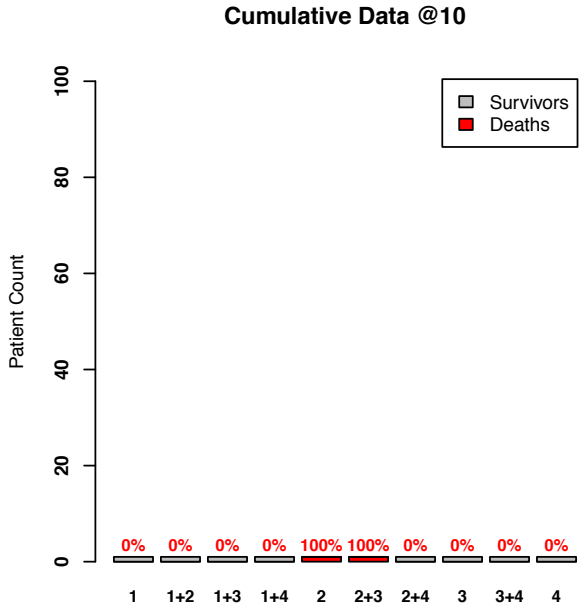
- Time:
  - Incorporate time "buckets" to model time trend or 'drift'

$$[\lambda] \sim NDLM\left(0,\tau^2\right)$$

Example Trial

Regimens		Agents			
		1	2	3	4
Agents	1				
	2				
	3				
	4				


New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @10
Survivors
Deaths
Patient Count
0
20
40
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80
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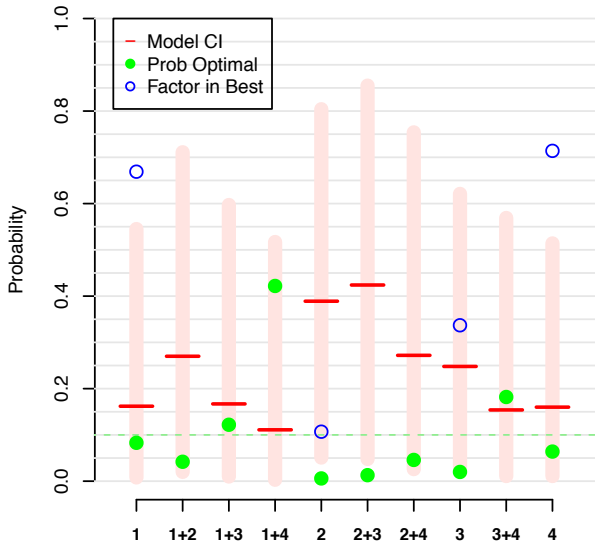
Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
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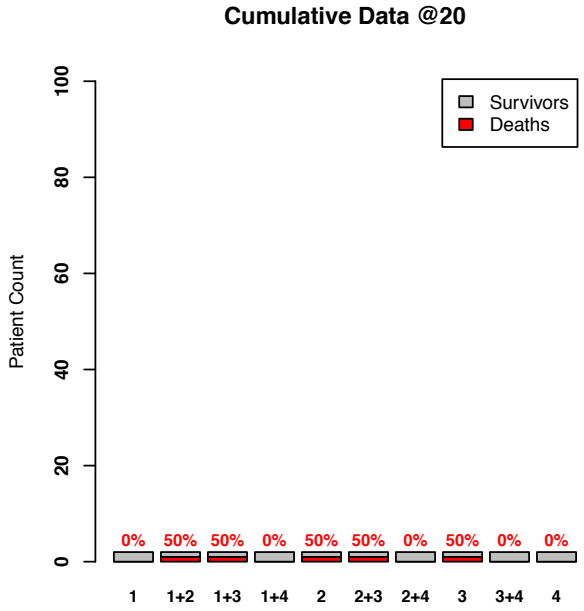
1+3
1+4
2
2+3
2+4
3
3+4
4


New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @20
Survivors
Deaths
Patient Count
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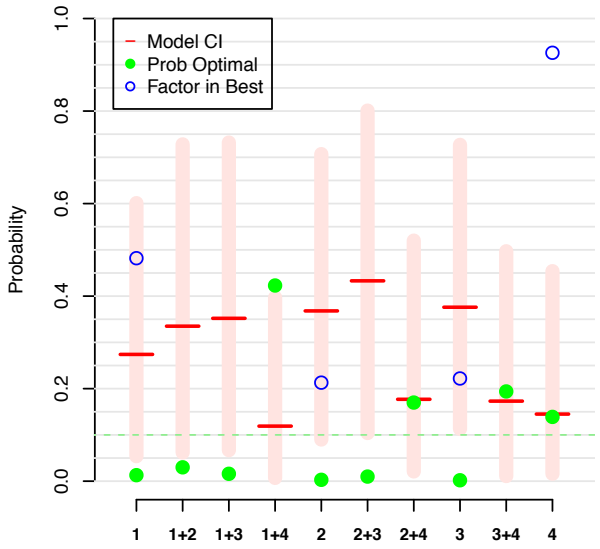
Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
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2+4
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New Data
Deaths
Survivors
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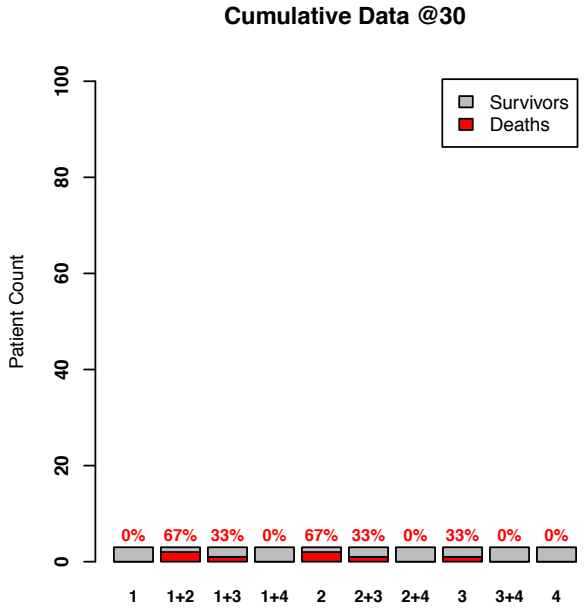
Cumulative Data @30
Survivors
Deaths
Patient Count
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20
40
60
80
100
0%
67%
33%
0%
67%
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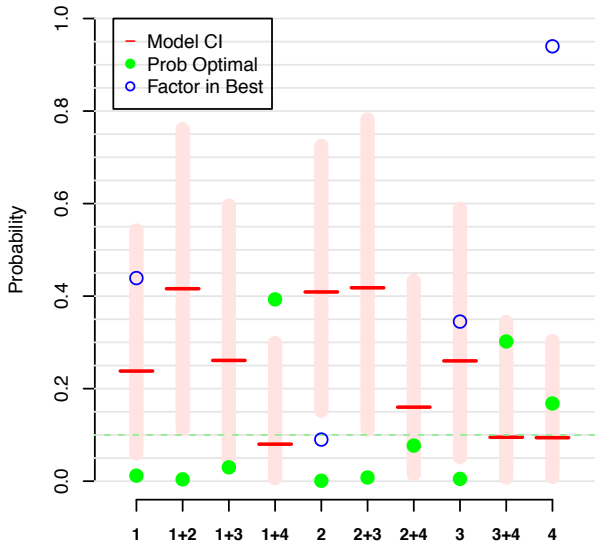
Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
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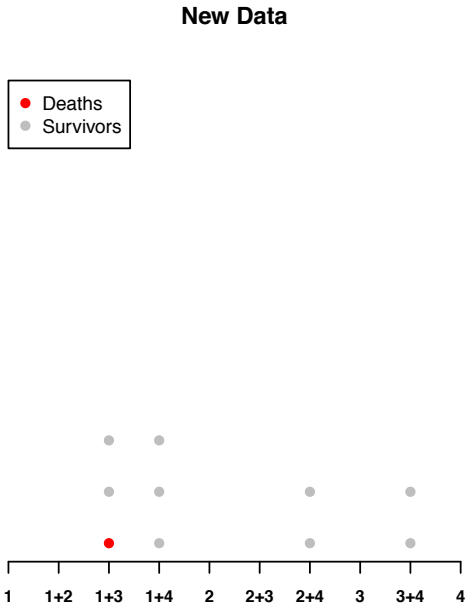
New Data
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Survivors
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1+2
1+3
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2
2+3
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3+4
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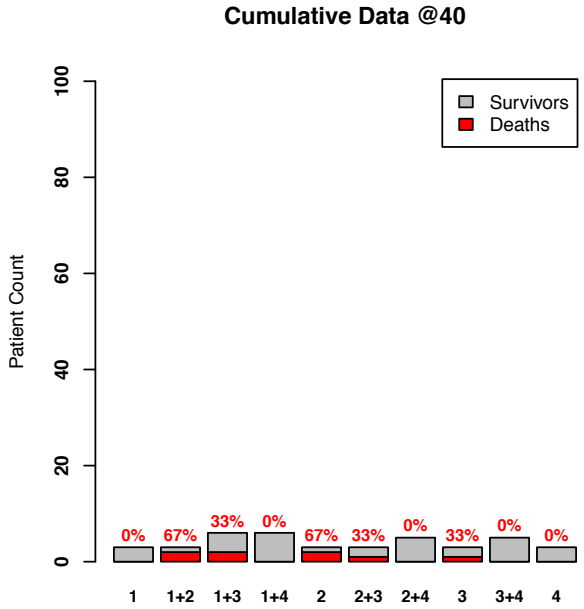
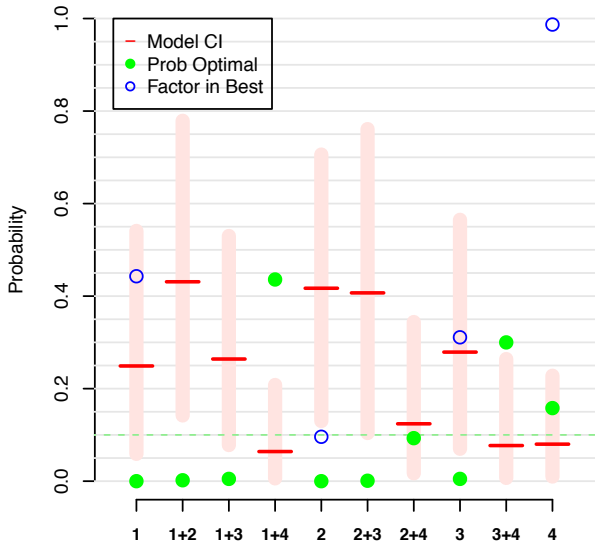
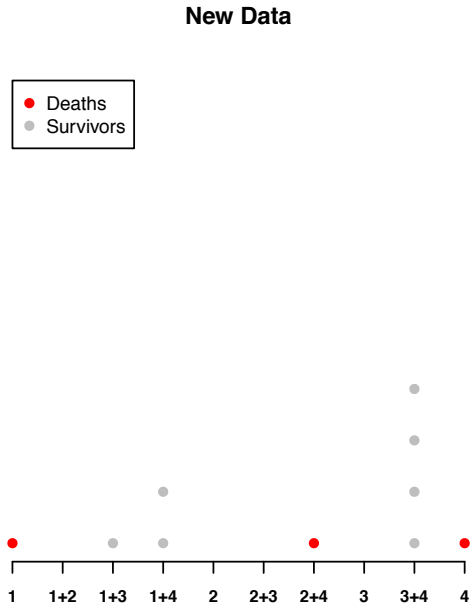
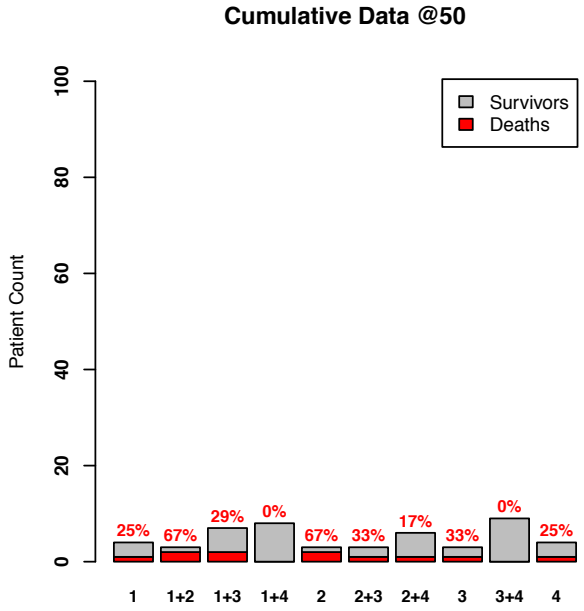
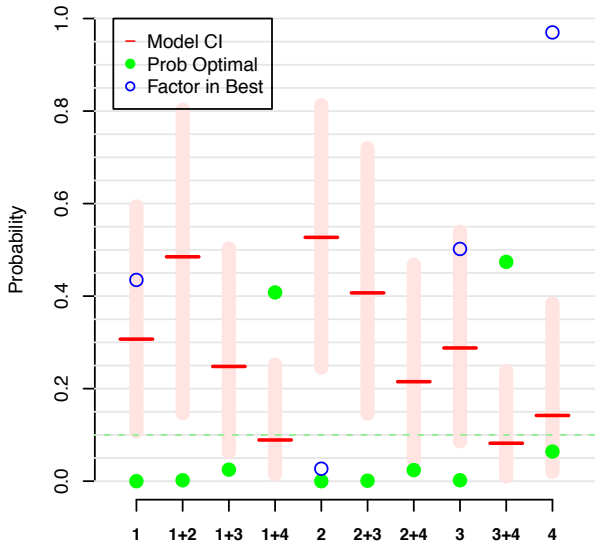
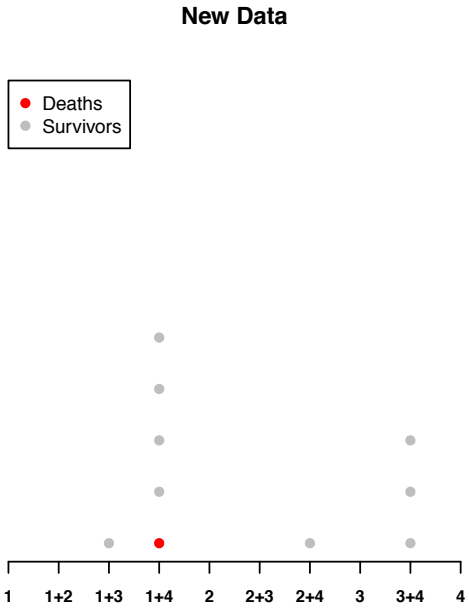

Cumulative Data @40
Survivors
Deaths
Patient Count
0
20
40
60
80
100
0%
67%
33%
0%
67%
33%
0%
33%
0%
0%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

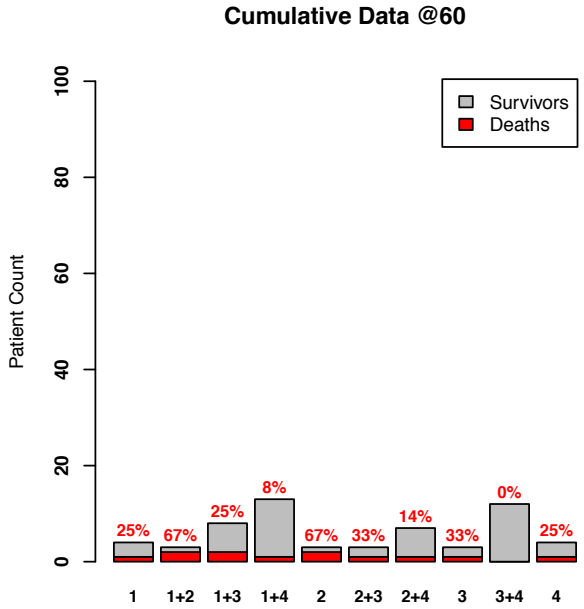

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

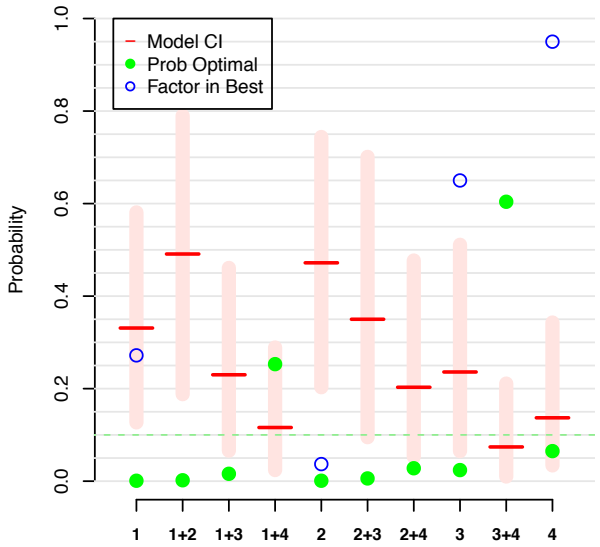

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

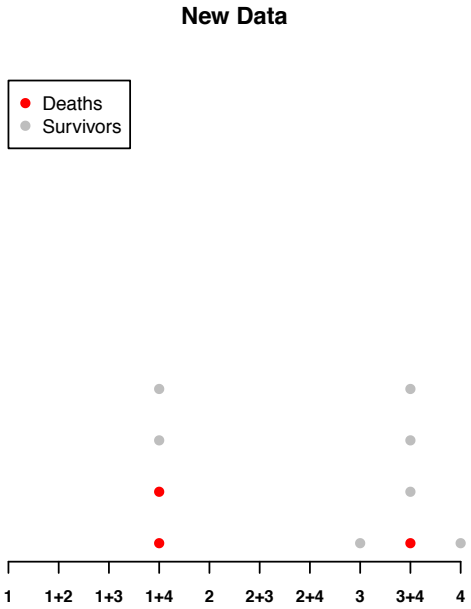

Cumulative Data @50
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
29%
0%
67%
33%
17%
33%
0%
25%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

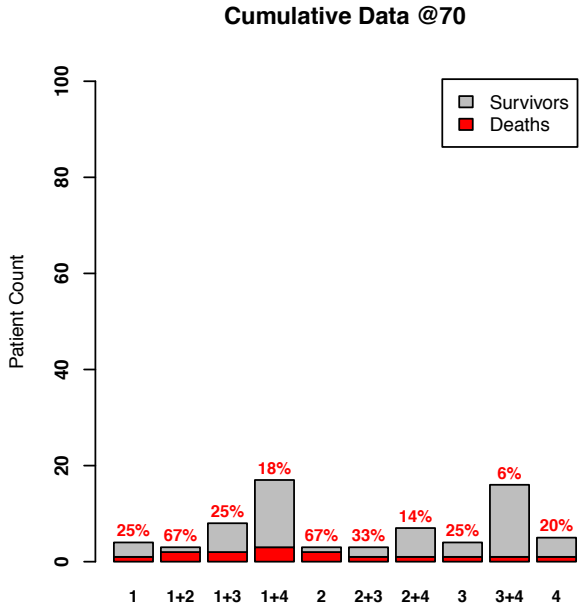

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

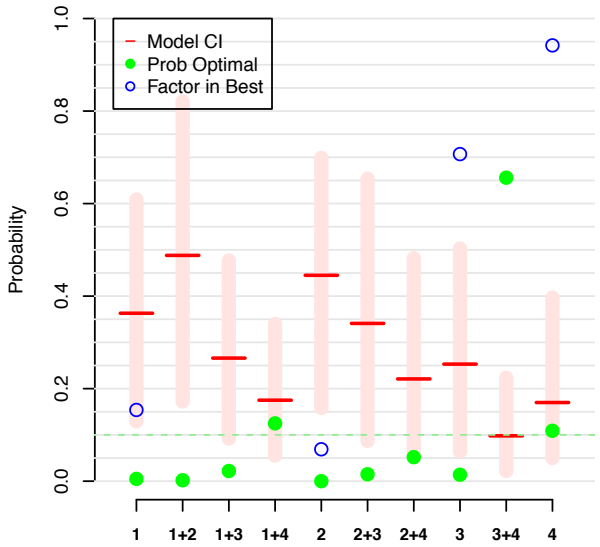

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

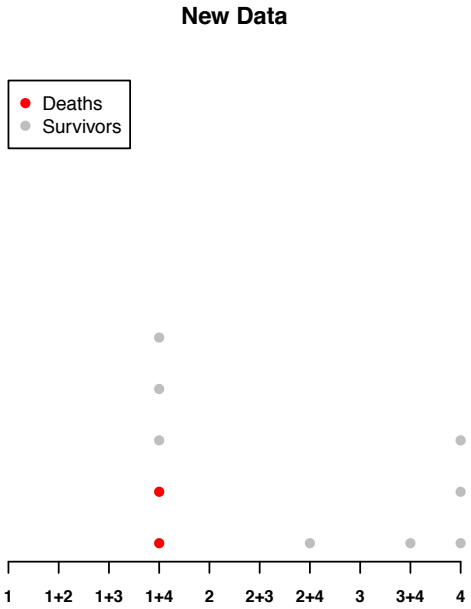

Cumulative Data @60
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
25%
8%
67%
33%
14%
33%
0%
25%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

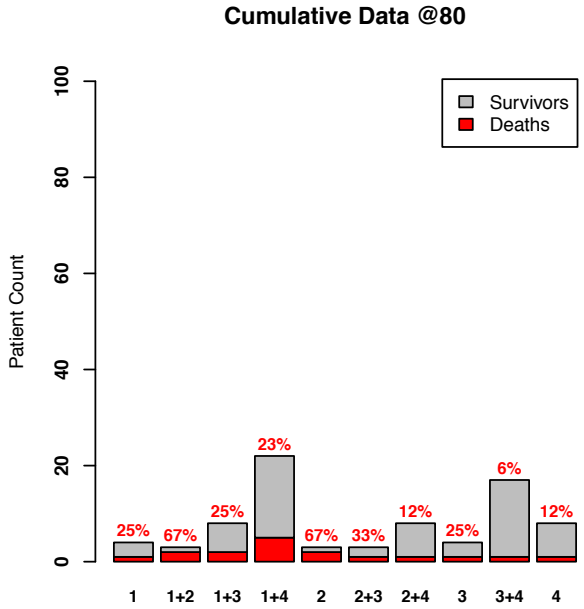

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

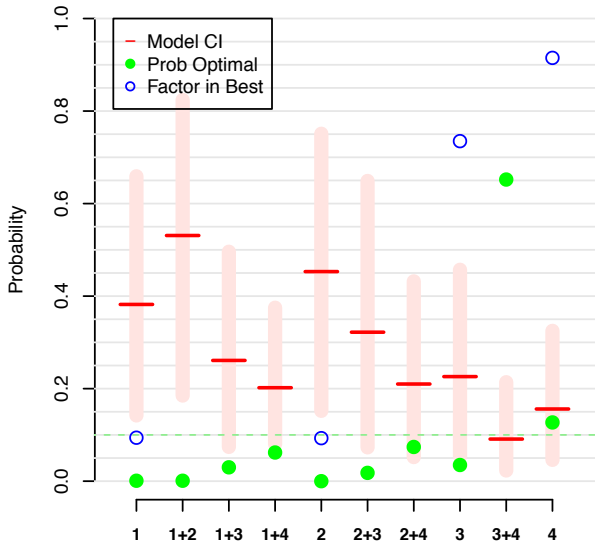

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

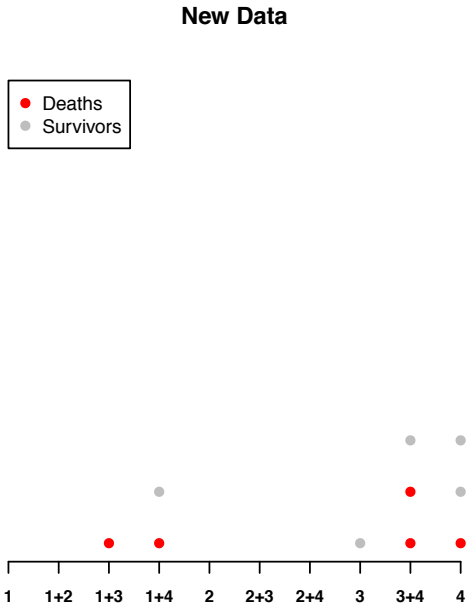

Cumulative Data @70
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
25%
18%
67%
33%
14%
25%
6%
20%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

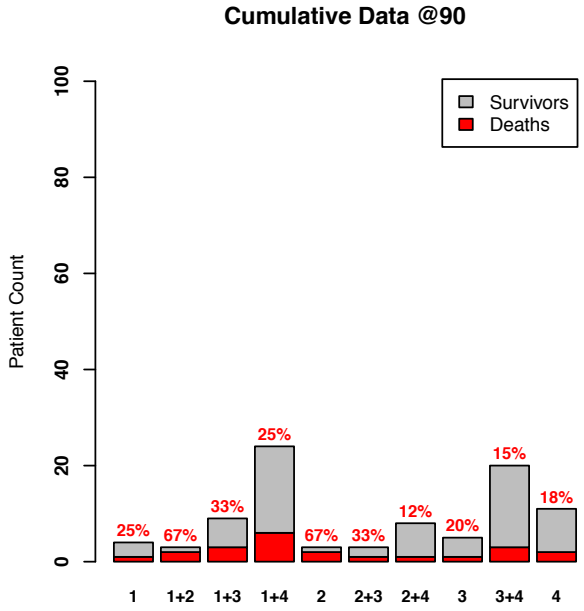

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

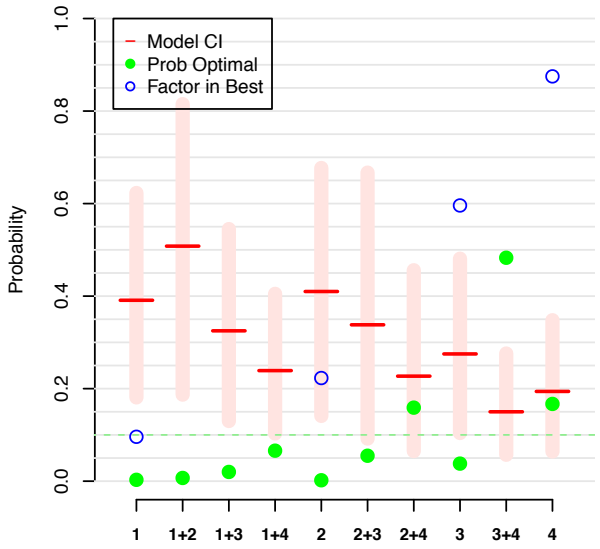

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

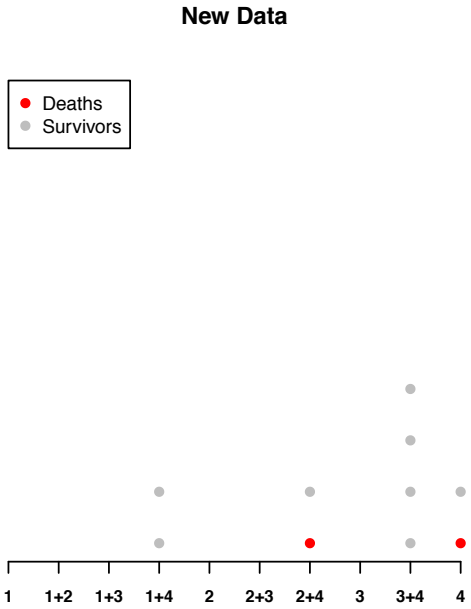

Cumulative Data @80
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
25%
23%
67%
33%
12%
25%
6%
12%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

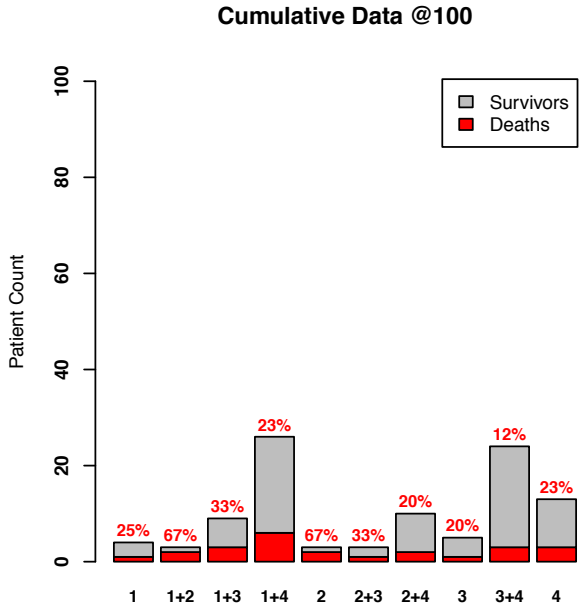

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

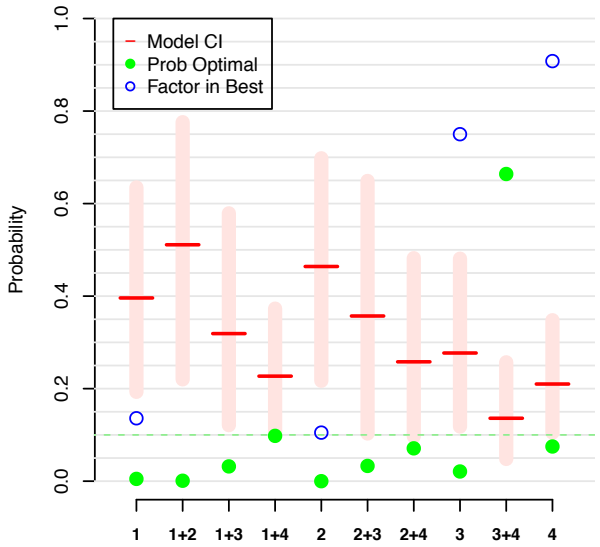

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

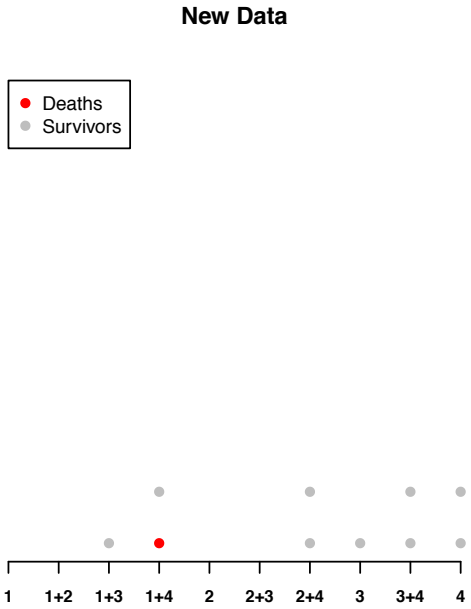

Cumulative Data @90
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
33%
25%
67%
33%
12%
20%
15%
18%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

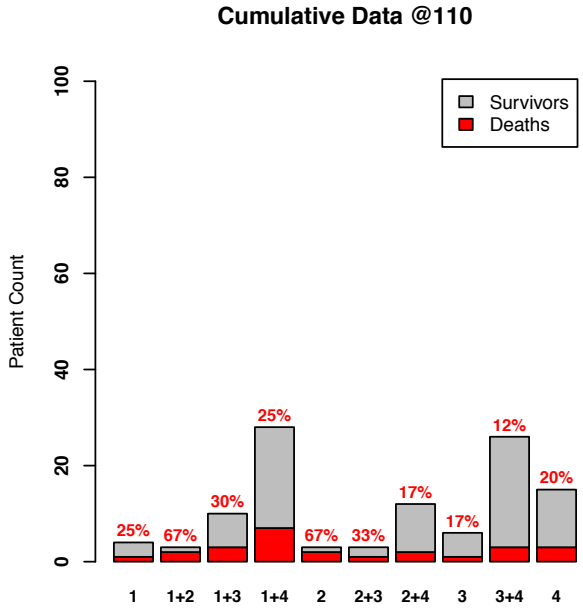

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

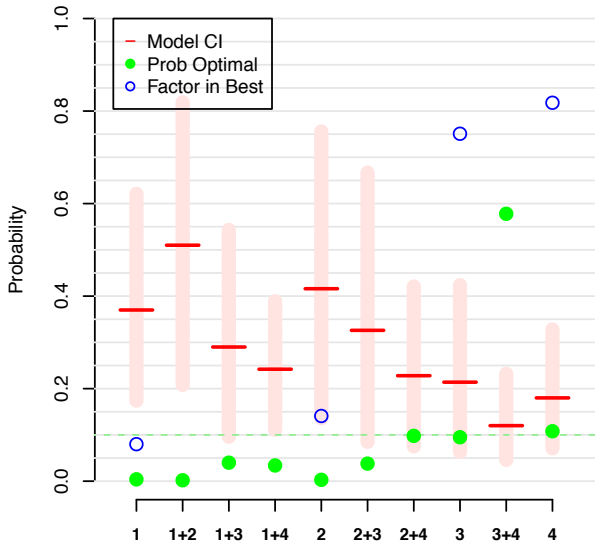

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

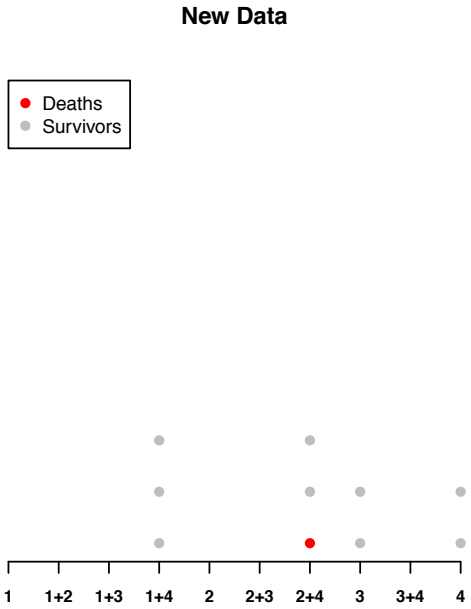

Cumulative Data @100
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
33%
23%
67%
33%
20%
20%
12%
23%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

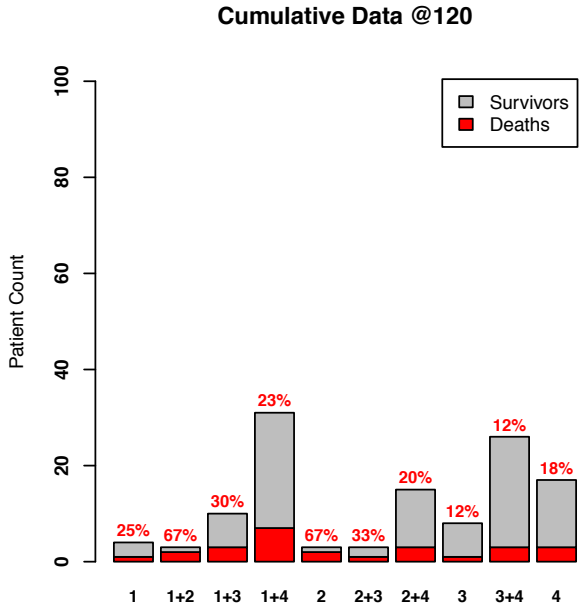

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

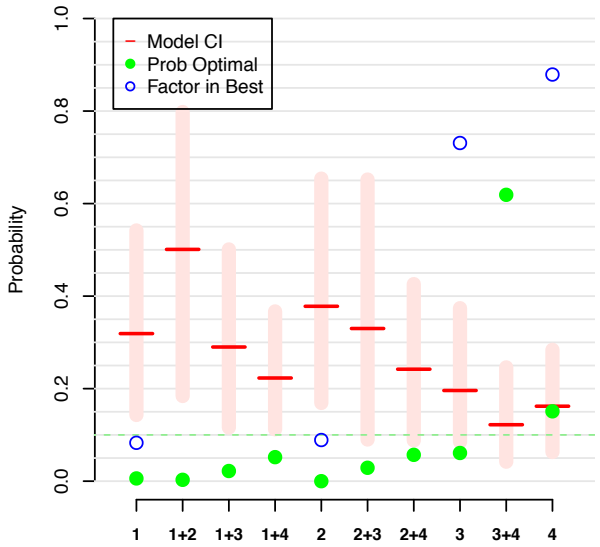

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @110
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
30%
25%
67%
33%
17%
17%
12%
20%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

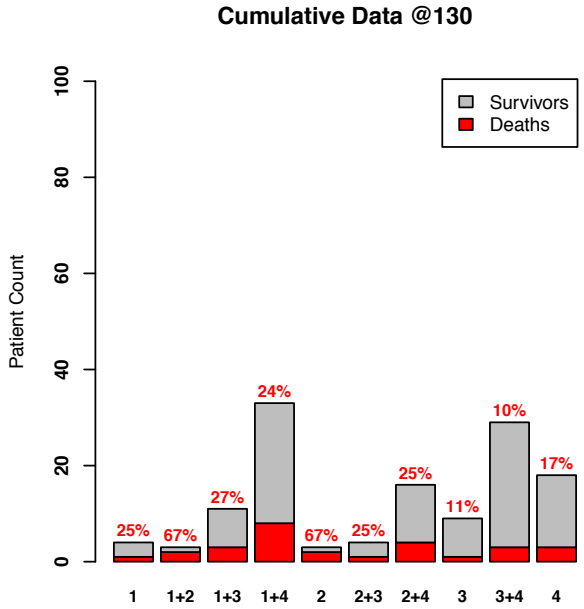

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

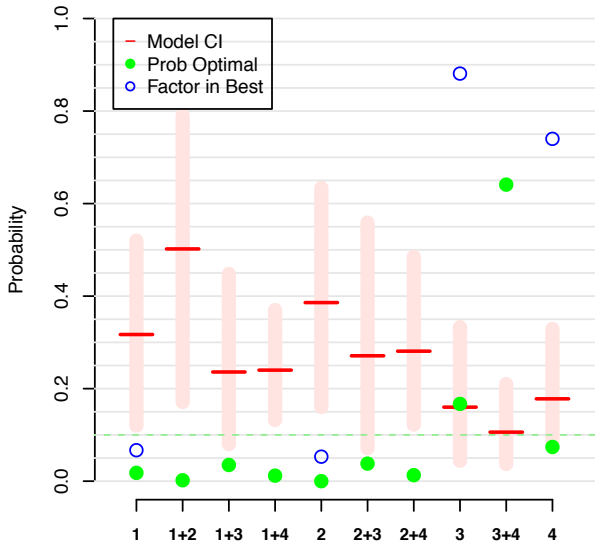

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

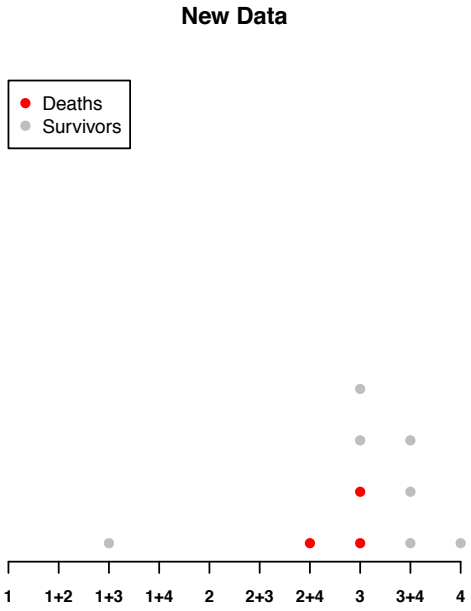

Cumulative Data @120
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
30%
23%
67%
33%
20%
12%
12%
18%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

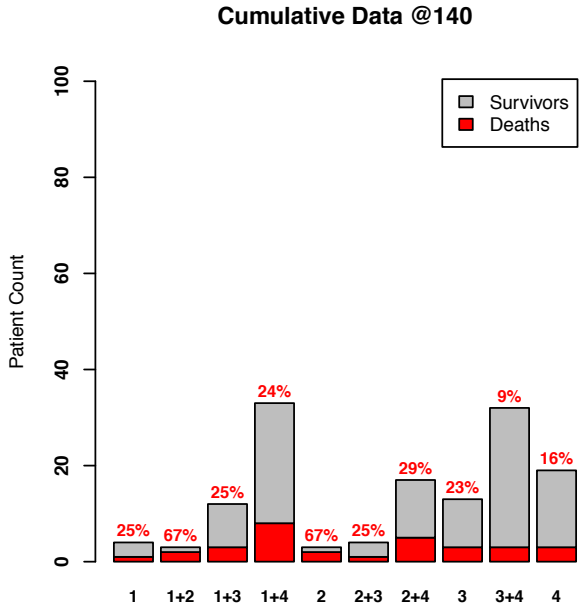

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

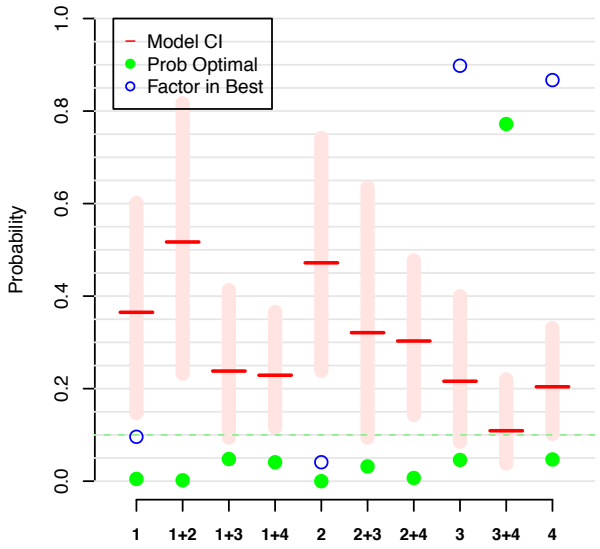

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

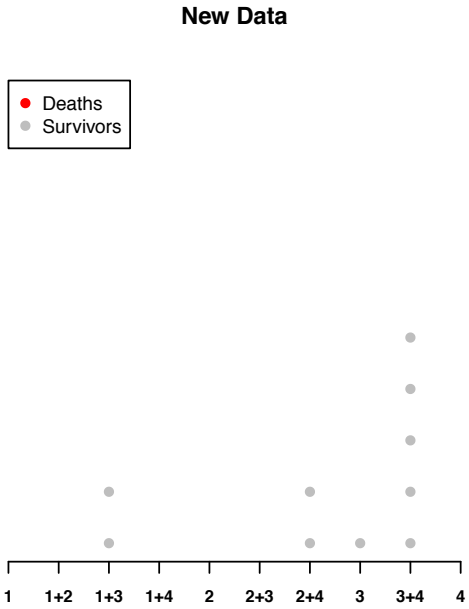

Cumulative Data @130
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
27%
24%
67%
25%
25%
11%
10%
17%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

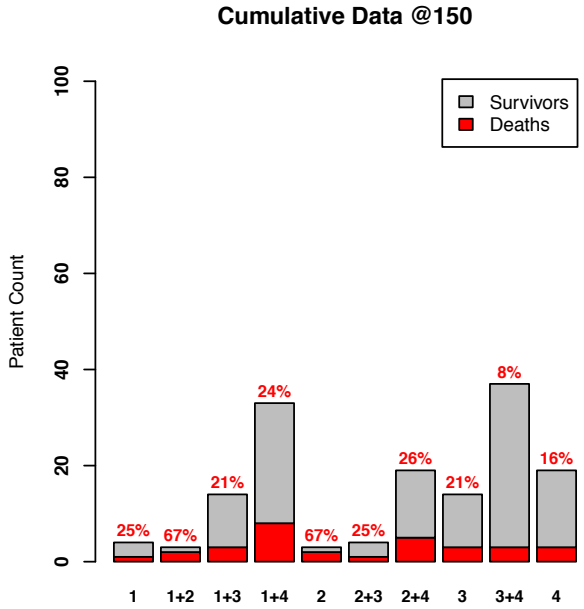

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

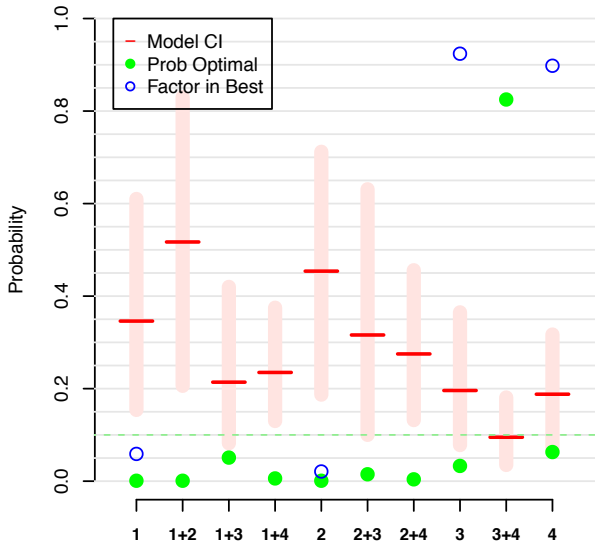

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

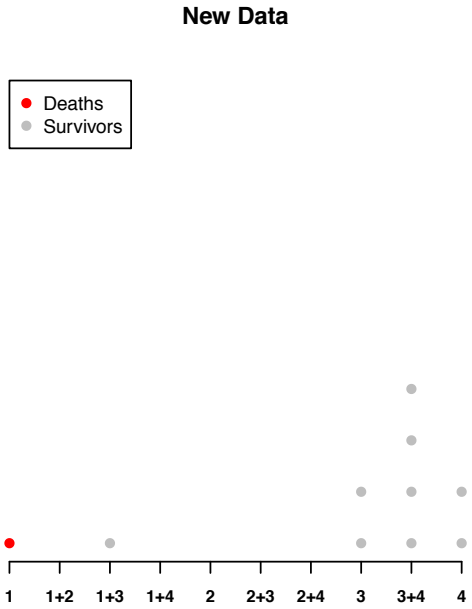

Cumulative Data @140
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
25%
24%
67%
25%
29%
23%
9%
16%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

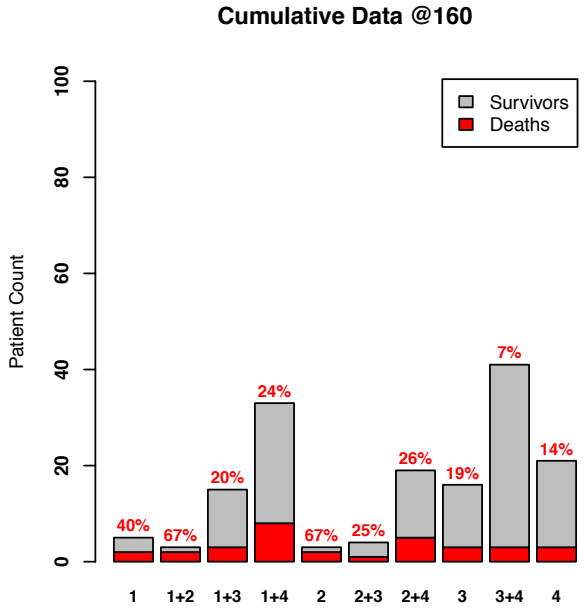

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

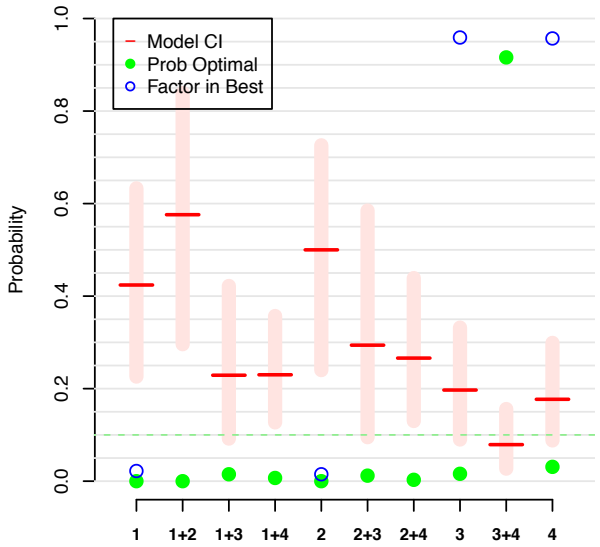

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

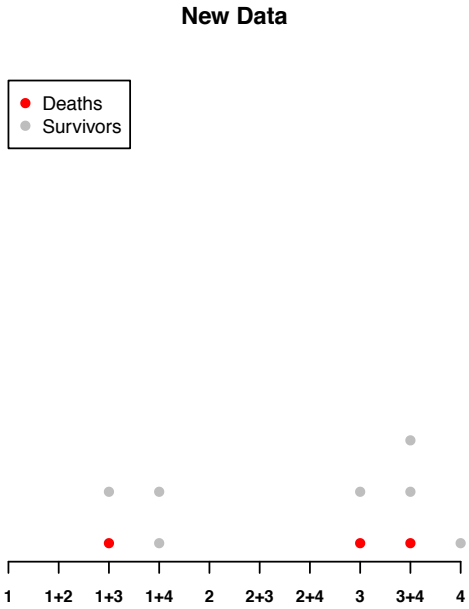

Cumulative Data @150
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
21%
24%
67%
25%
26%
21%
8%
16%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

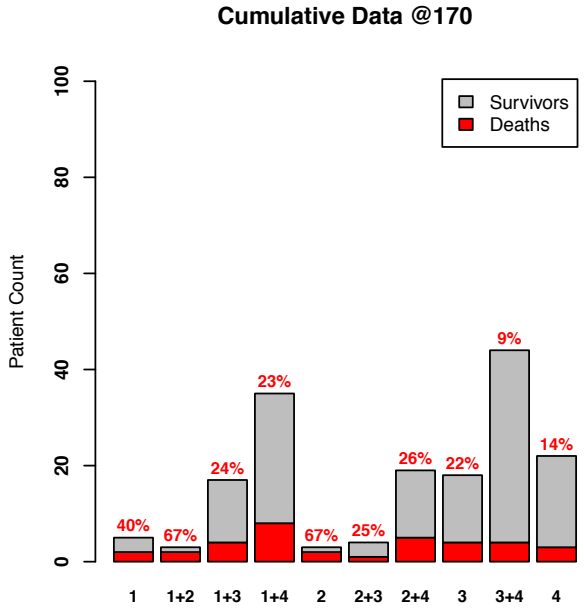

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

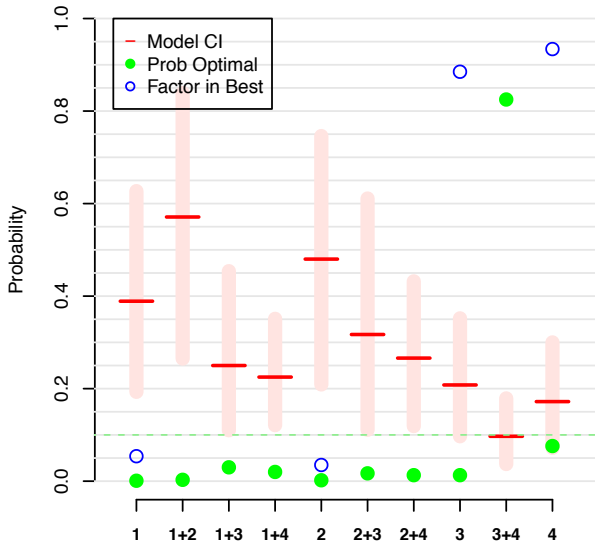

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @160
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
20%
24%
67%
25%
26%
19%
7%
14%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

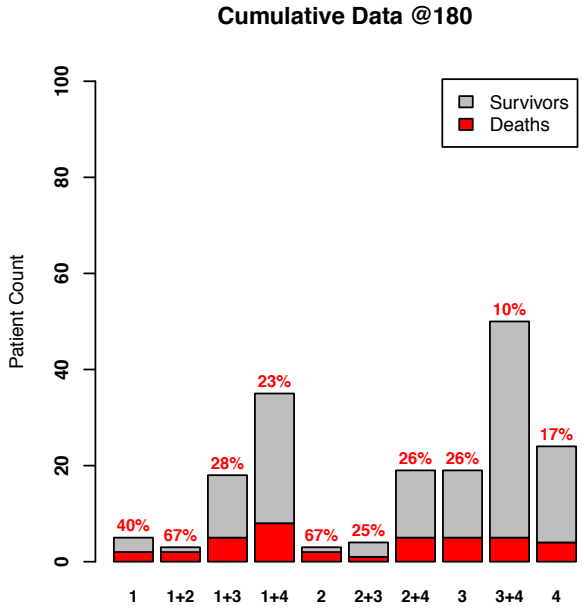

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

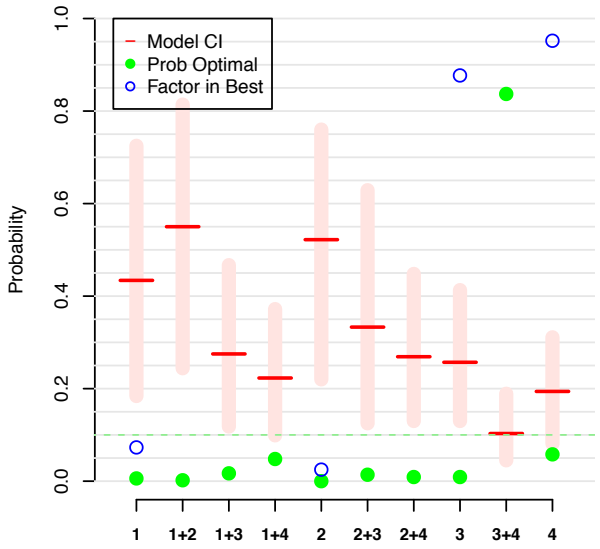

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

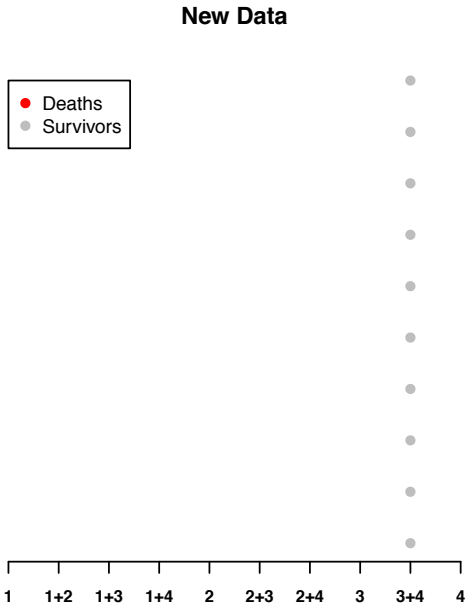

Cumulative Data @170
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
24%
23%
67%
25%
26%
22%
9%
14%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

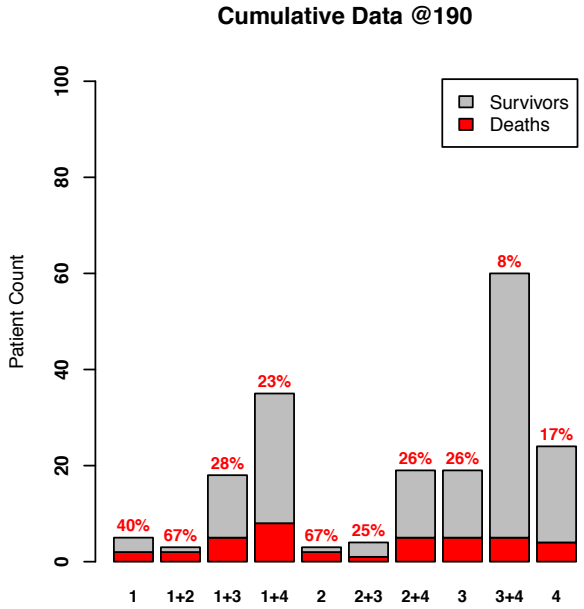

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

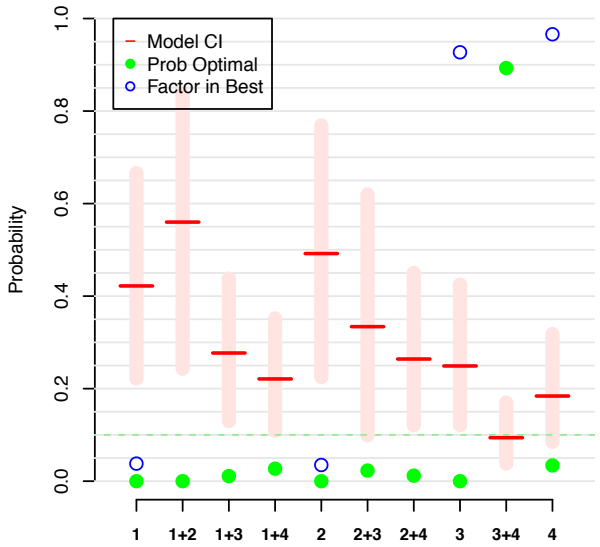

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

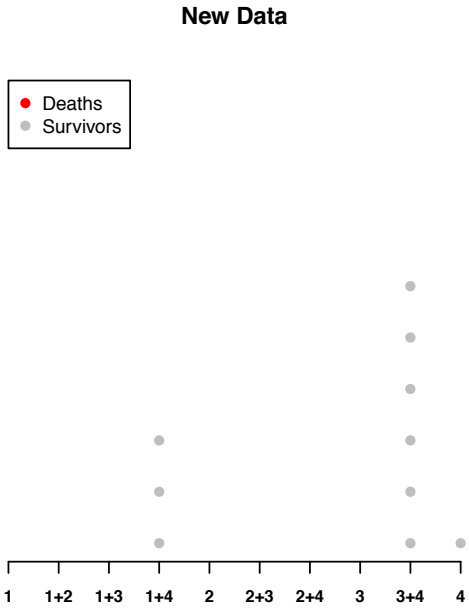

Cumulative Data @180
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
28%
23%
67%
25%
26%
26%
10%
17%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

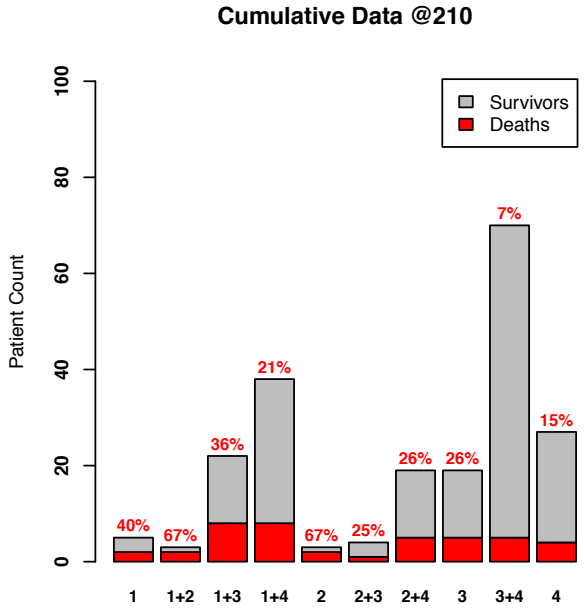

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

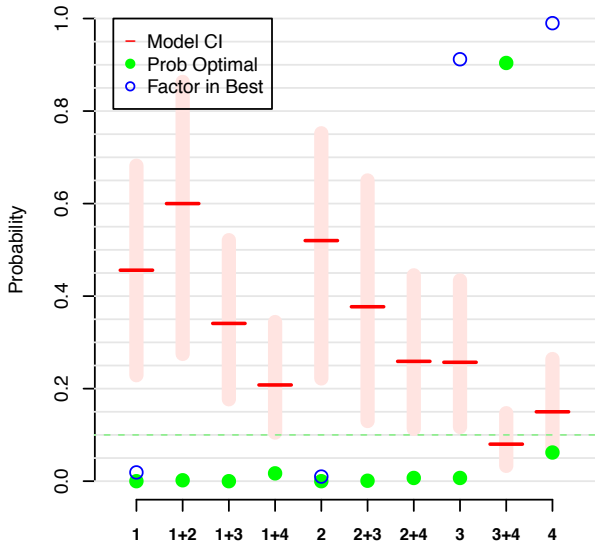

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

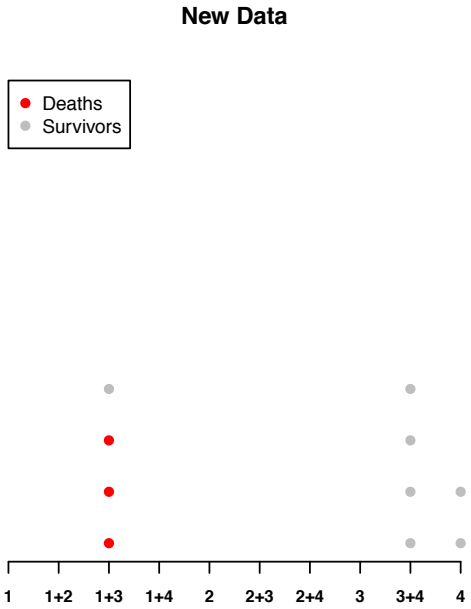

Cumulative Data @190
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
28%
23%
67%
25%
26%
26%
8%
17%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

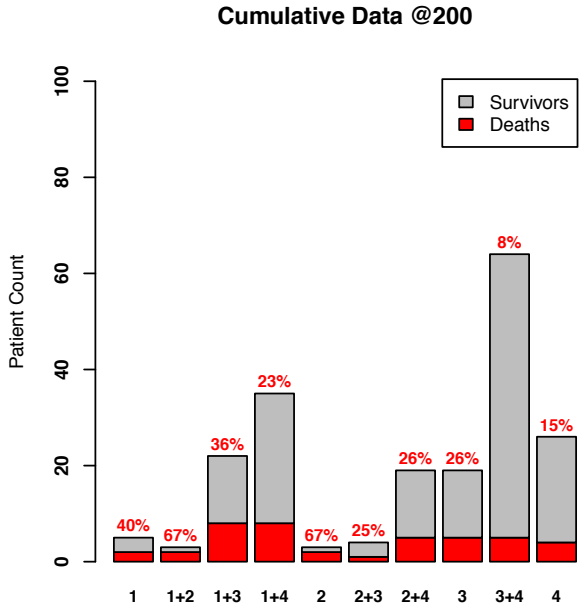

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

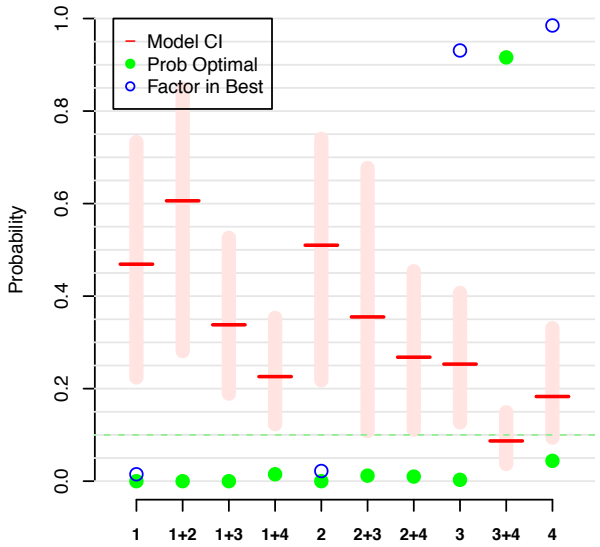

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

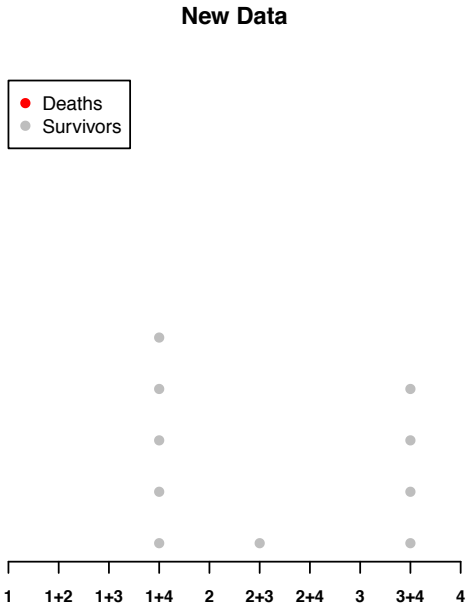

Cumulative Data @210
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
36%
21%
67%
25%
26%
26%
7%
15%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

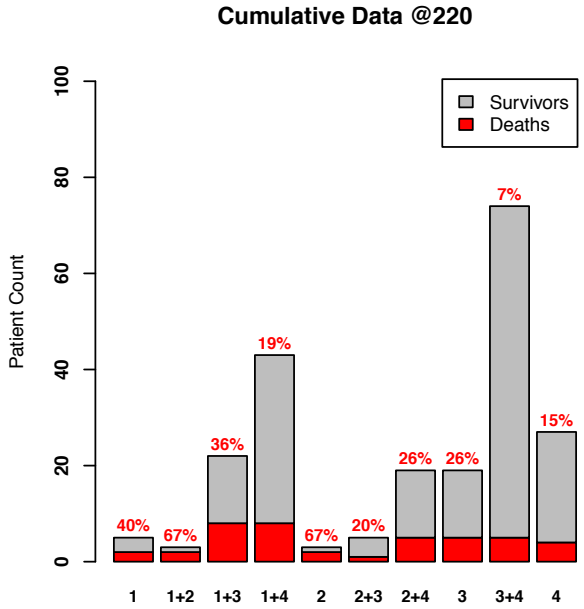

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

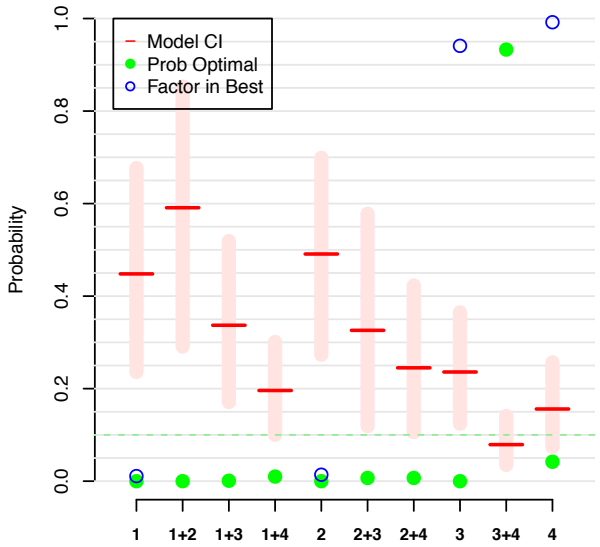

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @200
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
36%
23%
67%
25%
26%
26%
8%
15%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

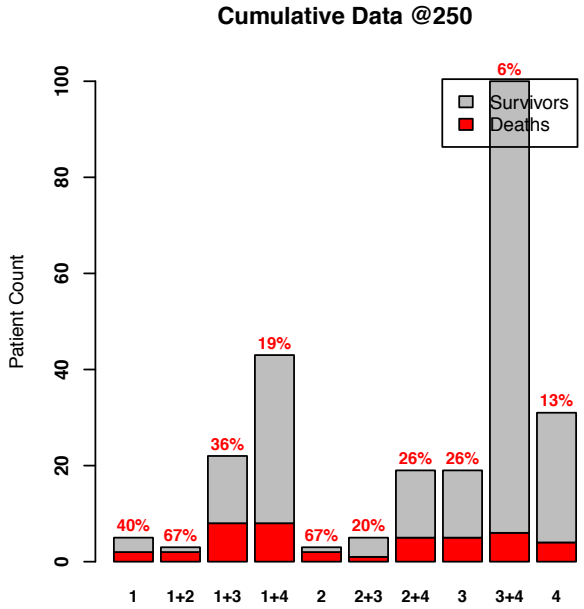

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

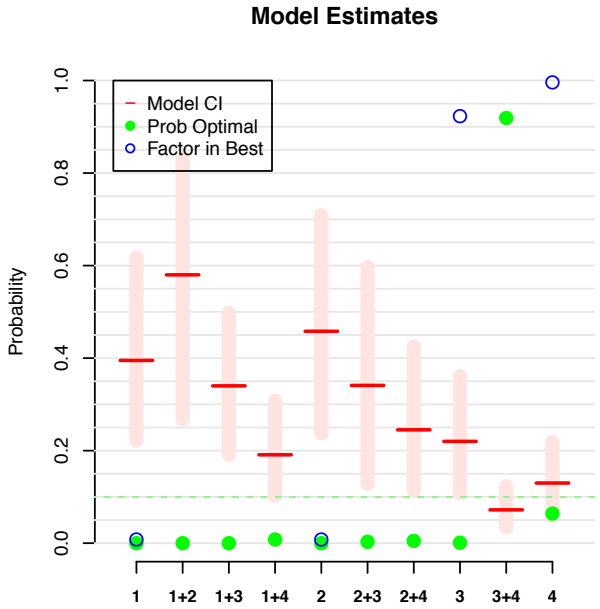

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

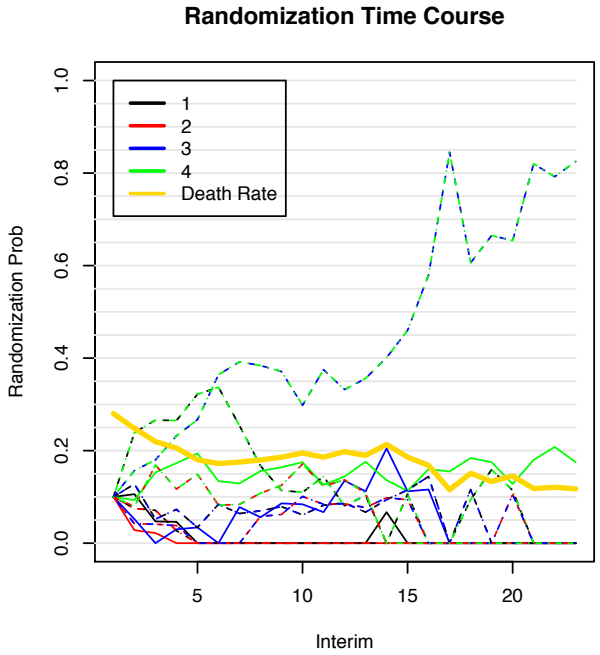

Cumulative Data @220
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
36%
19%
67%
20%
26%
26%
7%
15%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

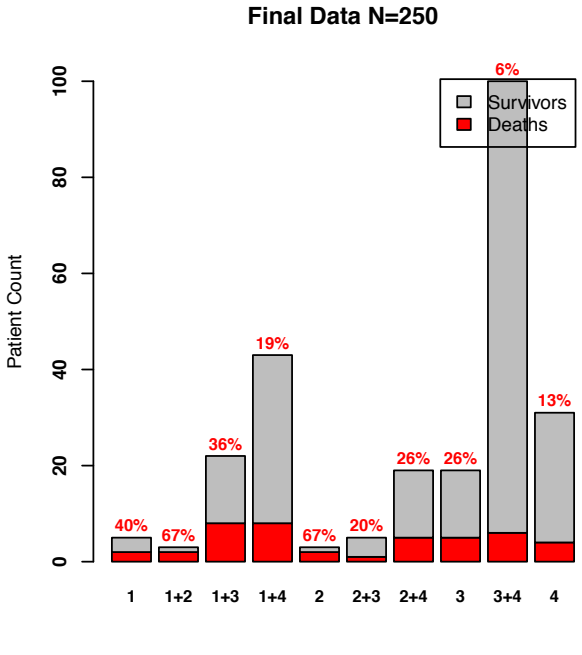

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

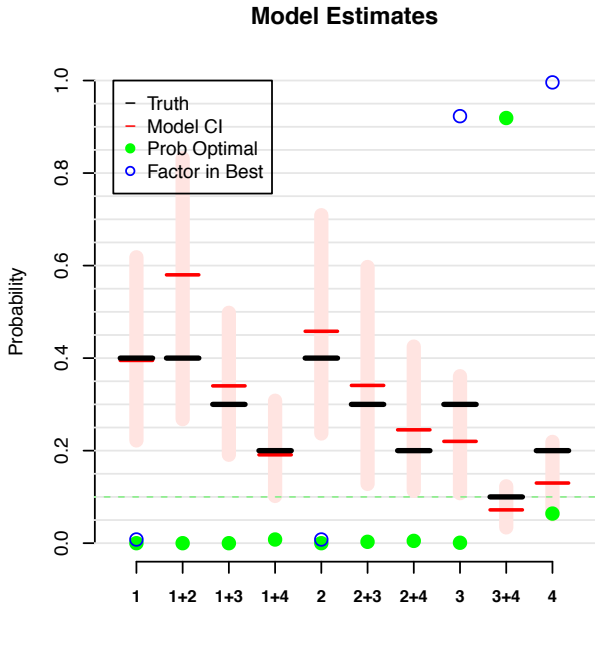

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

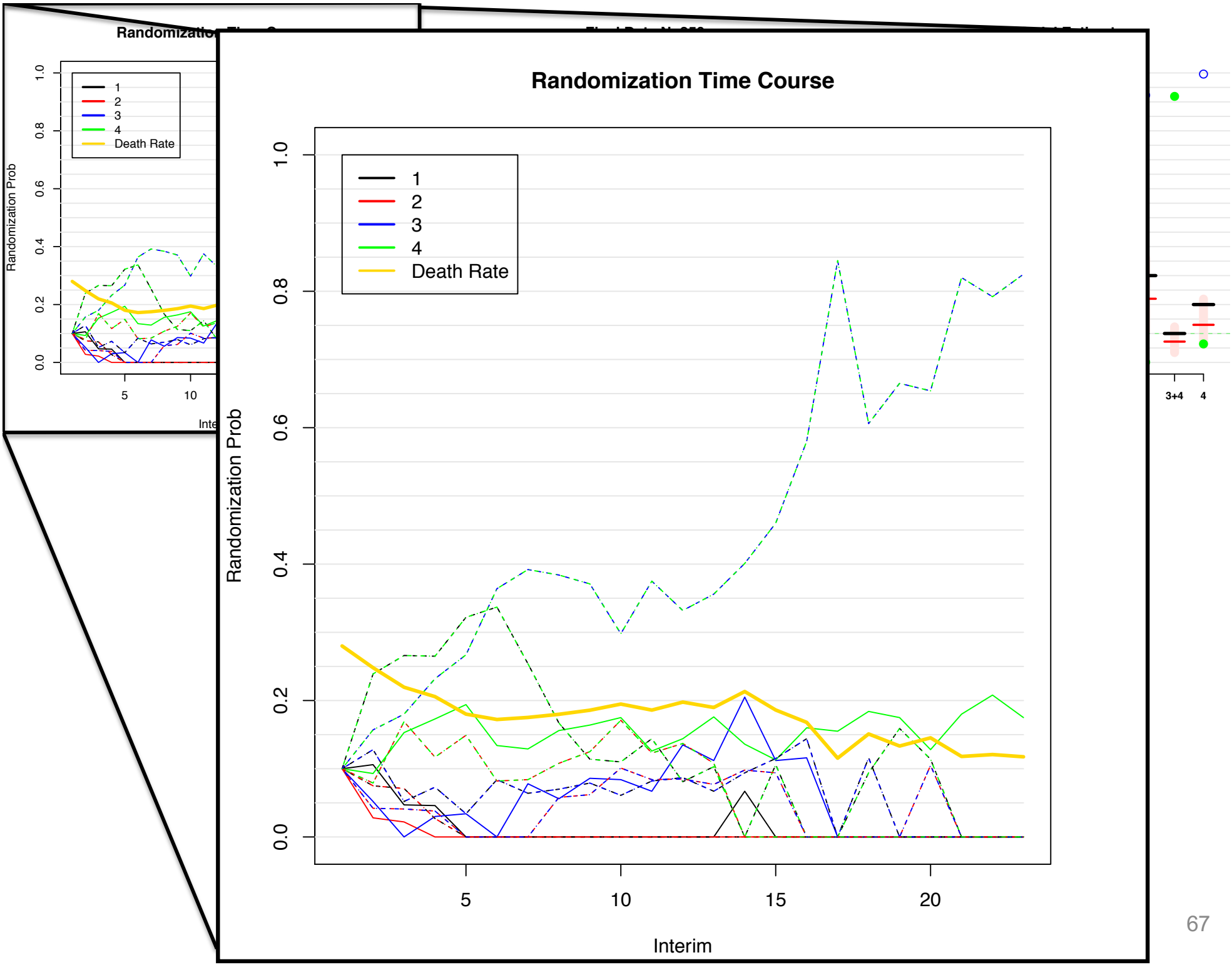

Cumulative Data @250
Patient Count
0
20
40
60
80
100
Survivors
Deaths
40%
67%
36%
19%
67%
20%
26%
26%
6%
13%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

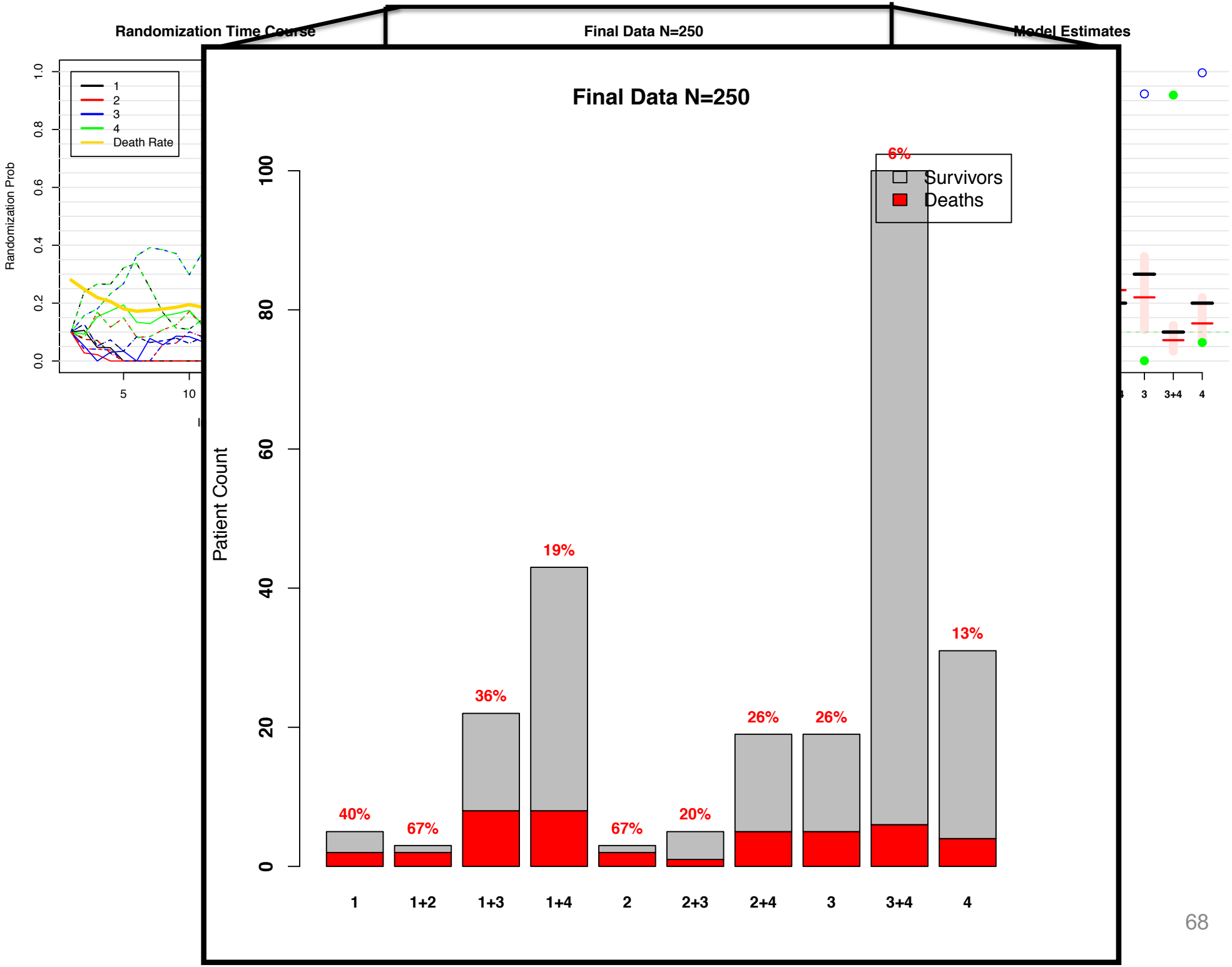

Model Estimates
Probability
0.0
0.2
0.4
0.6
0.8
1.0
Model CI
Prob Optimal
Factor in Best
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

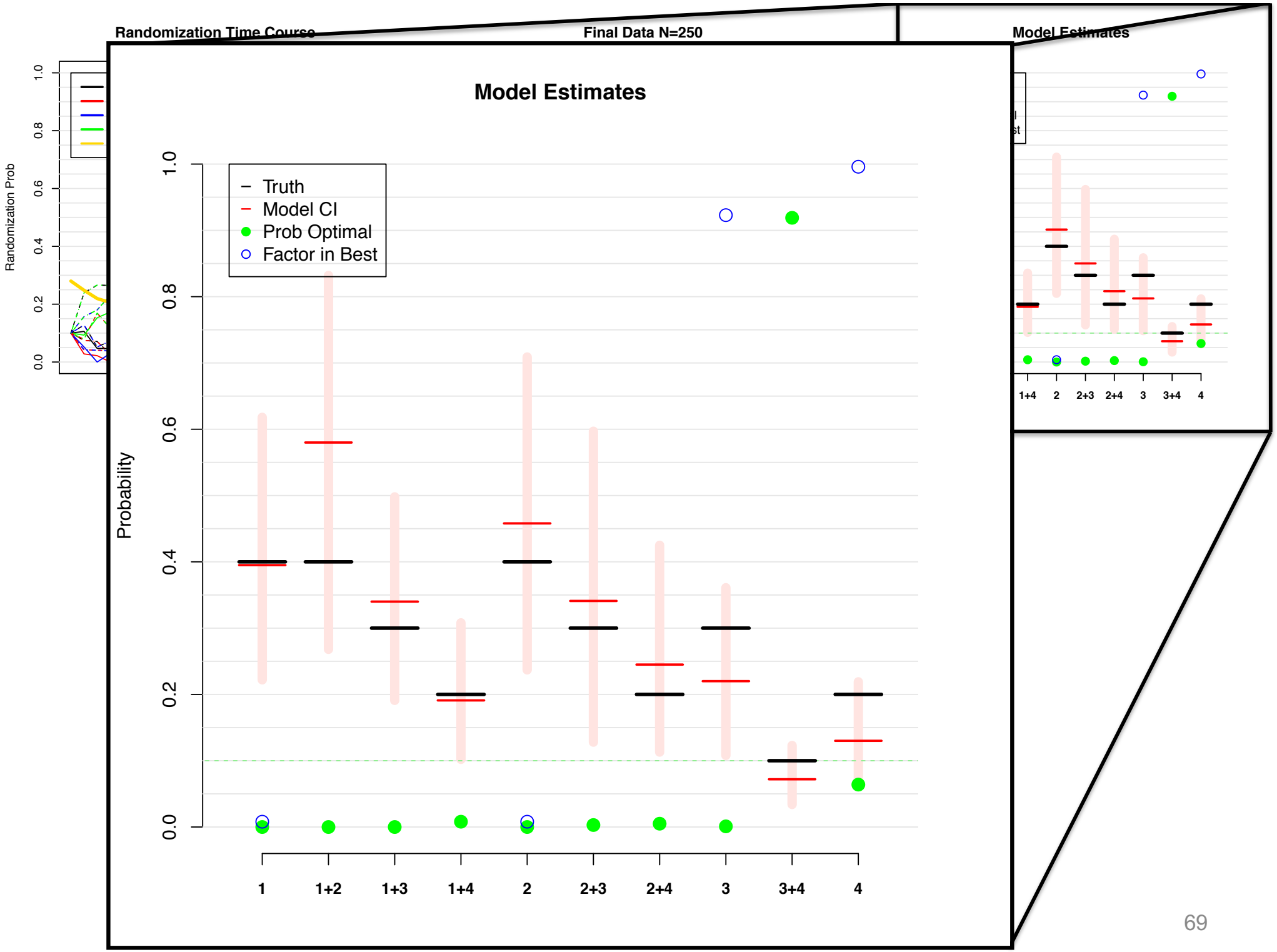

Randomization Time Course
Randomization Prob
Interim
1
2
3
4
Death Rate
0.0
0.2
0.4
0.6
0.8
1.0
5
10
15
20


Final Data N=250
Patient Count
Survivors
Deaths
0
20
40
60
80
100
40%
67%
36%
19%
67%
20%
26%
26%
6%
13%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

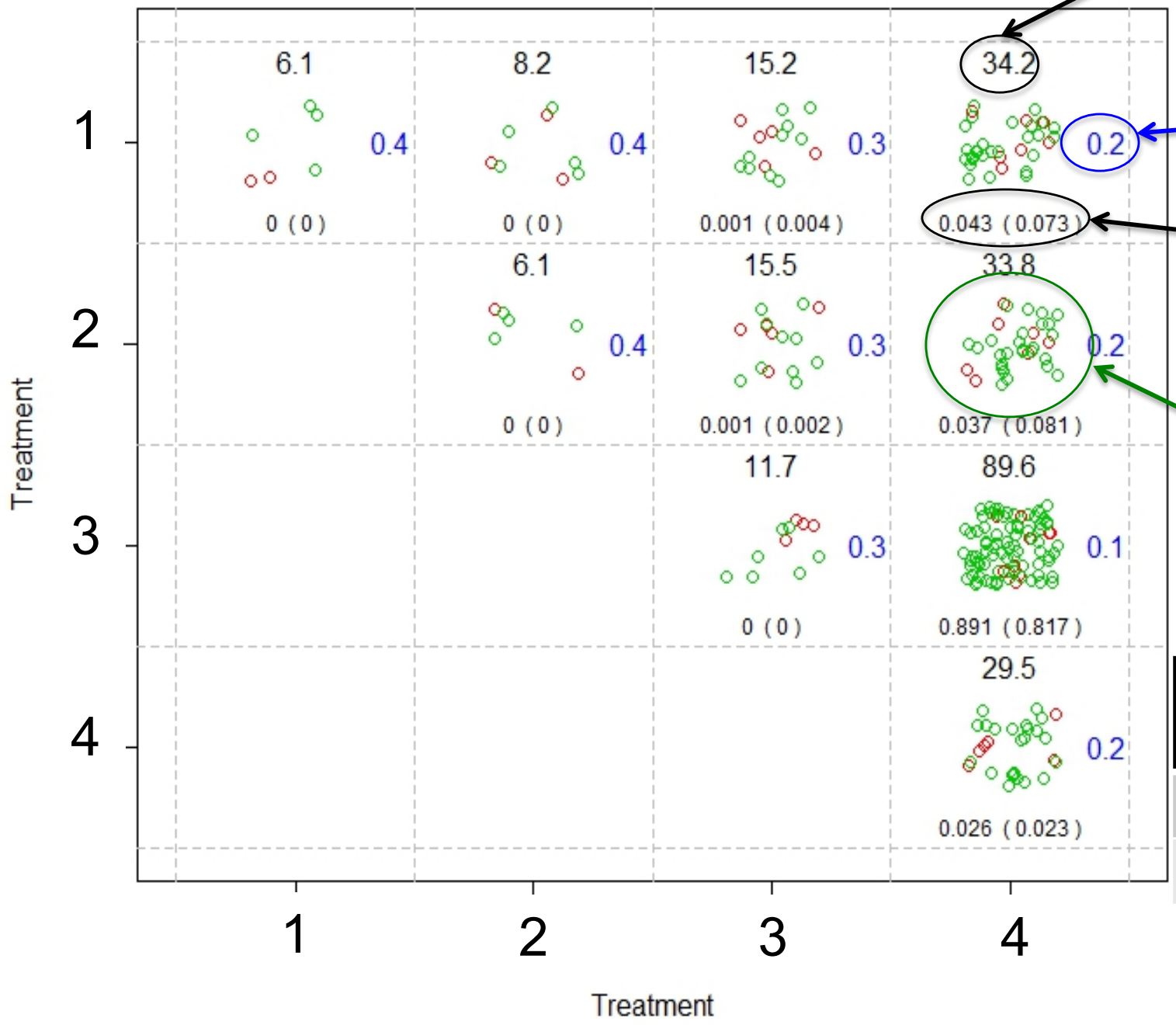

Model Estimates
Probability
Truth
Model CI
Prob Optimal
Factor in Best
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Randomization Time Course
Randomization Prob
Interim
1
2
3
4
Death Rate
0.0
0.2
0.4
0.6
0.8
1.0
5
10
15
20
3+4
4

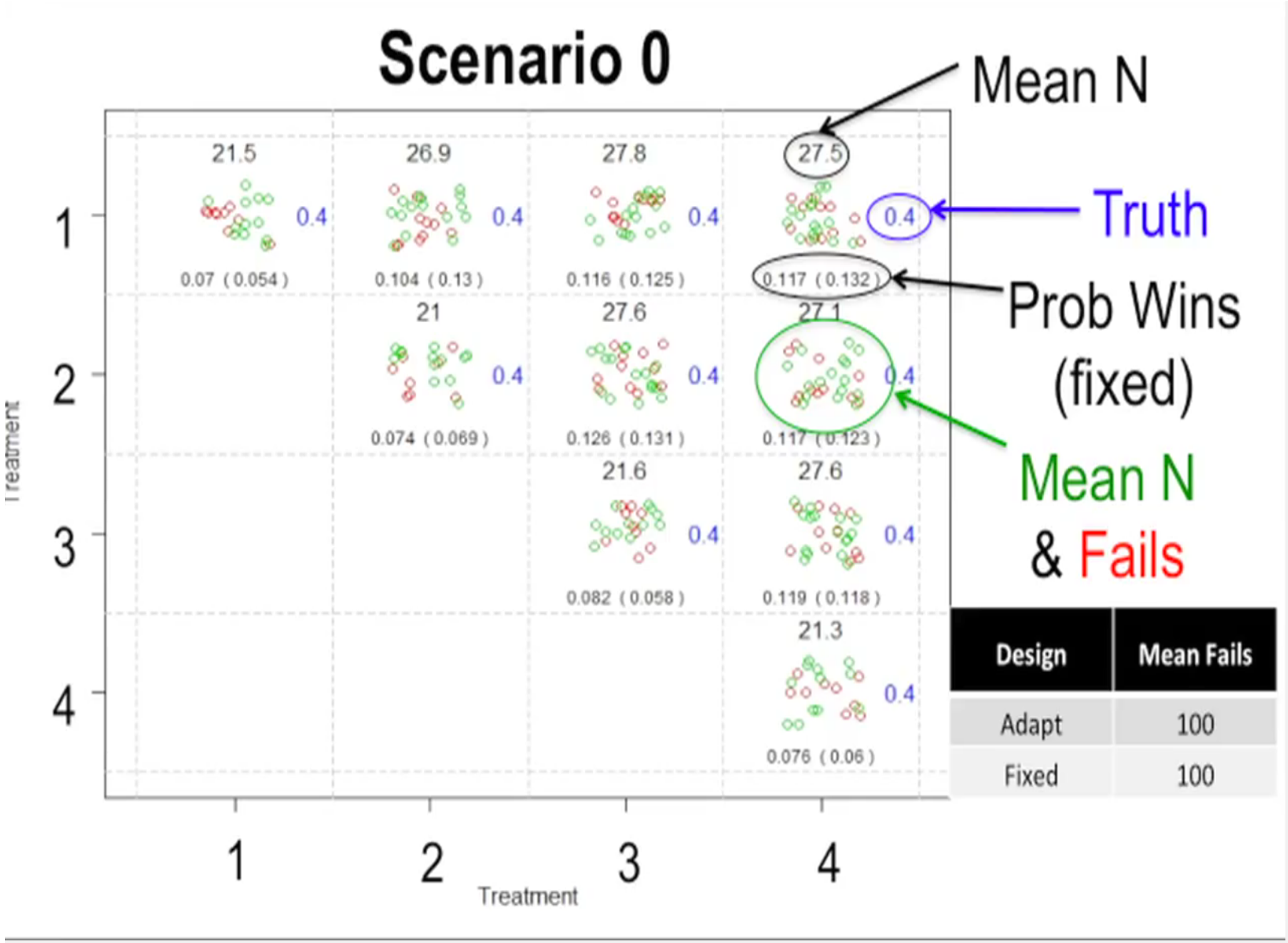

Randomization Time Course
Final Data N=250
Model Estimates
Randomization Prob
1
2
3
4
Death Rate
Final Data N=250
Patient Count
Survivors
Deaths
40%
67%
36%
19%
67%
20%
26%
26%
6%
13%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Randomization Time Course
Randomization Prob
0.0
0.2
0.4
0.6
0.8
1.0
Final Data N=250
Model Estimates
Truth
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4
Model Estimates
1+4
2
2+3
2+4
3
3+4
4

Scenario 3



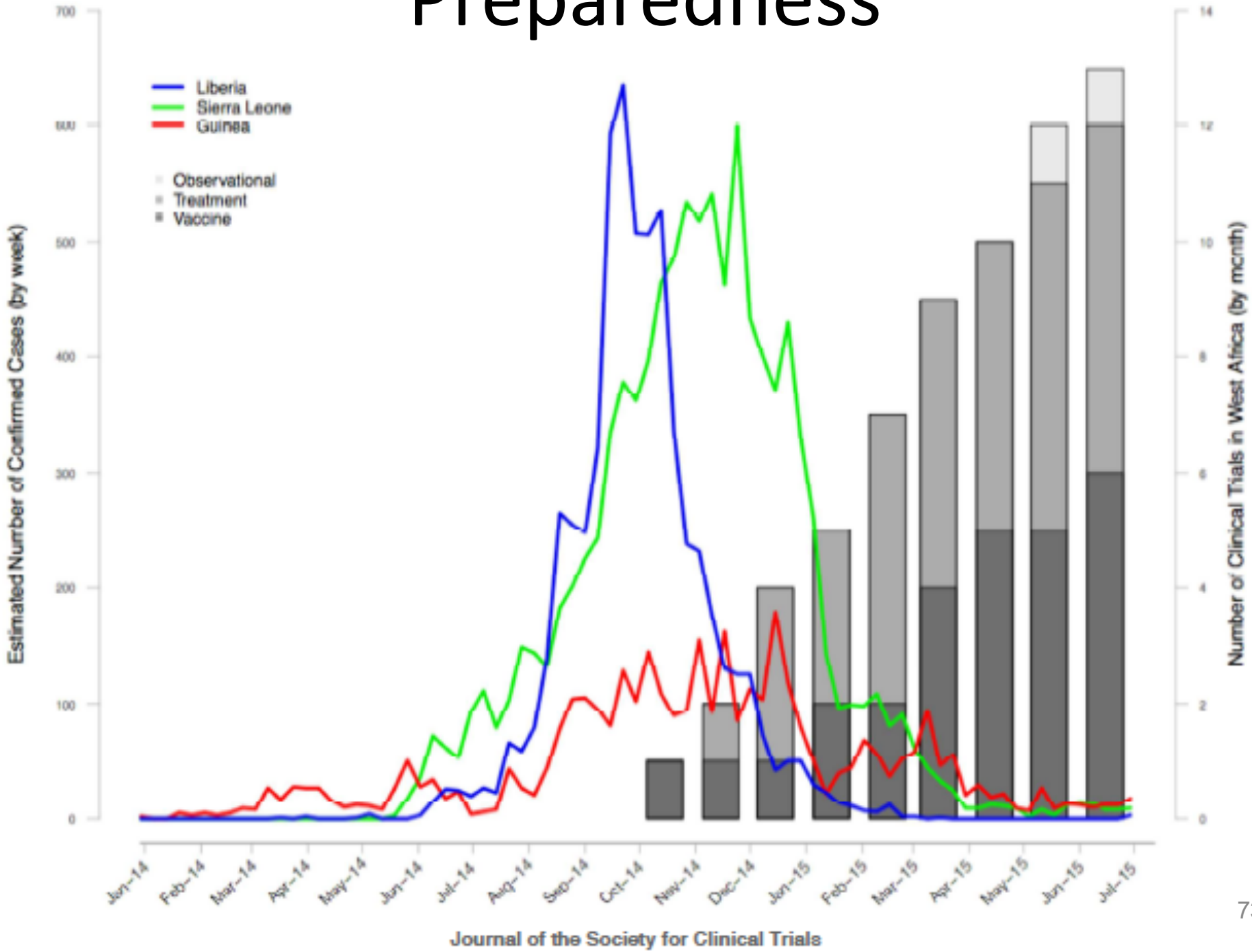
Design	Mean Deaths
Adapt	49.4
Fixed	69.9



Design	Mean Fails
Adapt	100
Fixed	100

The model adjusts for time trends by modeling the patient drift within "buckets" or months.

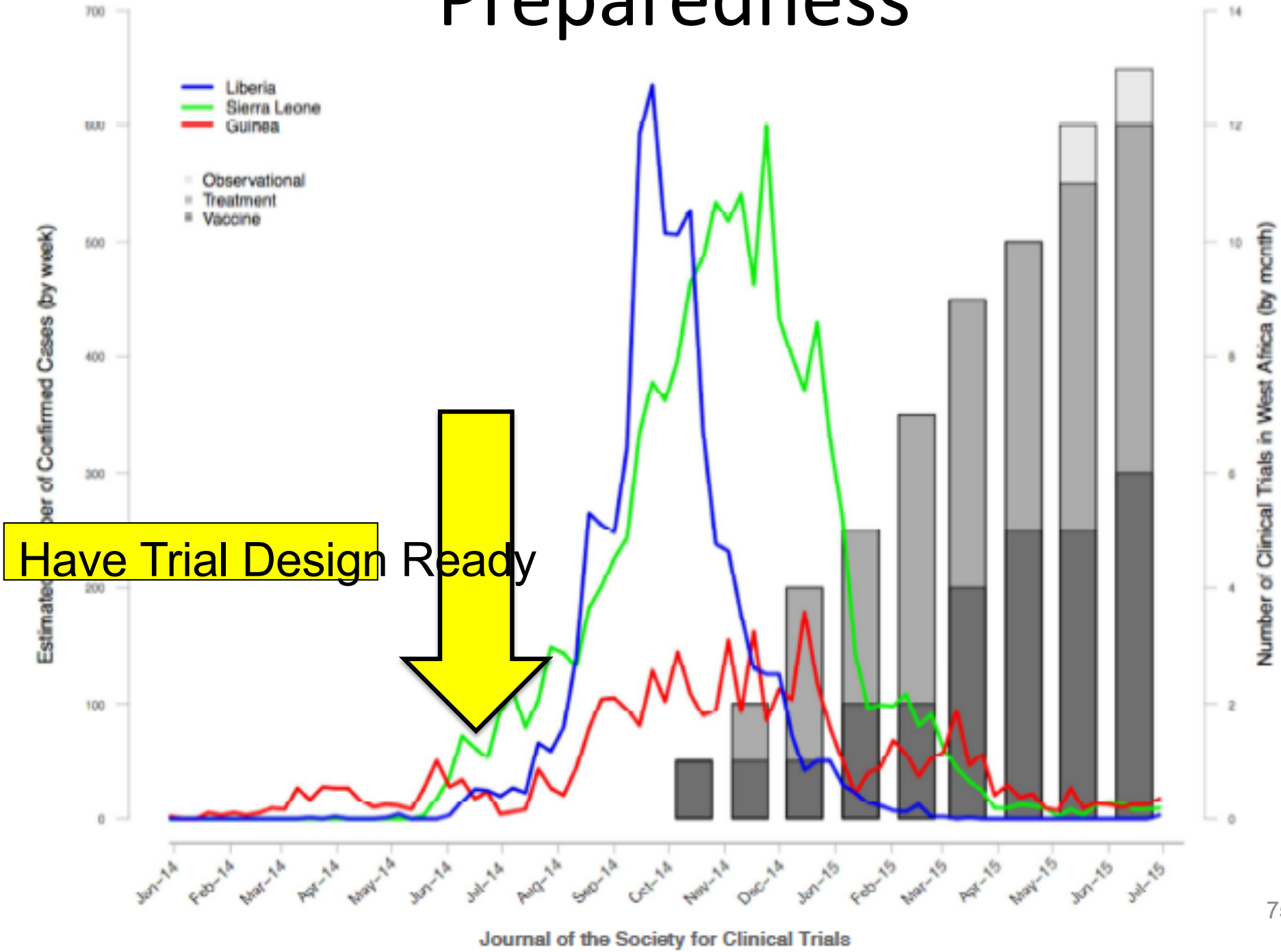
Preparedness



Preparedness

- Can we construct a master protocol to be “on-the-shelf” for the next pandemic?
- The design can be mapped out to handle a large class of possible outbreaks
  - Very easily customizable
  - Get software for simulations premade – “on-the-shelf”
- Do the groundwork at WHO/Ethical boards/Countries on readiness plans?

Preparedness



Have Trial Design Ready

Summary

- Incredibly powerful design for finding effective therapies and combinations in the universe of treatments
  - Type III Error (the question never asked!)
- Allows the arms to evolve internally and externally to changing science
- Improved Embedded Care: Efficiently and quickly identifies best agents, *while treating patients more effectively*
- Have design ready—on the shelf for next pandemic
  - A number of parameters can be optimized quickly
  - Protocol ready (add appendices)
  - Models + simulations ready

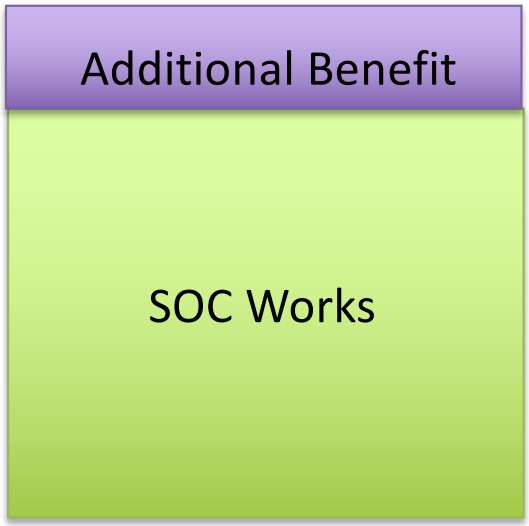
The Role of Biomarkers in Treatments & Trials

Testing a New Treatment

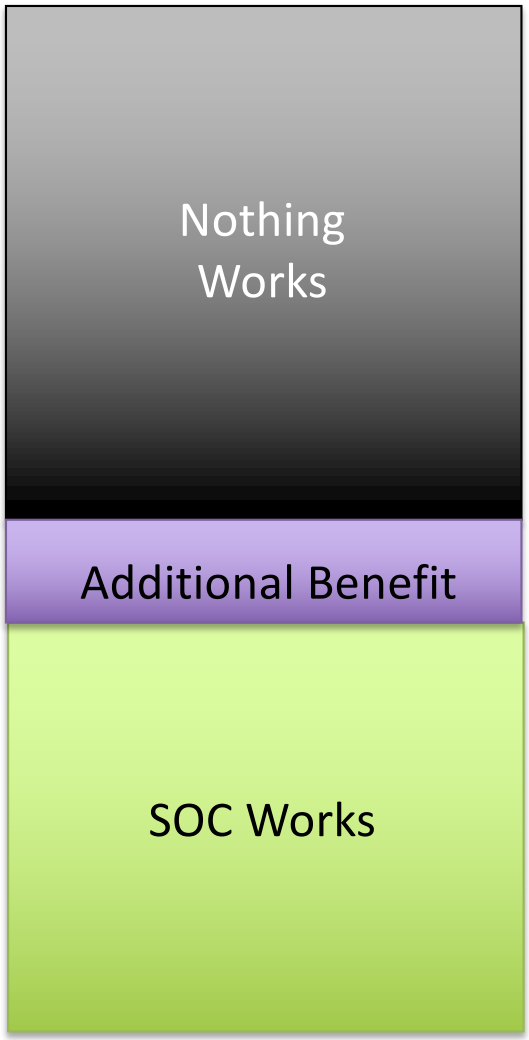
- Standard of Care works in 40%

10% of Patients Benefit

- Standard of Care works in 40%
- New therapy works in 50%

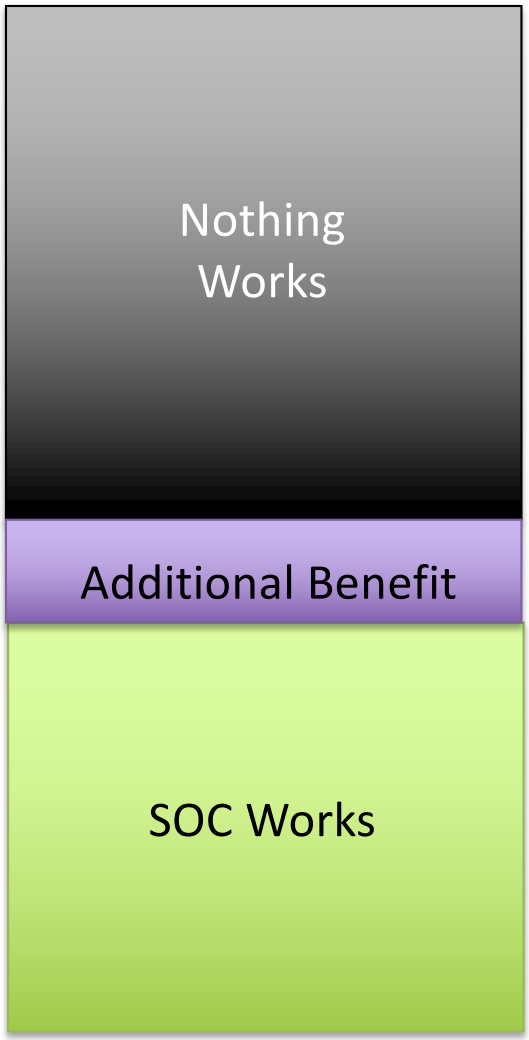


50% still untreatable



- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

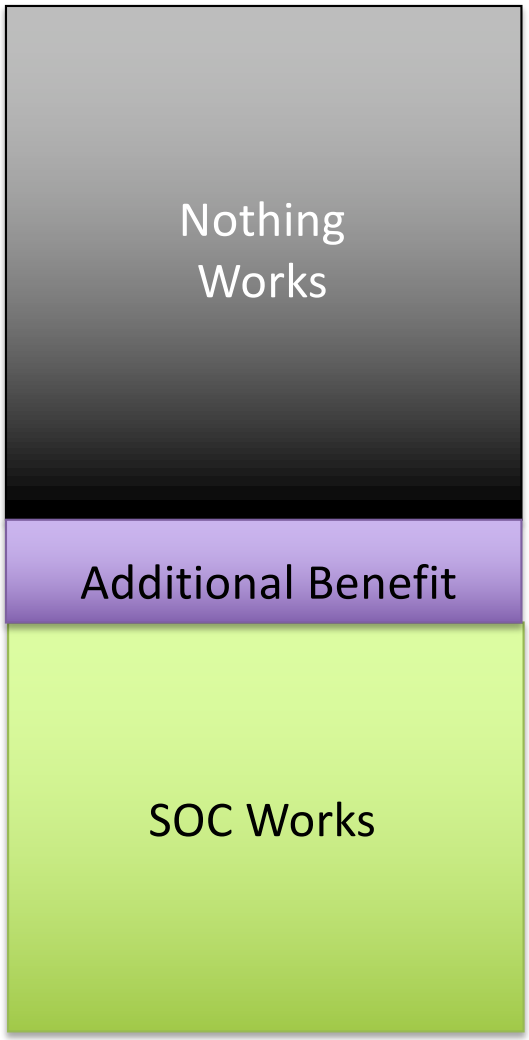
50% still untreatable



- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

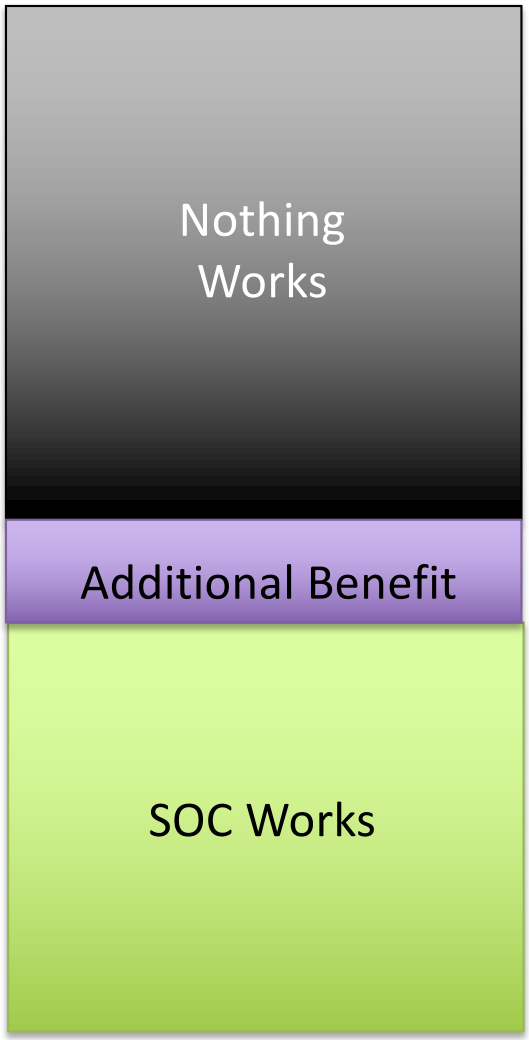
- How many patients do we need to have 90% chance to see a ‘statistically significant’ difference?

Need 1036 patients for 90% Power



- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

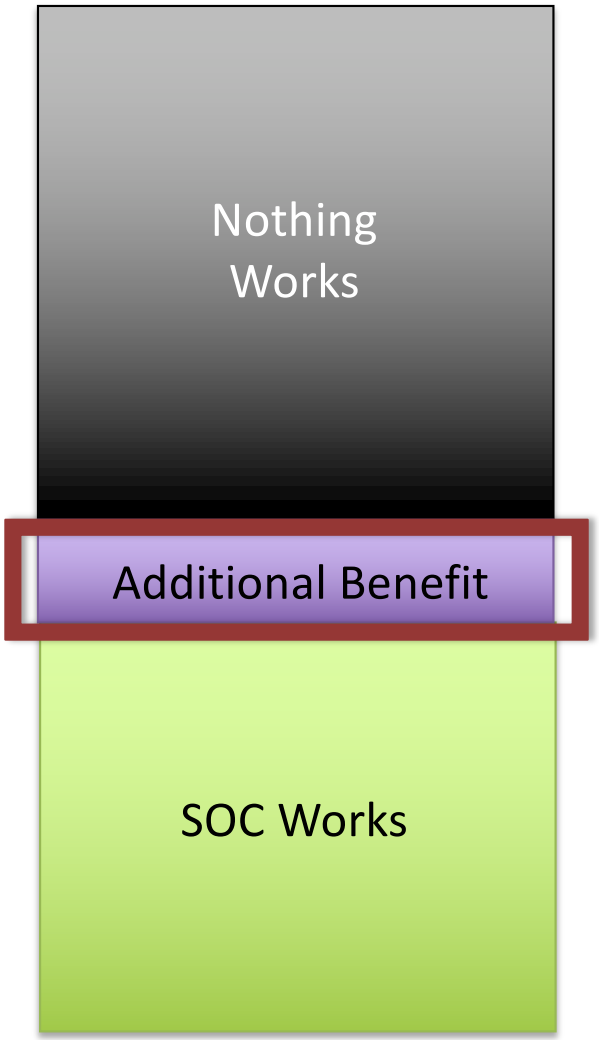
Need 1036 patients for 90% Power



- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

- 90% of patients you enroll tell you nothing

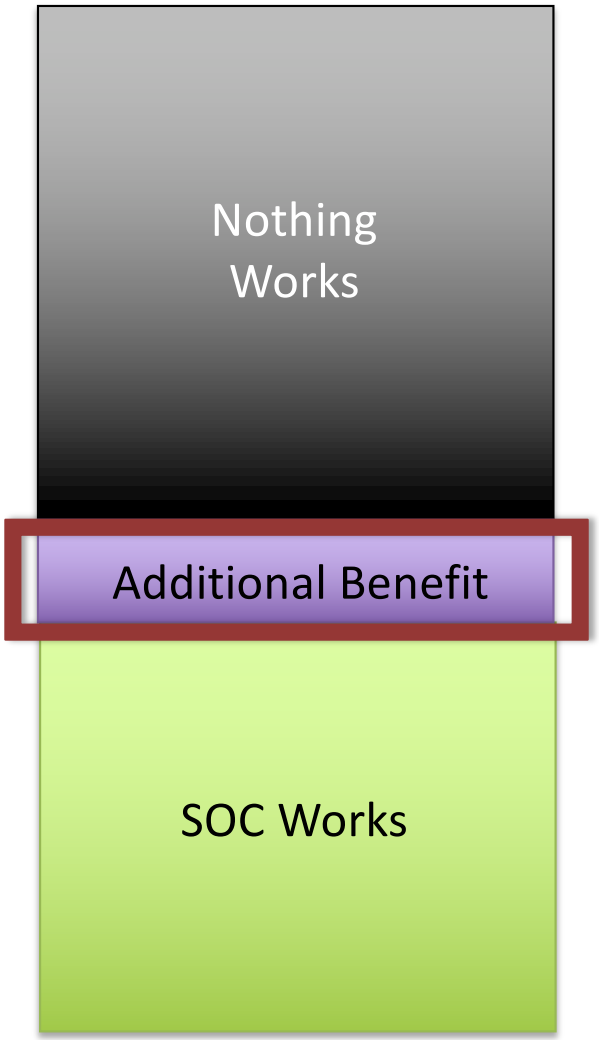
Need 1036 patients for 90% Power



- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

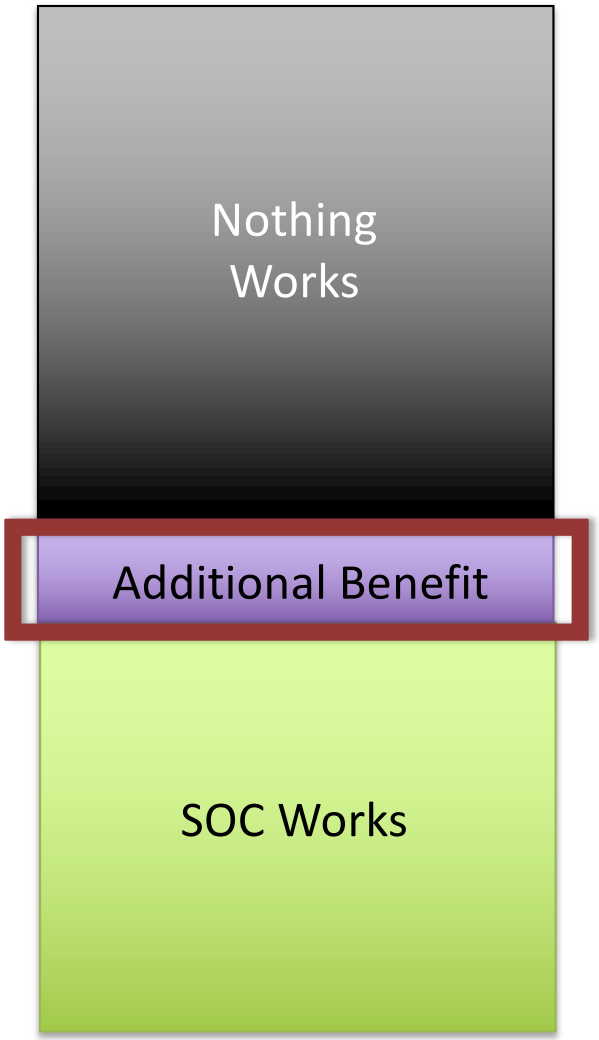
- 90% of patients you enroll tell you nothing
- What if you knew which 10% of patients benefited?

What if you KNEW which 10% Benefit



- If you just enrolled the purple patients how many patients do you need for 90% power?

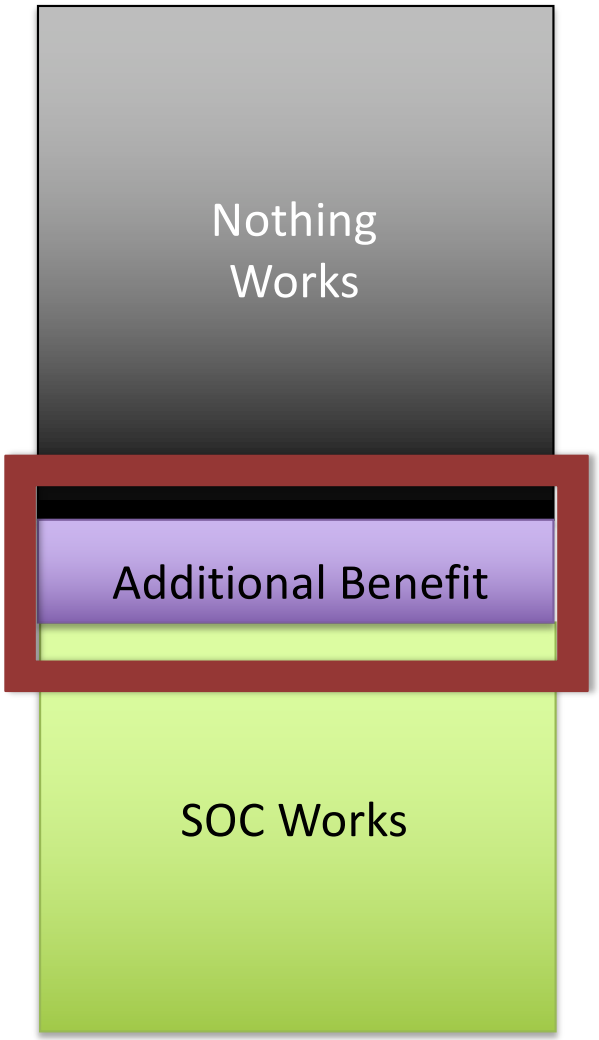
What if you KNEW which 10% Benefit



- If you just enrolled the purple patients you need 8 patients for 100% power
- If you could perfectly predict
  - 0/4 on standard of care
  - 4/4 on new treatment
  - Fisher's exact test p-value = 0.029

sorta

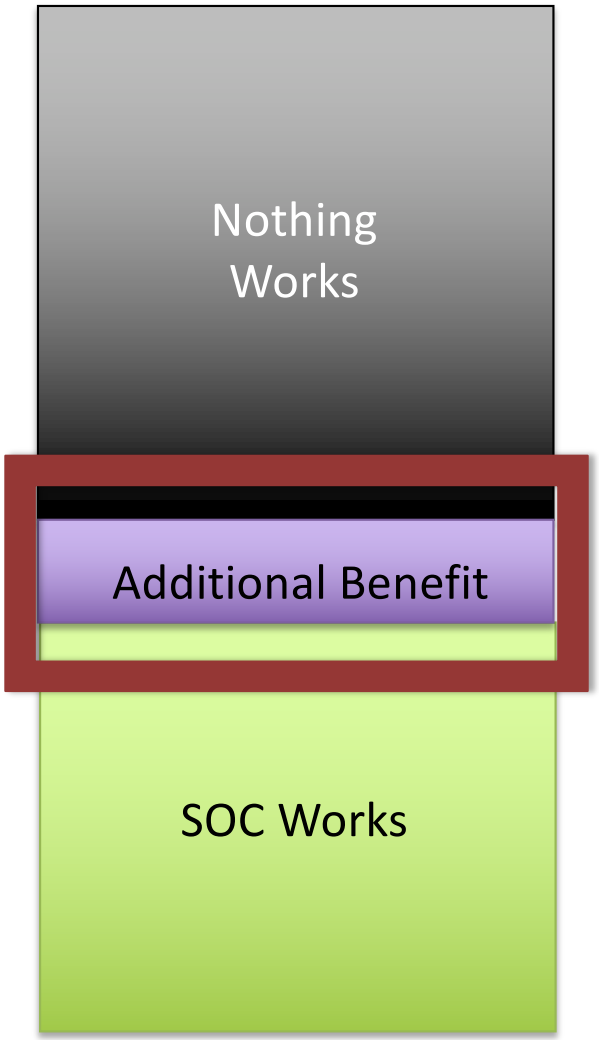
What if you^KNEW which 10% Benefit



- Enroll 20% to capture the 10%
- 25% cured by SOC
- 25% still not cured
- 50% of enrolled patients benefit

sorta

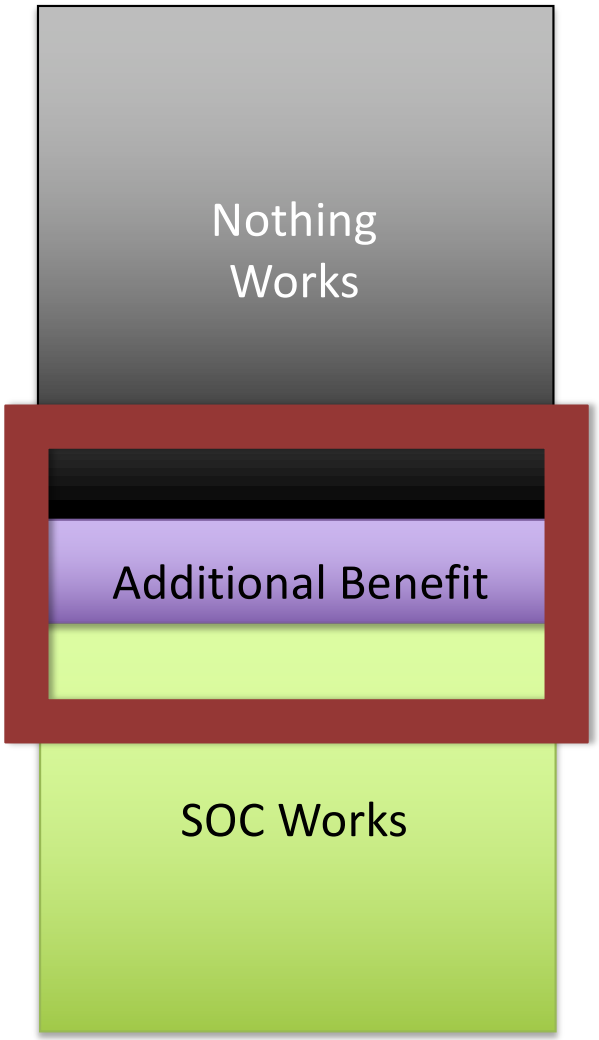
What if you^KNEW which 10% Benefit



- Enroll 20% to capture the 10%
- 25% cured by SOC
- 25% still not cured
- 50% of enrolled patients benefit
- Need 36 patients for 90% power

kinda sorta

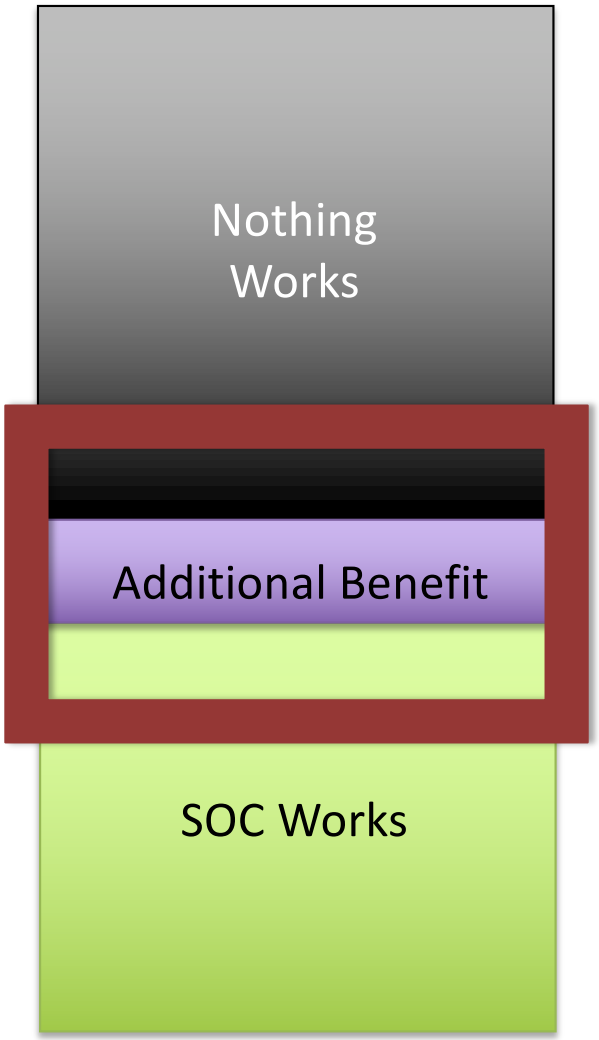
What if you^KNEW which 10% Benefit



- Enroll 30% to capture the 10%
- 33% cured by SOC
- 33% not cured
- 33% of enrolled patients benefit

kinda sorta

What if you^KNEW which 10% Benefit



- Enroll 30% to capture the 10%
- 33% cured by SOC
- 33% not cured
- 33% of enrolled patients benefit
- Need 90 patients for 90% power

Learn & Confirm Using Biomarkers

- Make confirmatory trials dramatically smaller
  - Or learn & confirm within a trial
- Lead us toward personalized medicine
  - What works best in whom?
- May require larger platforms trials, data sharing & adaptive randomization to efficiently identify
- Different drugs work in different types of patients
  - Not one trial, one patient type
  - Learn, confirm, perpetually

Challenges in Platform Trials

- Complexity in trial implementation and planning
- Collaborations across sponsors - who initiates the planning?
- Timely communication between participating sites and data coordinating units
- Sponsors sacrifice autonomy in running the trial
- Determining shared costs
- Identifying what to report when
  - iSpy2 has rules for ‘graduating’
  - When to report subgroup results broadly?

Platform Trial Efficiencies

- Useful for evaluating combinations of treatments and for direct comparisons between competing treatments
- Do not require a new trial infrastructure for every treatment under investigation
- Implemented or planned in many diseases
  - Breast cancer
  - Lung cancer
  - Brain cancer
  - Pandemic influenza
  - Community acquired pneumonia
  - Alzheimer's
  - Ebola
  - Melanoma
  - Scleroderma
  - President's Council of Advisors on Science and Technology (PCAST) included a call for antibiotic platform trials

ESSET Code

Definitions, Trial Parameters

```
rm(list=ls())
## All times in months
library(VGAM)
v = list(
  ### Event, success probabilities for IV, IV+2nd therapy, Oral, Oral + 2nd therapy
  S3 = c(## There are success rates for the four groups
     0.50,      # fPHT
     0.50,      # LVT
     0.50       # VPA
  ),

  # Maximum sample size & max sample size for Stage 1
  MaxN = 795,
  # Priors
  a = rep(1, 3),
  b = rep(1, 3),
  # First look and look every
  firstlook = 300,
  firststop = 400
  lookevery = 100,
  # Min to randomized
  minpr = 0.05,
  # simulations
  nsims = 1000,
  badlim = 0.25,
  # critv to (a) for 'best'
  #          (b) for 'worst'
  #          (c) to stop for futility (i.e Pred prob a winner or loser id'd)
  #          (d) for worse than 25%
 critv = c(.975, .975, 0.05, 0.05)
)
```

Response Rates

MaxN

Priors

Sample Size &
Timing of Looks

Critical values for stopping

```
simtrials <- function(v){

  co <- ppcutoffs(v$critv[3])

  #out.mat
  # (1) N
  # (2-4) N per group
  # (5-7) Rank as 1, 2, 3 (according to prob best)
  # (8)   Sig best (1 2 or 3 or 0 if none)
  # (9)   Sig worst (1 2 or 3 or 0 if none)
  # (10) Final conclusion
  #           1 = overall futility stop,
  #           2 = stop early for winner
  #           3 = stop early for winner & loser
  #           4 = stop early for loser and futility (not possible in ours)
  #           5 = max overall futility
  #           6 = max and loser
  #           7 = max and winner
  #           8 = max & winner & loser
  #  (11-13) Final Pr(best)
  #  (14-16) Final Pr(2nd)
  #  (17-19) Final Pr(worst)
  #  (20-22) Successes per group
  #  (23-25) Ever drop arm? (rand goes to 0 at any pt)
```

Creates a big matrix to store simulation results

```
out.mat <- matrix(NA, nrow=v$nsims, ncol=25)
  for(s in 1:v$nsims){
    ad <- c(1,1,1)
    ## Rand assignment for first FirstLook pts & generate outcome
    group <- rep(NA, v$MaxN)
    group[1:v$firstlook] <- rand.new(v$firstlook, c(1,1,1))
    y <- rep(NA, v$MaxN)
    y[1:v$firstlook] <- sim.endpoint(group[1:v$firstlook], v$S3)
    look1 <- interim(v$firstlook, y, group, v, co)
#    print(round(look1,3))
    # Track if arm every dropped
    ad <- ad * as.numeric(look1[12:14]>0)
    n.now <- v$firstlook
    print(c(s,n.now))
 ## Now loop through Stage 1
    while(look1[1]==1){
      new <- min(v$MaxN-n.now, v$lookevery)
      group[(n.now+1):(n.now+new)] <- rand.new(new, look1[12:14])
      y[(n.now+1):(n.now+new)] <- sim.endpoint(group[(n.now+1):(n.now+new)], v$S3)
      look1 <- interim(n.now+new, y, group, v, co)
#      print(round(look1,3))
      ad <- ad * as.numeric(look1[12:14]>0)
      n.now <- n.now+new
      print(c(s,n.now))
    }
```

Simulate group assignment & response to tx

First interim look

Simulate group assignment & response to tx

Do interim looks

```
    mx <- look1[3:5];    mn <- look1[6:8]
    winner <- ifelse(max(mx) > v$critv[1], (1:3)[mx==max(mx)], 0)
    loser <-  ifelse(max(mn) > v$critv[2], (1:3)[mn==max(mn)], 0)
   if(look1[2]==1){
       whystop <- 1    ## futility
     }else if(look1[2]==3){
       if(loser>0){
         whystop <- 3
       }else{
         whystop <- 2
       }
     }else if(look1[2]==2){
       if(winner==0 & loser==0)   { whystop <- 5}
       else if(winner>0 & loser>0){ whystop <- 8}
       else if(winner>0)          { whystop <- 7}
       else if(loser>0)           { whystop <- 6}
       else{print("error why stop at max?")}
       else{print("error, why did trial stop?")}

 out.mat[s,1:25] <- c(n.now, look1[18:20], order(mx), winner, loser,
                 whystop,look1[c(3,4,5,9,10,11,6,7,8,15,16,17)],1-ad)
}
    out.mat <- data.frame(out.mat)
    names(out.mat) <- c("N","N1","N2","N3",…
     return(out.mat)
```

See if best or worst identified

See if stopping rules met

Print out simulation results

```
sumtrial <- function(outmat){
  mat <- matrix(nrow=4, ncol=9)
  out <- table(factor(outmat[,10], levels=1:8))
#               Ntotal SDN phat Rank1  Rank2  Rank3  SigBest SigWorst Drop
#      fPHT
#      LVT
#      VPA              --
#      Total
  mat[1:3,1] <- apply(outmat[,2:4], 2, mean)
  mat[1:3,2] <- apply(outmat[,2:4], 2, sd)
  mat[1:3,3] <- c(mean(outmat[,20]/outmat[,2]), mean(outmat[,21]/outmat[,3]),
mean(outmat[,22]/outmat[,4]))
  mat[1,4:6] <- table(factor(outmat[,5], levels=3:1))/dim(outmat)[1]
  mat[2,4:6] <- table(factor(outmat[,6], levels=3:1))/dim(outmat)[1]
  mat[3,4:6] <- table(factor(outmat[,7], levels=3:1))/dim(outmat)[1]
  mat[1:3,7] <- table(factor(outmat[,8], levels=1:3))/dim(outmat)[1]
  mat[1:3,8] <- table(factor(outmat[,9], levels=1:3))/dim(outmat)[1]
  mat[1:3,9] <- apply(outmat[,23:25], 2, mean)
  mat[4,1] <- mean(outmat[,1])
  mat[4,2] <- sd(outmat[2])
  mat[4,3] <- mean(rowSums(outmat[,20:22]) / rowSums(outmat[2:4]))
  mat[4,4:6] <- NA
  mat[4,7] <- sum(mat[1:3,7])
  mat[4,8] <- sum(mat[1:3,8])
  mat[4,9] <- NA
  mat <- data.frame(mat)
  names(mat) <- c("N","SD","Phat","Best","Mid","Worst","SigBest","SigWorst","Drop")
  dimnames(mat)[[1]] <- c("fPHT","LVT","VPA","Total")
  return(list(out, mat))
}
```

Takes the results of ‘simtrials’ and Produces prettier output

```
interim <- function(N, y, group, v, co){
   ## Runs trial returns:
   #  (1) go (0=stop, 1=keep going)
   #  (2) why stop (1=3-way fut, 2=max n, 3=1 winner)
   #  (3-5) Pr each is best
   #  (6-8) Pr each is worst
   #  (9-14) x/N for each group
   #  (15-17) rand probs
   ns <- table(factor(group[1:N], levels=1:3))
   tab <- table(factor(group[1:N],levels=1:3), factor(y[1:N], levels=0:1))
   post1 <- rbeta(10000, v$a[1]+tab[1,2], v$b[1]+tab[1,1])
   post2 <- rbeta(10000, v$a[2]+tab[2,2], v$b[2]+tab[2,1])
   post3 <- rbeta(10000, v$a[3]+tab[3,2], v$b[3]+tab[3,1])
   vr <- as.numeric(( (v$a+tab[,2])*(v$b+tab[,1])) / ((v$a+v$b+ns)^2 * (v$a+v$b+ns+1)))
   top <- apply(cbind(post1,post2,post3), 1, max)
   bot <- apply(cbind(post1,post2,post3), 1, min)

   best <- c(mean(post1==top), mean(post2==top), mean(post3==top))
   worst <- c(mean(post1==bot), mean(post2==bot), mean(post3==bot))
   middle <- 1-best-worst

   toobad <- 1-c(pbeta(v$badlim, v$a[1]+tab[1,2], v$b[1]+tab[1,1]),
                 pbeta(v$badlim, v$a[2]+tab[2,2], v$b[2]+tab[2,1]),
                 pbeta(v$badlim, v$a[3]+tab[3,2], v$b[3]+tab[3,1]))

   wt <- sqrt(best * vr / as.numeric(ns));     wt <- wt/sum(wt)
   wt[wt < v$minpr] <- 0;    wt[toobad < v$critv[4]] <- 0
   if(sum(wt) > 0){
   wt <- wt/sum(wt)
   }
```

Does interim analysis
Calc posteriors, new rand probs,
Pred prob of success at max

Calc posteriors

Calc prob each is best & worst

Calc Pr(p<0.25)

Calc new rand prob

```
 #####PRED PROBS; only do if all 3 arms left
   if((N >= v$firststop) & (N < v$MaxN) & (prod(wt>0)> 0)){
     drop <- 0
     left <- v$MaxN - N
     left <- ceiling(rep(left/3, 3))
     ns.total <- ns+left
     winlose <- 0
     counter <- 1

     while((winlose < co[counter,1]) & (winlose >= co[counter,2]) & (counter < 1000)){
       y.end <- tab[,2] + rbetabin.ab(3, left, v$a+tab[,2], v$b+tab[,1])
       post1f <- rbeta(10000, v$a[1]+y.end[1], v$b[1]+ns.total[1]-y.end[1])
       post2f <- rbeta(10000, v$a[2]+y.end[2], v$b[2]+ns.total[2]-y.end[2])
       post3f <- rbeta(10000, v$a[3]+y.end[3], v$b[3]+ns.total[3]-y.end[3])
       topf <- apply(cbind(post1f,post2f,post3f), 1, max)
       botf <- apply(cbind(post1f,post2f,post3f), 1, min)
       bestf <- c(mean(post1f==topf), mean(post2f==topf), mean(post3f==topf))
       worstf <- c(mean(post1f==botf), mean(post2f==botf), mean(post3f==botf))
       winlose <- winlose + ifelse((max(bestf)>v$critv[1]) | (max(worstf)>v$critv[2]),
1, 0)
       counter <- counter + 1
#       print(c(winlose/counter, counter))
     }
     ppwin <- winlose/counter
   }else{
     drop <- 1
     ppwin <- v$critv[3]+1 #  If missing just make bigger than the crit value.
   }
```

Calc pred prob of success
At Max N

```
  ## Stopping:
  if(N < v$firststop){
    go <- 1
    whystop <- NA
  }else if(N >= v$MaxN){
    go <- 0
    whystop <- 2
  }else if(max(best) > v$critv[1]){
    go <- 0
    whystop <- 3
  }else if(ppwin < v$critv[3]){
    go <- 0
    whystop <- 1
  }else if(wt[1]==0 & wt[2]==0 & wt[3]==0){
    go <- 0
    whystop <- 1
  }else{
    go <- 1
    whystop <- NA
  }

  return(as.numeric(c(go, whystop, best, worst, middle, wt, tab[,2], ns, ppwin, drop)))
}
```

Track IF stop
And WHY stop

Summary:
Big Picture

Big Summary

- Think deeply about every question
  - Try to understand the clinical aide as much as you can
- Ask "What do you REALLY want to know?"
  - "Are you sure?"
  - "What else?"
  - A good trial can answer more than one question
- Ask yourself and your collaborators beforehand
  - "If this trial (or a future trial in the process) fails to answer our questions, what are would be likely to say we wish we'd have done differently?"

Big Summary

- Think deeply about every question
  - Try to understand the clinical aide as much as you can
- Ask "What do you REALLY want to know?"
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Big Summary

- Ask yourself what information is necessary to answer the primary question(s)
  - Think about how the info we collect might change as we answer the primary questions
  - Think about which design assumptions are least reliably known
- Ask what will we know and when will we know it
  - Can longitudinal models improve upon slow info
  - Can biomarkers improve upon slow info
- Continually ask whether we know the answer
  - Or whether we're likely to know the answer if we stop enrolling now and follow everyone enrolled
  - Or whether we're likely to ever know given our resource constrains

Big Summary

- Act naturally
- Be creative
- Our tool kit is FAR bigger than we think
- Our constraints are far fewer than we think
- Remember what the real question is
- Almost every research question is unique

  so why isn't every trial design unique?

Great Irony of Biostatistics

- Our job is to identify whether the newest, latest, greatest medical technologies are safe & efficacious and what works best for whom
  - Laser therapies, Whole genome diagnostics
  - Immunotherapies for cancer, etc

- Many statisticians believe our 'technologies' were as good as can be by 1933 or 1977 and nothing better can be invented

Great Irony of Biostatistics

- Anna Barker @ GBM AGILE kickoff:
  "Randomized clinical trials are 70 years old…what other technology doesn't change in 70 years? Meanwhile, cancer biology is moving at light speed and potential treatments have to wait in the queue."

- Take away: Realize the constraints (lack of) computing played on statistical methodology – and realize we are no longer constrained

Thanks for a great class

What did you like?
What worked?
What did not?