Innovative Trial Design: Opportunities for Global Health

Scott Berry, PhD

October 2, 2017

Austin Bradford Hill

Credited with designing the first randomized clinical trial in humans

Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. BMJ. 1948; 2:769-782.

Born	8 July 1897
Died	18 April 1991 (aged 93)
Nationality	United Kingdom
Occupation	Epidemiologist statistician
Known for	"Bradford Hill" criteria
Awards	Guy Medal (Gold, 1953)

Table I.–*Condition on Admission*

General Condition	S Group	C Group	Max. Evening Temp. in First Week*	S Group	C Group	Sedimentation Rate	S Group	C Group
Good .	8	8	98-98·9° F. (36·7-37·15° C.)	3	4	0-10	0	0
Fair . .	17	20	99-99·9° F. (37·2-37·75° C.)	13	12	11-20	3	2
Poor . .	30	24	100-100·9° F. (37·8-38·25° C.)	15	17	21-50	16	20
			101° F (38·3° C.) +	24	19	51+	36	29
Total	55	52	Total	55	52	Total	55	51†

* Temperature by mouth in all but six cases.

† Examination not done in one case.

Table II.–*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement . .	28	*51%*	4	*8%*
Moderate or slight improvement	10	*18%*	13	*25%*
No material change	2	*4%*	3	*6%*
Moderate or slight deterioration	5	*9%*	12	*23%*
Considerable deterioration . .	6	*11%*	6	*11%*
Deaths	4	*27%*	14	*27%*
Total	55	*100%*	52	*100%*

Randomized clinical trials

- Incredible innovation in health care and science
- Pre-1948 relied on anecdote and observational studies
- Ushered in a complete change to pharmaceutical/device development

- For 50 years the ‘science of the clinical trial’ barely changed
- Trials are “long boxes” designed to answer a single question
  - “Not sustainable” —Janet Woodcock, FDA

We are now innovating trial design science

Adaptive design

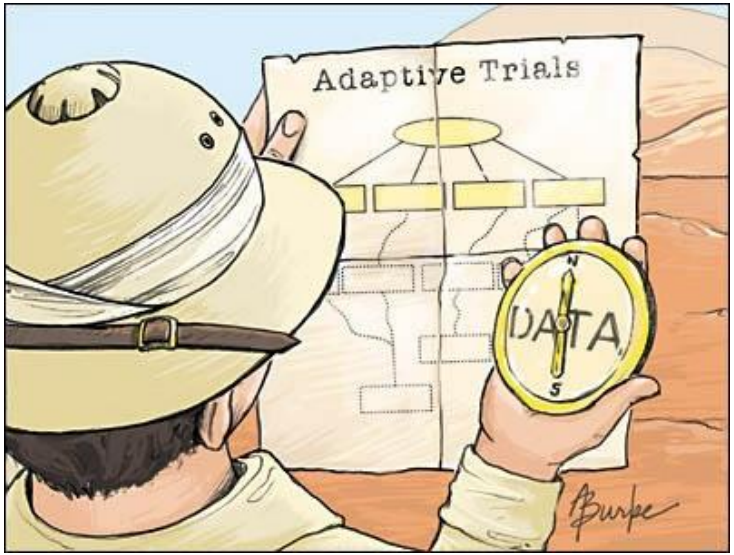


Photo credit: Burke, Alison, *JAMA* 2006; 296:1955-1957.

- A design that has pre-specified dynamic aspects that are determined by the accruing information
- Adaptive… “by design”

Adaptive design: promise

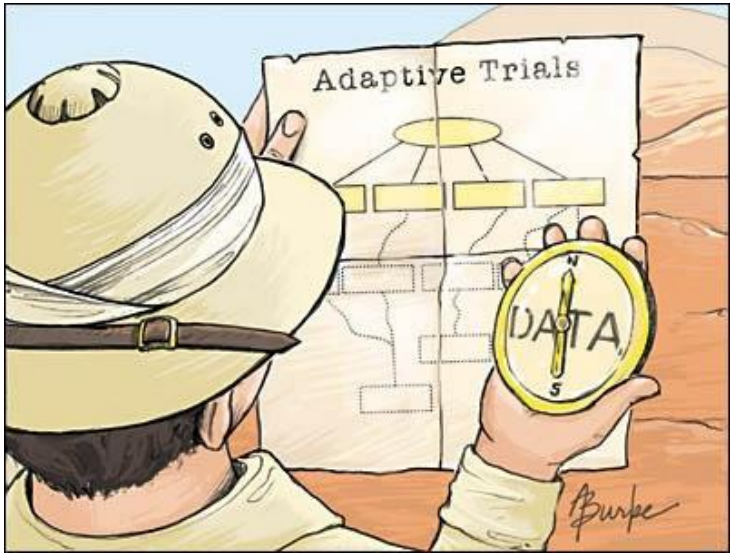
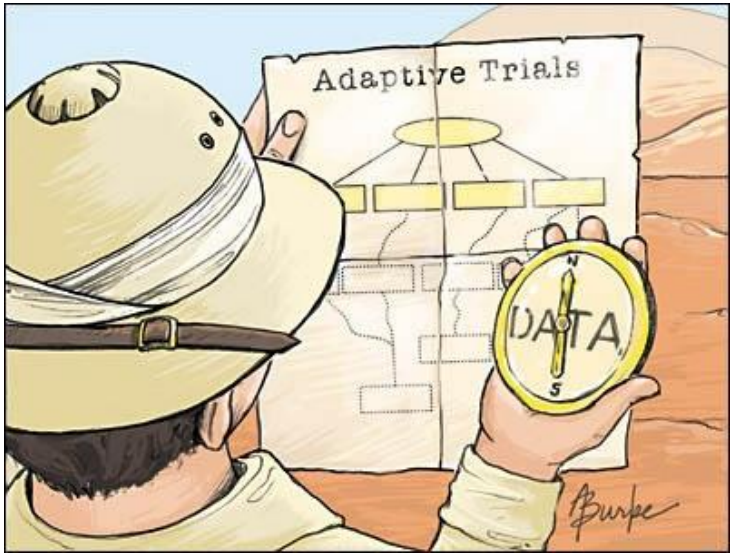


Photo credit: Burke, Alison, *JAMA* 2006; 296:1955-1957.

During the trial things are learned that – if known before the trial began – you would have changed the design.

- Learning: Formal modeling from accruing data
  - Dose-response models, Longitudinal models, prediction, imputation, biomarkers,…
- Change: The dynamically moving aspects of the trial:

Common adaptations



- **Sample size selection**:
  - Right-size sample size (ie, Goldilocks trial design[1])
- **Winning the trial** (hit success boundaries)
- **Futility**
- **Changing arms** (doses/frequency/settings)
  - Add, drop, combine
- **Change randomization to arms**
- **Change patients**
  - Enrichment, expansion, basket trials
- **Change stages** (seamless designs)

Source[1]: Berry, SM, et al. *J Biopharm Stat*. 2014;24(3):685-705.
Photo credit: Burke, Alison, *JAMA* 2006; 296:1955-1957.

Dulaglutide Example

Journal of Diabetes Science and Technology
Volume 6, Issue 6, November 2012
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SYMPOSIUM

An Adaptive, Dose-Finding, Seamless Phase 2/3 Study of a Long-Acting Glucagon-Like Peptide-1 Analog (Dulaglutide): Trial Design and Baseline Characteristics

Mary Jane Geiger, M.D., Ph.D.,[1] Zachary Skrivanek, Ph.D.,[1] Brenda Gaydos, Ph.D.,[2] Jenny Chien, Ph.D.,[1] Scott Berry, Ph.D.,[3] Donald Berry, Ph.D.,[3,4] and James H. Anderson, Jr., M.D.[5]

Abstract

Dulaglutide (dula, LY2189265) is a once-weekly glucagon-like peptide-1 analog in development for the treatment of type 2 diabetes mellitus. The first adaptive, dose-finding, inferentially seamless phase 2/3 study was designed to support the development of this novel diabetes therapeutic. The study is divided into two stages based on two randomization schemes: a Bayesian adaptive scheme (stage 1) and a fixed scheme (stage 2). Stage 1 of the trial employs an adaptive, dose-finding design to lead to a dula dose-selection decision or early study termination due to futility. If dose selection occurs, the study proceeds to stage 2 to allow continued evaluation of the selected dula doses. At completion, the entire study will serve as a confirmatory phase 3 trial. The final study design is discussed, along with specifics pertaining to the actual execution of this study and selected baseline characteristics of the participants.

J Diabetes Sci Technol 2012;6(6):PAGE NUMBERS

- Phase 2 trial with 7 doses; active comparator; placebo
- Response adaptive randomization
- Potential seamless shift to phase 3 between 200-400 enrolled
  - Analysis includes both phases
- Select 1 or 2 doses for phase 3
- Spawn additional phase 3 trials with selected doses
- Completely pre-specified algorithm drives all adaptations:
  - HbA1c, Weight, Heart rate, blood pressure

Dulaglutide Example

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J Diabetes Sci Technol 2012;6(6):PAGE NUMBERS

- Actual trial shifted to phase 3 at 200 subjects
- Selected two doses
- Spawned additional phase 3 trials
- Shortened development 12-18 months

Trulicity Example

FierceBiotech
THE BIOTECH INDUSTRY'S DAILY MONITOR

NEWS TOPICS ANALYSIS FEATUR

UPDATED: FDA hands Eli Lilly a big win, OKs dulaglutide for diabetes

September 18, 2014 | By John Carroll

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An embattled Eli Lilly ($LLY) won a major battle today, gaining the FDA's approval to market dulaglutide for Type 2 diabetes. It will be sold as Trulicity.

Lilly Diabetes President Enrique Conterno

With Novo Nordisk ($NVO) already digging in to defend its position around Victoza, the once-weekly treatment has been widely billed as a likely blockbuster. The Phase III program has long represented Eli Lilly's best shot at opening a major new market, though many analysts are still wondering just how much revenue can be gained in this already crowded field.

The market, though, is huge and growing as a tidal wave of diabetes rises around the world.

"Bernstein's Tim Anderson now projecting $1.3 billion in 2020"

--Q4 2016 already beat that projection

Traditional “standard” trial design

- Single treatment
- Homogeneous patients
- Single question

	Treatment
Type A	

Basket trial design

- Single Treatment
- Multiple Subgroups of interest:
  - Severity of disease
  - Genetic markers
  - Demographic covariates
  - MOA related
  - Timing of Intervention

	Treatment
Type A	
Type B	
Type C	
…	
Type K	
…	

Adaptive platform trial design

- “Master Protocol”
- Perpetual Trial?

	Tx 1	Tx 2	…	Tx N	…
Type A					

Abbreviations: Tx, treatment.

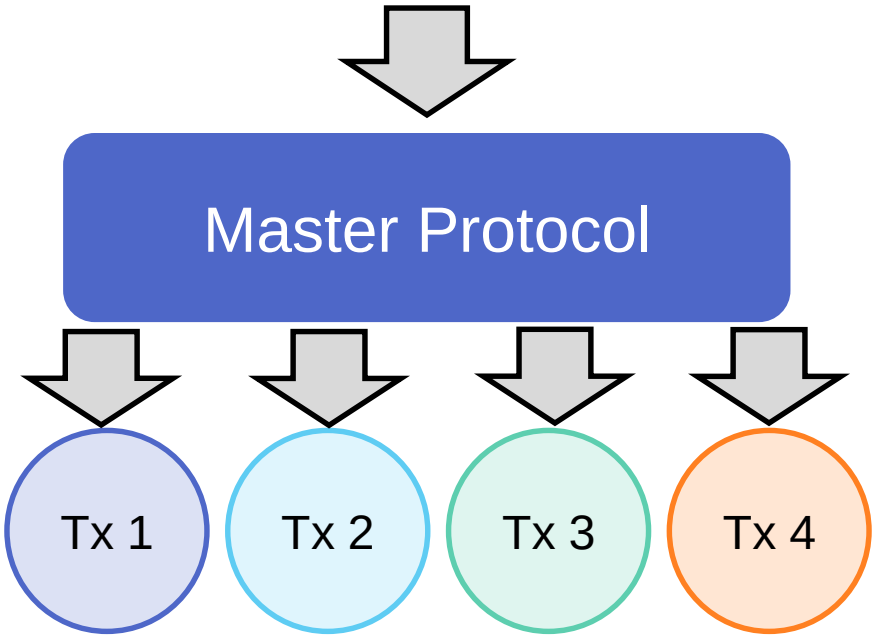
Adaptive platform (basket) trial design

	Tx 1	Tx 2	…	Tx N	…
Type A					
Type B					
…					
Type K					
…					

Abbreviations: Tx, treatment.

Adaptive platform trial design: Master protocol

- There is one Protocol
- The master protocol assigns patients
- Protocol is disease focused
- No treatment names in protocol
- What happens to patients/arm appendix
- Potentially evolving arms



Abbreviations: Tx, treatment.

Adaptive platform trial design: ebola case study

CLINICAL TRIALS

Clinical Trials
2016, Vol. 13(1) 22–30

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.

Adaptive platform design: EV-003

Master protocol: Trial goal is to find the best way to treat Ebola

- Reviewed and approved by:
  - Duke University IRB
  - University of Sierra Leone ethics committee
- Multiple Agents:
  - Combination + Single agents
  - Trial arms evolve, trial is perpetual

Regimens		Agents			
		Tx 1	Tx 2	Tx 3	Tx 4
Agents	Tx 1	■			
	Tx 2		■		
	Tx 3			■	
	Tx 4				■

Abbreviations: IRB, institutional review board; RAR, responsive adaptive randomization, Tx, treatment.

Adaptive platform design: EV-003

Master protocol: Trial goal is to find the best way to treat Ebola

- Primary Endpoint is 14-day mortality
- Response Adaptive Randomization:
  - Assigns treatment regimens that are performing better using primary endpoint data
- Prospective rules to remove; graduate arms

Regimens		Agents			
		Tx 1	Tx 2	Tx 3	Tx 4
Agents	Tx 1	■			
	Tx 2		■		
	Tx 3			■	
	Tx 4				■

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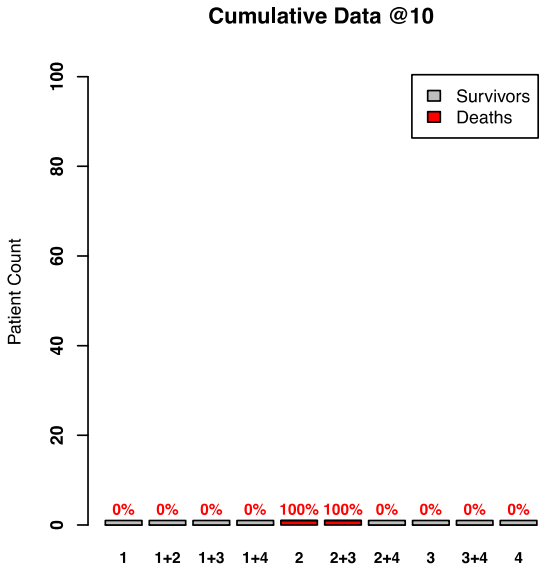

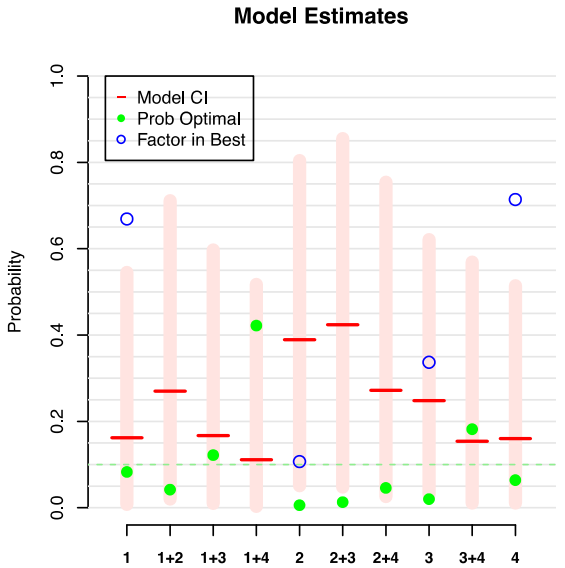

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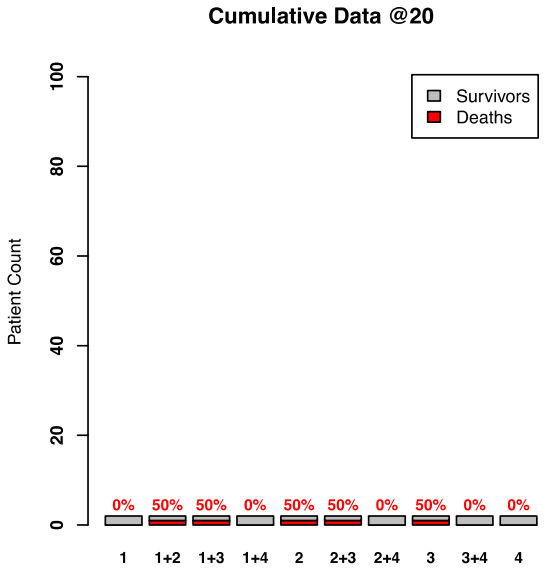

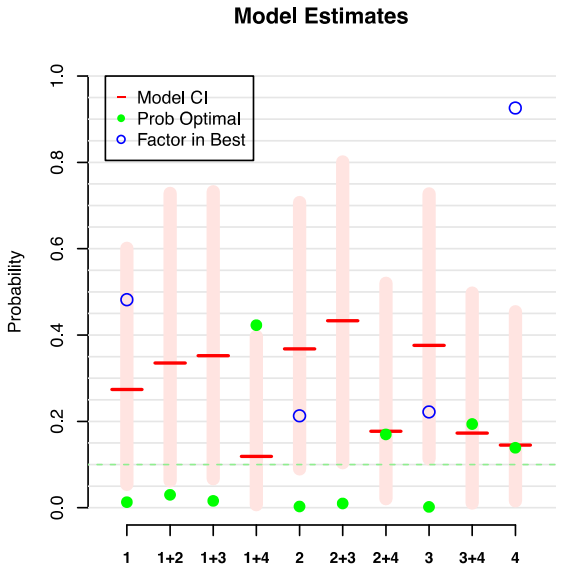

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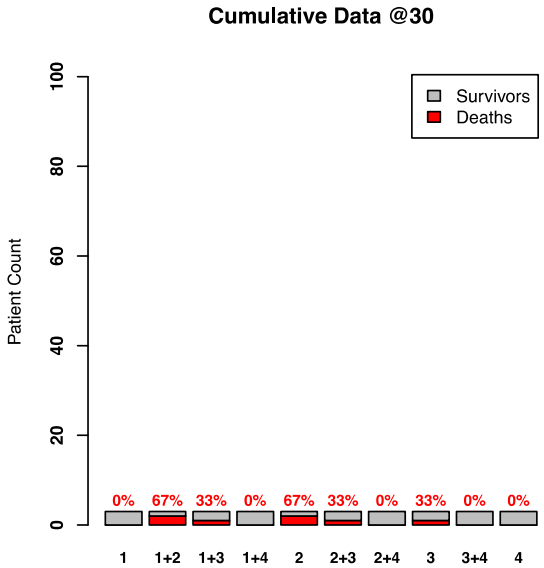

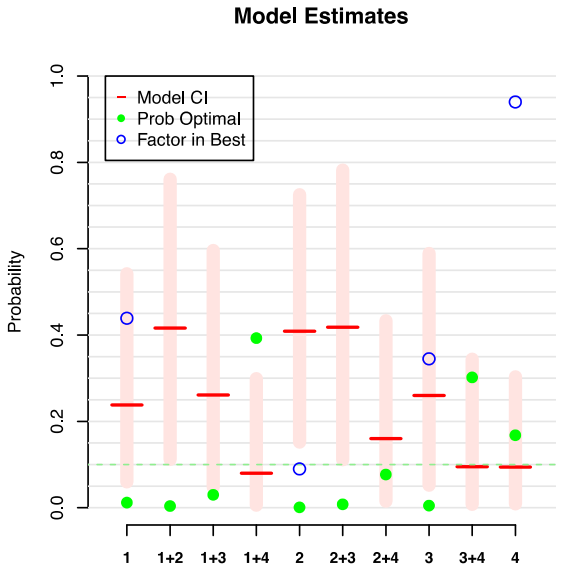

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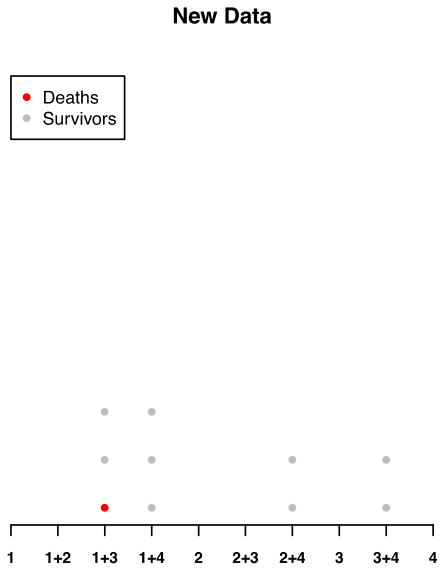

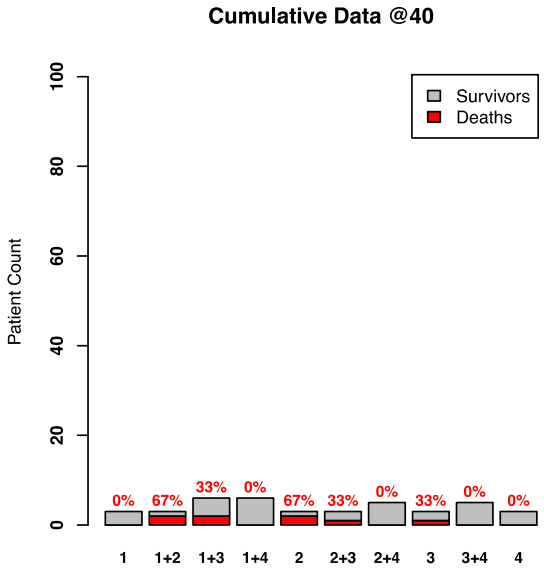

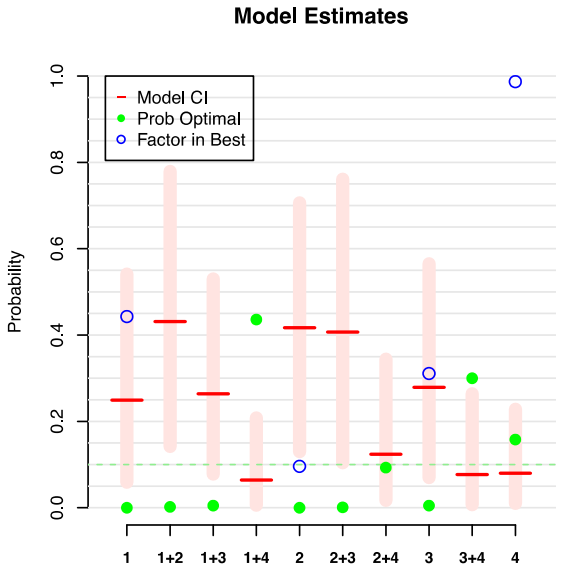

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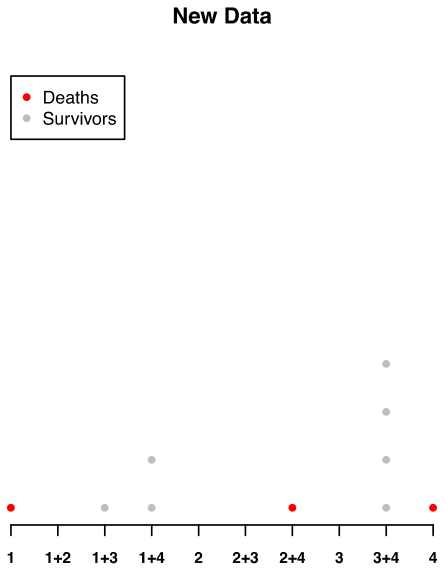

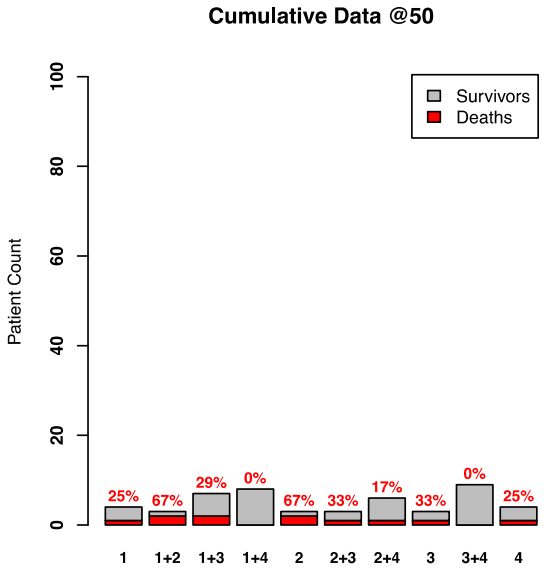

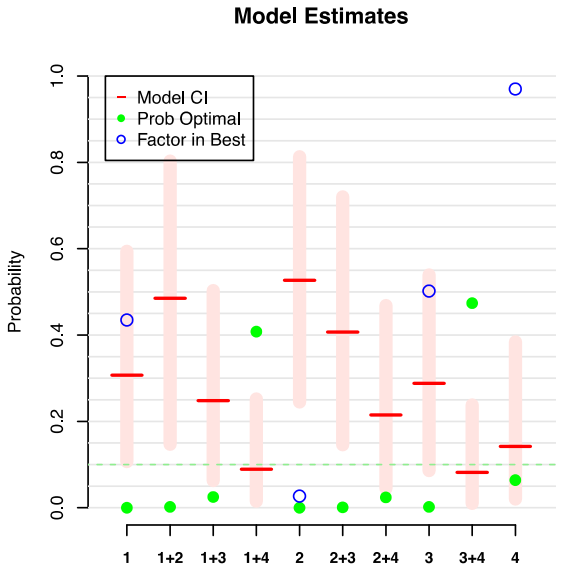

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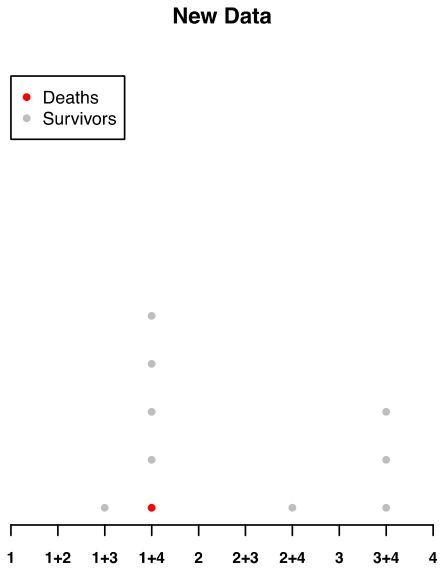

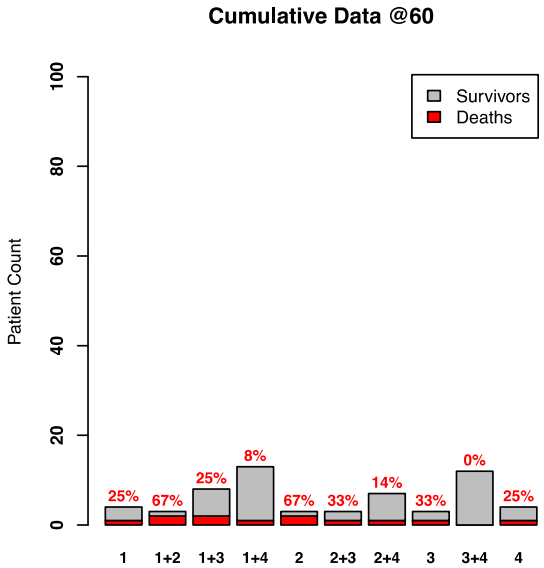

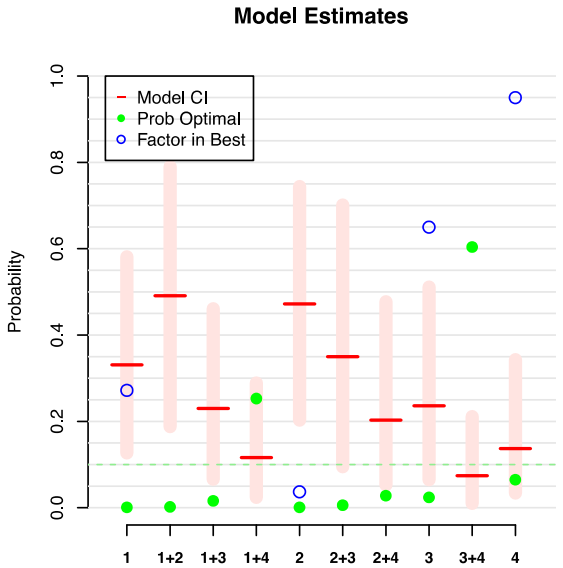

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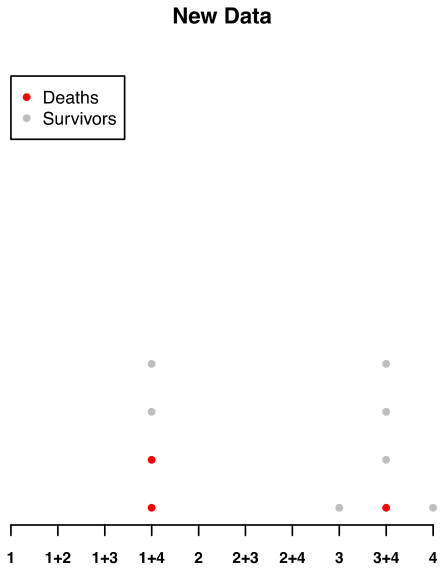

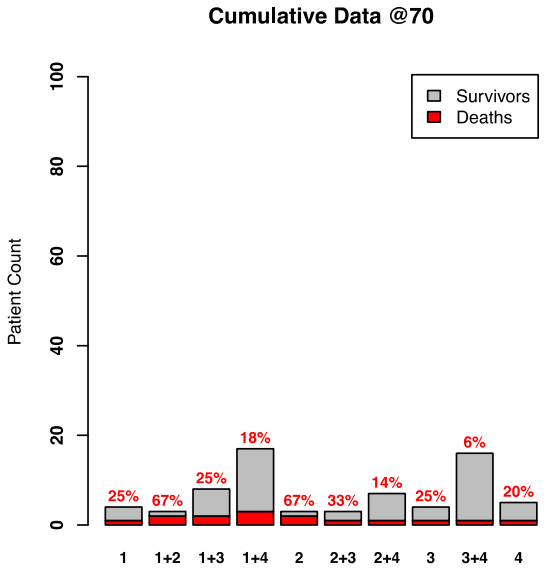

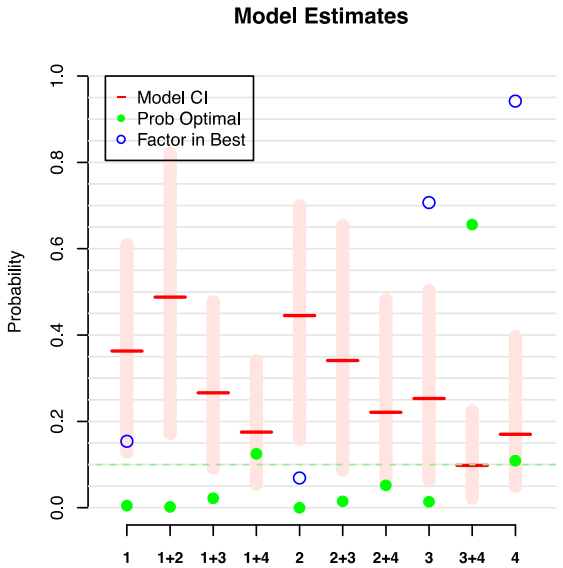

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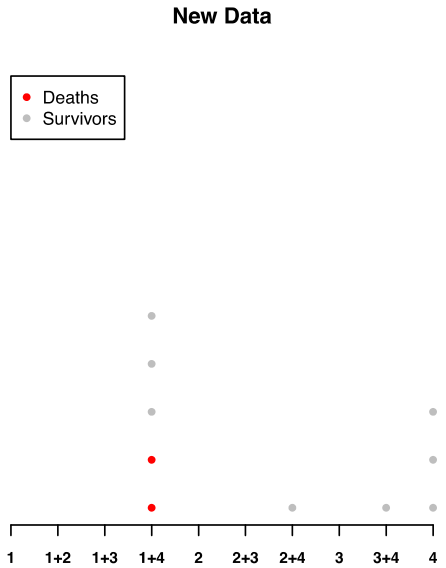

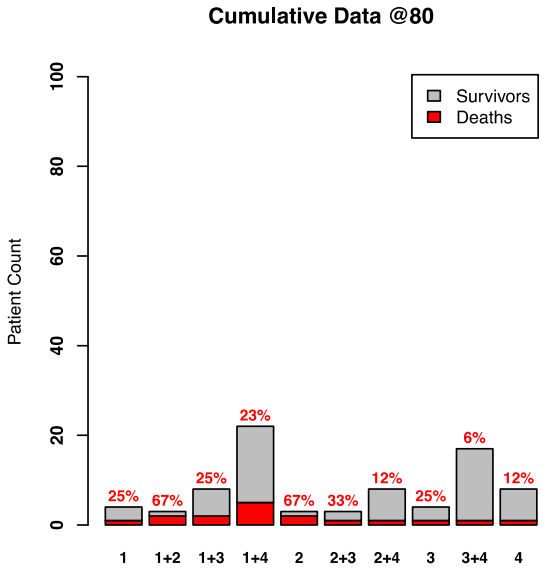

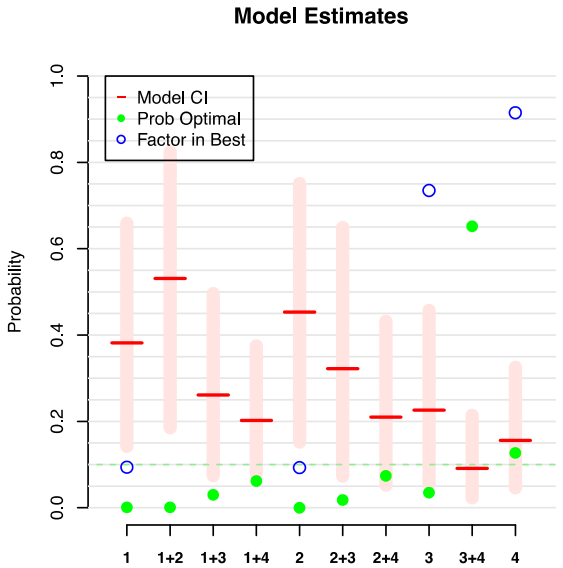

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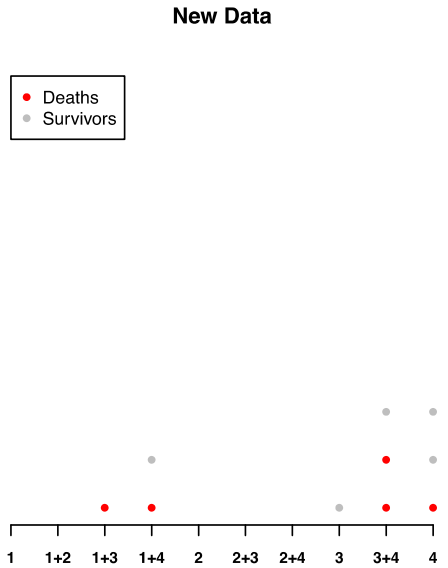

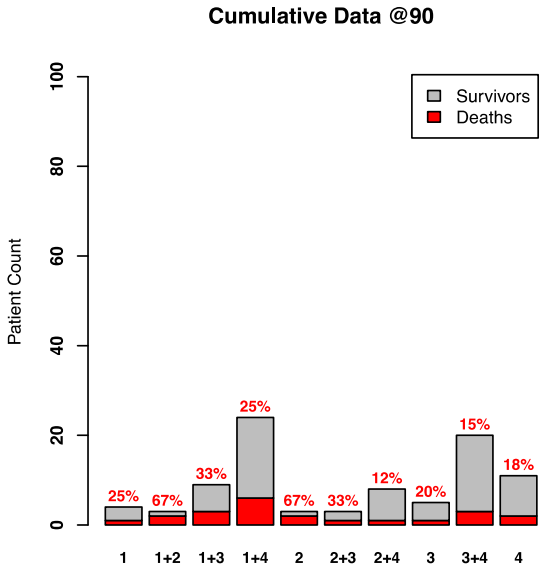

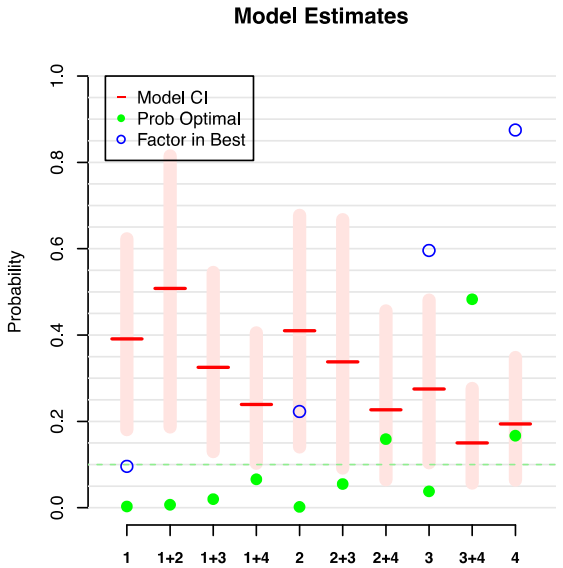

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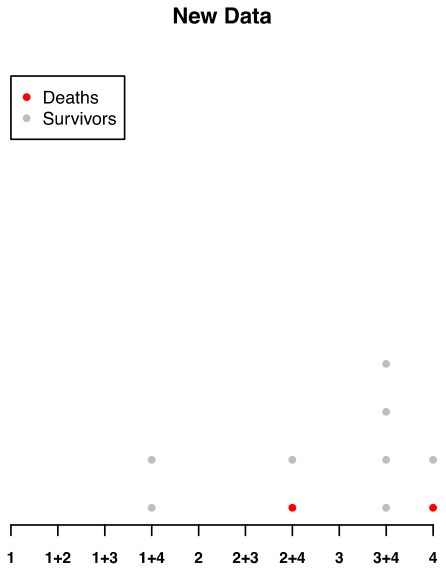

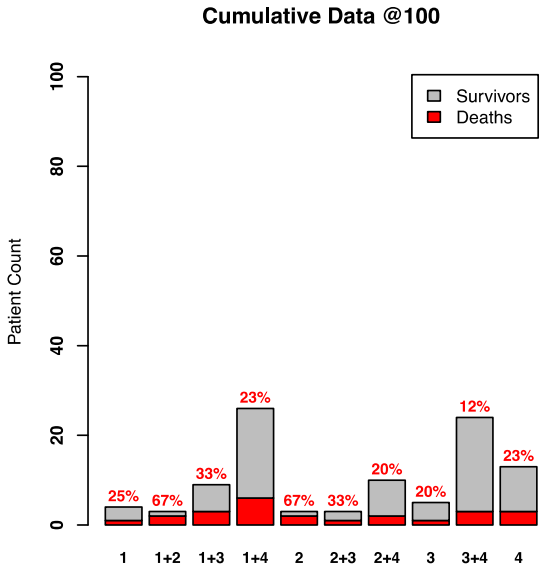

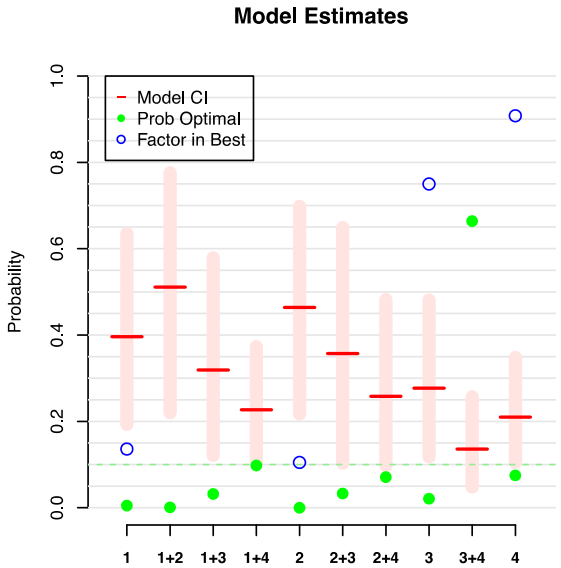

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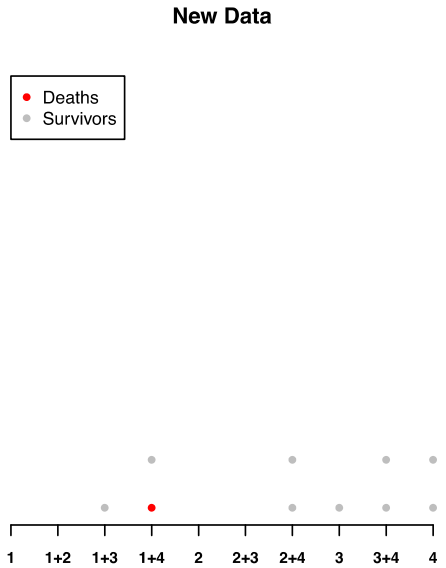

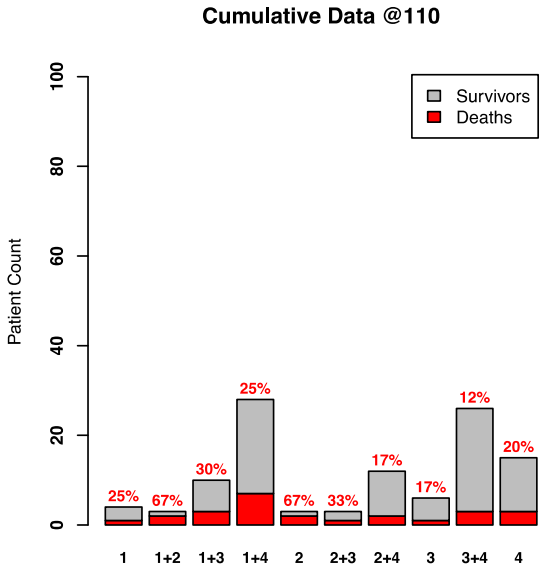

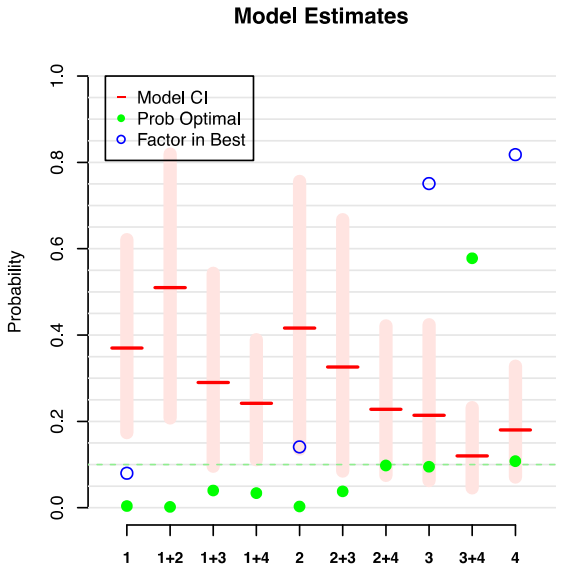

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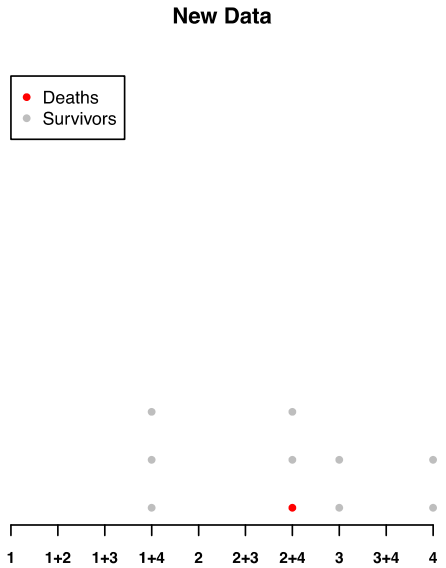
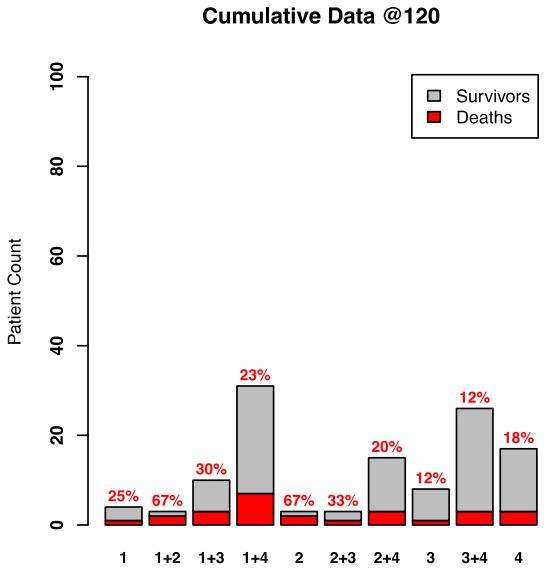
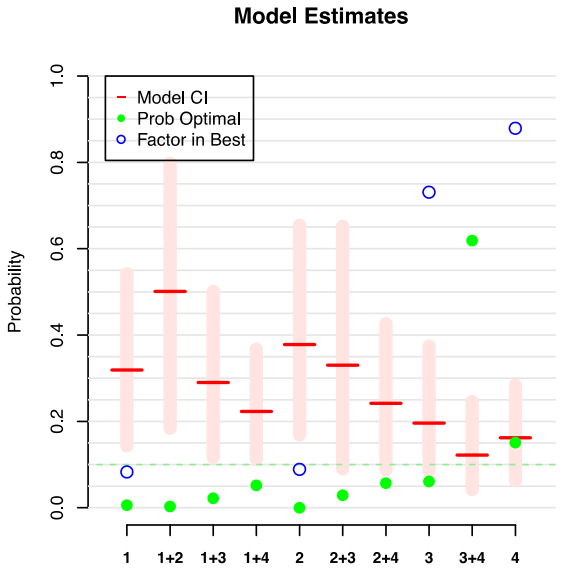
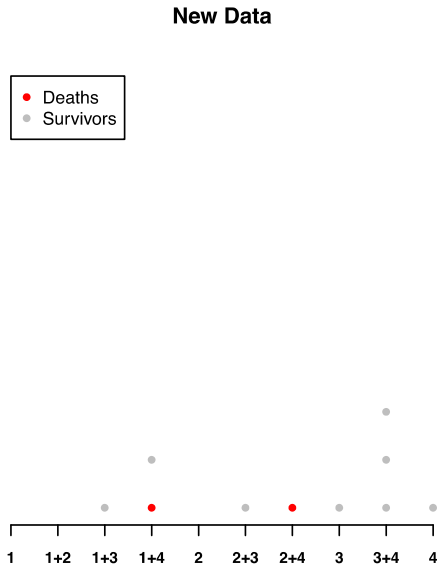
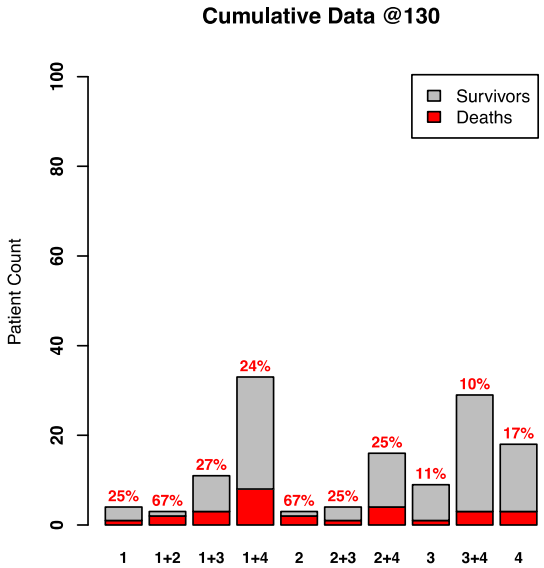


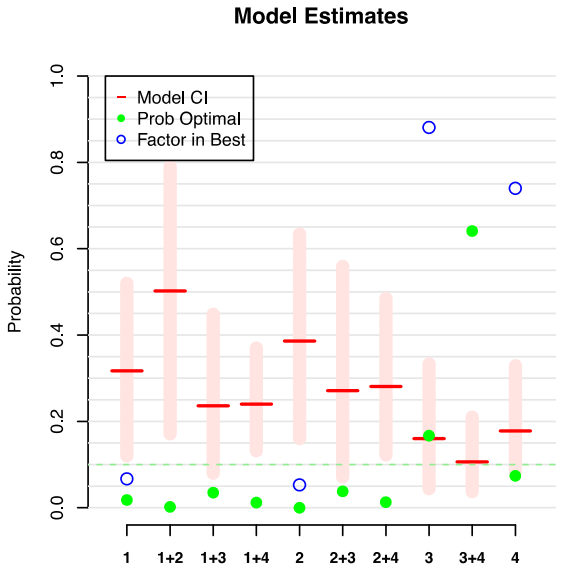




Adaptive platform design: EV-003







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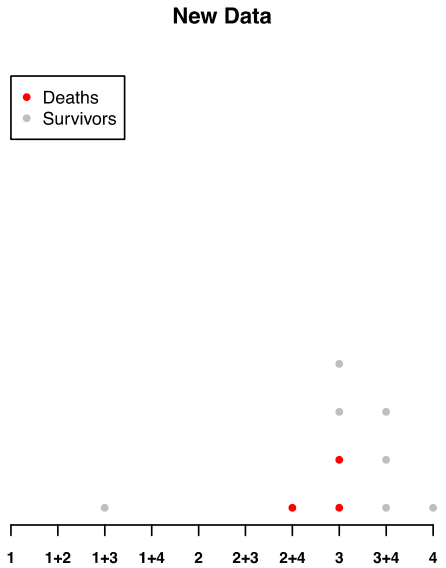

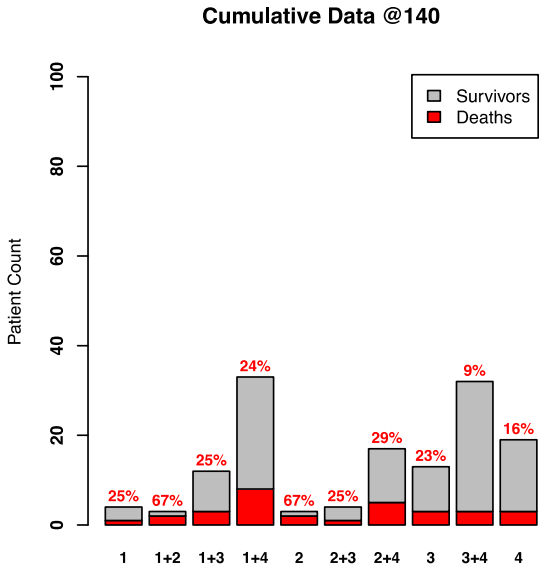

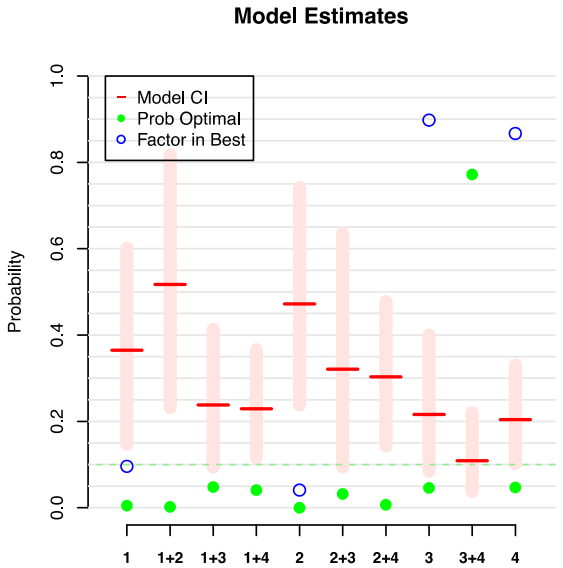

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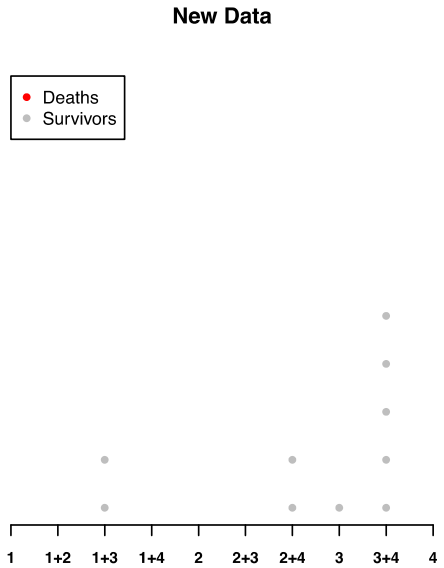

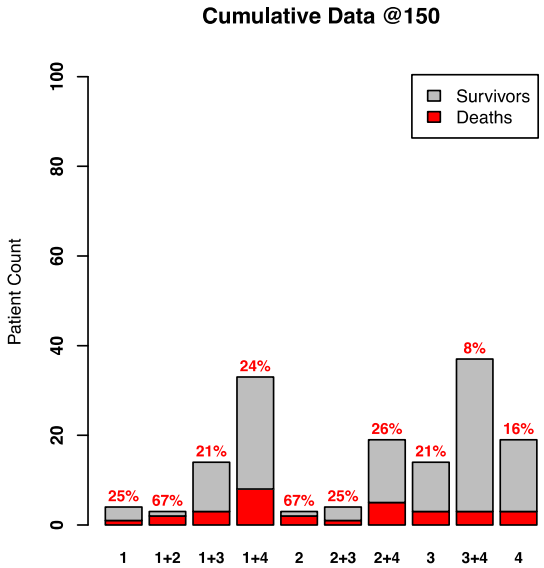

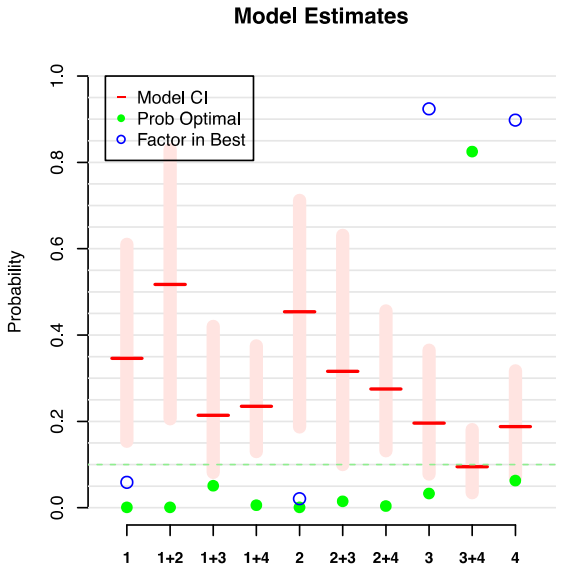

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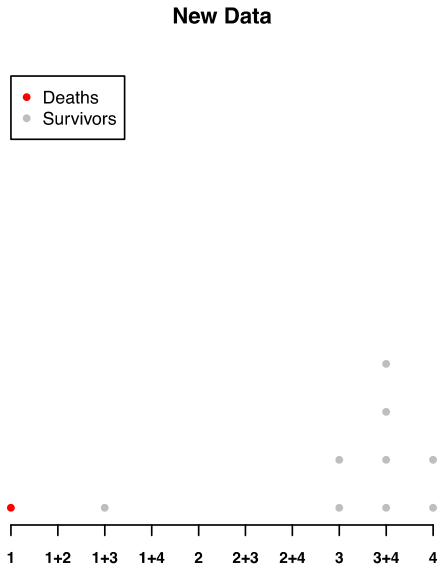
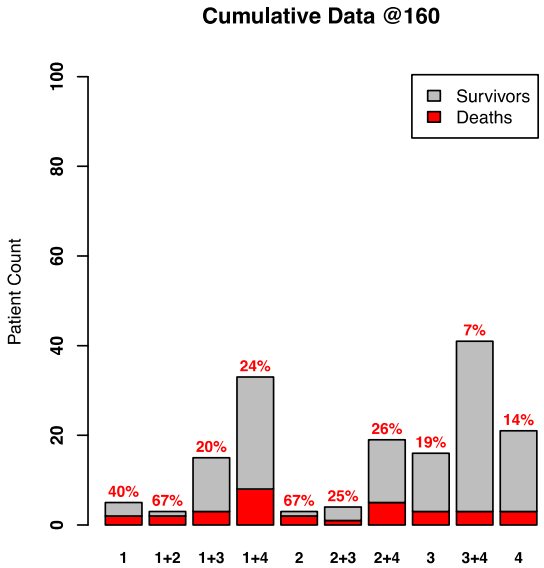
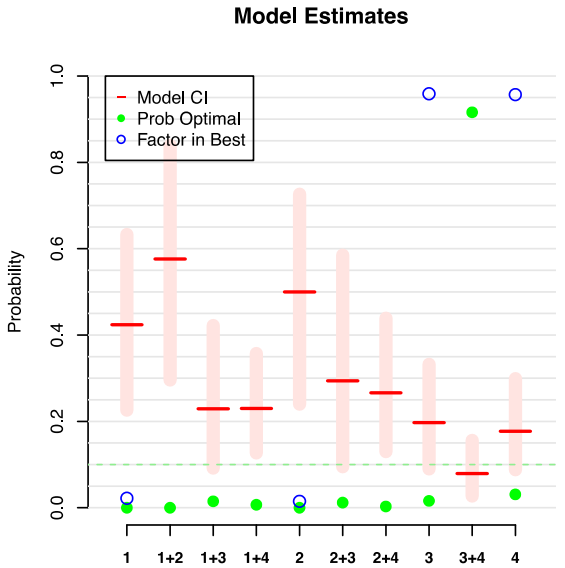
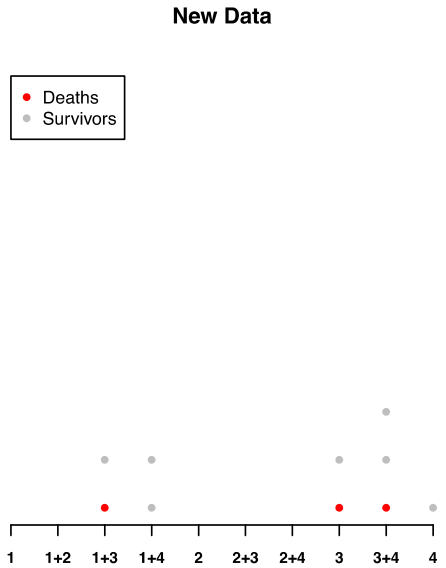
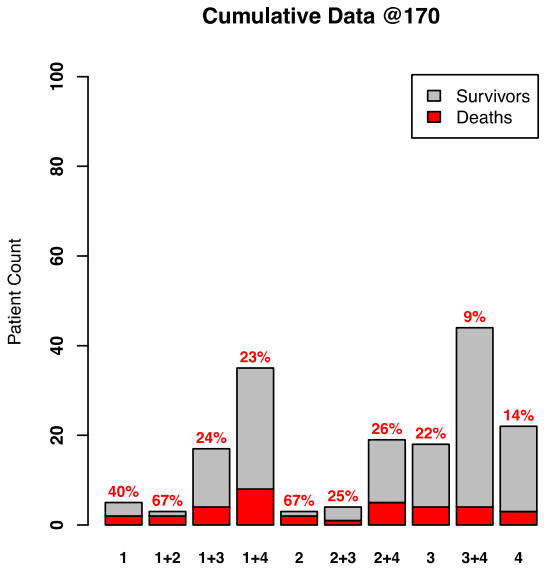


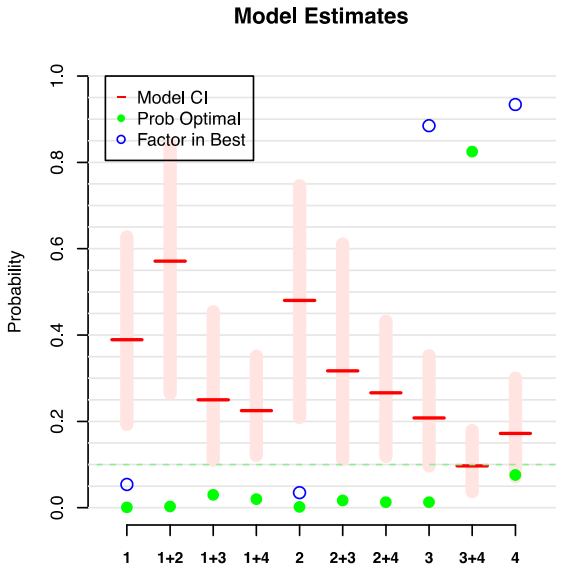




Adaptive platform design: EV-003







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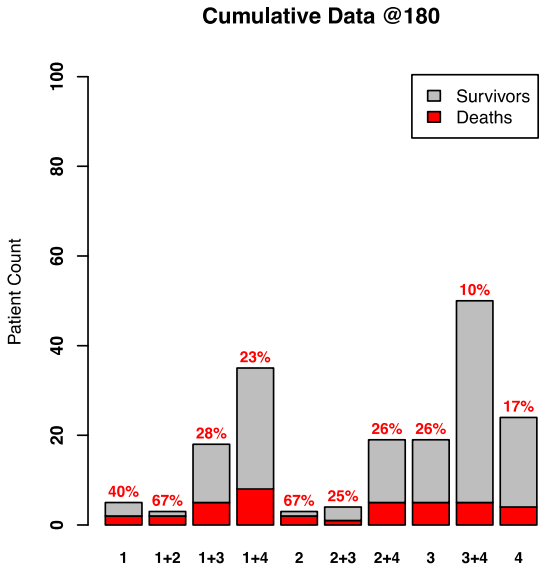

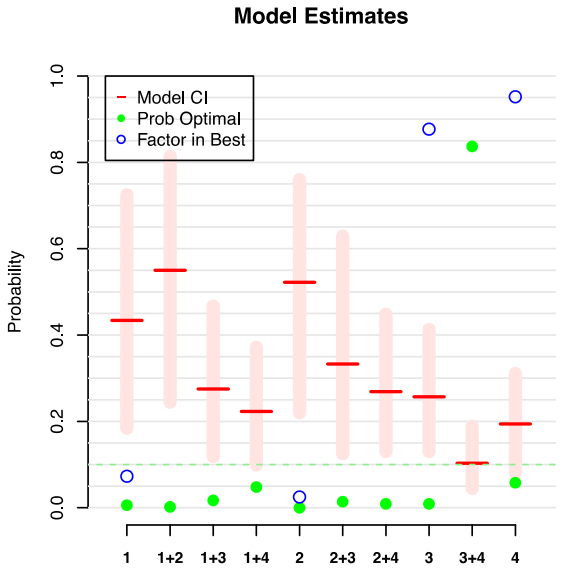

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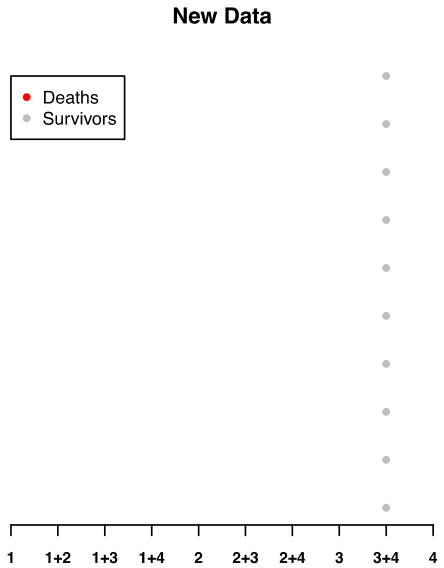

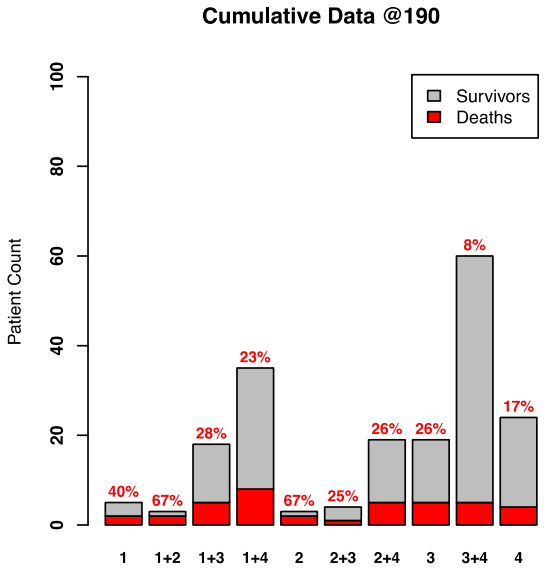

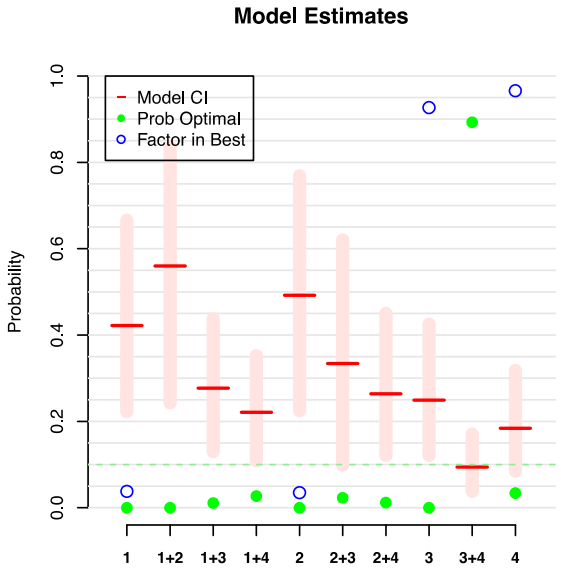

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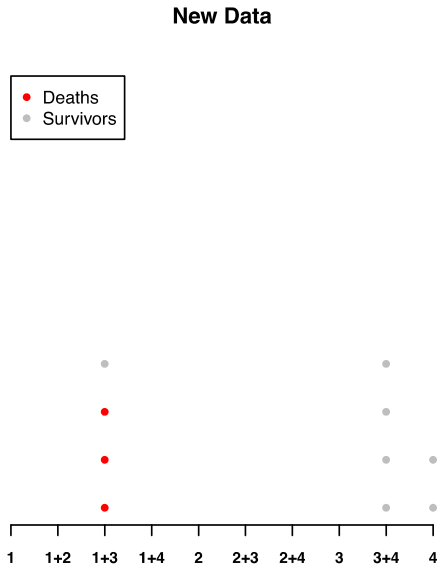

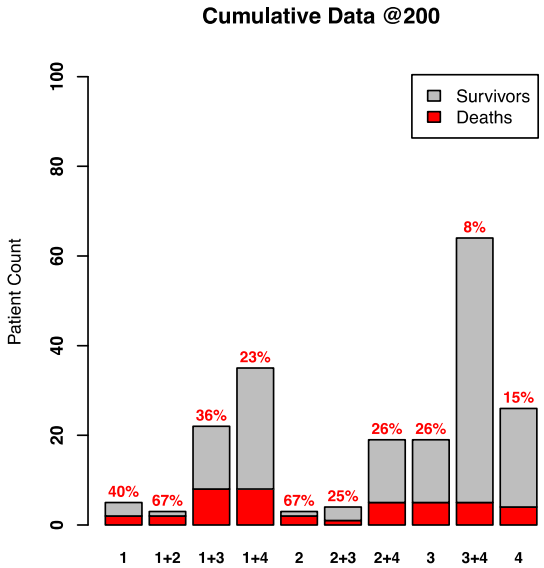

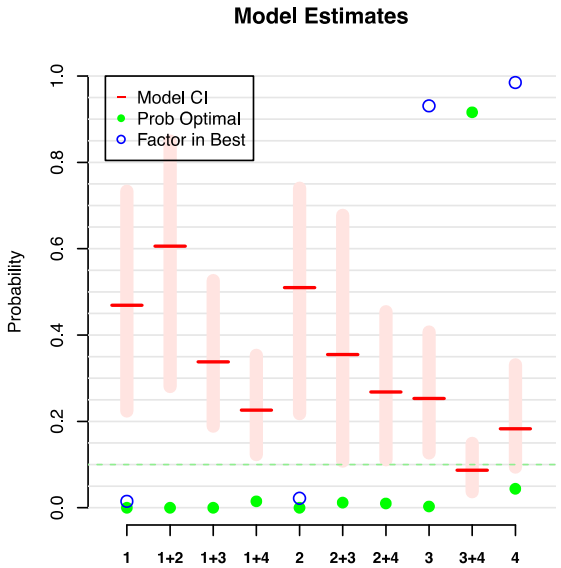

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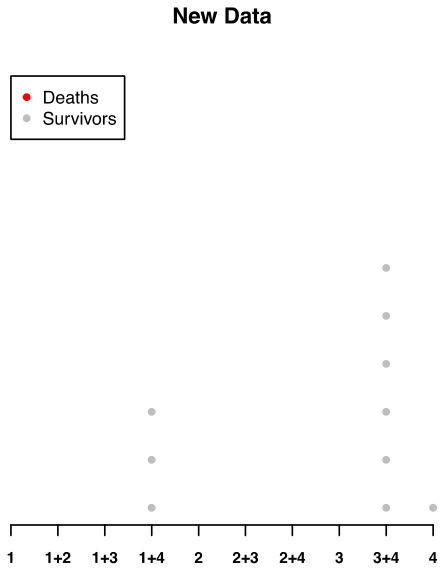

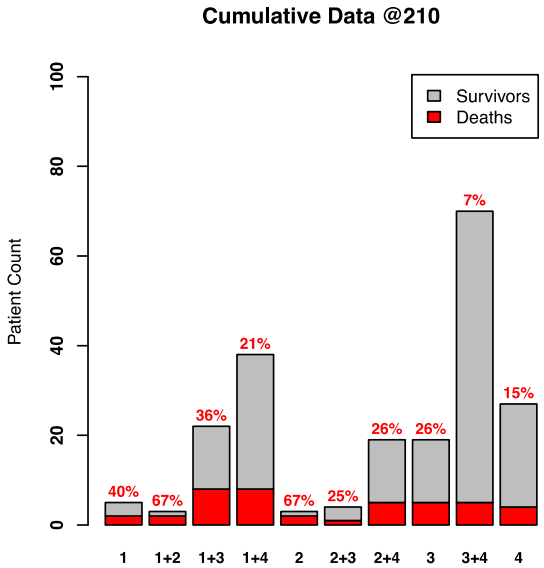

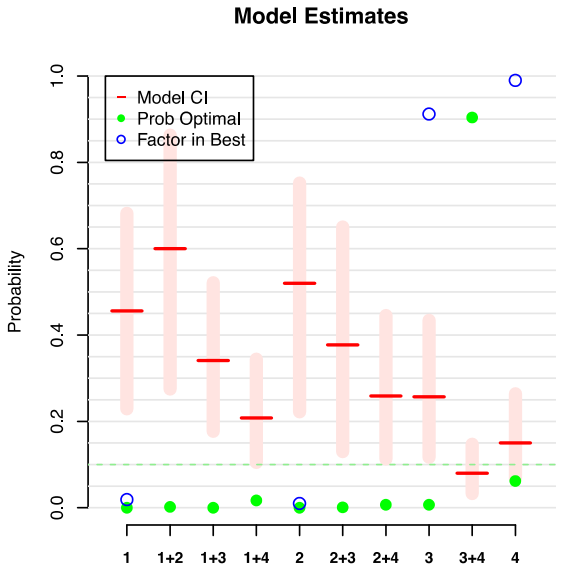

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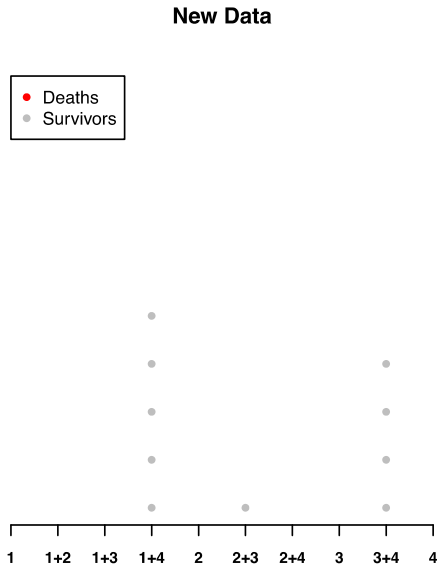

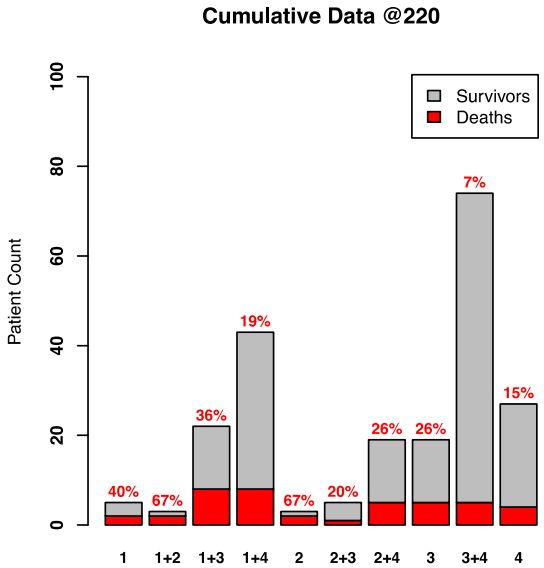

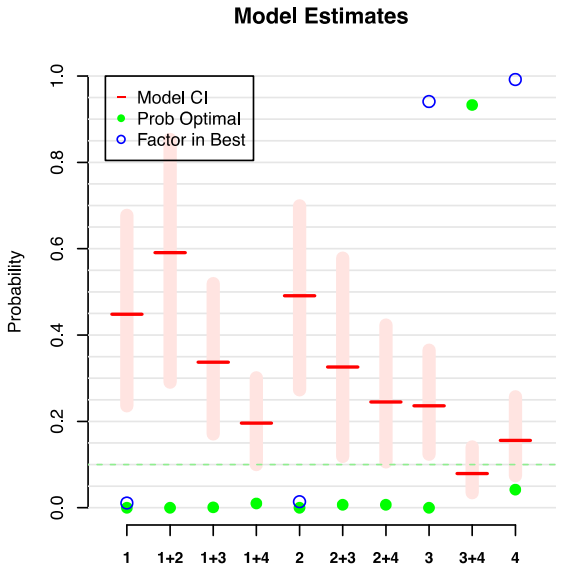

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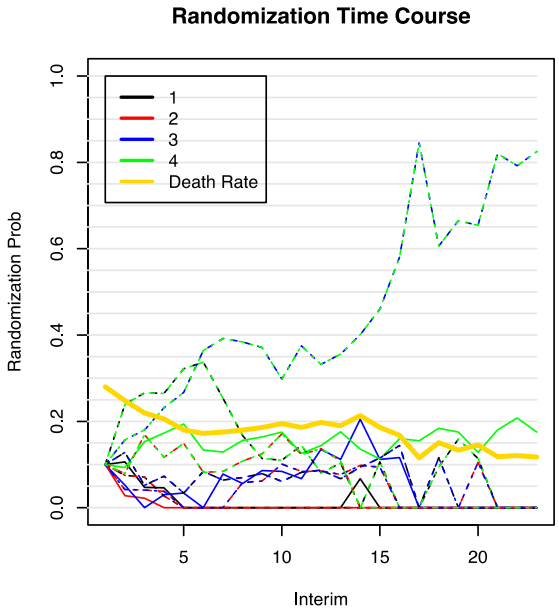

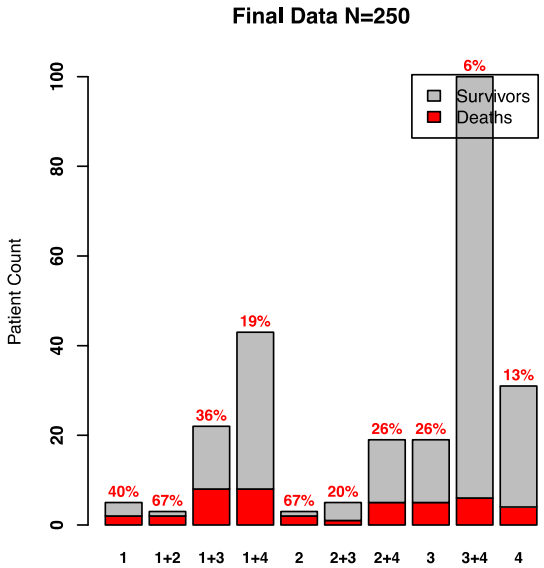

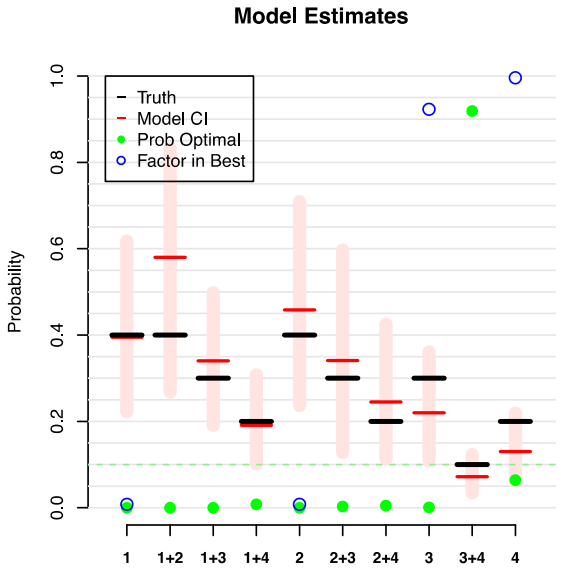

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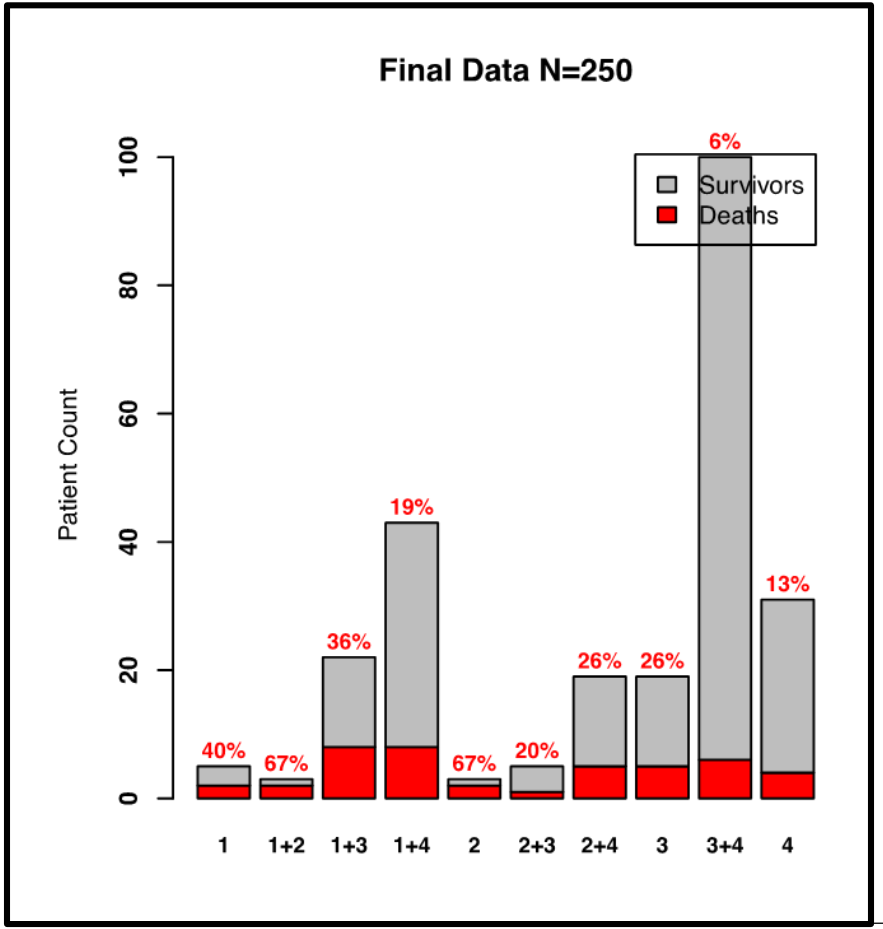
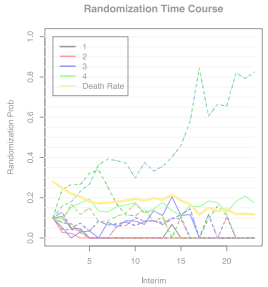
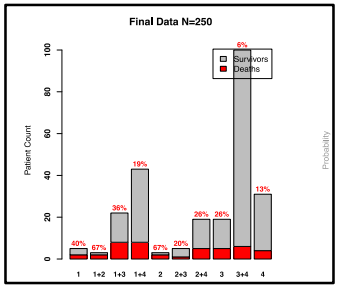
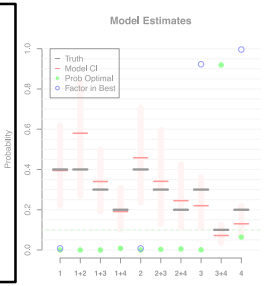
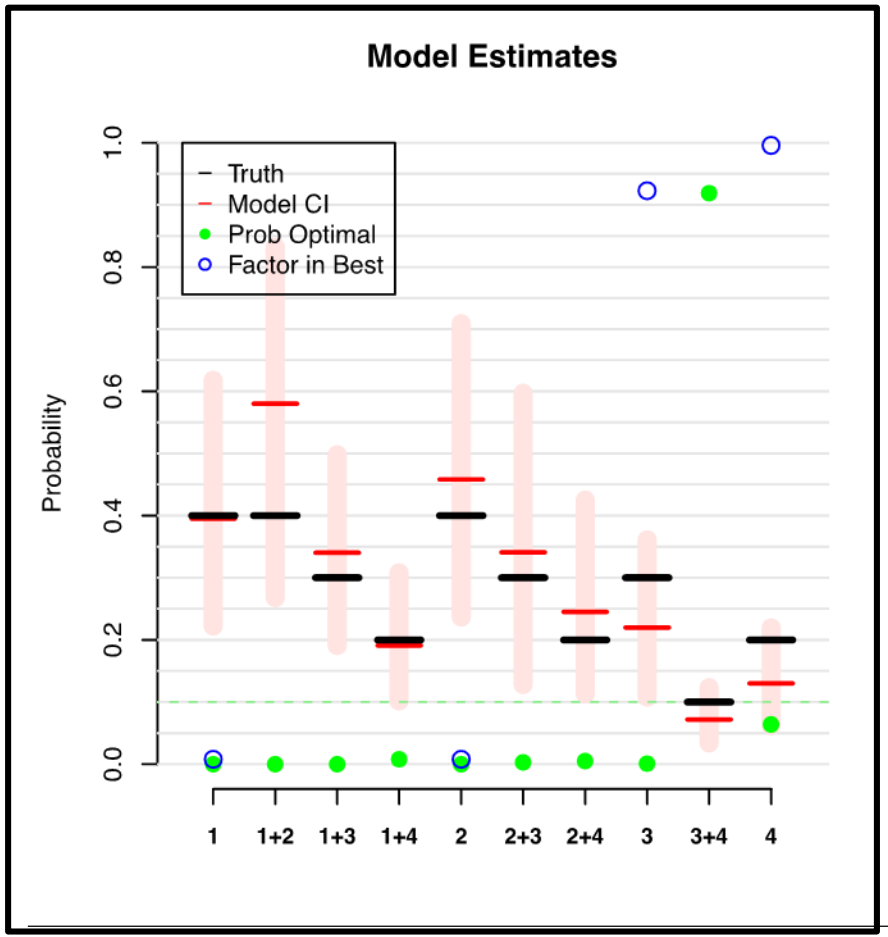


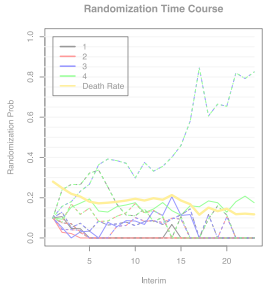


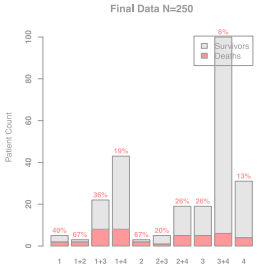


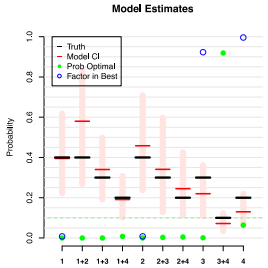


Adaptive platform design: EV-003

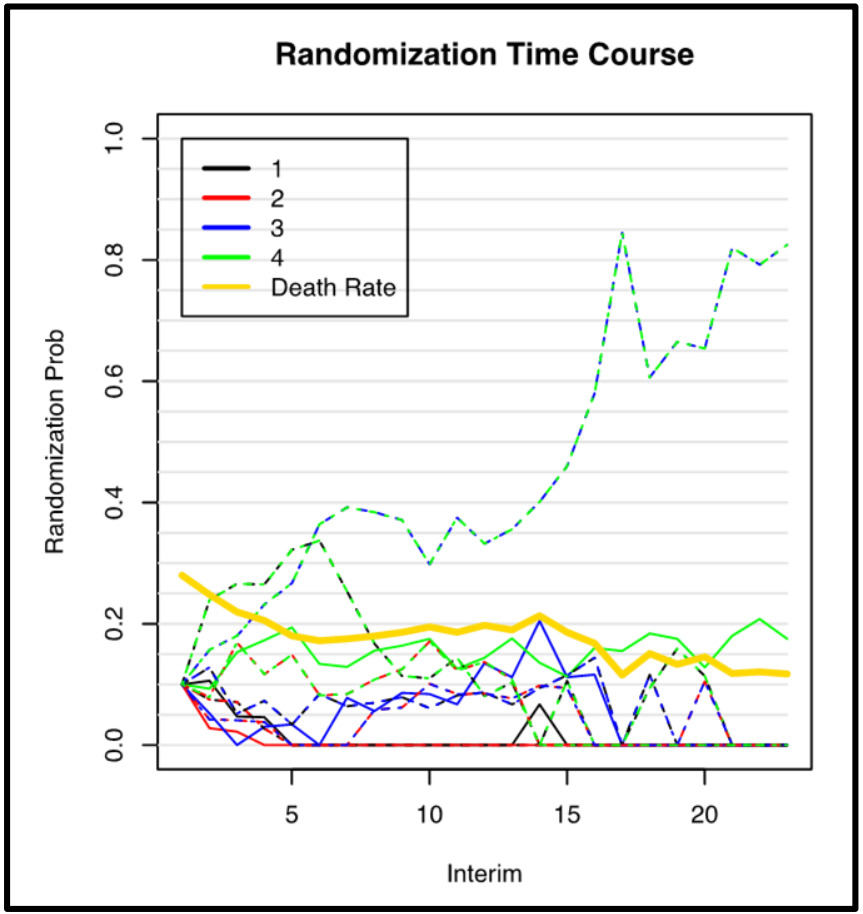


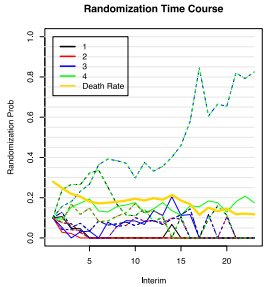


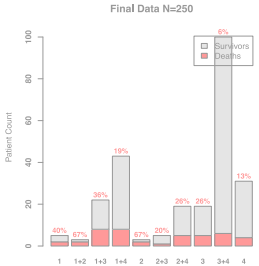


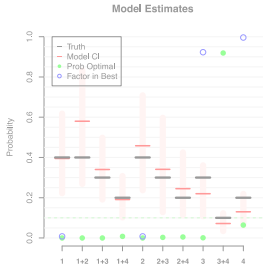


Adaptive platform design: EV-003

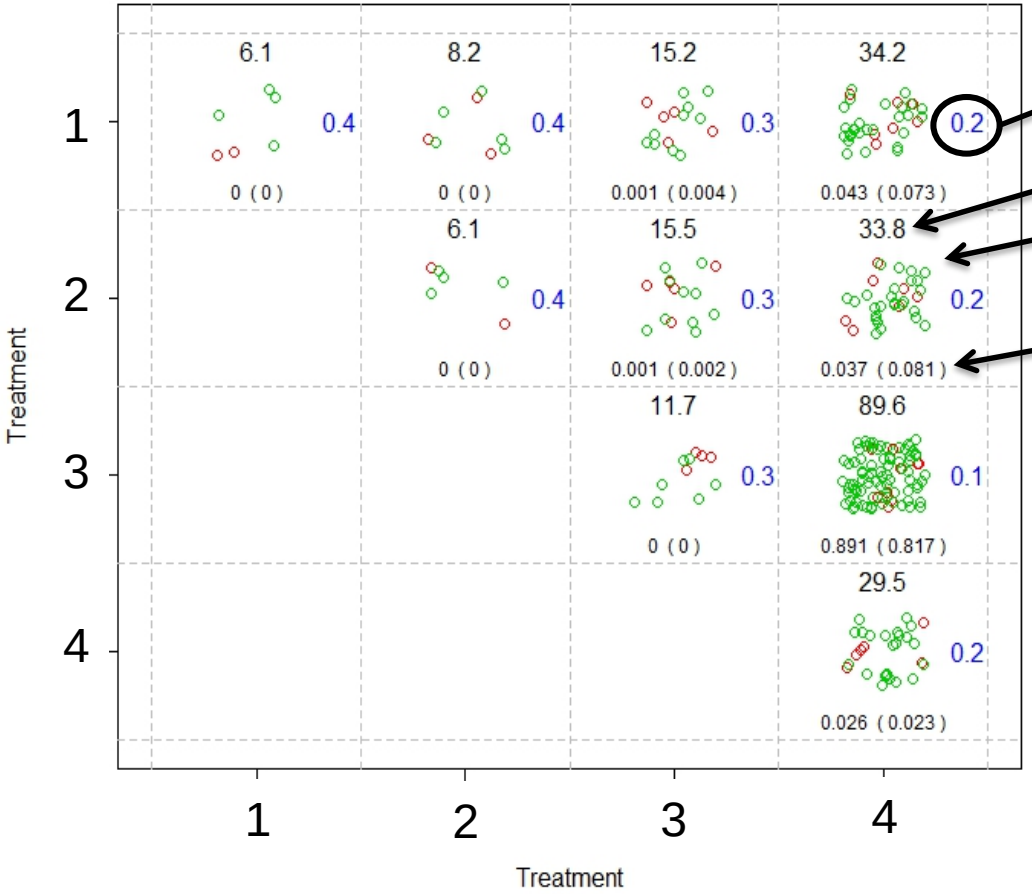








Adaptive platform design: EV-003; Scenario 3



True mortality rate

Mean sample size

Distribution of Success/Fail

Probability Win (No RAR)

Design	Mean Deaths
Adaptive	49.4
Fixed	69.9

Adaptive platform design: Efficiencies

Approach	N Trials	# Tx	N	Fails	Mean Years	% Process Good Tx	% Good Tx Win	% Ineffective Wins
Traditional 2-arm	9.8	9.8	1966	1357	12.0	78	82	2.5%
Bayes Adaptive Closed	3.4	13.7	971	663	5.5	82	76	2.5%
Bayes Open	1	13.1	849	579	4.2	85	91	2.2%
Bayes Open With RAR	1	18.2	640	431	3.2	87	85	2.3%

Source: Saville and Berry (2016) “Efficiencies of Platform Clinical Trials: A Vision of the Future” Clinical Trials.
Abbreviations: Tx, treatment.

Adaptive platform design: Examples

- iSpy-2 (Neoadjuvant breast cancer)
- Precision Promise (Pancreatic cancer)
- GBM-AGILE (GBM)
- IMI-EPAD (Alzheimer’s disease)
- DIAN-TU (Dominantly inherited Alzheimer’s Disease)
- ADAPT (Anti-biotics)
- PPMD (Duchesne MD)
- REMAP-CAP

Adaptive platform design: Examples

REMAP-CAP

- Treatment of severe community acquired pneumonia
- Multiple domains of treatment:
  - Anti-biotic (5), immunomodulation (2), extended macrolide (2), ventilator (4?), evolves as trial goes
- Embedded within the ICUs throughout EU, Australia, NZ
- Response adaptive randomization to a regimen for each patient as a function of their shock status
- Superiority/inferiority/equivalence claims for interventions by shock status:
  - Announce to world – already implemented in the sites in the trial

Adaptive platform design: REMAP

Randomized **E**mbedded **M**ultifactorial **A**daptive **P**latform

VIEWPOINT

Fusing Randomized Trials With Big Data
The Key to Self-learning Health Care Systems?

Derek C. Angus, MD, MPH
Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; and Associate Editor, *JAMA*.

Randomized clinical trials (RCTs) have revolutionized medicine by providing evidence on the efficacy and safety of drugs, devices, and procedures. Today, more than 40 000 RCTs are reported annually, their quality continues to increase, and oversight mechanisms ensure adequate protection of participants. However, RCTs have at least 4 related problems: (1) they are too expensive and difficult; (2) their findings are too broad (average treatment effect not representative of benefit for any given individual) and too narrow (trial population and setting not representative of general practice); (3) randomizing patients can make patients and physicians uncomfortable, especially when comparing different types of existing care; and (4) there are often long delays before RCT results diffuse into practice.

access to massive amounts of data, the Achilles' heel is lack of causal inference. No matter how detailed the measurement and how sophisticated the adjustment for all known variables, big data cannot eliminate unmeasured factors coincident with a particular treatment assignment that could explain an apparent change in outcome.[2]

Thus, each approach has complementary strengths: RCTs offer causal inference, and big data offers the potential for low-cost, high-volume, nuanced answers with immediate feedback. Rather than debate which is better, the greatest promise may come from fusing them.

Fixing Problem 1—Cost and Difficulty

Conducting RCTs as freestanding enterprises requires

Angus, *JAMA.* August 25, 2015. Volume 314, Number 8

ScienceInsider

BREAKING NEWS AND ANALYSIS FROM THE WORLD OF SCIENCE POLICY

Food and Drug Administration commissioner nominee Scott Gottlieb at his 5 April Senate confirmation hearing.

AARON P. BERNSTEIN/REUTERS/Newscom

Congress and FDA nominee heap love on 'adaptive trials'

By Kelly Servick | Apr. 7, 2017 , 5:45 PM

PERSPECTIVE

I-SPY 2 — THE FUTURE OF PHASE 2 DRUG DEVELOPMENT?

STATISTICS IN MEDICINE

I-SPY 2 — A Glimpse of the Future of Phase 2 Drug Development?

David Harrington, Ph.D., and Giovanni Parmigiani, Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

PDUFA VI

4. Enhancing Capacity to Review Complex Innovative Designs

To facilitate the advancement and use of complex adaptive, Bayesian, and other novel clinical trial designs, FDA will conduct the following activities during PDUFA VI:

a. FDA will develop the staff capacity to enable processes to facilitate appropriate use of these types of methods. This staff will support the computationally intensive review work necessary to evaluate complex adaptive, Bayesian, and other novel clinical trial designs, with a particular focus on clinical trial designs for which simulations are necessary to evaluate the operating characteristics.

Opportunities for Global Health

- Create “Disease Focused” standing clinical trials for numerous global health initiatives
  - Treatment agnostic trials with multiple (combination) treatments
- Improve the condition for current participants
- Improve the science of learning
- **Greatly improve the future for the human condition**