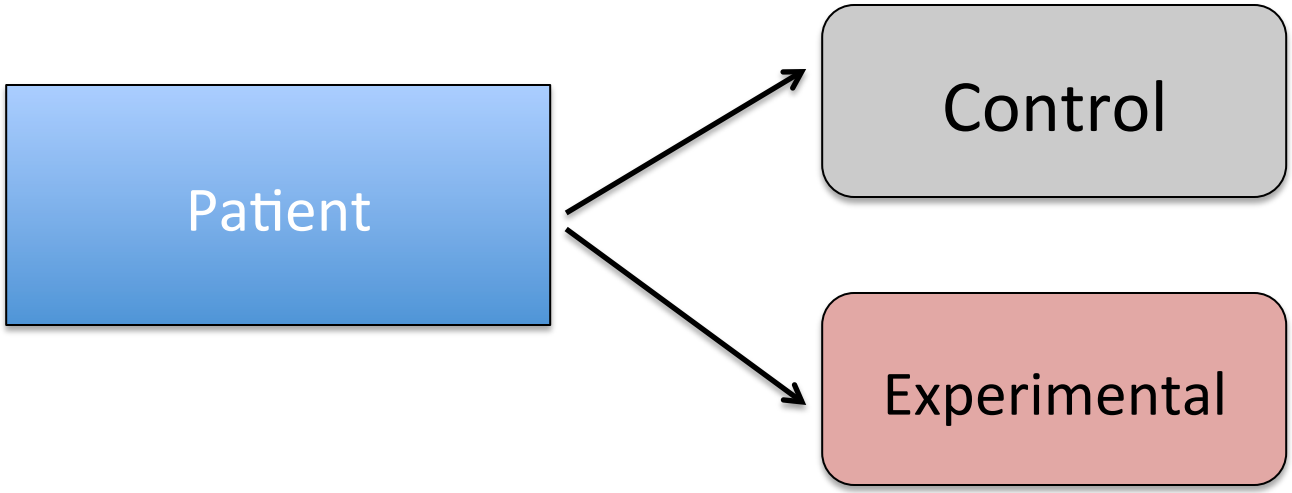
# An Adaptive Platform Trial For EBOLA: Application to Future Pandemics

Scott M. Berry
Berry Consultants
Adjunct KUMC
scott@berryconsultants.com

@statberry

# What is a Platform Trial?

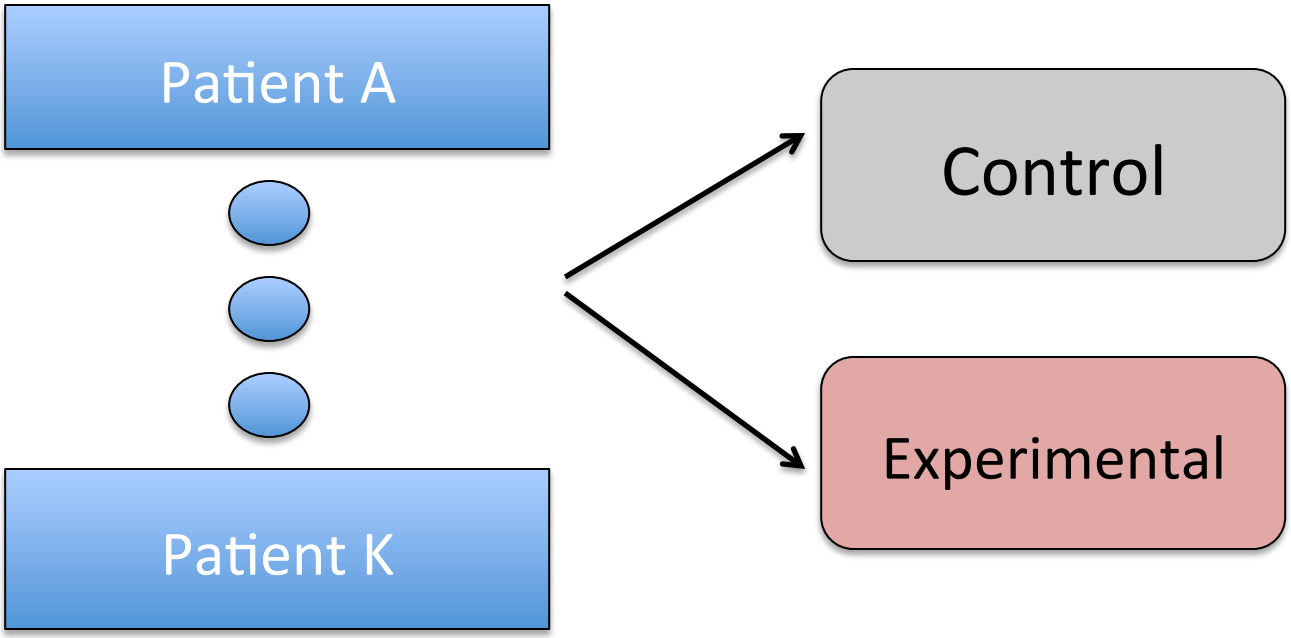
- Traditional Trial:




- Single treatment, homogenous patients: One question

# What is a Platform Trial?

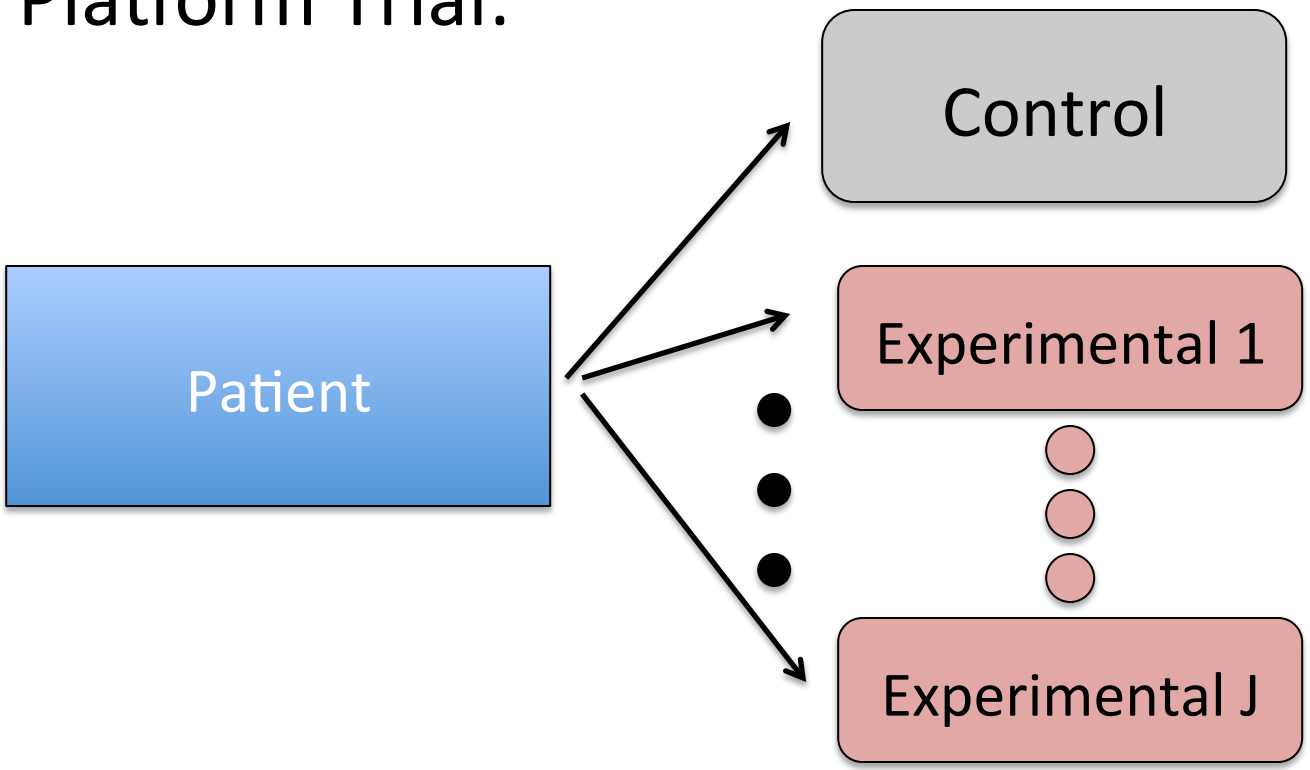
- Basket Trial:




- Single treatment, heterogeneous patients: K correlated questions

# What is a Platform Trial?

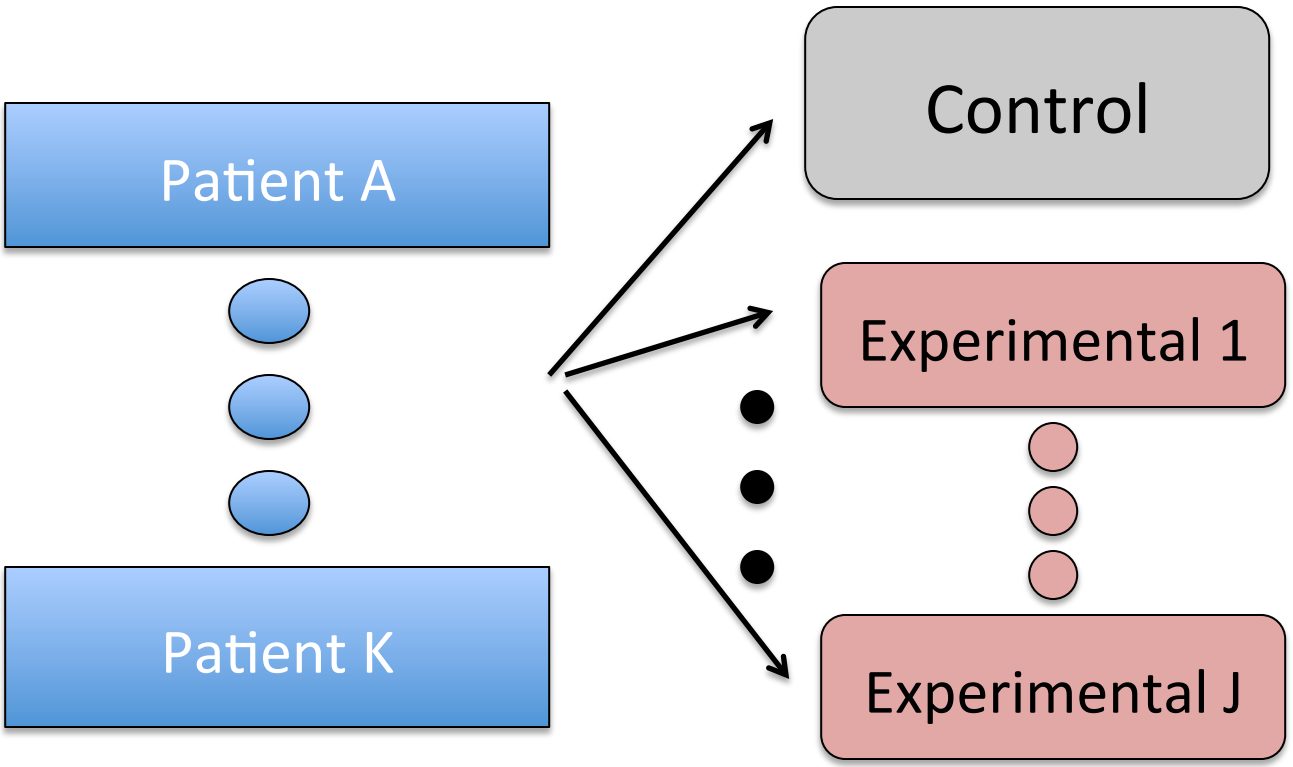
- Platform Trial:




- J treatments, Homogeneous patients, J questions

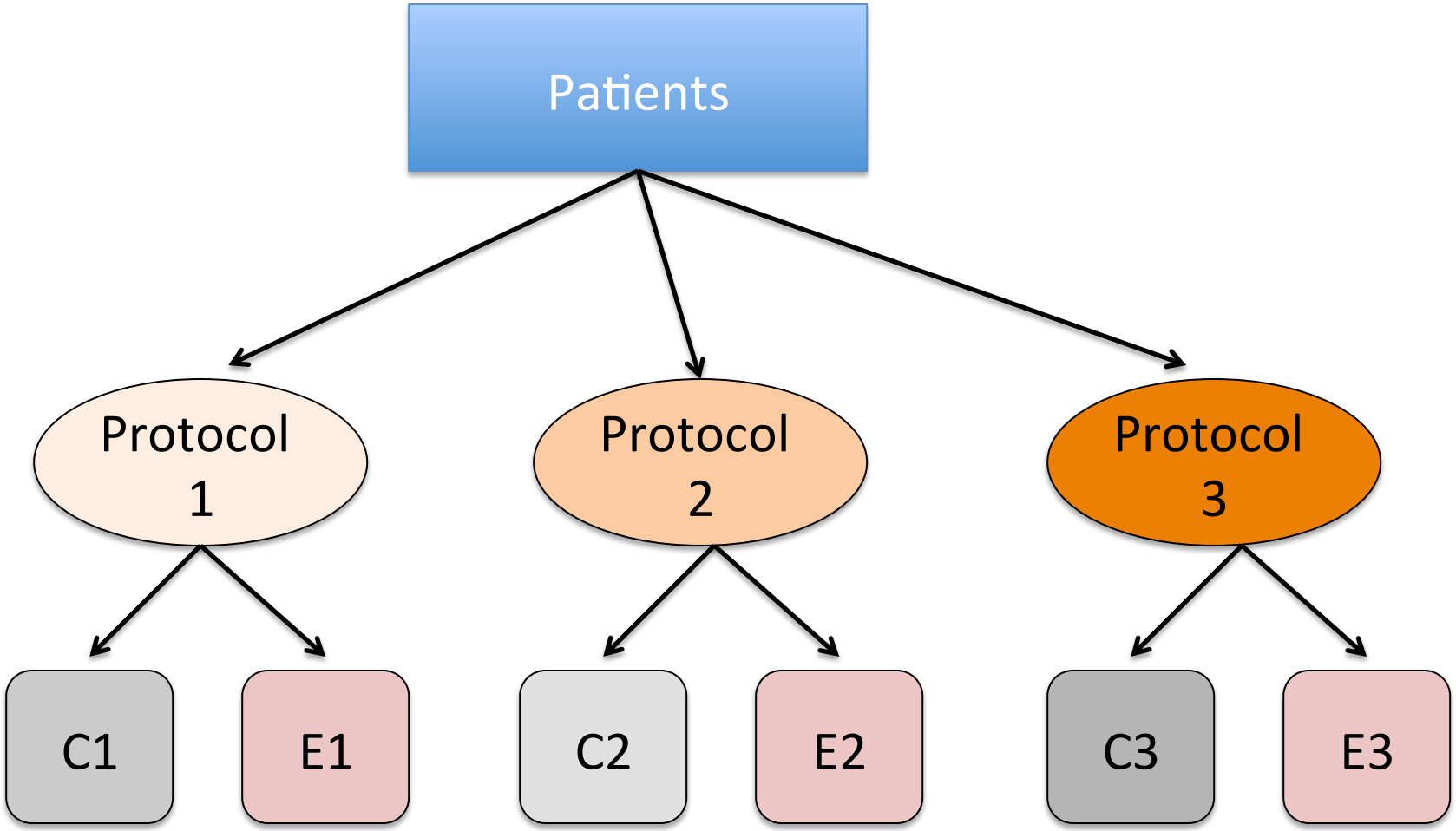
# What is a Platform Trial?

- Basket/Platform Trial:

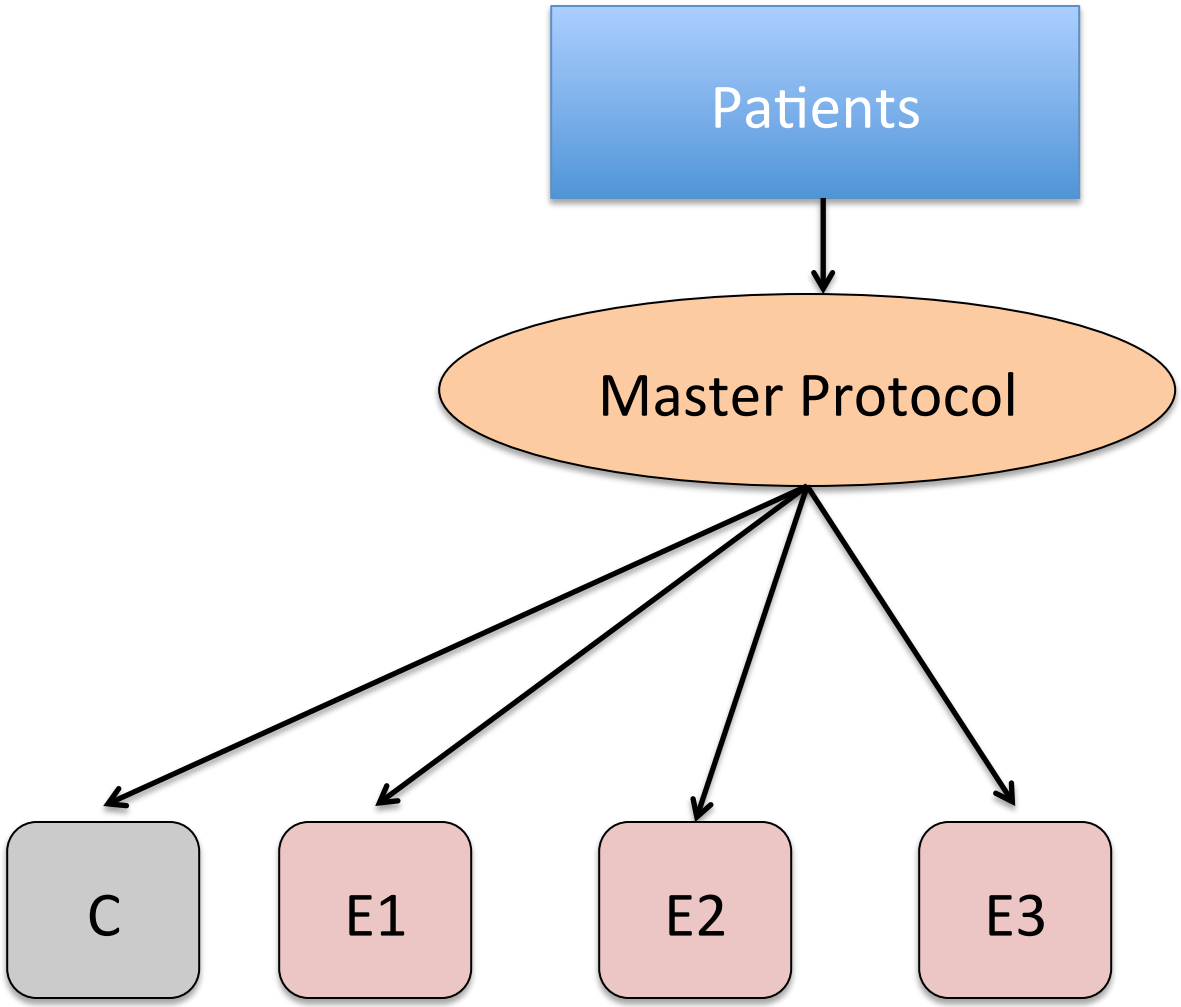



- J treatments, heterogeneous patients, JxK questions

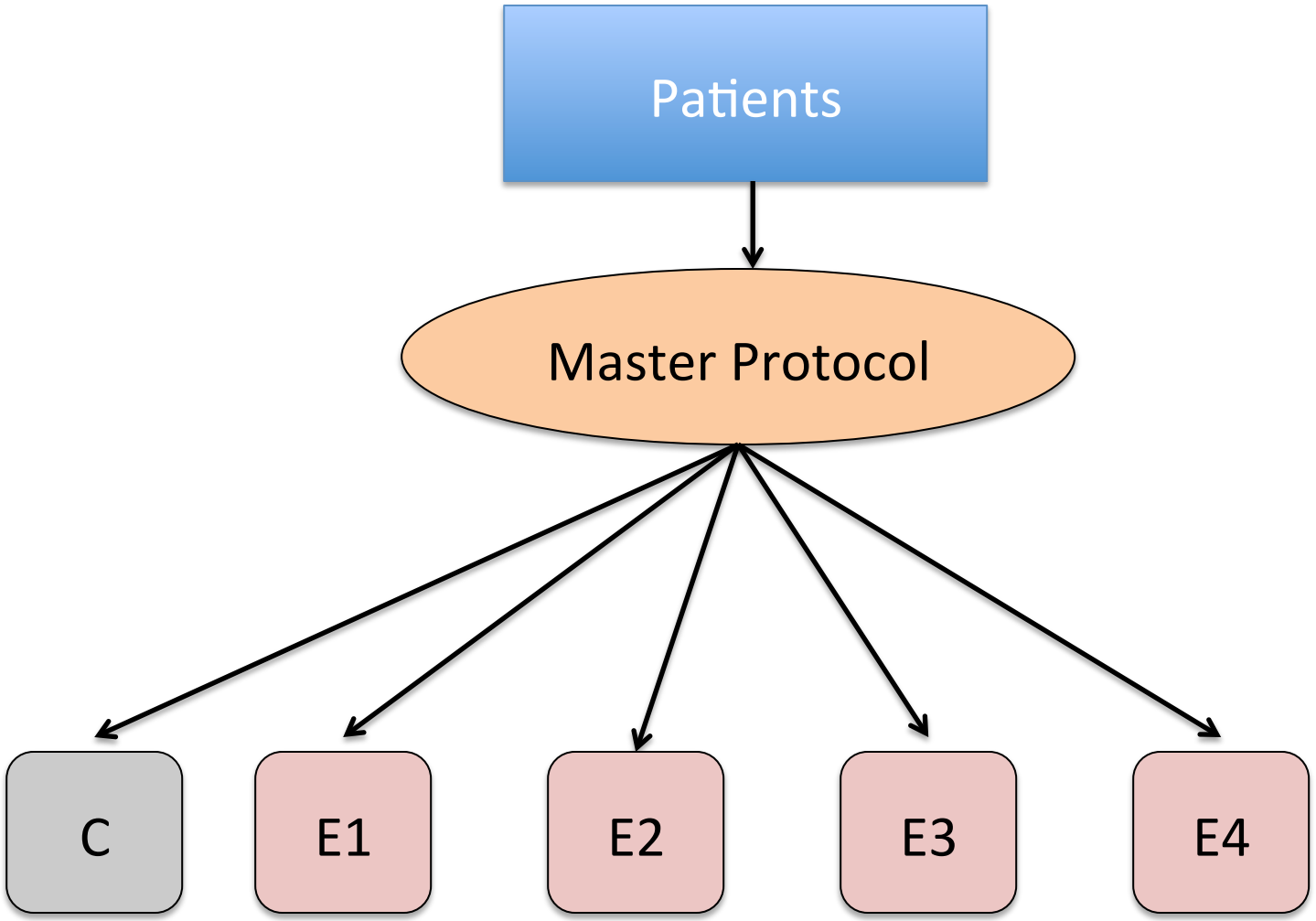
# Co-Operative Group



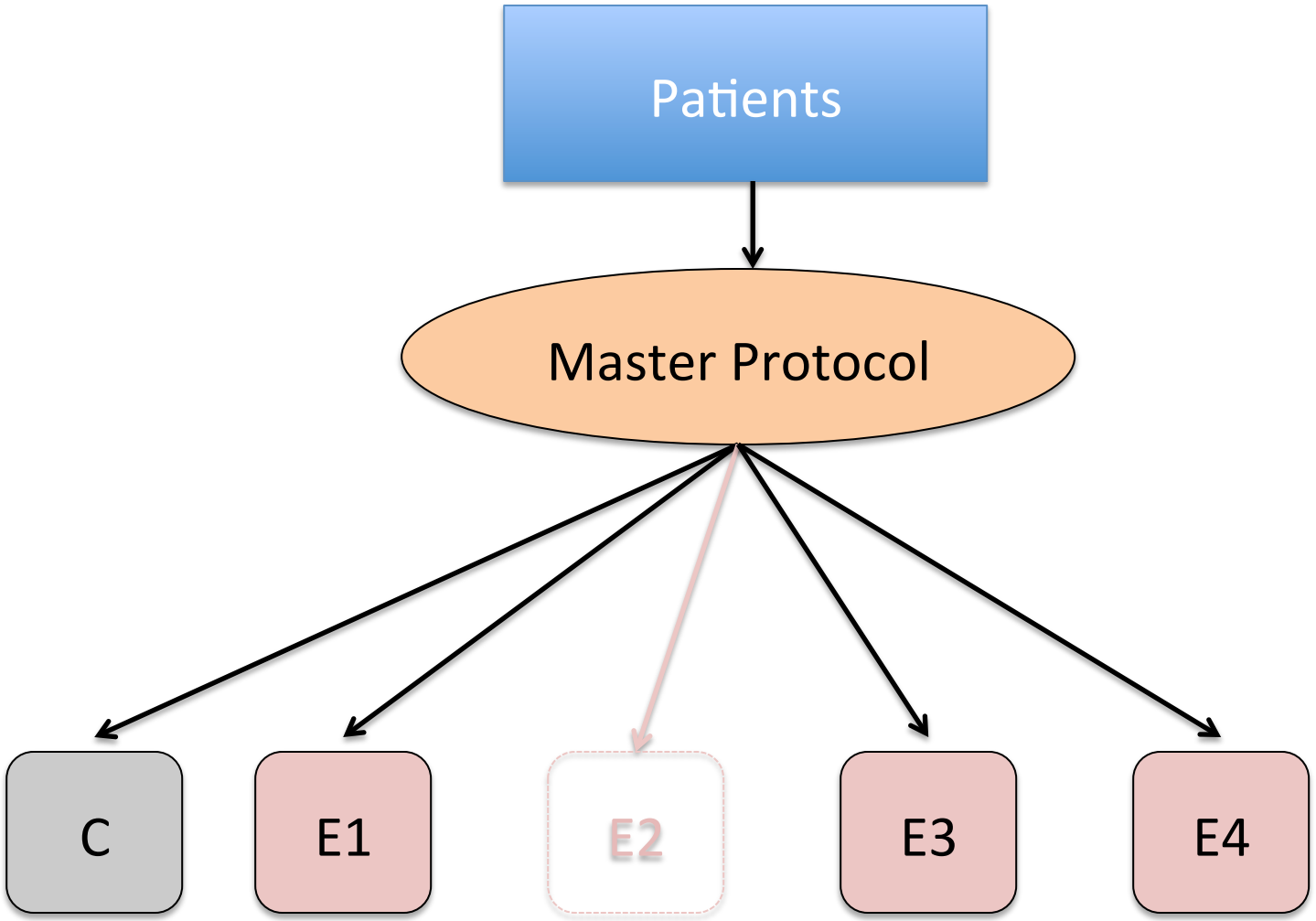
# Platform Trial/Master Protocol



# Platform Trial/Master Protocol



# Platform Trial/Master Protocol



# Platform Trial/Master Protocol

- Perpetual Trial/Process
- Evolving Treatments, Patients
- Adaptive allocation
  - Response adaptive randomization
  - Removing Arms/Graduating Arms
  - Combining Arms
- Strong central model (run by algorithm, not committees)
- Protocol has no treatment names!
  - Arm appendices

# Combination Adaptive Platform

- Gates Foundation Funded
- Built flexibly for k agents, provide example for 4 active agents:
  - 1; 2; 3; 4
- Treatment regimens:
  - Single-agents and **all** two-way combinations

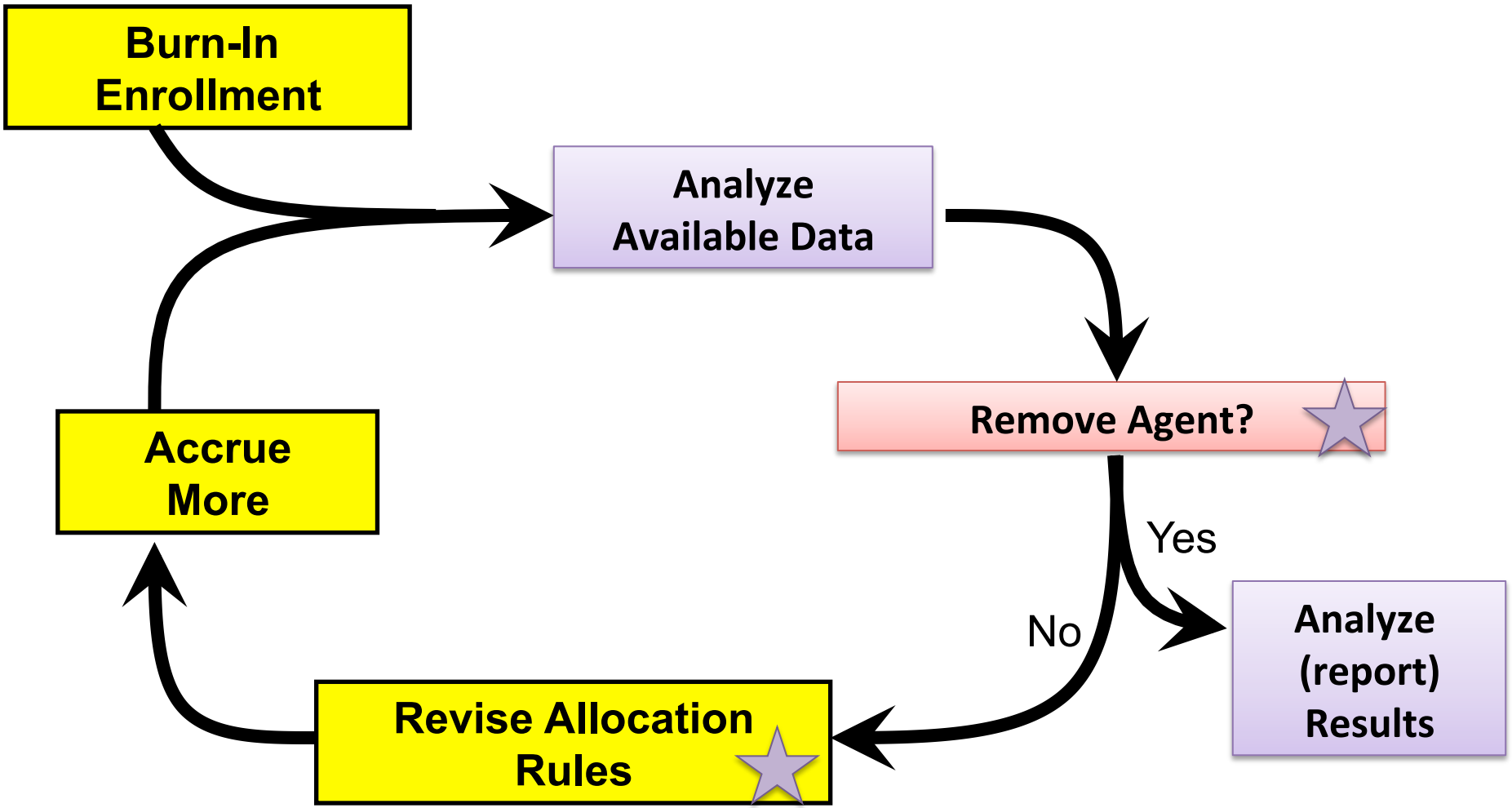
# Regimens

| Regimens | | Agents | | | |
|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 |
| Agents | 1 | | | | |
| | 2 | | | | |
| | 3 | | | | |
| | 4 | | | | |

# Design Details

- Endpoint: Mortality
- Start with a burn-in period to all 10 *regimens*
  - Equal randomization to 10 arms
  - For 30 subjects (an example period of time)
  - *This is flexible!*
- After Burn-In
  - Response adaptive randomization (RAR)
  - Proportional to probability regimen is optimal
    - Adjusted for information
  - Continue perpetually

# Trial Perpetual Design



# Statistical Model

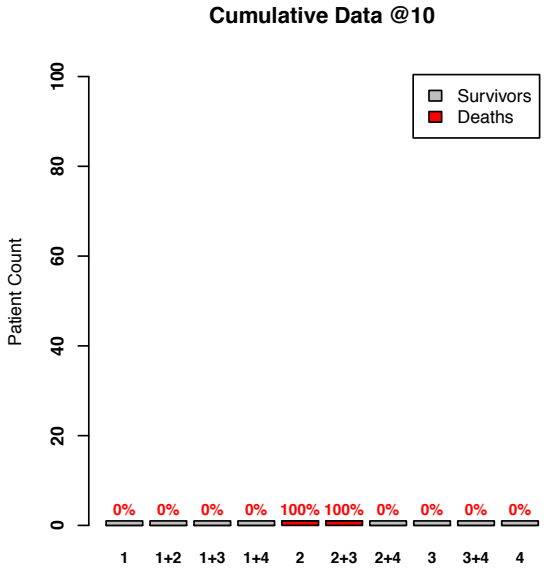
**Analyze Available Data**

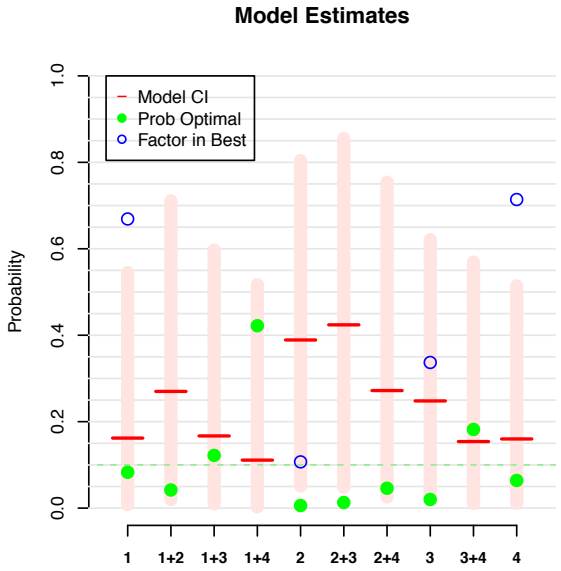
$$\log\left(\frac{p}{1-p}\right) = \alpha + \sum_{X=1}^{4}[X] + \sum_{X=1}^{4}\sum_{Y=X+1}^{D}[X,Y]$$

- Factor for each active agent (4)
- An interaction between each agent (6)
- Priors:

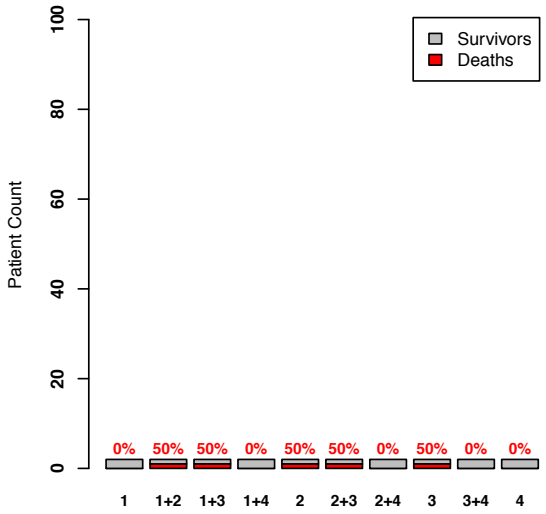
$$[X] \sim N\left(0, 2^2\right) \qquad [X,Y] \sim N\left(0, 1^2\right)$$

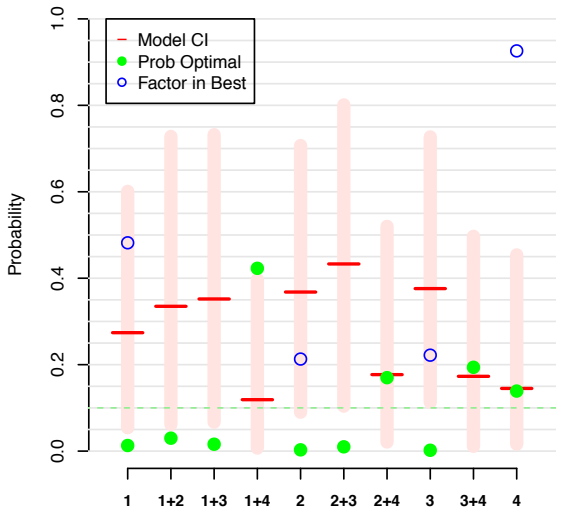

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @10
Survivors
Deaths
Patient Count
0
20
40
60
80
100
0%
0%
0%
0%
100%
100%
0%
0%
0%
0%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

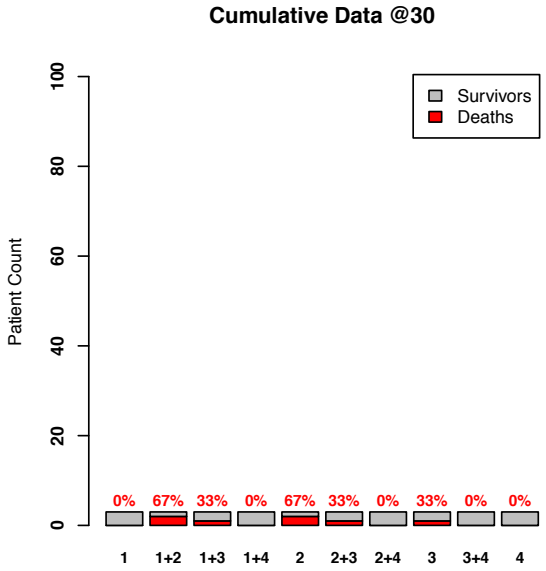

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

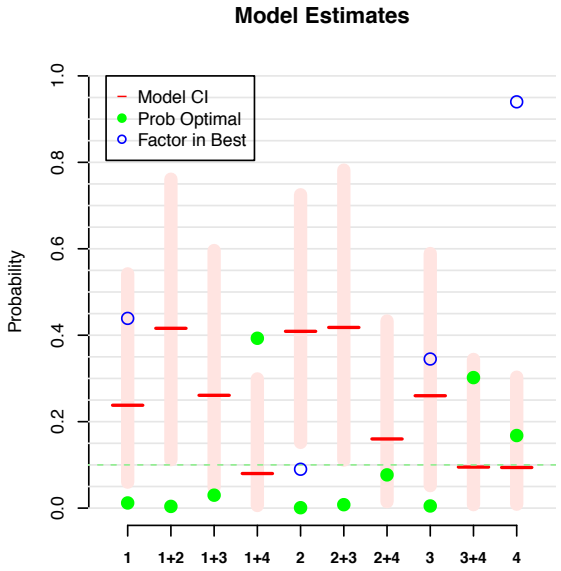

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

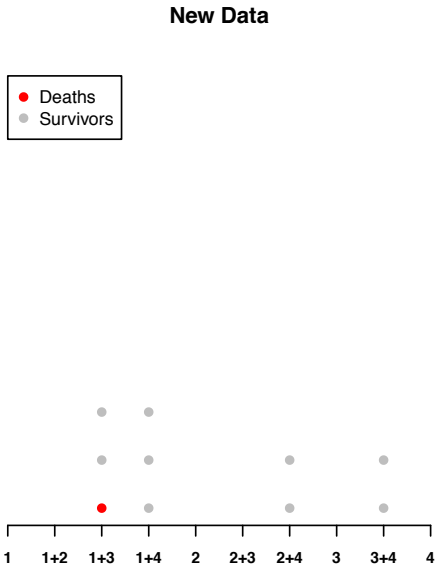

Cumulative Data @20
Survivors
Deaths
Patient Count
0
20
40
60
80
100
0%
50%
50%
0%
50%
50%
0%
50%
0%
0%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

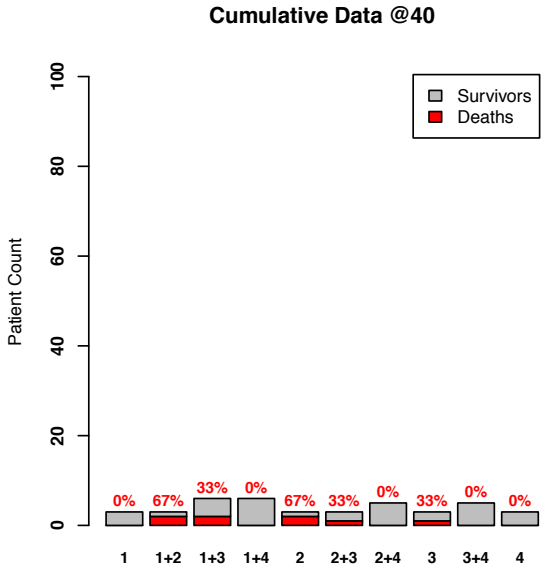

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

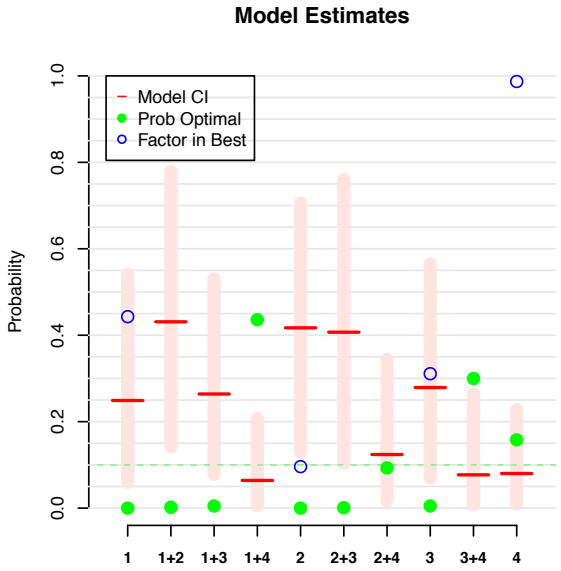

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

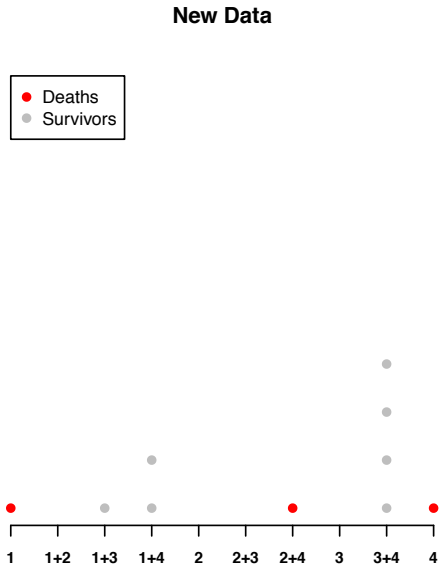

Cumulative Data @30
Survivors
Deaths
Patient Count
0
20
40
60
80
100
0%
67%
33%
0%
67%
33%
0%
33%
0%
0%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

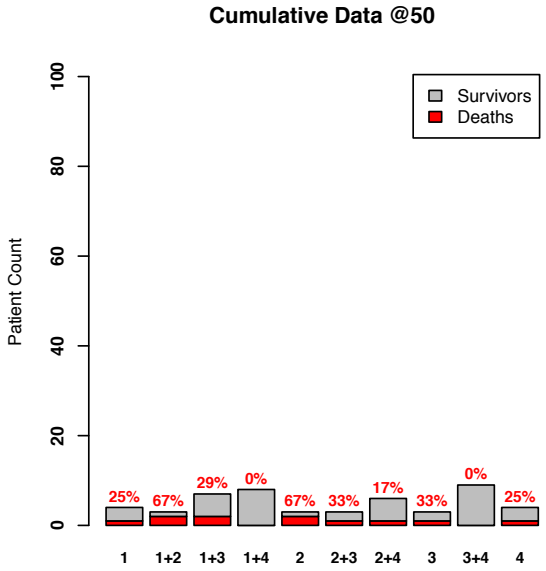

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

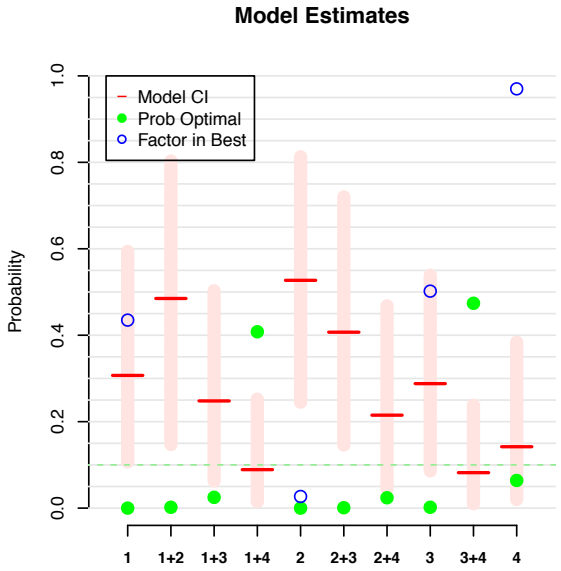

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

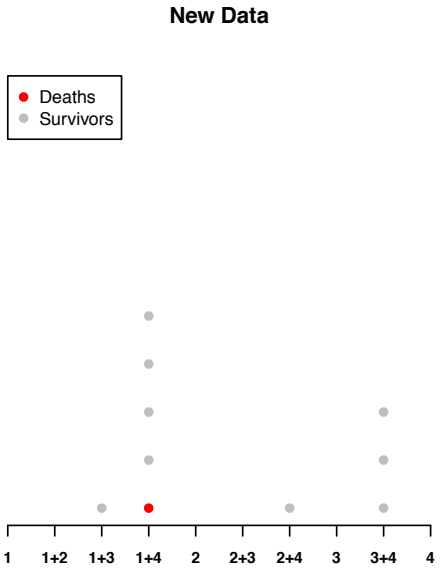

Cumulative Data @40
Survivors
Deaths
Patient Count
0
20
40
60
80
100
0%
67%
33%
0%
67%
33%
0%
33%
0%
0%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

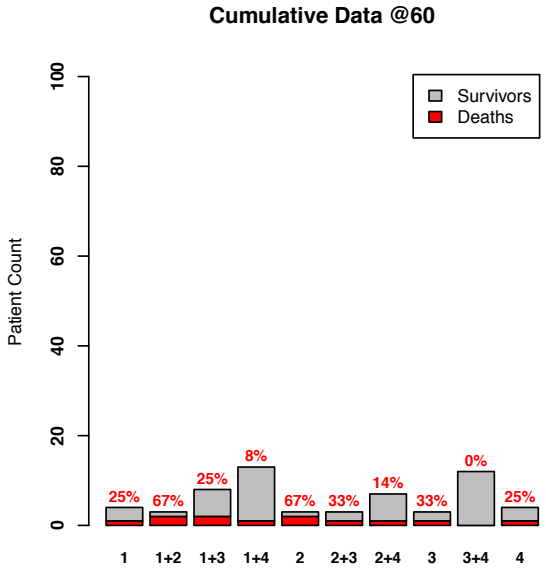

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

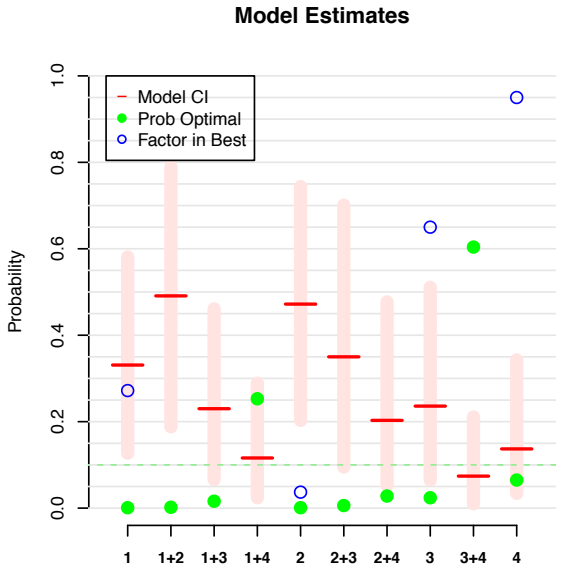

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

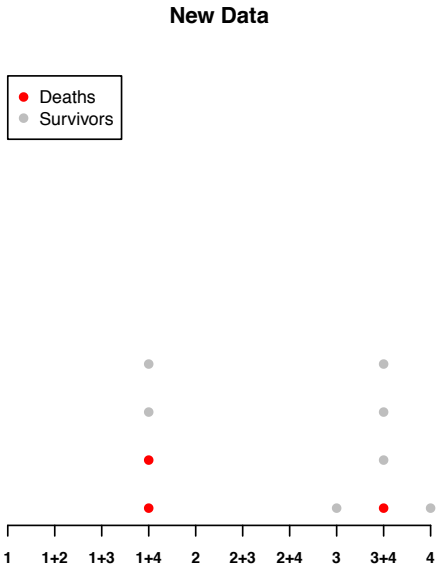

Cumulative Data @50
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
29%
0%
67%
33%
17%
33%
0%
25%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

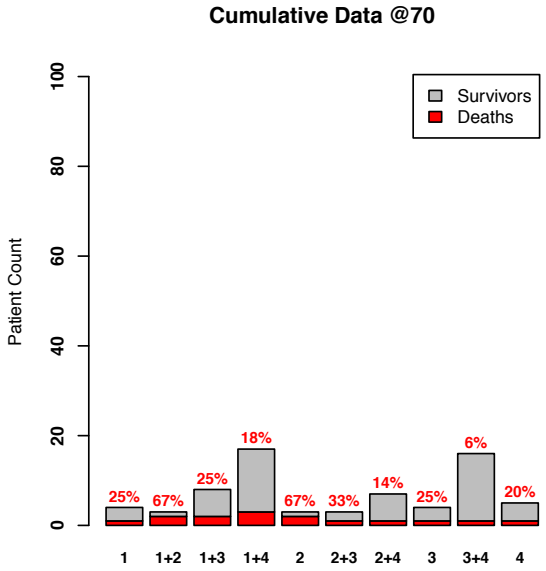

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

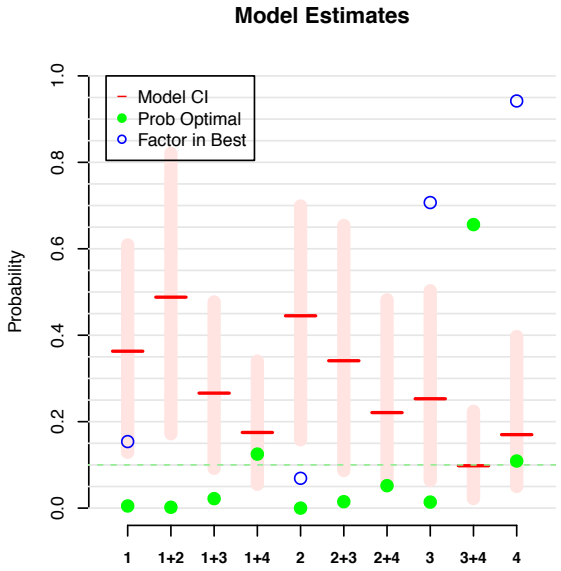

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

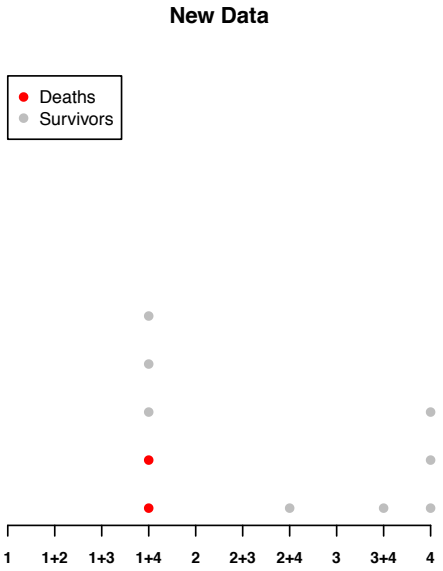

Cumulative Data @60
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
25%
8%
67%
33%
14%
33%
0%
25%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

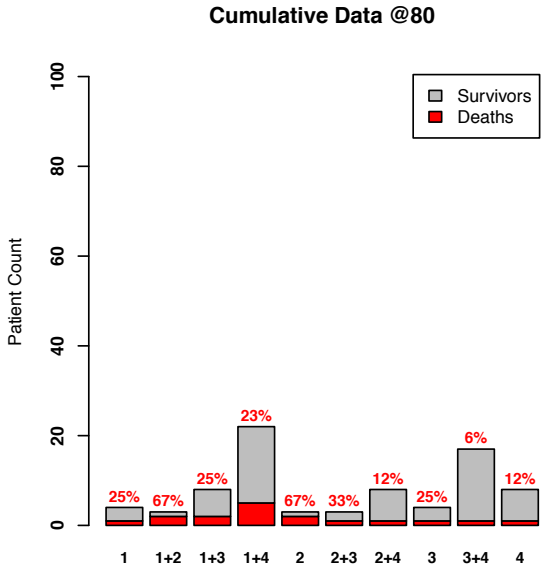

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

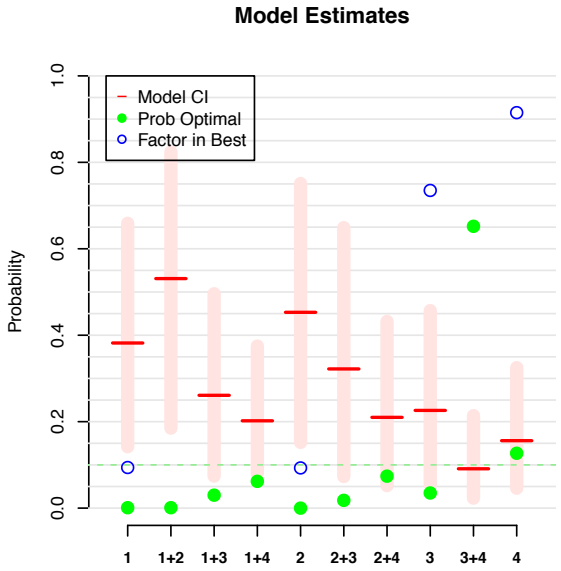

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

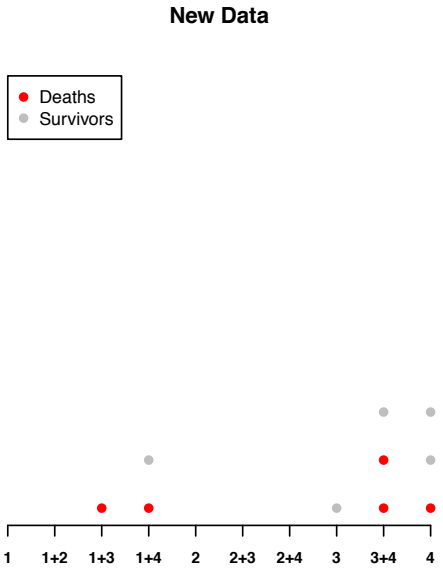

Cumulative Data @70
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
25%
18%
67%
33%
14%
25%
6%
20%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

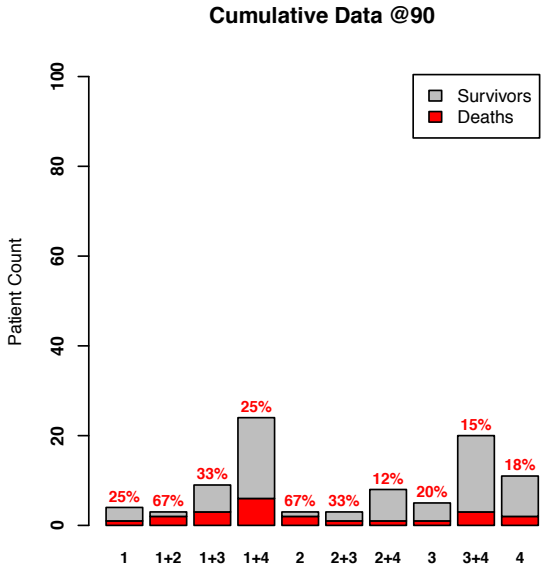

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

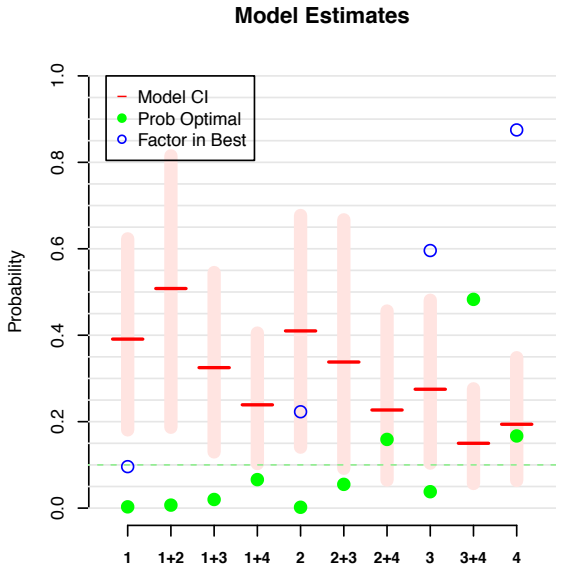

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

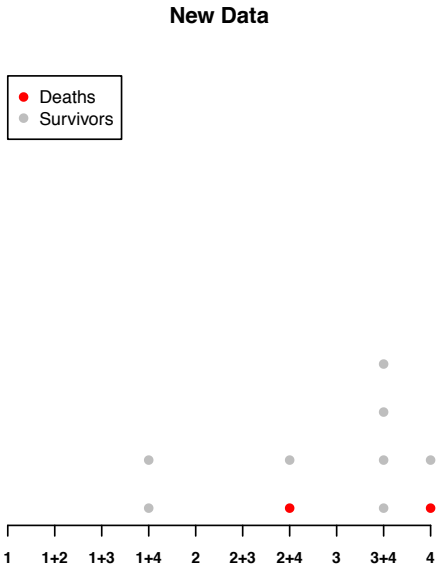

Cumulative Data @80
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
25%
23%
67%
33%
12%
25%
6%
12%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

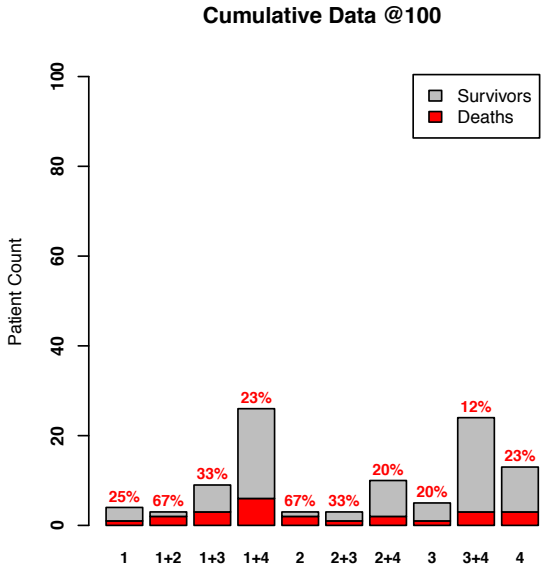

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

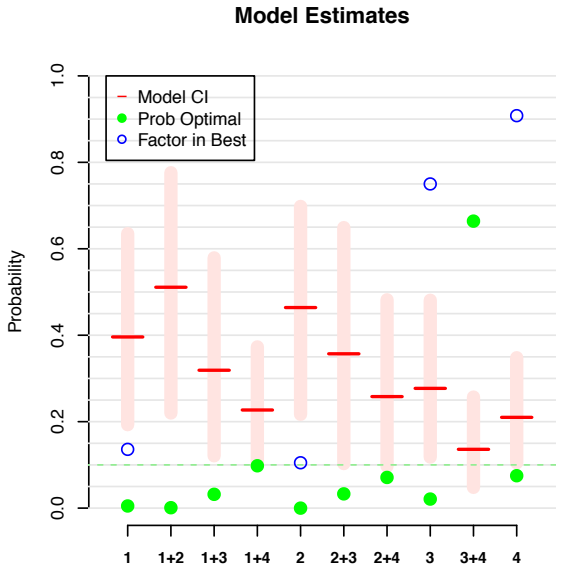

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


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

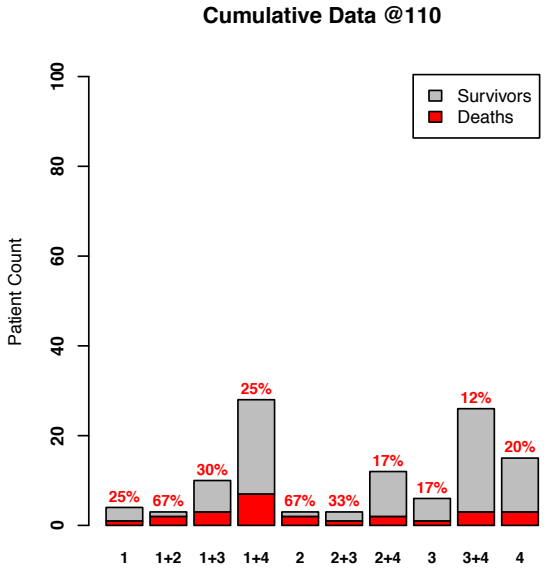

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

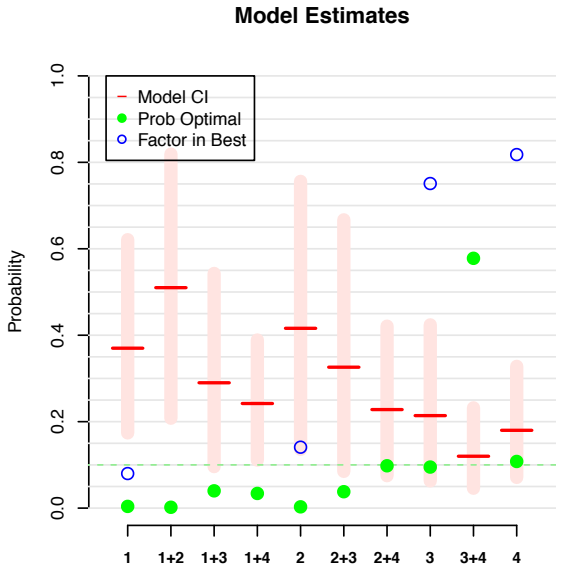

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

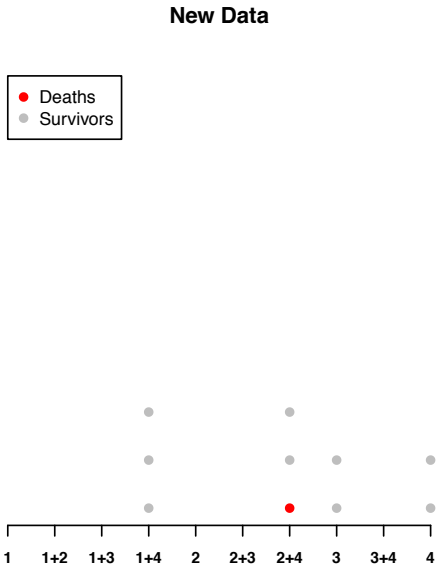

Cumulative Data @100
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
33%
23%
67%
33%
20%
20%
12%
23%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

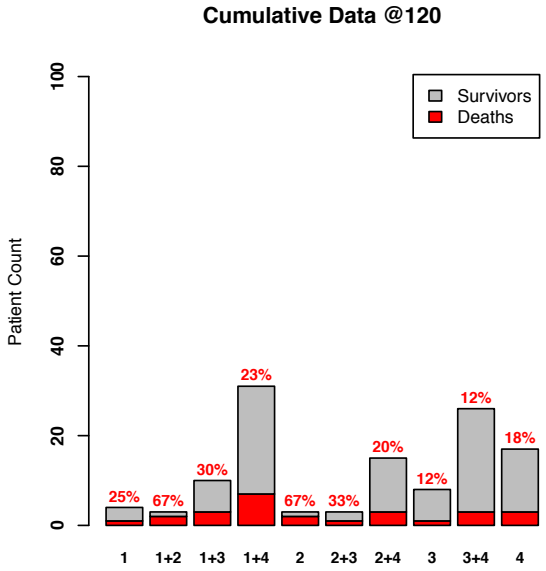

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

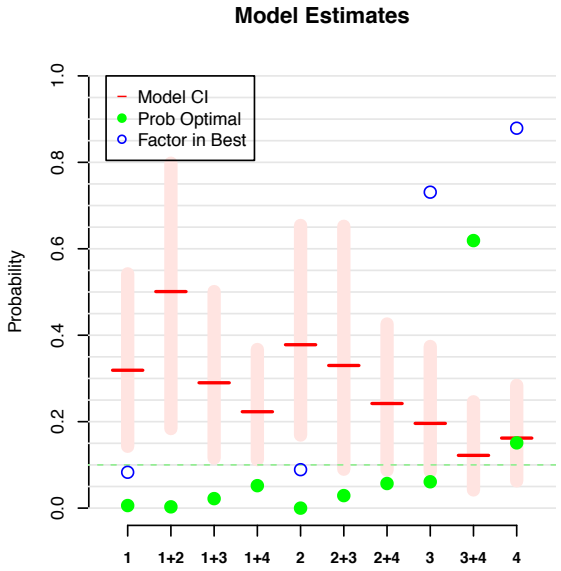

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

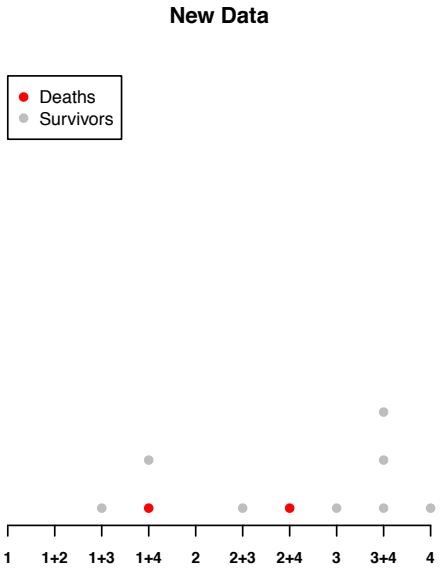

Cumulative Data @110
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
30%
25%
67%
33%
17%
17%
12%
20%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

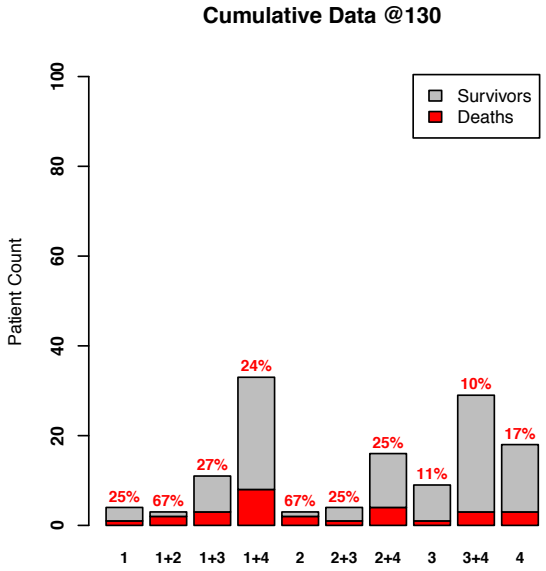

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

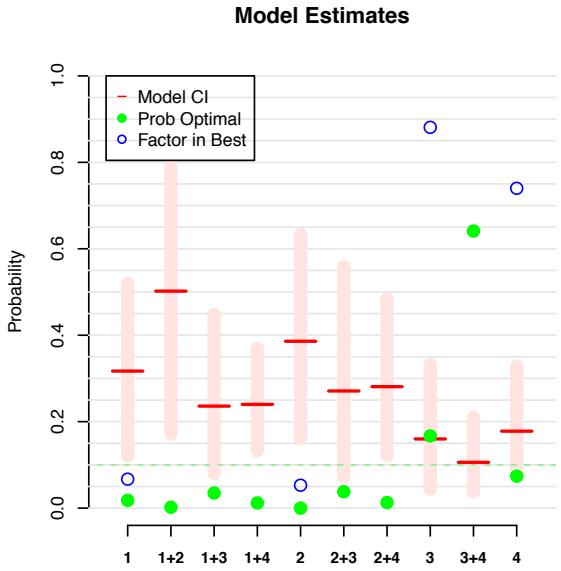

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

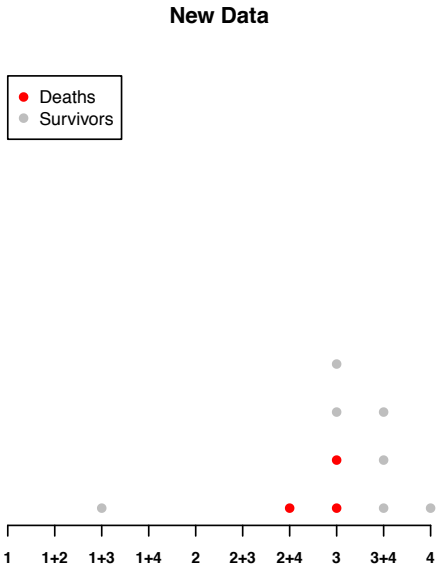

Cumulative Data @120
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
30%
23%
67%
33%
20%
12%
12%
18%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

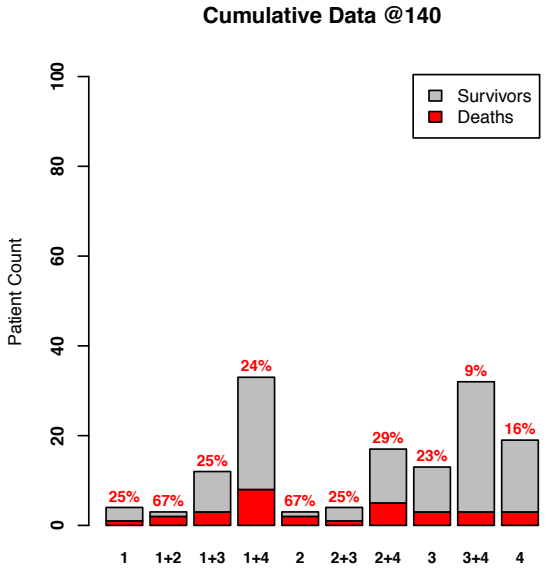

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

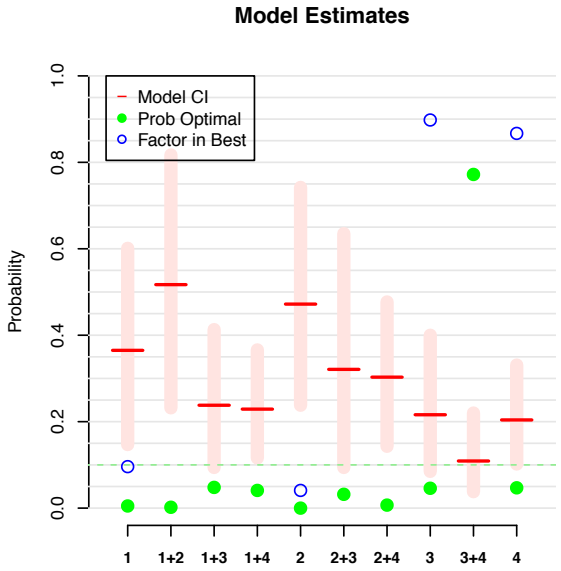

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

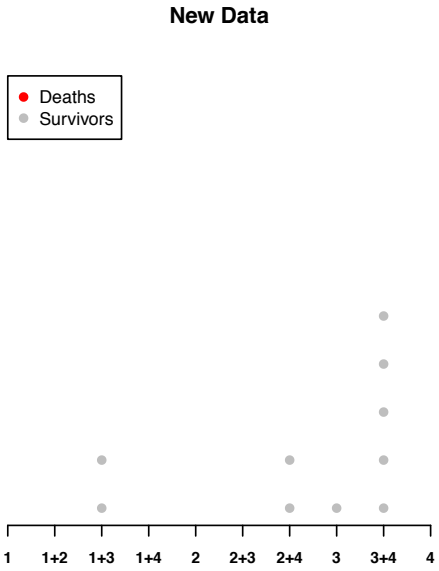

Cumulative Data @130
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
27%
24%
67%
25%
25%
11%
10%
17%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

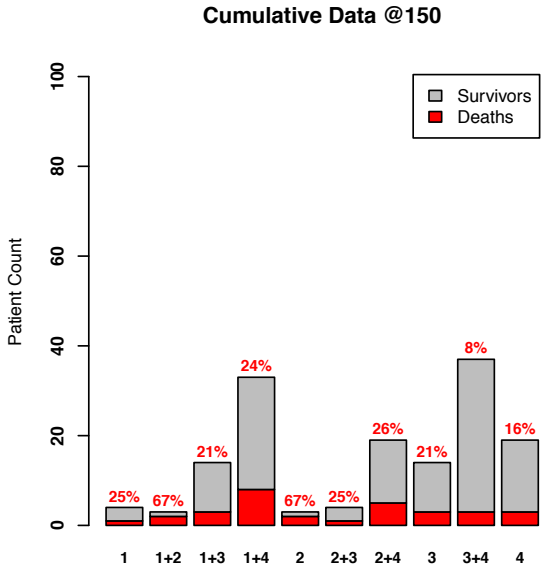

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

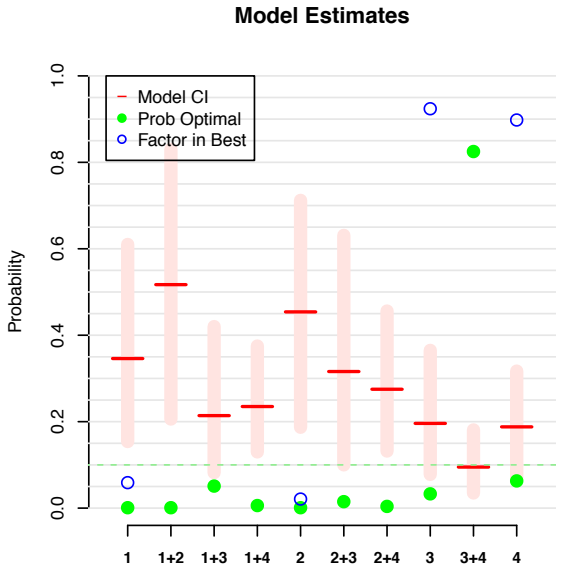

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

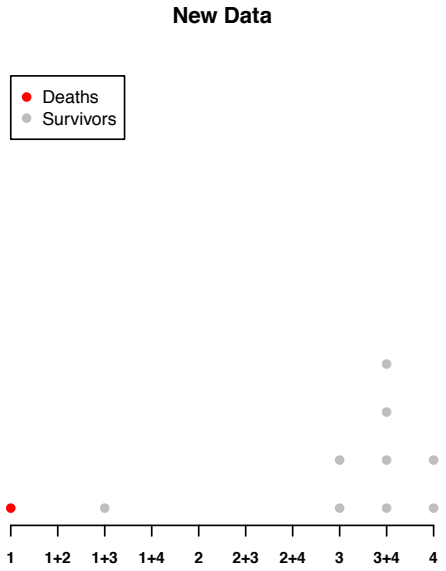

Cumulative Data @140
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
25%
24%
67%
25%
29%
23%
9%
16%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

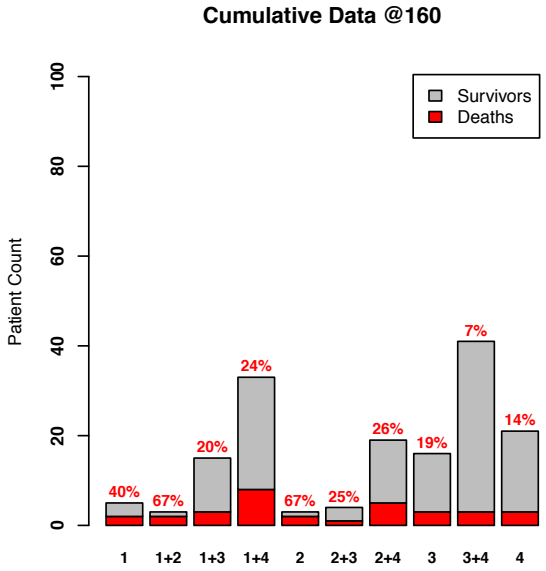

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

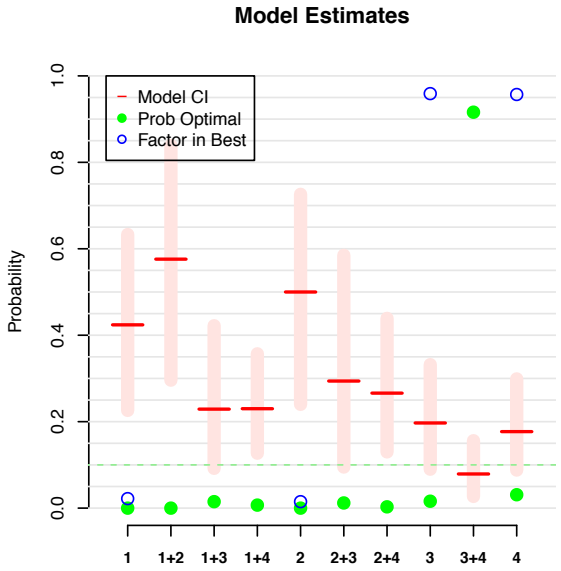

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

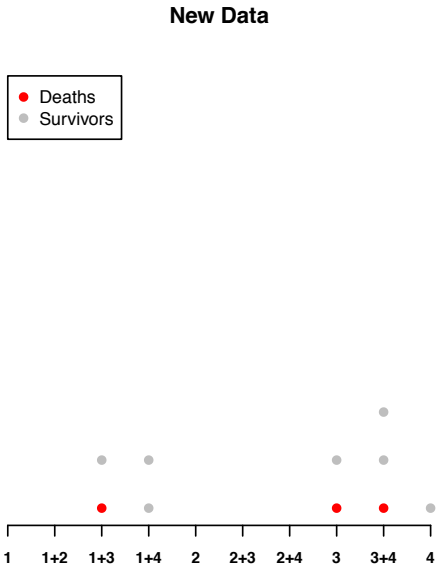

Cumulative Data @150
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
21%
24%
67%
25%
26%
21%
8%
16%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

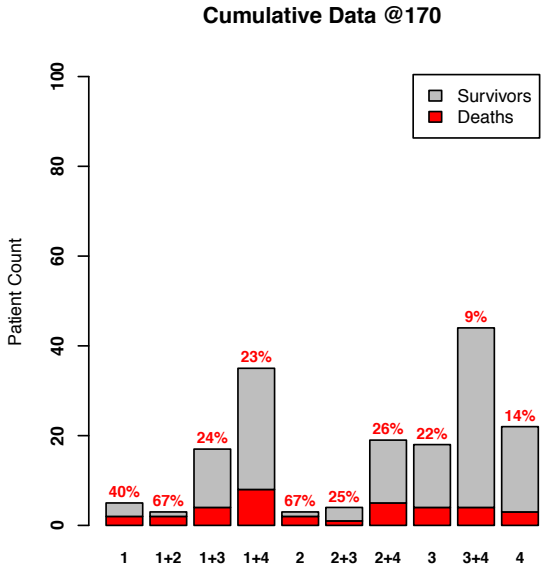

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

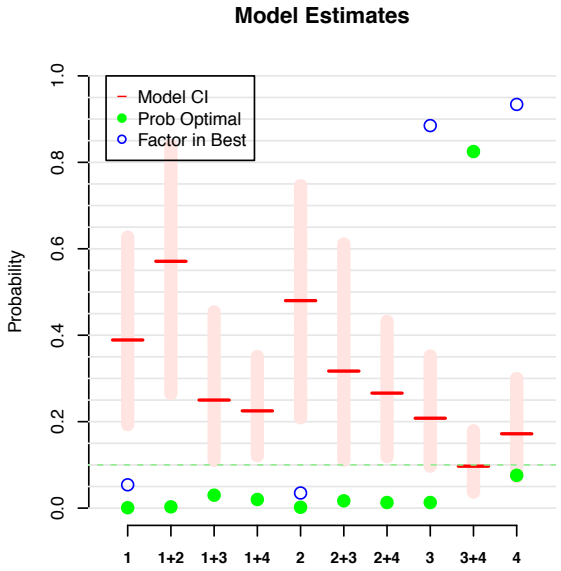

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


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

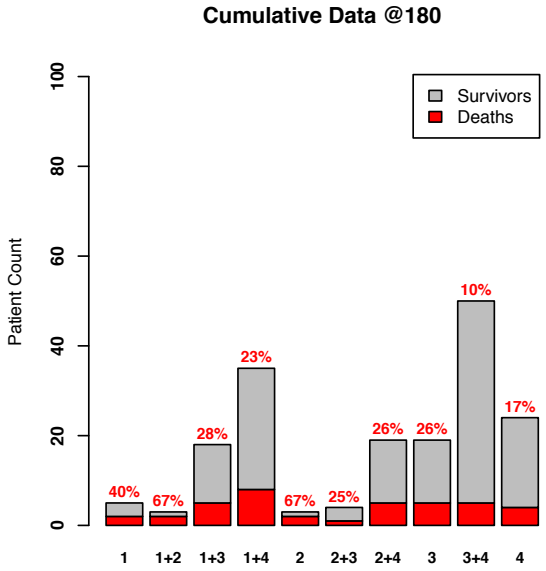

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

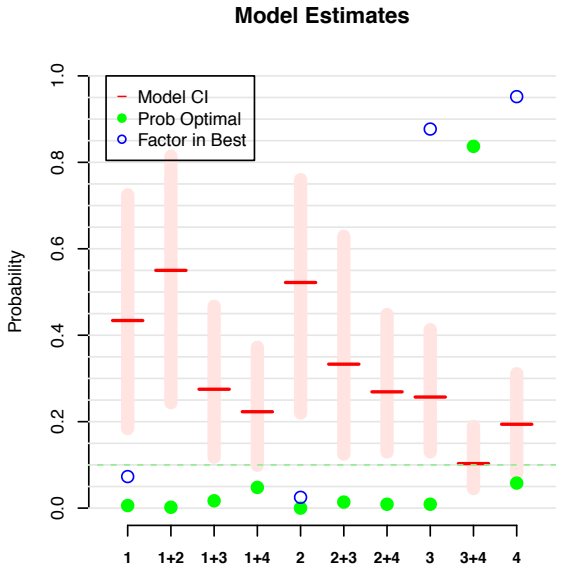

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

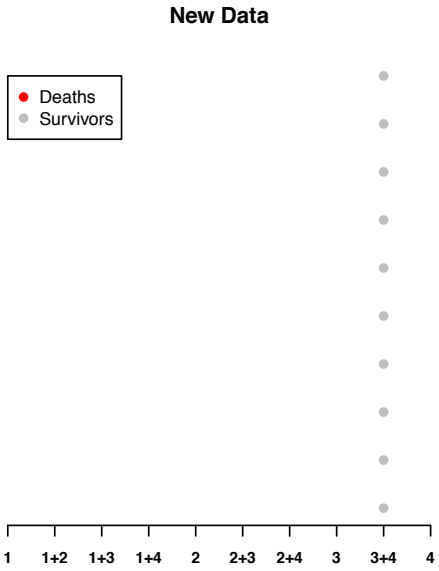

Cumulative Data @170
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
24%
23%
67%
25%
26%
22%
9%
14%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

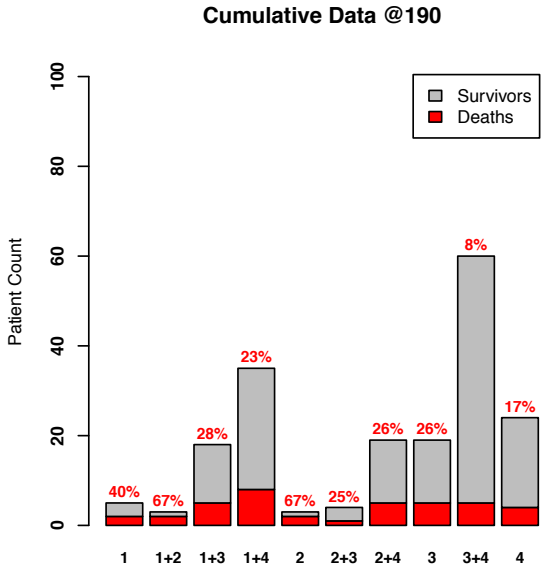

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

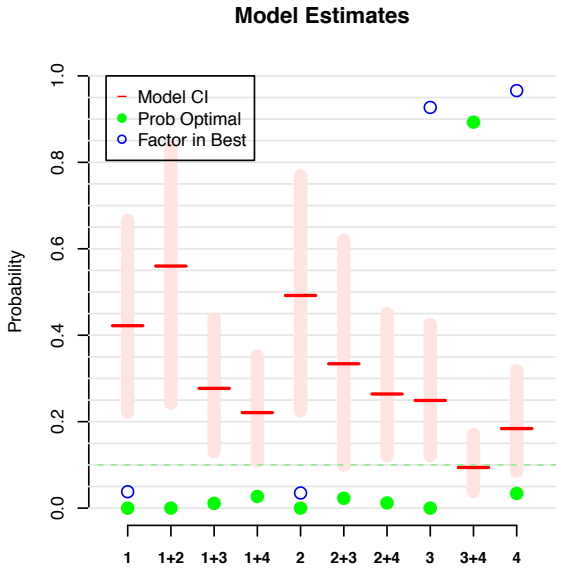

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

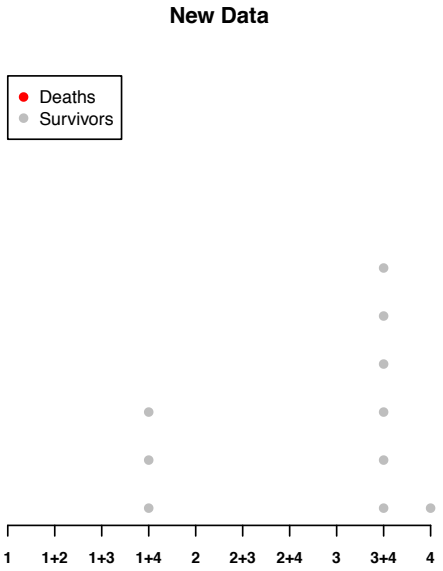

Cumulative Data @180
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
28%
23%
67%
25%
26%
26%
10%
17%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

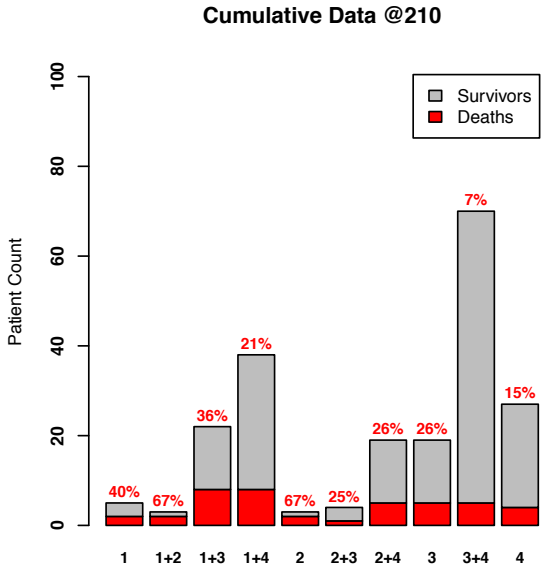

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

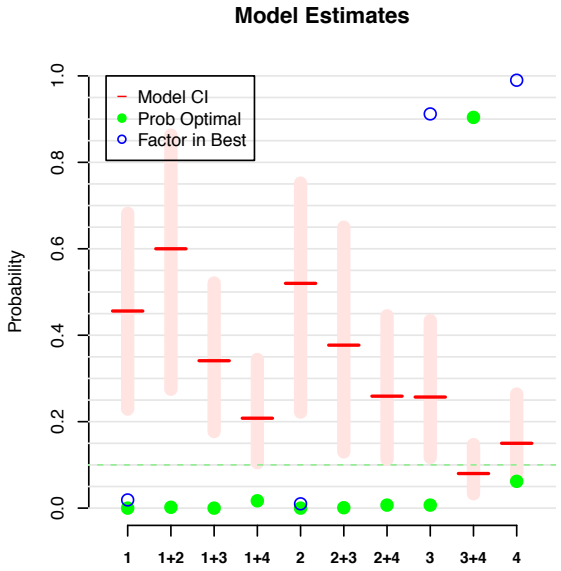

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

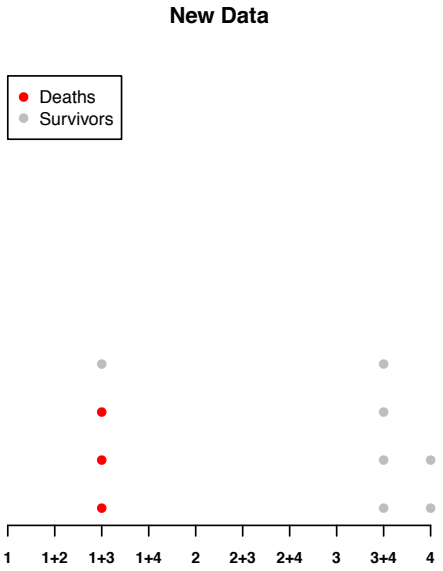

Cumulative Data @190
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
28%
23%
67%
25%
26%
26%
8%
17%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

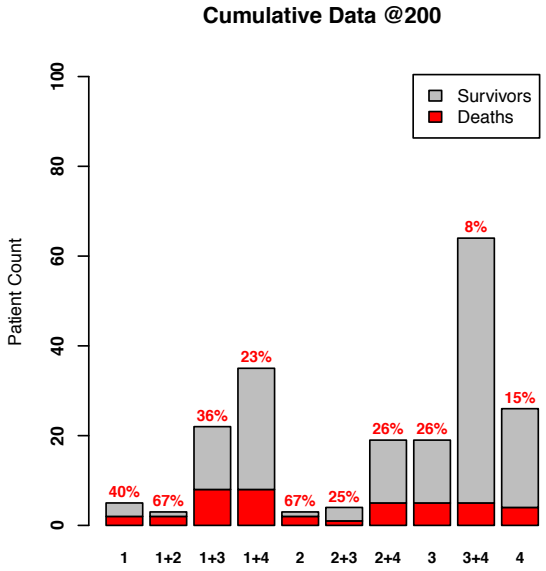

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

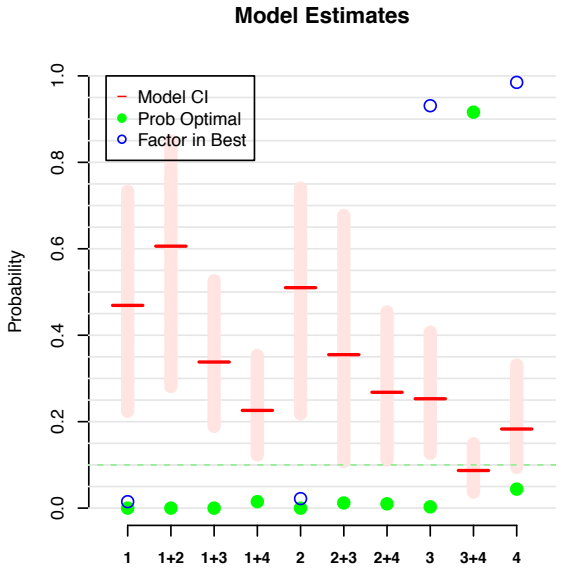

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

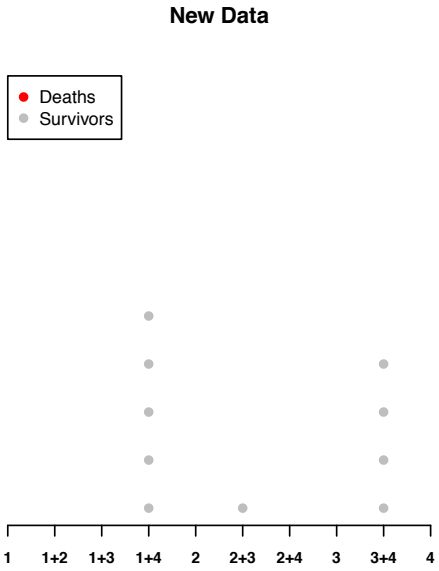

Cumulative Data @210
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
36%
21%
67%
25%
26%
26%
7%
15%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

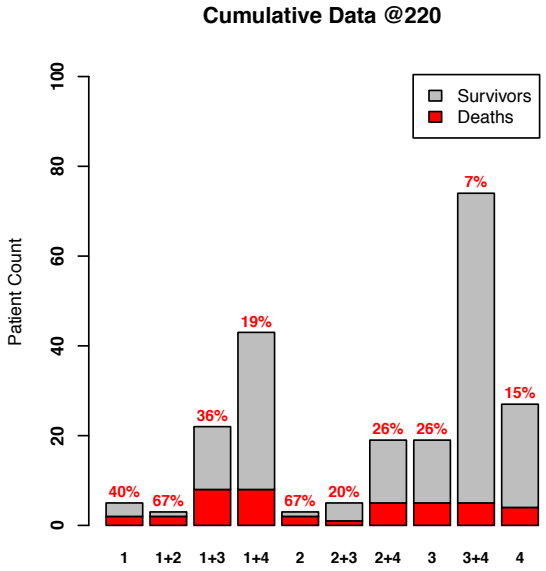

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

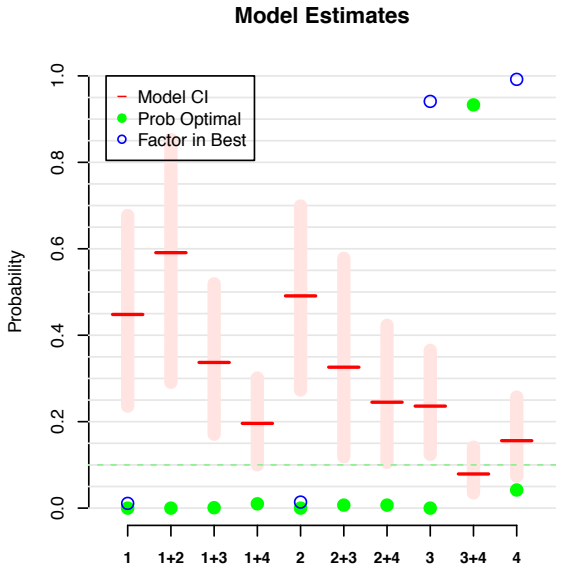

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

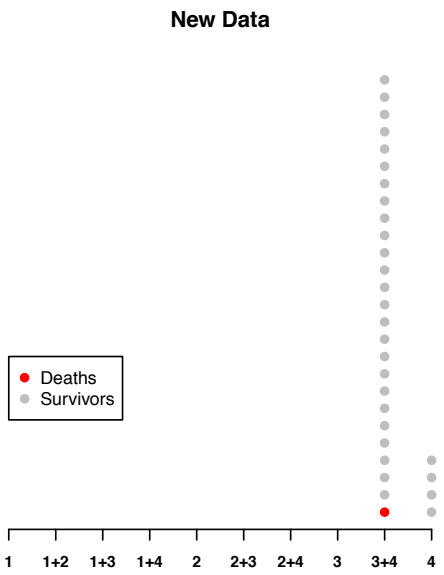

Cumulative Data @200
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
36%
23%
67%
25%
26%
26%
8%
15%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

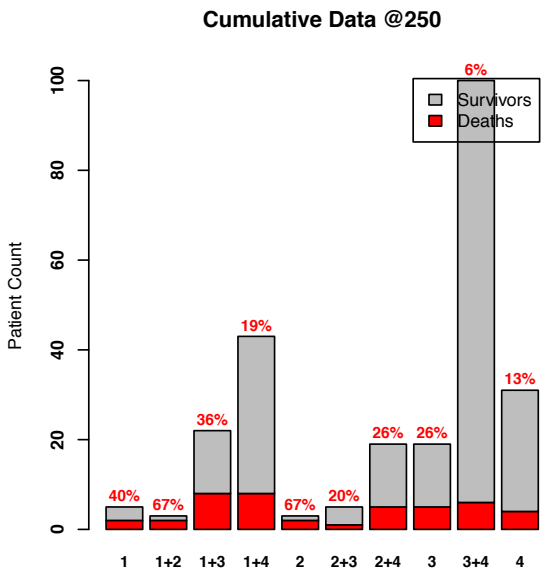

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

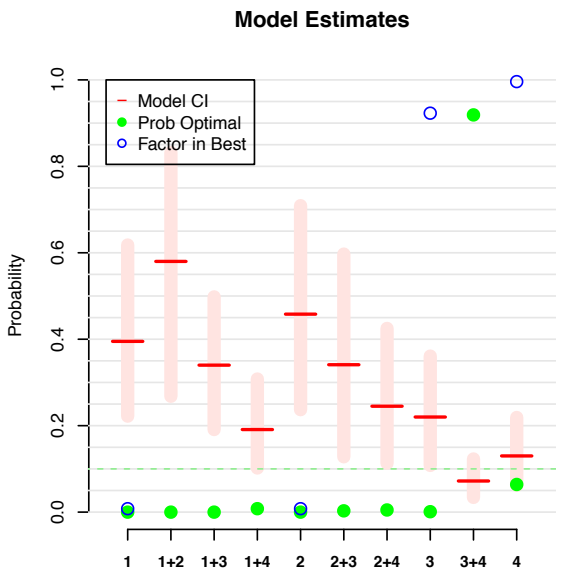

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

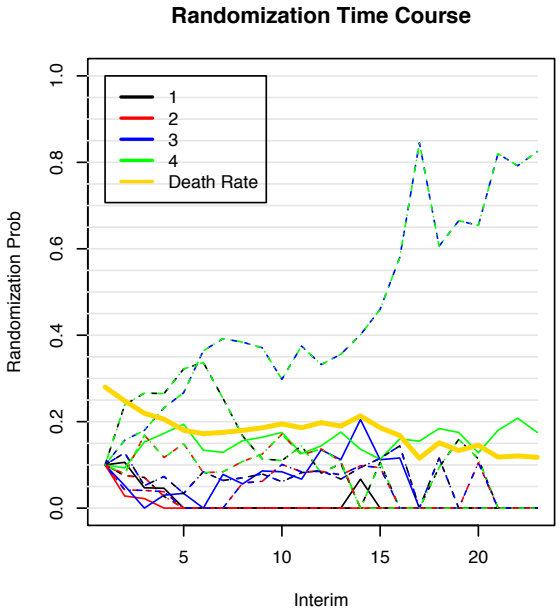

Cumulative Data @220
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
36%
19%
67%
20%
26%
26%
7%
15%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

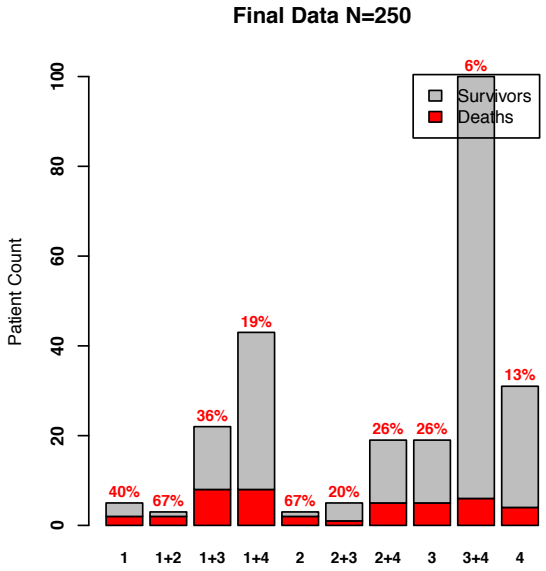

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

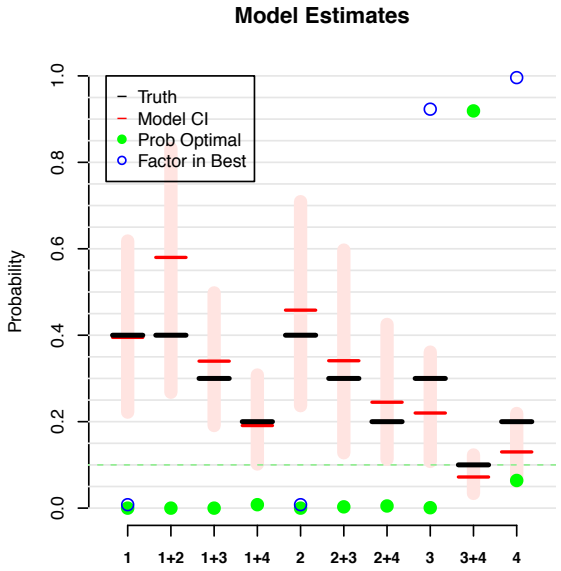

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


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

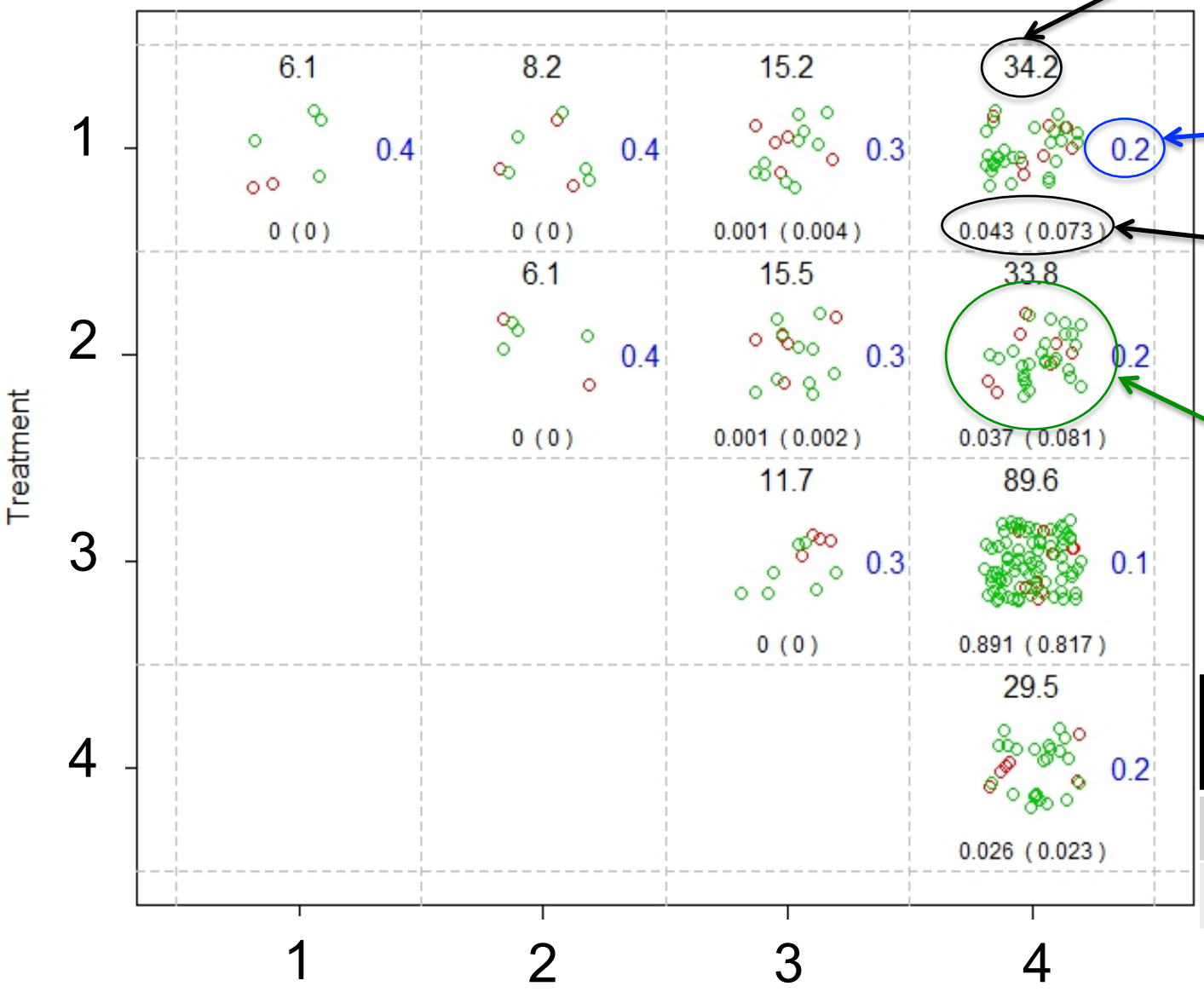

Model Estimates
Probability
0.0
0.2
0.4
0.6
0.8
1.0
Model CI
Prob Optimal
Factor in Best
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


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

# Scenario 3




Mean N

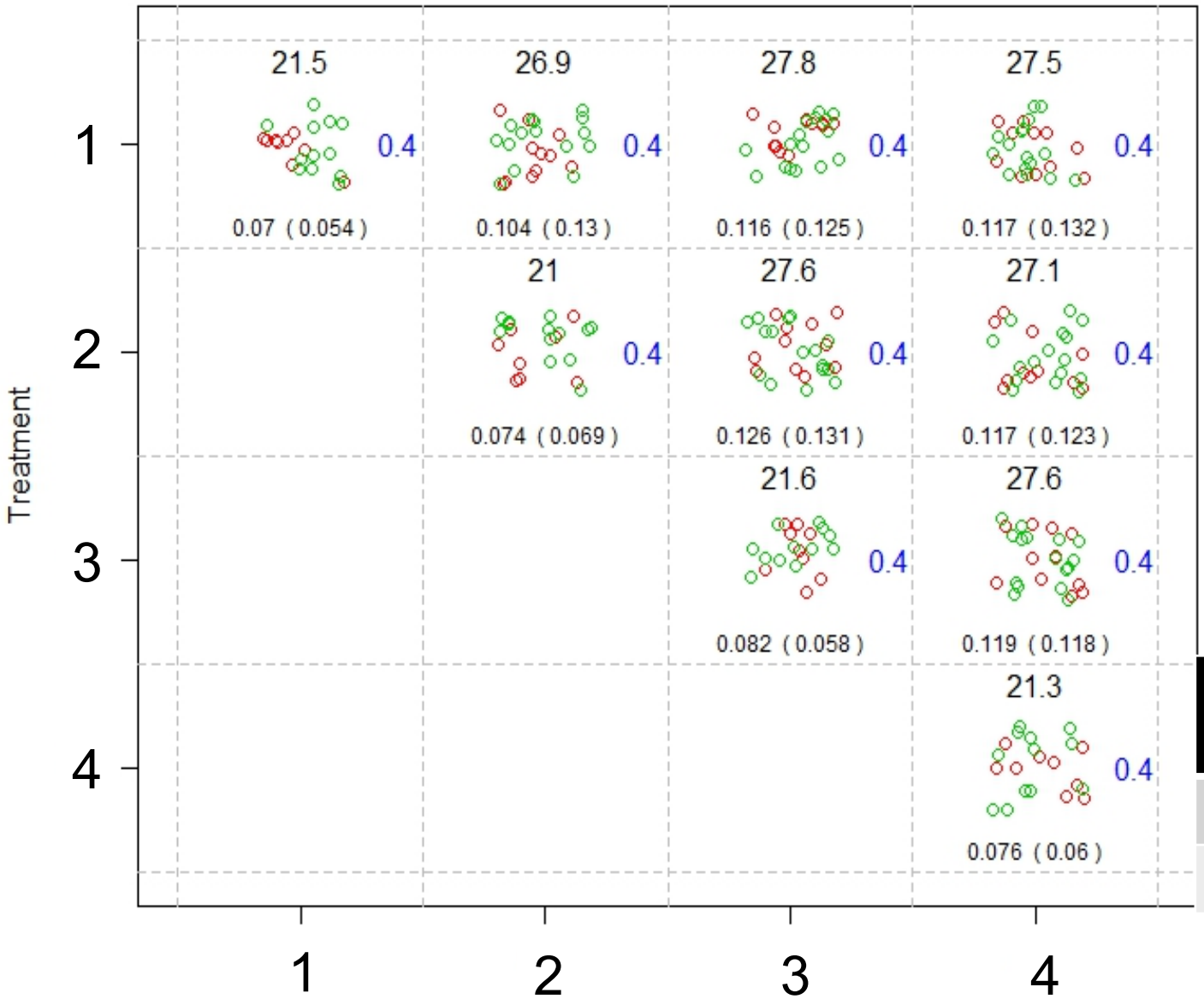
Truth

Prob Wins (fixed)

Mean N & Fails

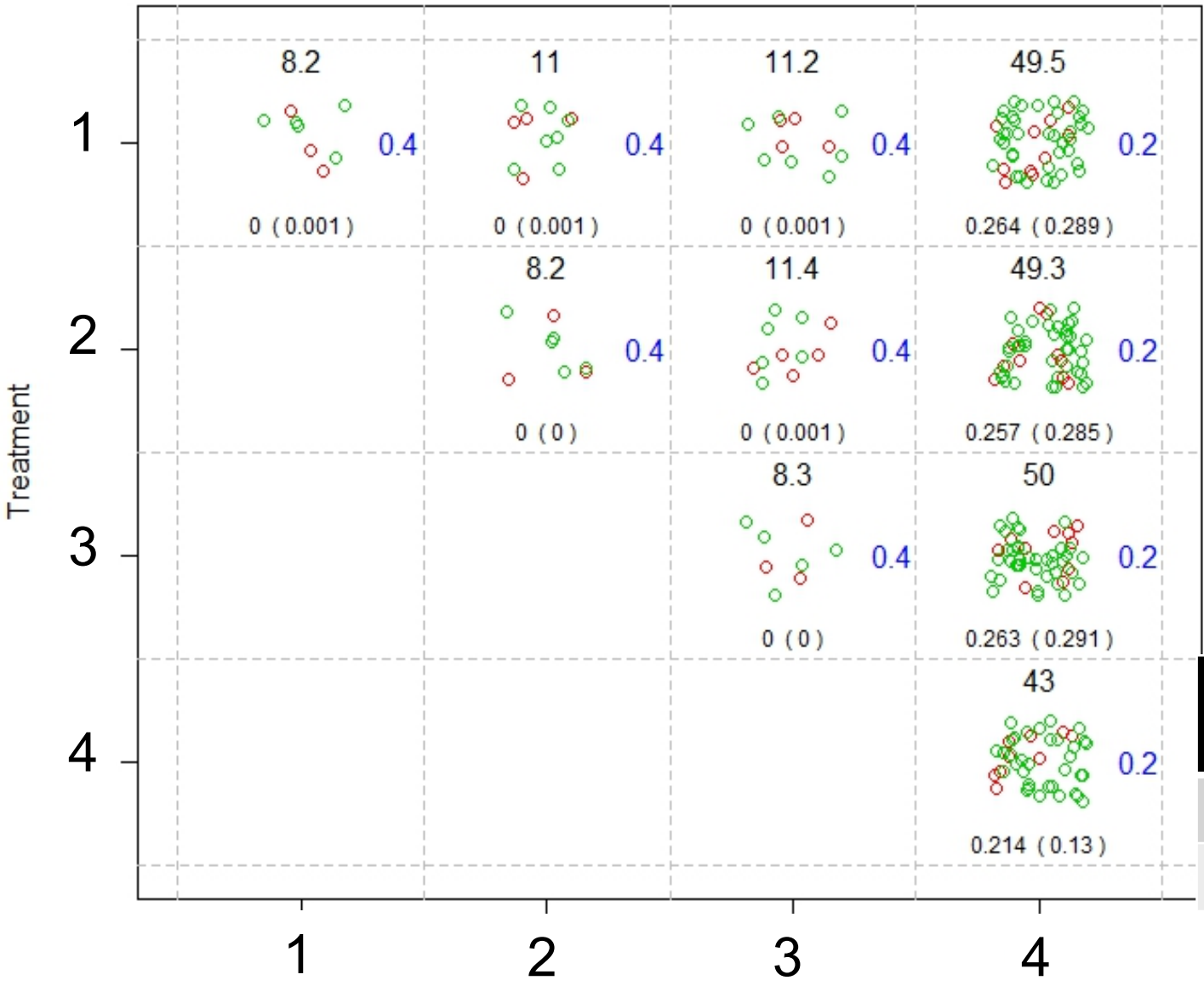
| Design | Mean Fails |
|---|---|
| Adapt | 49.4 |
| Fixed | 69.9 |

# Scenario 0



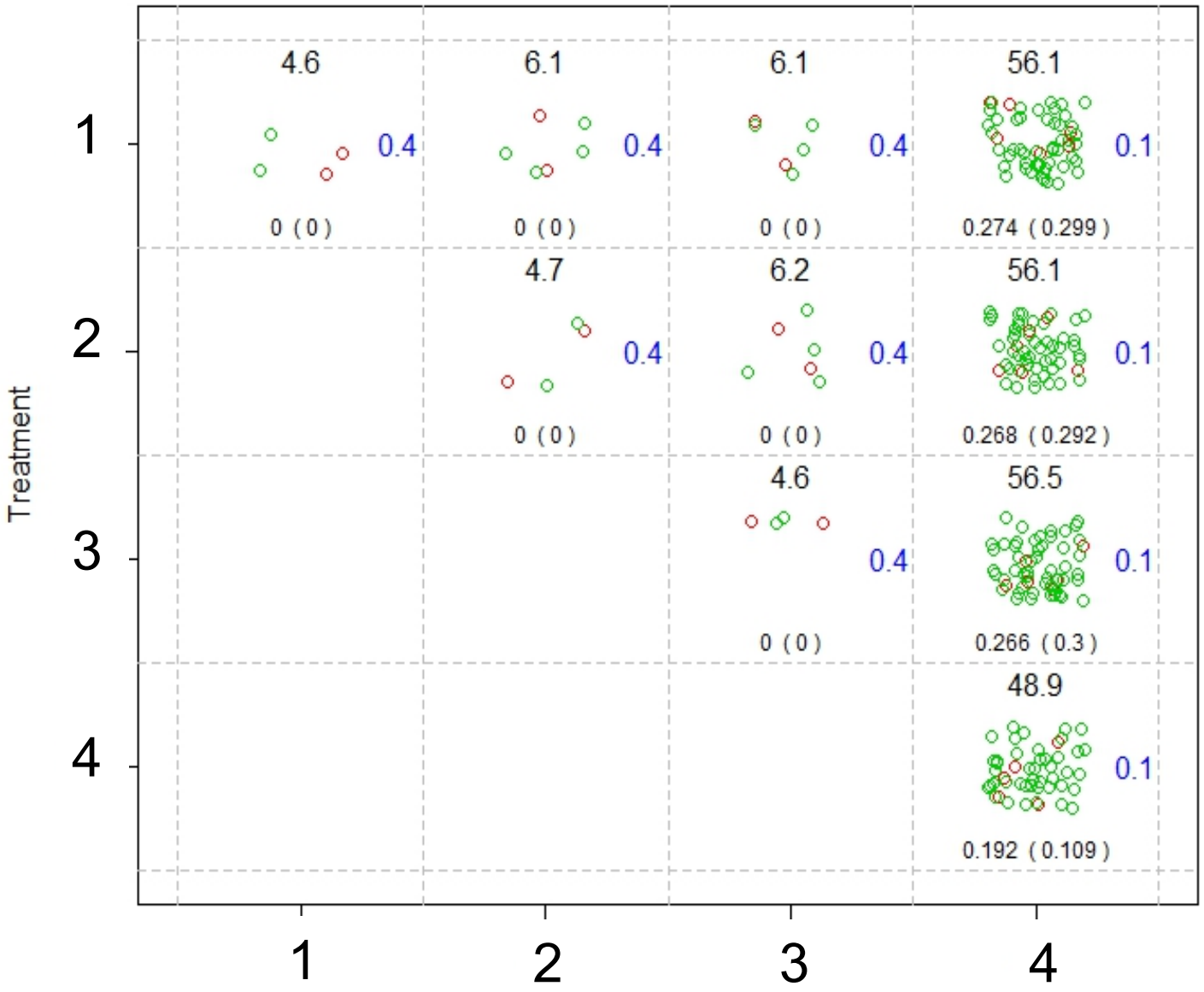

| Design | Mean Fails |
|---|---|
| Adapt | 100 |
| Fixed | 100 |

# Scenario 1



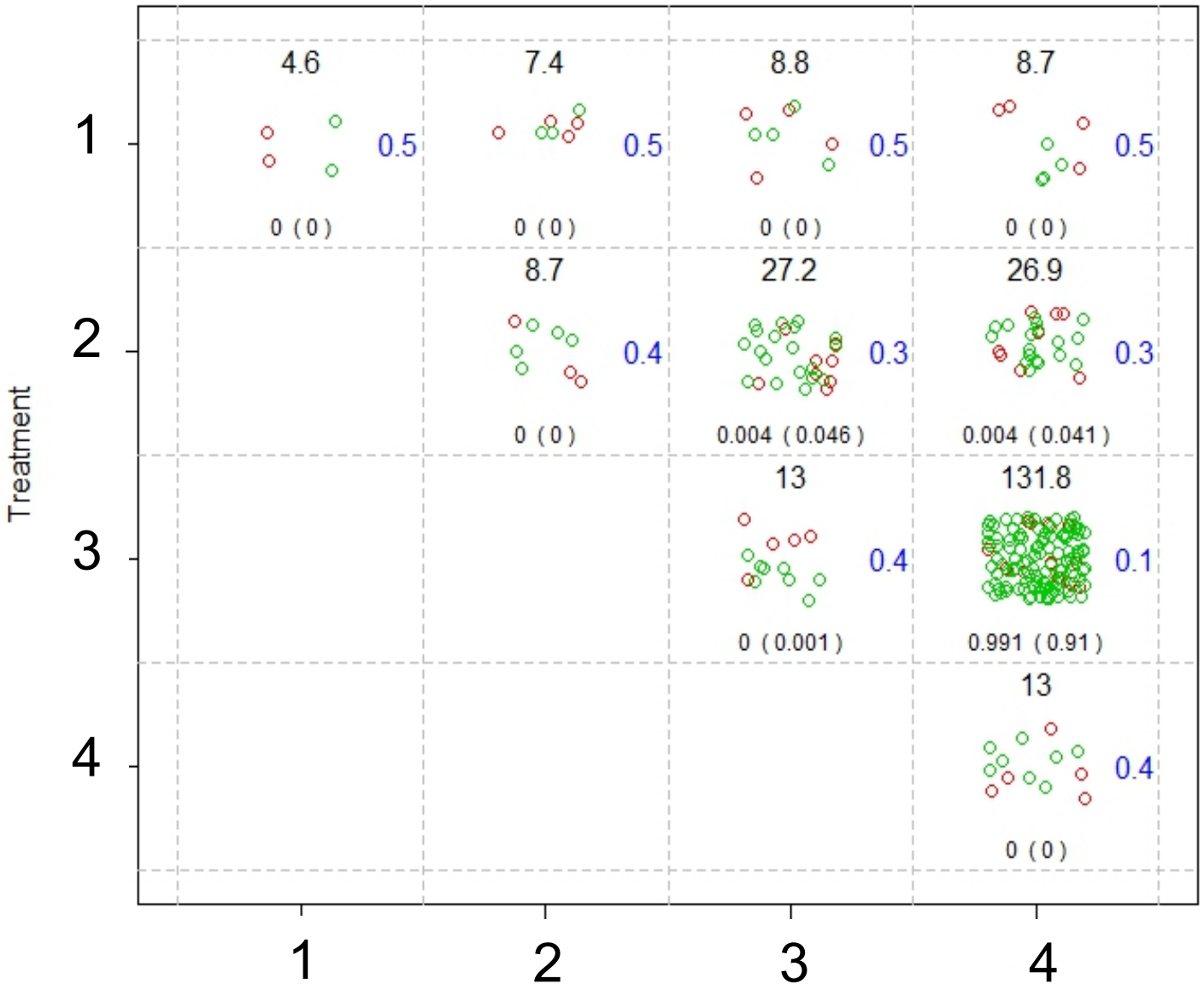

| Design | Mean Fails |
|---|---|
| Adapt | 61.6 |
| Fixed | 79.9 |

# Scenario 2



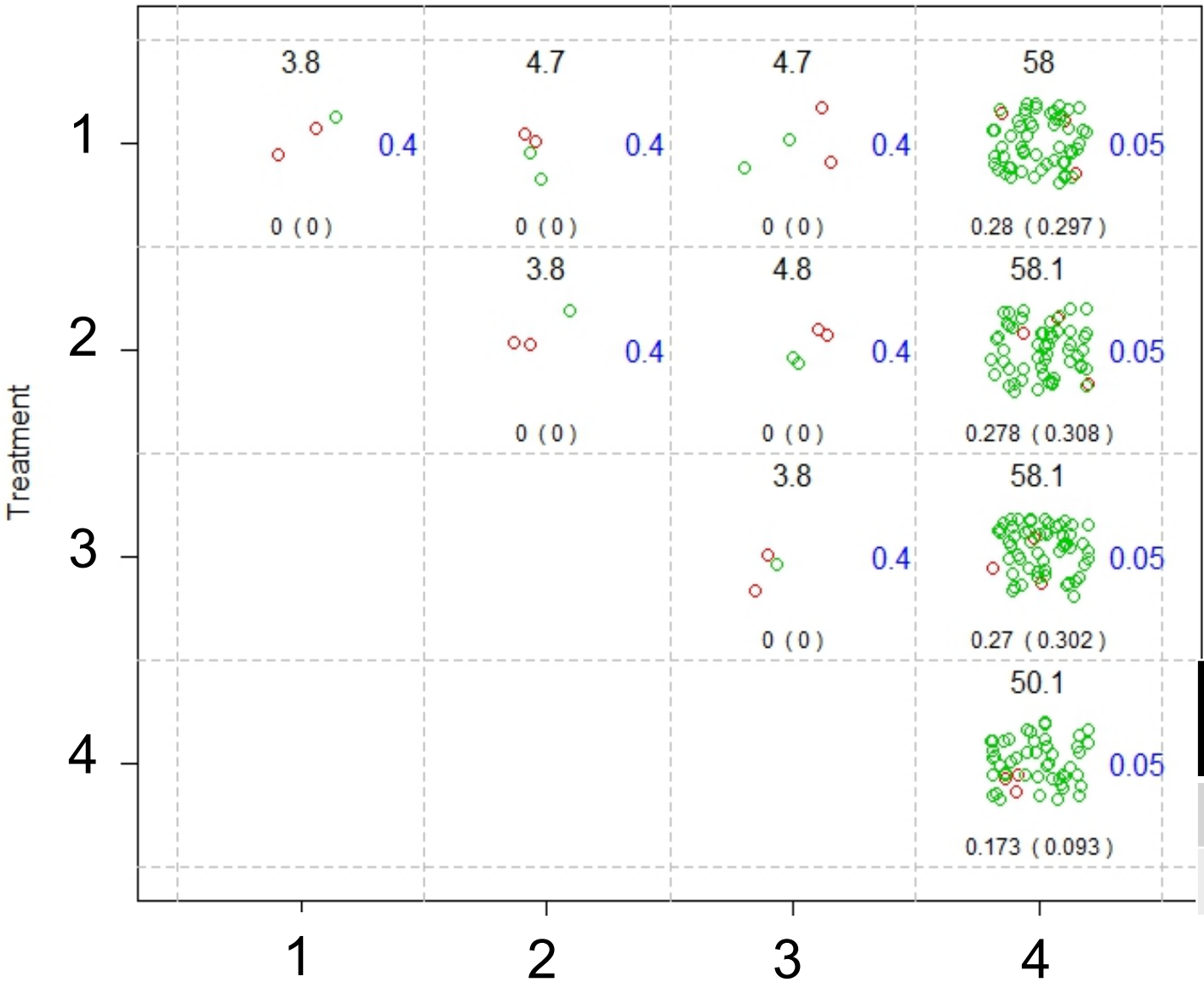

| Design | Mean Fails |
|---|---|
| Adapt | 34.7 |
| Fixed | 69.9 |

# Scenario 4



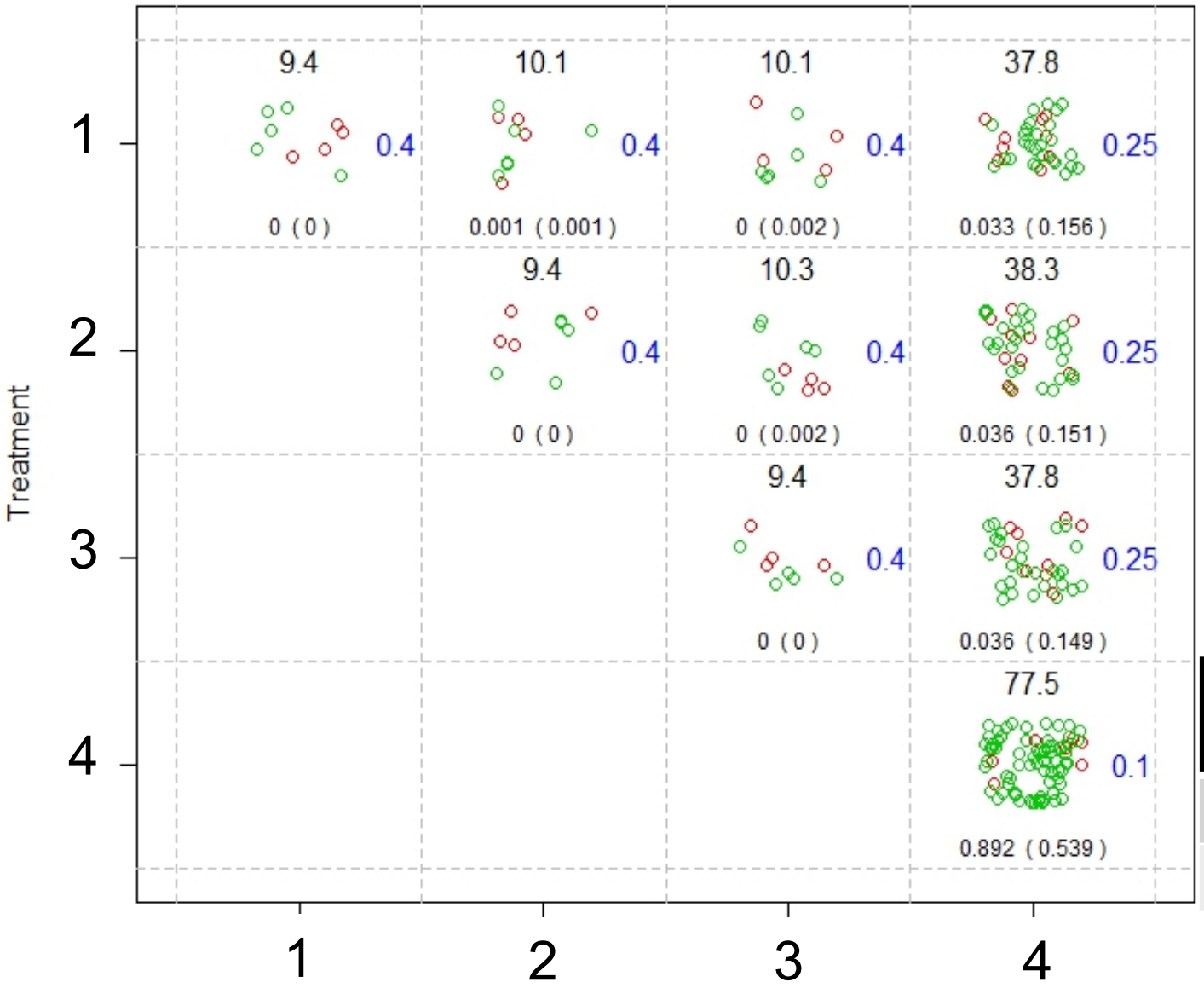

| Design | Mean Fails |
|---|---|
| Adapt | 58.0 |
| Fixed | 97.3 |

# Scenario 5



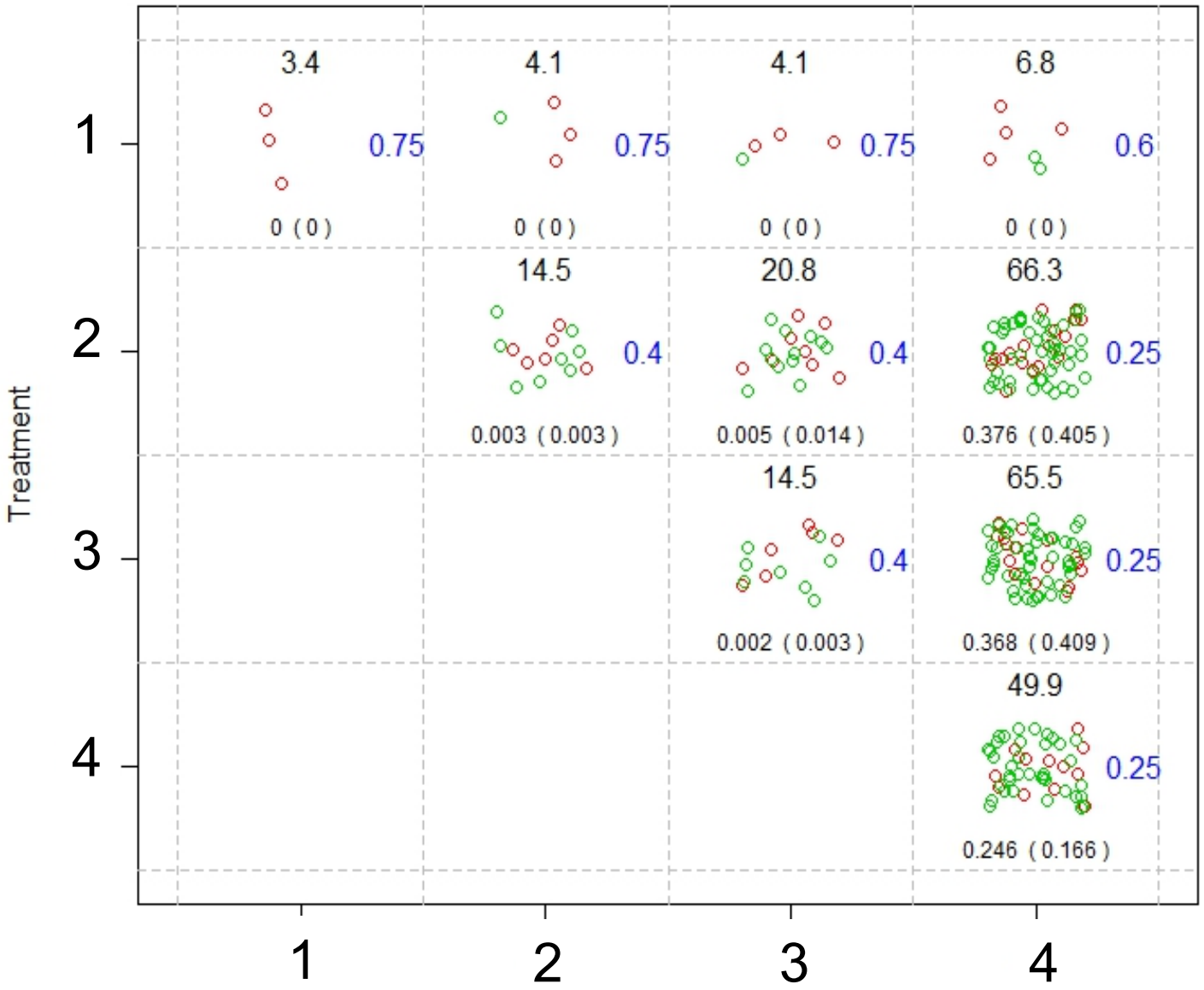

| Design | Mean Fails |
|---|---|
| Adapt | 21.5 |
| Fixed | 64.9 |

# Scenario 6




| Design | Mean Fails |
|---|---|
| Adapt | 59.7 |
| Fixed | 81.1 |

# Scenario 7




| Design | Mean Fails |
|---|---|
| Adapt | 78.1 |
| Fixed | 119.8 |

# What Happened

- Full protocol constructed, complete details, no treatments in protocol
- Appendices for each agent
- Changed burn-in to solo agents + SOC arm fixed at 20% (drop when inferior)
- Construction of this powerful platform trial stopped the disease!!!

# Application to Pandemic

- A protocol like this could sit on the shelf, ready to go immediately when needed
- Heck design could be pre-approved!
- PREPARE
  - EU
  - Canada + Australia/NZ + US ???

# PREPARE

- EU funded group charged with being prepared for a pandemic [www.prepare-europe.eu](http://www.prepare-europe.eu)
- Herman Goosens (Antwerp) is PI
- PREPARE CAP/FLU
  - Trial + CE + Process for care + readiness
- CAP: 2 or 3 interventions from 3 domains – 8 to 12 regimens to start

PREPARE NEWSLETTER

1st Edition
September 2014

Also available online at: www.prepare-europe.eu

PREPARE kick-off meeting Antwerp - February 2014

## Editorial

*Herman Goossens, PREPARE Coordinator, University Hospital and University Antwerp*

***In recent years several epidemics have posed considerable threats to public health, in Europe and beyond. The clinical research response to these epidemics has all-too-often proven to be fragmented, cumbersome and too delayed to generate data in time to provide evidence for clinical management of patients and for informing public health responses.***

The PREPARE ("Platform for European Preparedness Against (Re-) emerging Epidemics") project has been funded by the European Commission and kicked-off in Antwerp in February 2014 to address this startling challenge. PREPARE's ambitious goal is to revolutionise the clinical research response to future epidemics and pandemics. More than 600 GPs in primary care and over 700 hospitals in Europe are integrating with Europe's finest fundamental and clinical scientists in the field of infectious diseases under the PREPARE banner. The forward thinking and imaginative European Union funding Framework has made this collaborative platform a unique reality. Since its inception, the PREPARE Consortium has already addressed challenges associated with several global infectious disease threats and WHO "Public Health Emergency of International Concern" (PHEIC), such as resurgence of MERS-CoV in the Middle East in April, PHEIC declared for poliovirus in May and PHEIC declared for Ebola virus in August. PREPARE has moved swiftly to develop an "Outbreak Clinical Research Response Mode" strategy for responding to such potential threats for Europe, and has established the "Outbreak Mode Committee", a standing committee to coordinate the PREPARE responses to infectious diseases threats for the EU (see page 4 and 5). Our bold ambition is to establish an new paradigm for epidemic and pandemic clinical research so that the processes of clinical research speed up to the extent that findings are generated in real time to inform practice when it is most useful, in the midst of the pandemic, rather than once the threat has passed. Prof. Jeremy Farrar, Director of the Wellcome Trust, whose foresight helped inspire the PREPARE platform, alludes to this on page 7 of this Newsletter. The many tasks achieved by the Workpackages and their (Co-)Leaders (see page 2 and 3) are evidence of the vitality and startlingly rapid progress of this Consortium. I would like to thank the PREPARE partners, clinical networks and associated organisations who have all worked so effectively during these first months of PREPARE. I hope you will enjoy reading our first Newsletter. There is a lot more information on our website! (www.prepare-europe.eu)

In this issue



PREPARE is funded by the European Commission under grant number 602525