Platform Trials: Impossibly Complex, or the future of clinical trials?

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The Status Quo

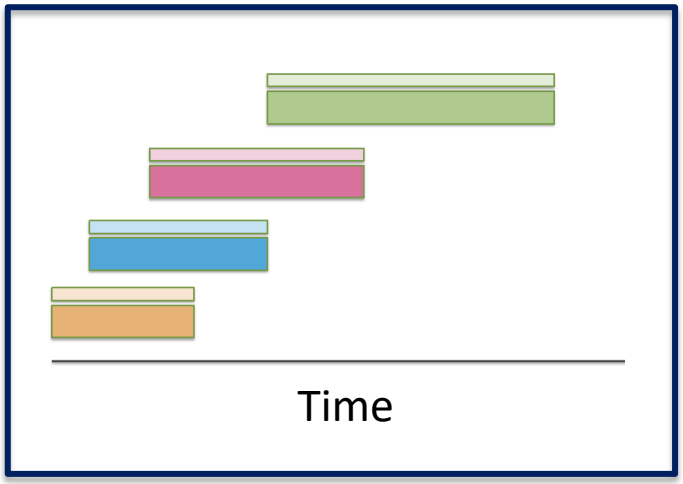
- We rebuild a new stadium every time we run a trial
- Rules are different in every match and nobody can watch the game

What if we had <u>one</u> arena and we all played at the same time, learning as we go along?

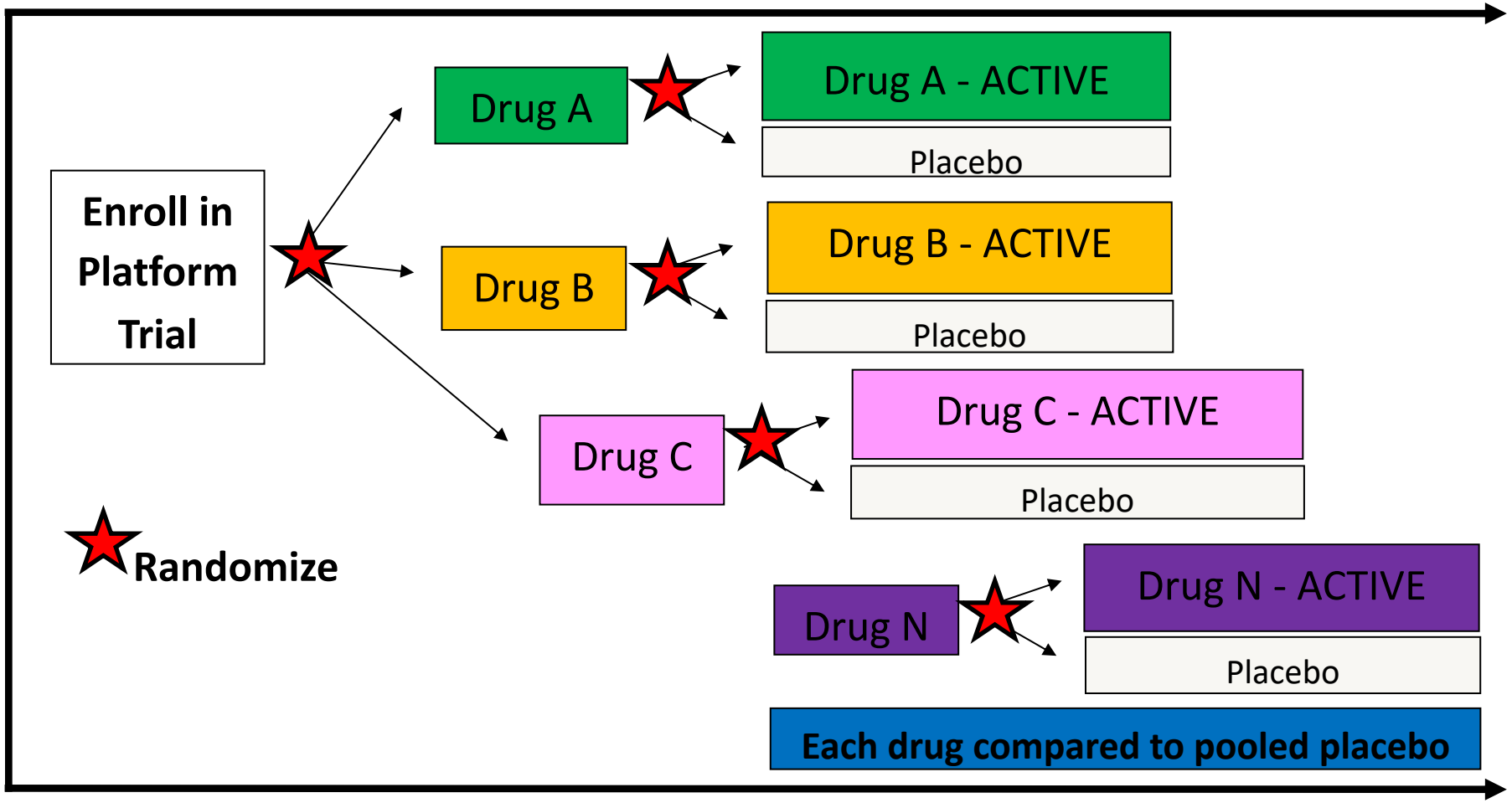
[Analogy adapted from Scott Berry, DIA Master Protocol Workshop 2018]

Platform Trial - definition

To study **multiple 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.



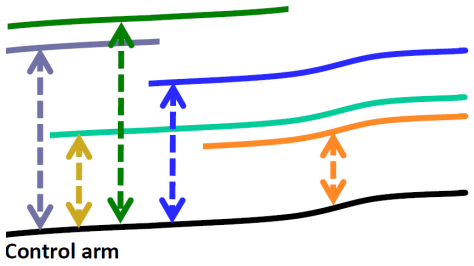
Platform Trial – patient experience



Platform Trial – basic characteristics

The trial is governed by a **Master Protocol** –
a common protocol for multiple drugs

- **Disease-focused** (agnostic to the experimental agents)
- **Describes the patient experience** (e.g., common schedule of activities; data and bio-sample collection- uniform across drugs)
- **Allows for sharing of controls/placebo groups**



- Experimental agents are added as “regimens” (AKA, appendix) by way of protocol **amendments**

THE EFFICIENCY OF TESTING MULTIPLE TREATMENTS

Synthetic Example

- Traditional Method

- 100:100 single trial, if effective “stop process”, if not “new treatment” run another trial
- Dichotomous outcome:
  - Assume control: 30% success rate
  - Effective therapies: 50% success rate
  - 0.025 type I error per trial
  - ~83% power
- Assume 90% of therapies are ineffective!

Different Strategies

- Sequence of Traditional 2-arm trials:
  - 100 per arm, 1:1, 0.025 type-1 error
- Sequence of Fixed 6-arm trials:
  - 100 per arm, common control, 0.025 type-1 error per treatment
- Sequence of 6-arm trials with interim for futility or success – every 150 subjects
- Open Platform of 6 arm trials
  - Interim every 150 subjects, futility or success per arm, replace arms that drop

Operating Characteristics

Approach	N Trials	# Trts	N	N non-resp	Mean Years	% Process ends with Good TRT	% A Good Trt Wins	% Ineffective Wins
Traditional 2-arm	9.8	9.8	1966	1357	12.0	78	82	2.5%
Closed Platform	2.5	12.7	1528	1045	8.0	86	83	2.7%
+Adaptive every 150	3.4	13.7	971	663	5.5	82	76	2.5%
Open Platform	1	13.1	849	579	4.2	85	91	2.2%

Saville and Berry (2016) "Efficiencies of Platform Clinical Trials: A Vision of the Future" Clinical Trials.

Operational and scientific efficiencies

- **Shared infrastructure**
  - ✓ **efficient start-up** - the time and effort required to start up a new regimen (i.e. adding a new drug) is minimized (sites always active, streamlined contracting).
  - ✓ **high-quality execution** - network of selected investigators and sites, uniform and standardized data and sample collection processes, recruitment and retention strategies (RRE committee).

- **Innovative Design**
  - ✓ **Sample size savings** from shared placebo
  - ✓ 3+:1 randomization appealing for patients!
  - ✓ Collect uniform data/samples from every participant to facilitate future trial adaptations and **accelerate disease learnings.**

Efficiencies

- ✓ **Sample size savings** from shared placebo
- ✓ **Shared infrastructure** means quicker time to start a new therapy
- ✓ **Less chance of being on placebo**: appealing for patients!
- ✓ Test more regimens **faster and reject inefficient regimens quicker**
- ✓ Better **disease learning.**

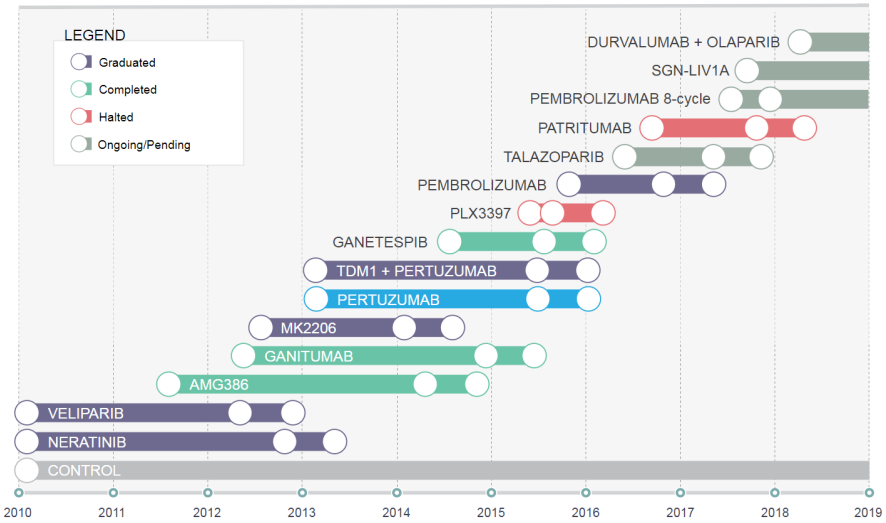
Multiple therapeutic areas

BREAST CANCER I-SPY 2 TRIAL

www.ispy2.org

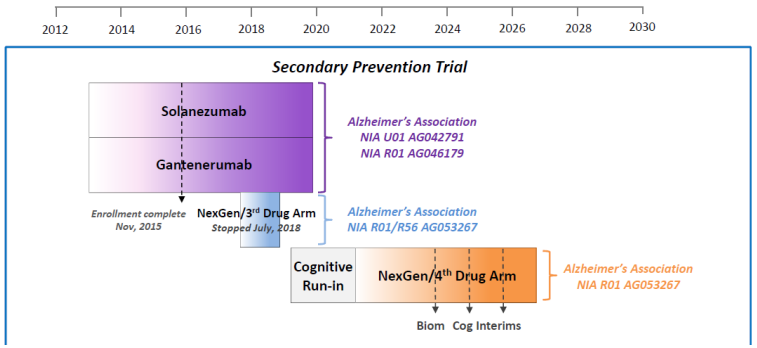
1400 patients enrolled

3 agents received accelerated approval



AbbVie
Amgen
AstraZeneca
Genentech/Roche
Merck
Pfizer
…

DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit



Lilly
Jannsen
Roche

Foundations + NIH + Industry

Platform Trial

Specific features driven by the goals of the platform:

- Inclusion/Exclusion criteria
- Flexibility and customization at the regimen level
- Borrowing of placebos
- Endpoints
- Subgroups & Randomization within subgroup
- Subgroup “signatures” for possible regimen success
- Exit criteria for regimens
- Frequency of interims
- Phase III cohort

Vocabulary Words

- Platform trial: Standing, perpetual clinical trial to investigate multiple therapies in parallel in a particular disease
- Master protocol: defines global rules that govern the therapies being investigated and how participants flow through the trial
- Appendix: The mechanism through which therapies are added to the platform and attached to the master protocol
- Regimen: An therapy being investigated along with the matched control. A regimen is described in an appendix. Within a regimen participants are randomized to control and investigational arms

Protocol Vs Appendix

- The master protocol specifies *global* rules
- A drug is added to the master protocol via an appendix
- The appendix specifies *local* rules particular to the drug being studied
- Appendices can accommodate the necessary flexibility to the sponsor and the agent under investigation
- Compromise between what is global and what is local
- Global rules to develop and protect the two biggest platform commodities – shared infrastructure and shared control

Protocol Vs Appendix

Master Protocol

- Trial Eligibility
- Visit schedule & data collection
- Minimums and Maximums
  - Sample Size
  - Follow-up Time
- Preferred
  - Endpoints and analyses
  - Futility Criteria
  - Success Criteria

Appendix Flexibility

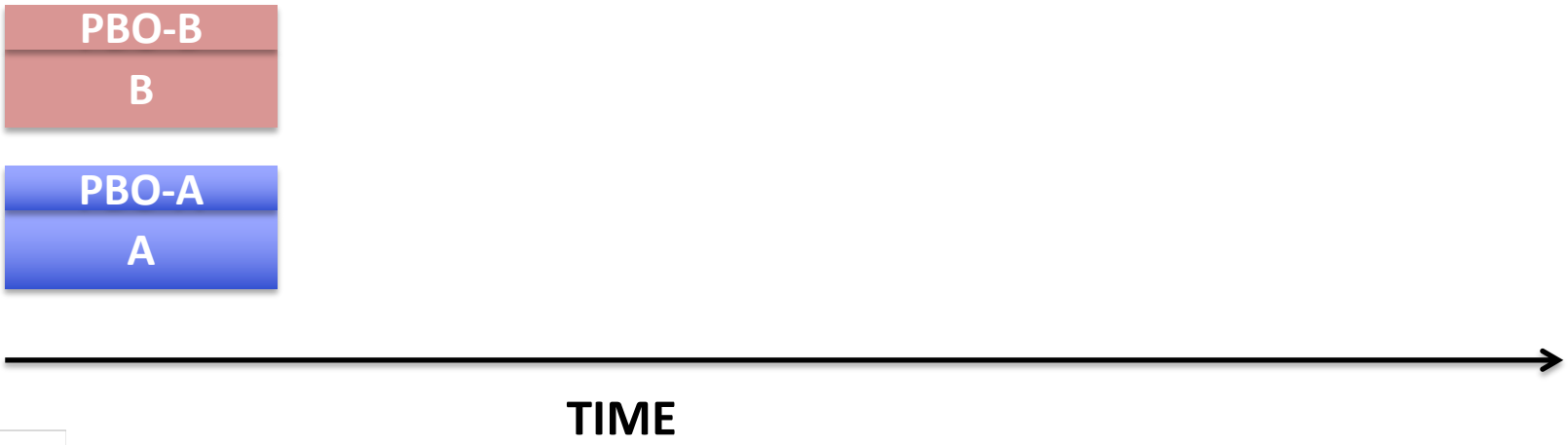
- Additional restrictions on Inclusion/exclusion
- Additional endpoints to be collected
- Specifics on
  - Sample size
  - Length of follow-up
  - Prespecified subgroups
  - Endpoints and analyses
  - Futility or other decision triggers

Key Challenge

- Find Balance of Synergy vs. Flexibility
  - What is specified in the Master Protocol vs. Appendix
  - Too much in the Master Protocol – hard to reach consensus
  - Too much left to the Appendix – lose efficiencies

EXAMPLE SPONSOR JOURNEYS

Example Sponsor Journeys

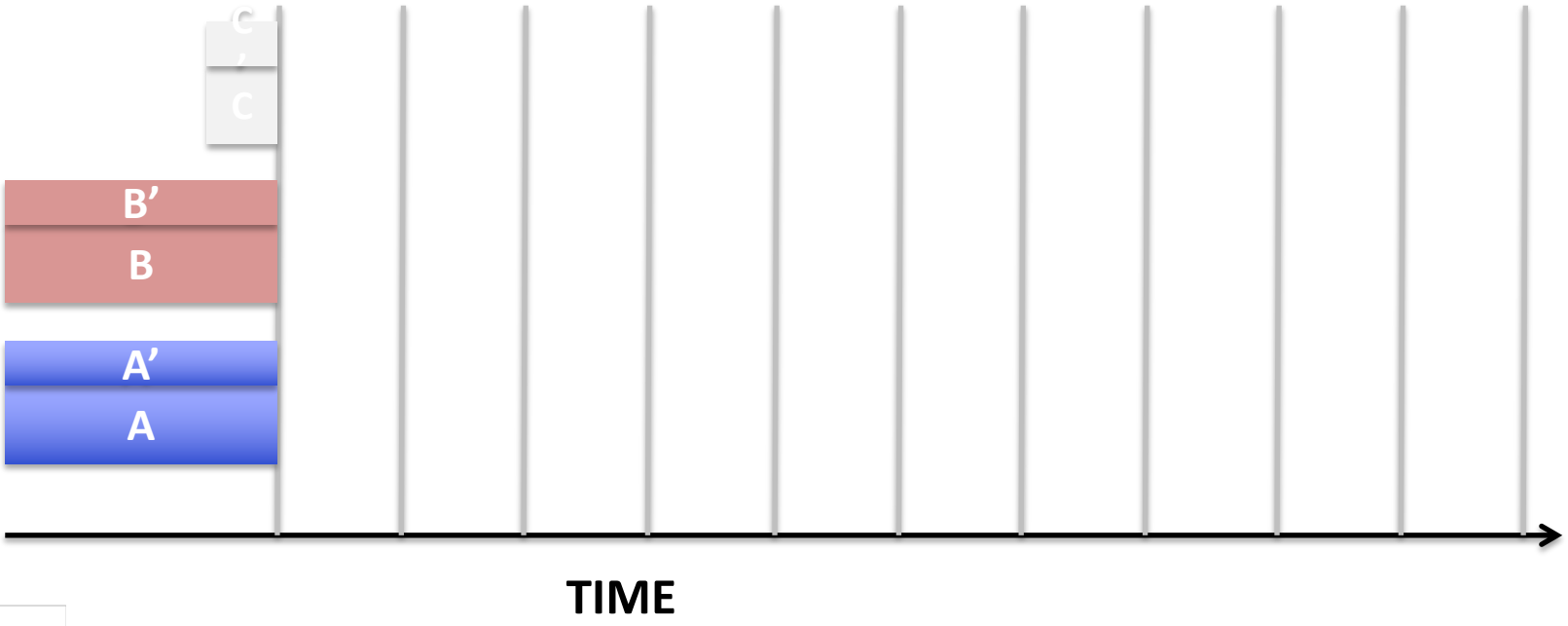


Example Sponsor Journeys

- Can add treatment regimens “as appropriate”
  - Available, Enrollment support, …
  - Not a protocol change!

Example Sponsor Journeys

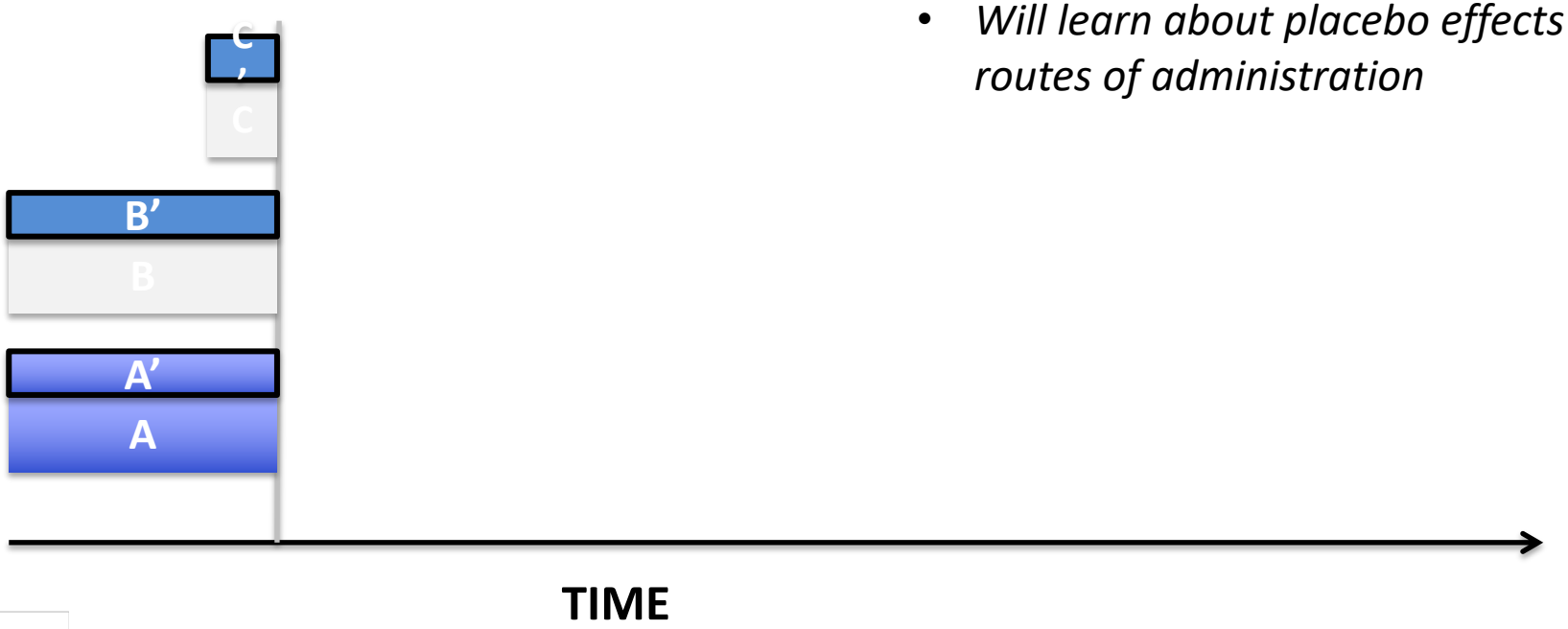
- Interim Analyses:
  - Occur every 3 months for platform
  - Some regimens “actionable” at interim



Example Sponsor Journeys

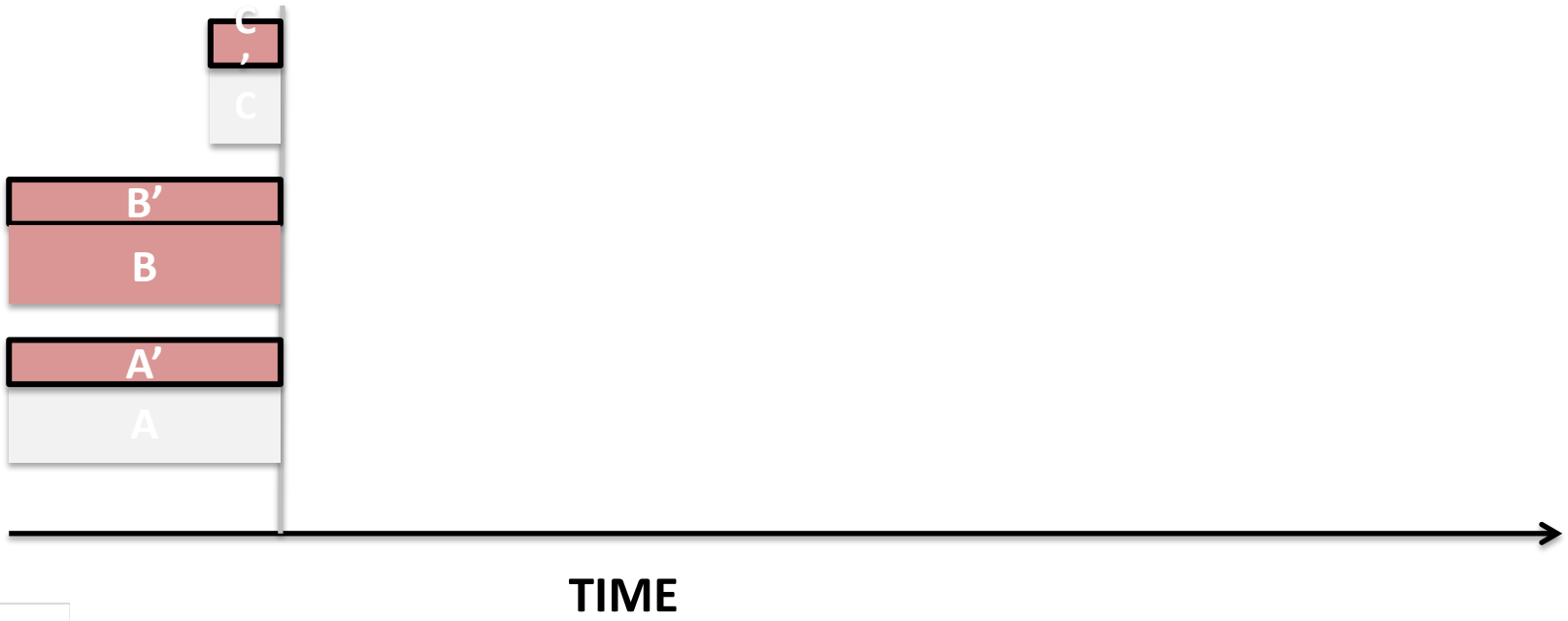
- Interim Analysis Regimen A:
  - Combine all control participants together for analyses for each regimen

- *Pool all routes of administration for the shared control*
- *Will learn about placebo effects in routes of administration*



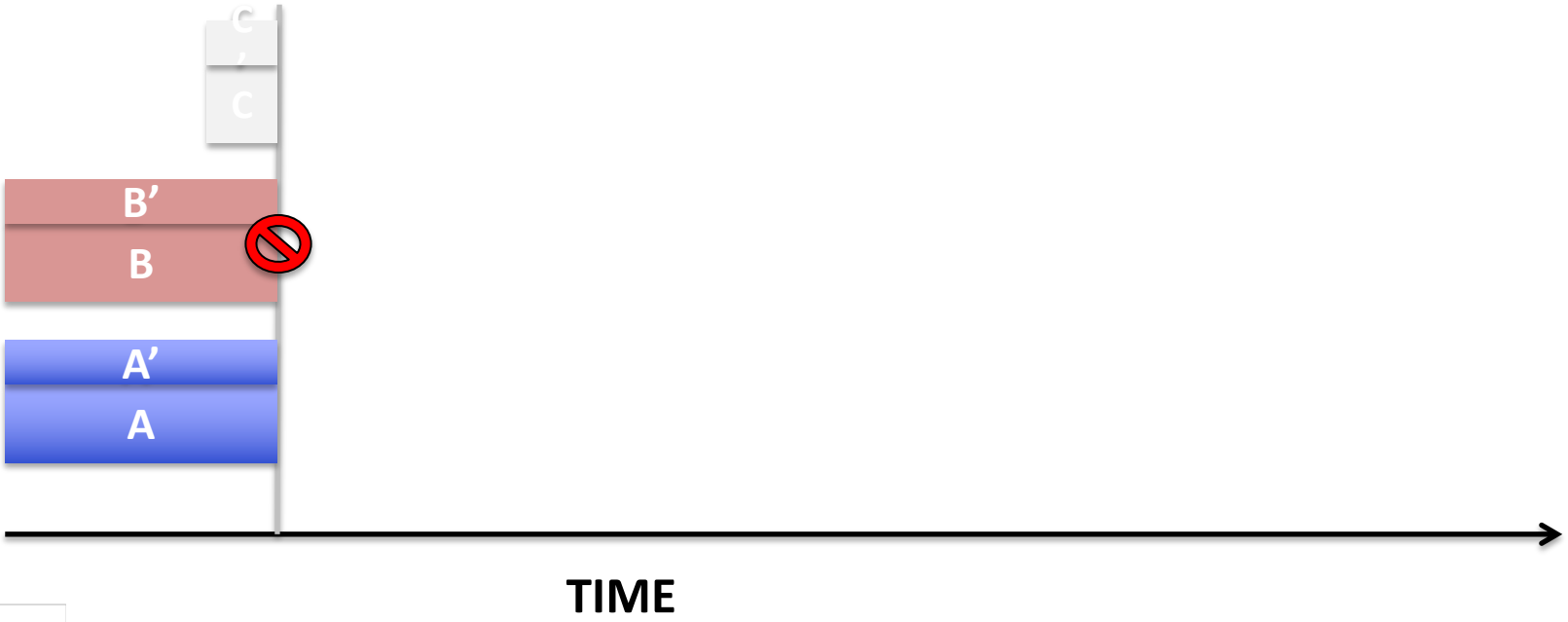
Example Sponsor Journeys

- Interim Analysis Regimen B:
  - Combine all control participants together for analyses for each regimen



Example Sponsor Journeys

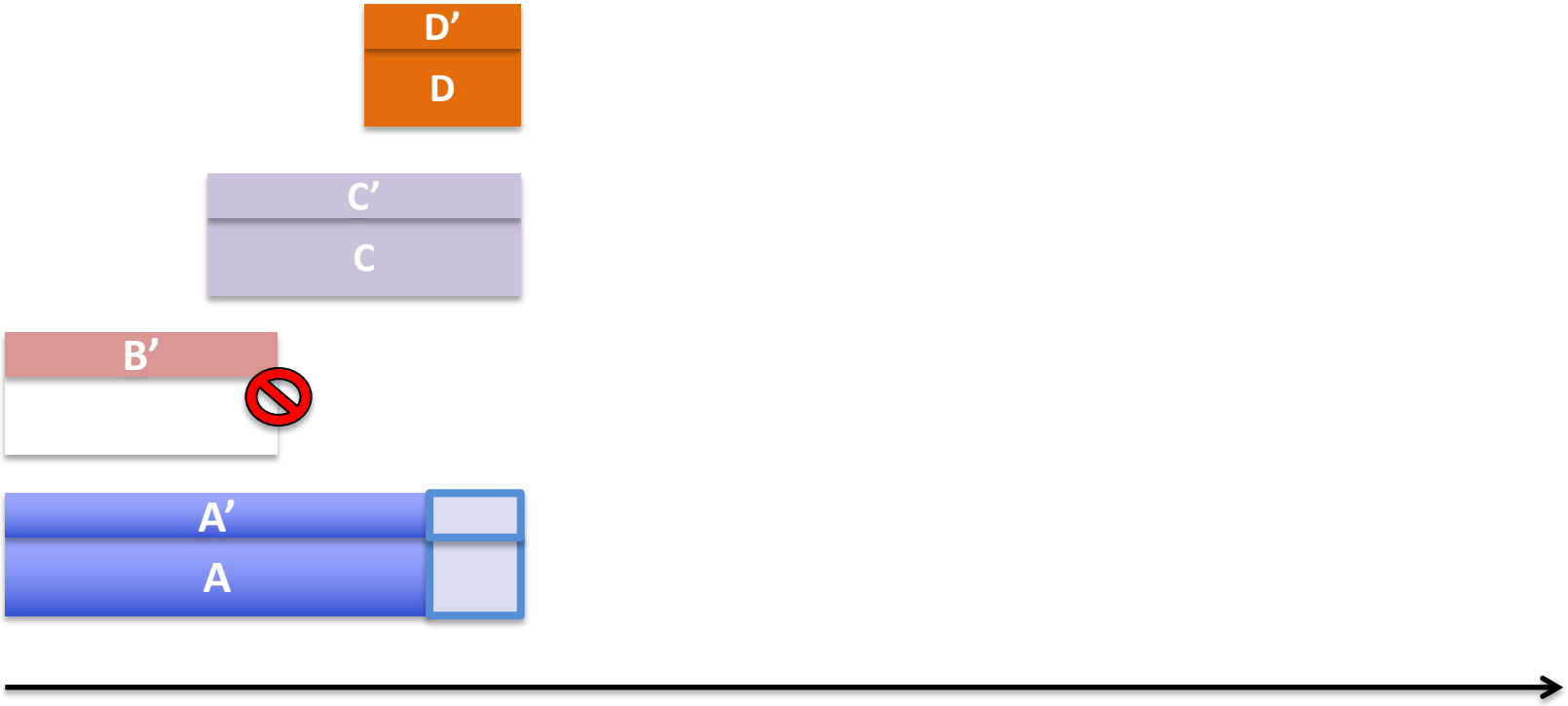
- Interim Analyses:
  - Drop a regimen for futility based on lack of efficacy
  - Option to re-randomize participants



Example Sponsor Journeys

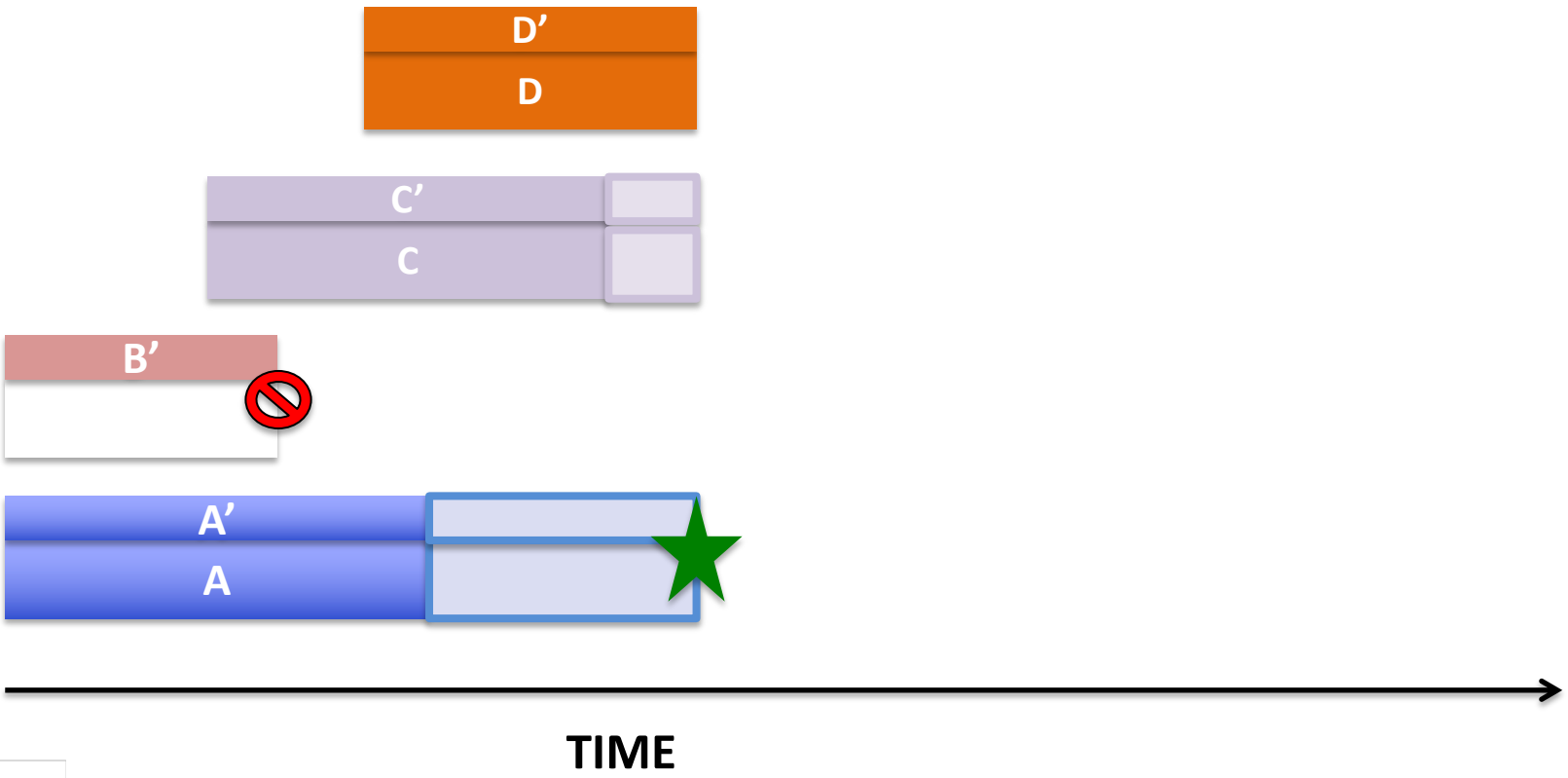
Example Sponsor Journeys

- Another regimen added ….
- Enrollment to A ended, still follow…



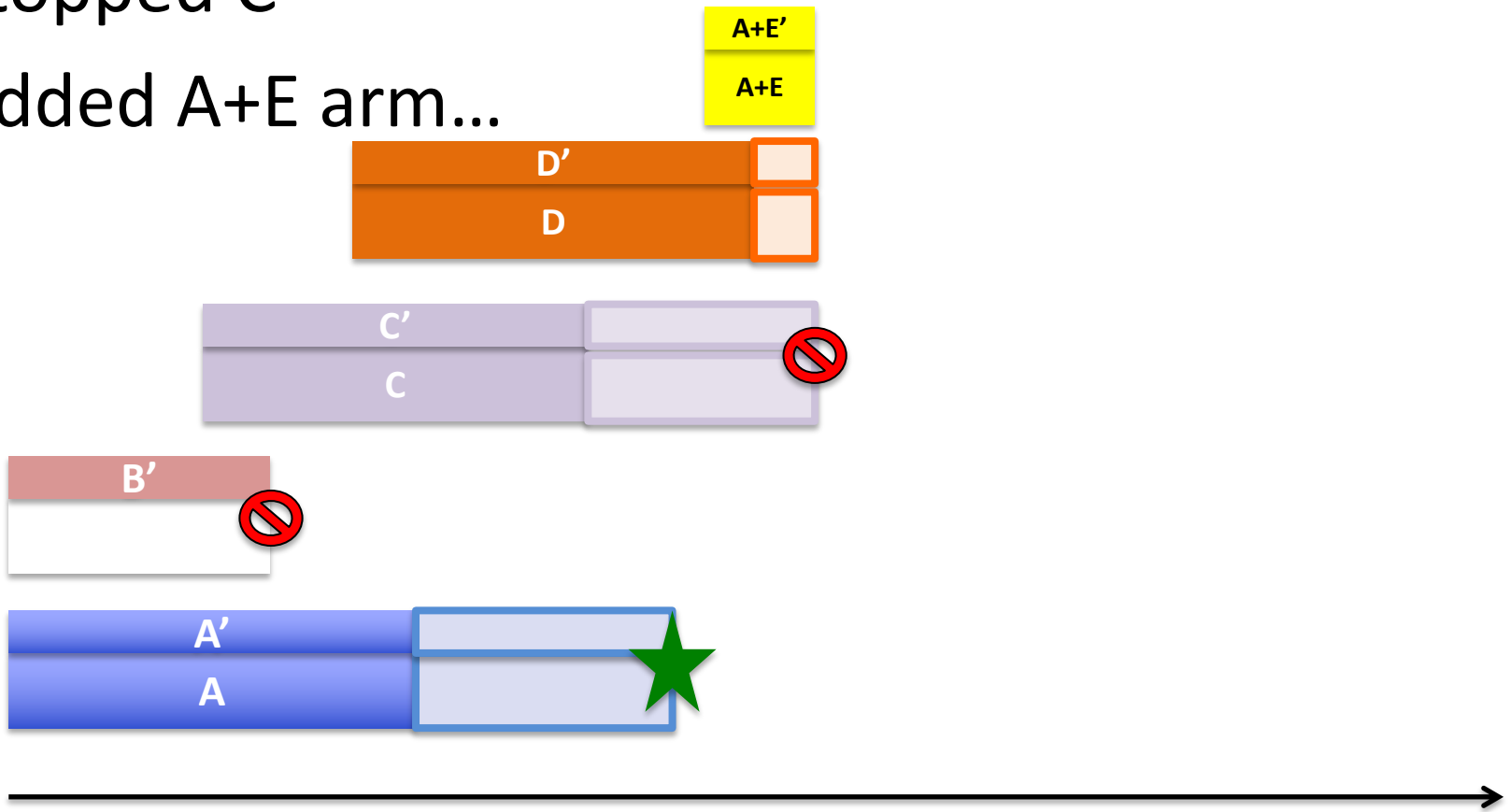
Example Sponsor Journeys

- Successful finding on endpoint for A



Example Sponsor Journeys

- Stopped C
- Added A+E arm…



EXAMPLES

Adaptive Platform Trials Planned or Running

- Cancer (breast, GBM, pancreas, melanoma, myeloma)
- Alzheimers
- Antibiotics
- Ebola
- Community acquired pneumonia
- Pandemic flu
- Muscular dystrophy
- Diabetes
- Cardiovascular Outcomes (diabetes, testosterone)

From Scott Berry

EPAD = European Prevention of Alzheimer's Dementia

DIAN = Dominantly Inherited Alzheimer Network

ARLG = Antibiotic Resistence Leadership Group

RAR = Response Adaptive Randomization

Exp = Expected

Features	iSpy2	REMAP-CAP	GBM-AGILE	EPAD	DIAN	PanCAN PP	ARLG AB	EBOLA	PREPARE FLU
Phase?	2	4	2/3	2	3	2/3	3	3+4	4
Master Protocol	Y	Y	Y	Y	N/SAP	Y	Y	Y	N
Mult Arms	Y	Y	Y	Y	Y	Y	Y	Y	N/Y
Embedding	N	Y	N	N	N/?	N/?	N	Y	Y
Multifactorial	N	Y	**Exp**	N	N	**Exp**	N	Y	N
Control?	Com	Y/N	Com	Com	Com	Com	Com	Both!	Y
Staggered Arms	Y	Y	Y	Y	Y	Y	Y	Y	N/Y
Blinding	N	N	N	Y	Y	N	?	N	N
Enrichment	Y	Y	Y	Y	N	Y	Y	N	N/Y
Interims	2w	M	M	3M	2Y	M	M	1w	N/Y
Primary Time	6M	2M	TTE	Var/4y	4y+	TTE	<1M	2w	1w
Bayesian	Y	Y	Y	Y	Y	Y	Y	Y	N
Adapt N	Y	E	Y	Flex/U	N	Y	Y	E	E
RAR	Y	Y	Y	N	N	Y	N	Y	N
Long. Model	Y	N/?	Exp	Y	Y	Exp	N	N	N
Time Machine	Y	Y	Y	N	N	Y	N	Y	**N**

IN THE BEGINNING: I-SPY 2

ISPY2: Phase II Trial in Neoadjuvant Breast Cancer

- Master protocol: Specifies most aspects
  - Primary endpoint and primary analysis
  - Sample size and follow-up time
  - Interim analysis schedule and criteria for futility / success
- Appendix: Discourage from deviations from the master protocol
- Personalized medicine vision: What drug works best for which participants?
  - Subgroups of interest are HER2+/-, ER +/-, and Mammoprint (high/low)
  - 8 total groups. Response adaptive randomization (RAR) within each of these groups
  - Success ("Graduation") in a "signature"
  - Signature = the HER2, ER, and Mammoprint groups where the drug is most active

And 8 patient subgroups

- Defined by
  - Hormone Receptor (HR)
  - HER2
  - 70gene MammaPrint status

	MP–		MP+	
	HR+	**HR–**	**HR+**	**HR–**
HER2+				
HER2–				

I-SPY2 Adaptive Process

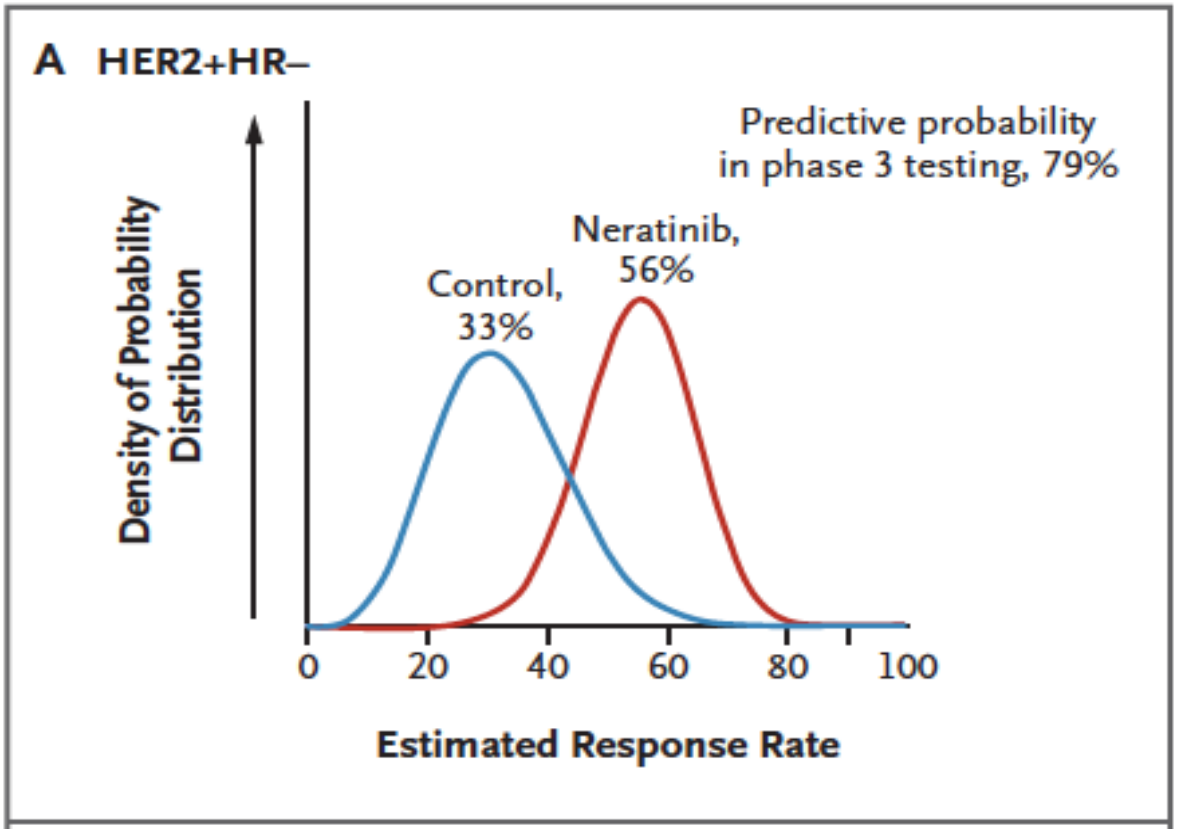
- Neoadjuvant breast cancer; PIs Esserman/Berry
- Primary endpoint: pCR (Longitudinal model MRI)
- 10 biomarker signatures
- Never-
- Operat ation
- First sponsor: FNIH (NCI, FDA, industry)
- Coordinated wi CDRH)—
  Regulatory pathway via pCR
- Current status: 1 s, 1 0 pts randomized, first 13
  exp drugs: neratinib, veliparib, AMG 52 AMG479,
  MK2206, pertuzumab, pertuzumab+T-DM1, ganetespib,
  pembrolizumab, P 44 397, talazopanib, patritumab, plus …

With different biomarker signatures and sample sizes

Graduated to phase 3

93 115 72 52 69 44

Neratinib's "graduation signature"

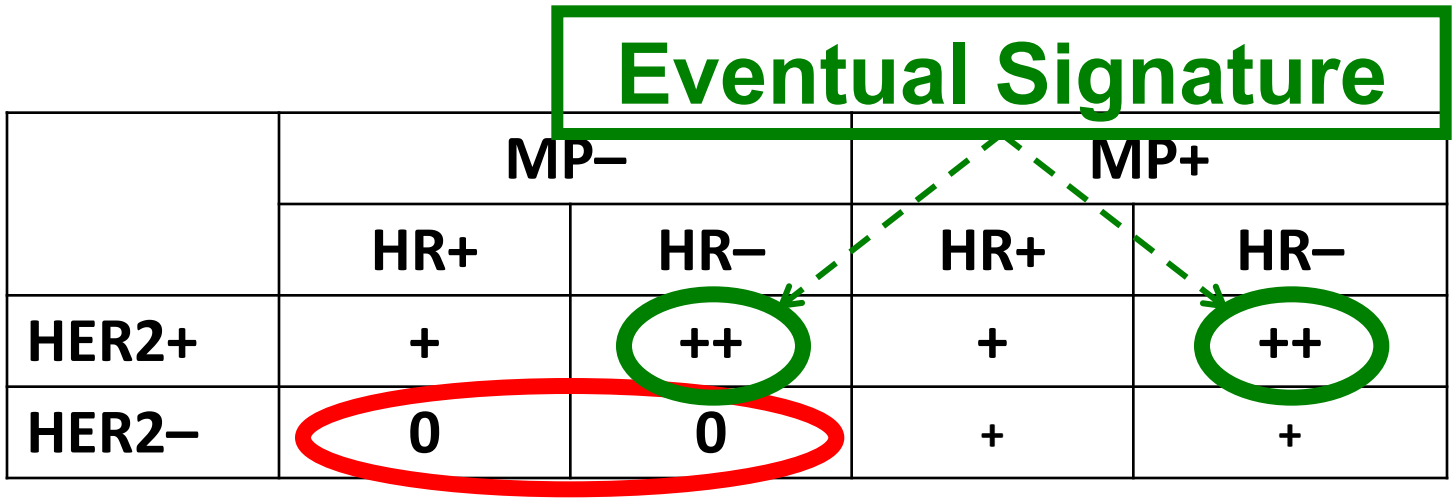


All 10 possible "signatures"

Table 2. Final Posterior and Predictive Probabilities of Neratinib Efficacy with Regard to 10 Biomarker Signatures.

Biomarker Signature	Estimated Rate of Pathological Complete Response (95% Probability Interval)		Probability of Neratinib Being Superior to Control	Predictive Probability of Success in Phase 3 Trial
	Neratinib	Control		
		percent		
Any	33 (24–40)	23 (14–33)	93	48
Hormone-receptor positive	23 (13–33)	16 (6–28)	81	40
Hormone-receptor negative	44 (30–55)	31 (17–45)	92	58
HER2 positive	39 (28–51)	23 (8–38)	95	73
HER2 negative	28 (15–37)	24 (13–35)	69	25
High-risk category 2 on 70-gene profile*	48 (30–60)	29 (11–48)	93	72
HER2 positive, hormone-receptor positive	30 (18–44)	17 (3–32)	91	65
HER2 positive, hormone-receptor negative	56 (37–73)	33 (11–54)	95	79
HER2 negative, hormone-receptor positive	14 (3–25)	16 (5–27)	42	14
HER2 negative, hormone-receptor negative	38 (22–50)	31 (15–46)	77	40

Randomization to neratinib part way through I-SPY 2



- **A nightmare in a 2-armed trial**
- **Easy in a platform trial: no amendment, nobody knew it happened**

Longitudinal Modeling
(MRI volume is auxiliary endpoint for adaptive decision making)

- **Assess predictability (depending on therapy) of pCR from interim MRI**
- **Borrow relationship (but discounting) from I-SPY 1**

Longitudinal Modeling and Time Machine in re Pembrolizumab

- Algorithm graduated pembro in TNBC when 1 patient through surgery, with estimated 60% pCR rate
- How is this possible?
  - MRIs available on about 30 pembro patients
  - Covariate modeling
  - Time machine: Previous controls showed a compelling ~20% pCR rate
- 4 months later, with half results final, estimated pCR rate: 60%
- Final answer (n = 29), estimated pCR rate: 60%

OTHER PLATFORM TRIALS DESIGNS AND THEIR DIFFERENCES

GBM Agile: Phase II/III Trial in GBM

- Master protocol: Specifies most aspects
  - Primary endpoint (overall survival) and primary analysis
  - Sample size and follow-up time
  - Interim analysis schedule and criteria for futility and success
- Appendix: Discourage from deviations from the master protocol
- Developing biomarkers
  - Drug may come in with biomarker that corresponds to the mechanism of action (MOA)
  - The marker becomes a randomization strata
  - Enroll in all groups, but RAR within the biomarker groups
  - Learn what works for what participants
  - Graduate phase II in a signature
  - Phase III trial then enrolls only in the signature

PANCAN: Phase II/III Trial in Pancreatic Cancer

- Very similar to GBM-Agile in most respects
- Allows re-randomization:
  - Once a participant progresses, they may be re-randomized
  - Participant cannot be randomized to control twice unless that is the only choice available to that participant
- Two control arms
  - One for each of the currently approved regimens
  - Experimental arms expected to have one of control regimens as their backbone
  - Compared to their backbone therapy alone

EPAD: Phase II Trial in Sporadic Alzheimer's

- Master Protocol:
  - Primary endpoint and analysis
  - Maximum sample size and length of follow-up
  - Interim analysis schedule and success / futility rules
- Appendix : Choose sample size and follow-up. Allow multiple doses, and specify randomization to the doses
- Subgroups: 4 pre-defined subgroups based on preclinical / prodromal and APOE4+/-
  - Appendices choose which subgroups they want to enroll in
  - Enrolling a subset of the prespecified subgroups is not allowed Appendix specific analyses may consider only the subset
  - Within each subgroup - equal randomization to all enrolling appendices

DIAN: Phase III Trial in Dominantly Inherited Alzheimer's

- Master Protocol:
  - Primary endpoint and analysis
  - Max Sample Size and length of follow-up
  - Interim analysis schedule and global success / futility rules
- Appendix: Choose Sample Size and length of follow-up
- Subgroups: No pre-specified subgroups. Enroll all-comers. Appendix specific analyses may consider only the subset

PPMD: Phase II, III, or II/III Trial in Duchenne's Muscular Dystrophy

- Master Protocol:
  - visit schedule and list of assessments
  - Preferred primary endpoint, primary analysis, sample size and max follow-up
- Appendix: May allow flexibility in terms of sample size, endpoints and analyses. Additional assessments may be added, but would be last priority
- Subgroups: Under discussion. Potentially
  - All participant have equal opportunity to be randomized to any appendix.
  - If a drug has a particular MOA, that can be an additional inclusion/exclusion for that appendix.

EBOLA

The Problem: Ebola Treatment Trial

- Acknowledge universe of possible treatments
  - Will evolve over time
  - Recognition that combinations may play an important role
- Is it ethical to assign subjects to placebo/SoC?
- Uncertainty over role / rate of response on SoC
- FDA insists on assignment to SoC
- 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

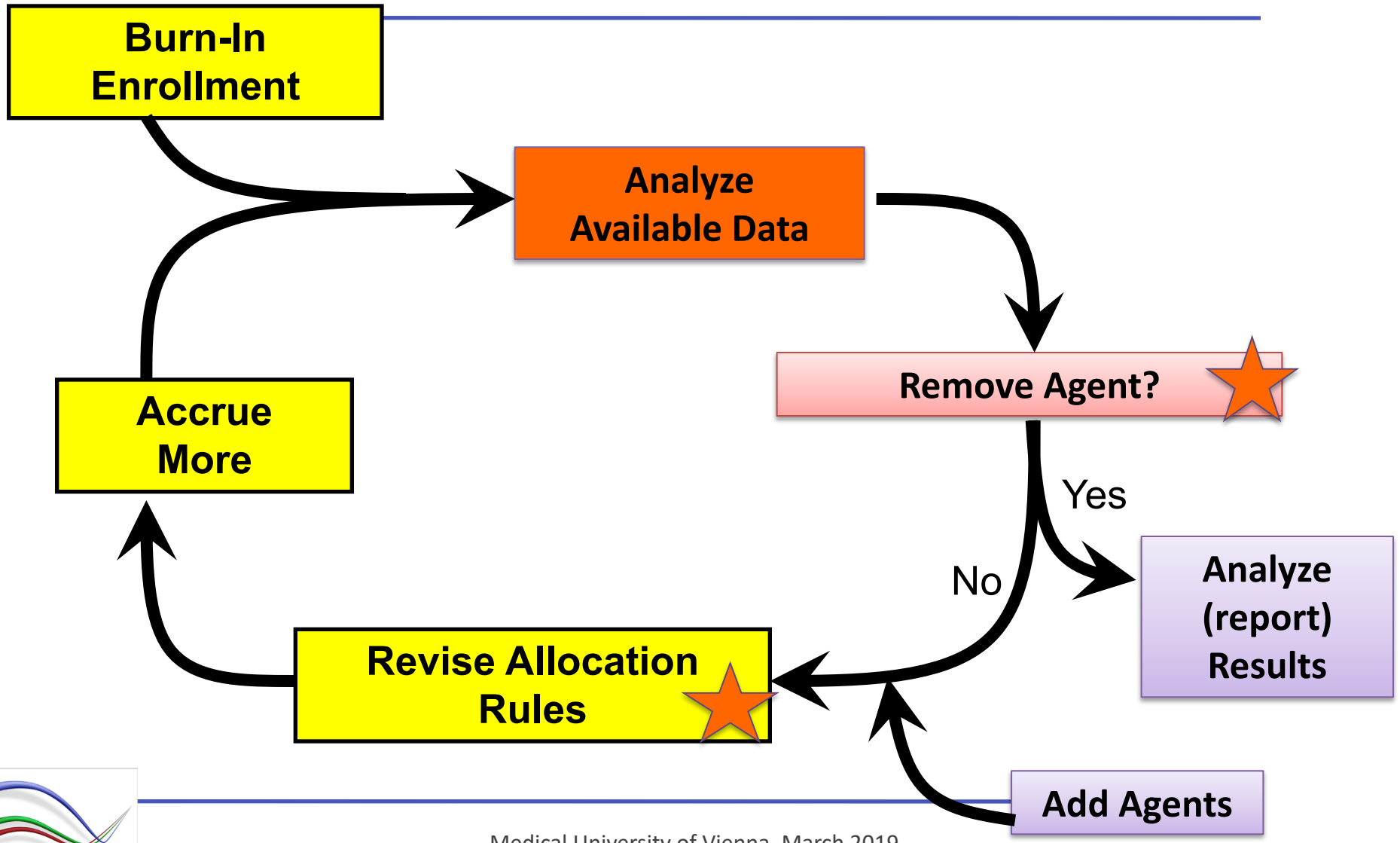
- Reviewed and approved by:
  - Duke University IRB
  - University of Sierra Leone ethics committee
- **Master Protocol** dictates trial behavior, each treatment included as an appendix
- Multiple Agents
  - Primary & Secondary agents
  - Combination + Single agents
- Response Adaptive Randomization (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)

Regimens		Treatments					
		P1	P2	P3	P4	S1	S2
Treatments	P1	■	■	■	■	■	■
	P2		■	■	■	■	■
	P3			■	■	■	■
	P4				■	■	■

Adaptive Platform Design



Berry Consultants
Statistical Innovation

Starting Structure

Burn-In Enrollment

- SOC arm is to be included, it gets a minimum of 20% allocation
- Allocate 40% of subjects to single-agent arms
- Allocate 40% to combination arms

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

- SOC gets a 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:

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

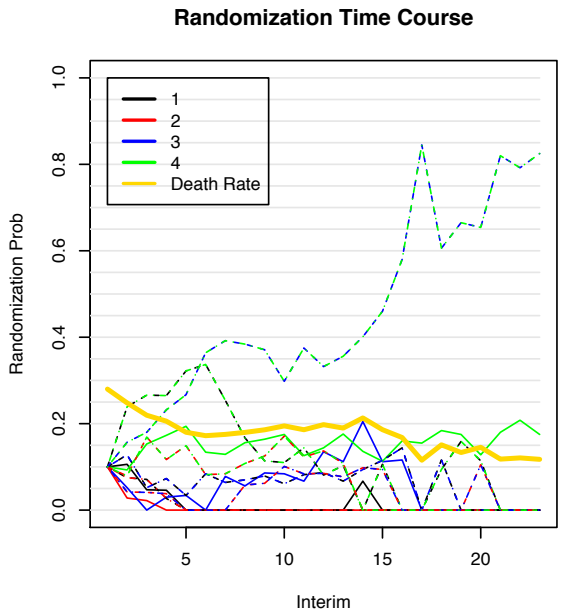
- Time:
  - Incorporate time "buckets"

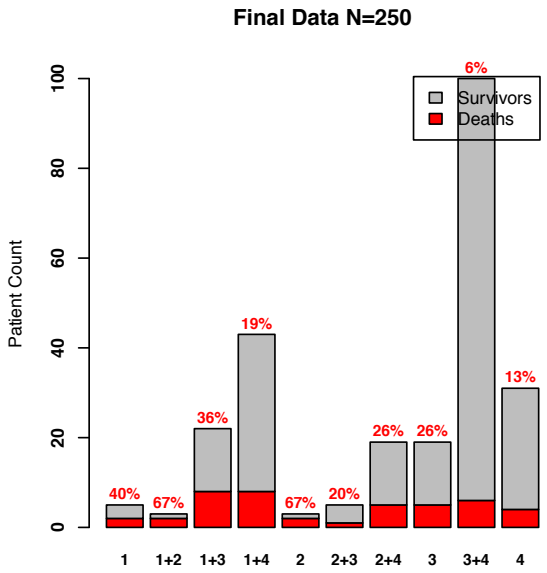
$$[\lambda] \sim NDLM(0,\tau^2)$$

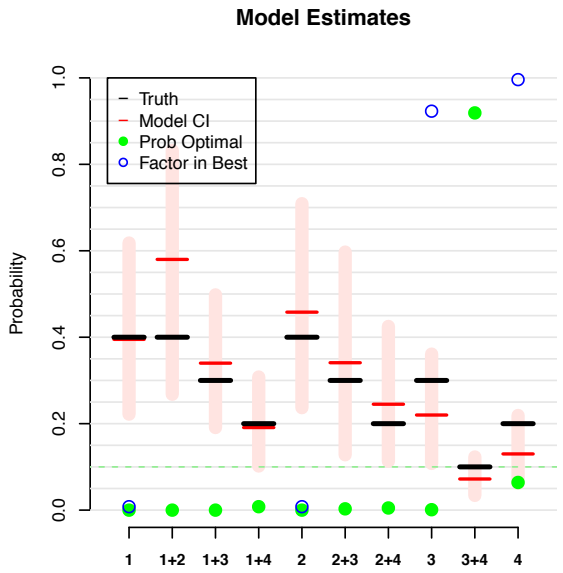
Example Trial

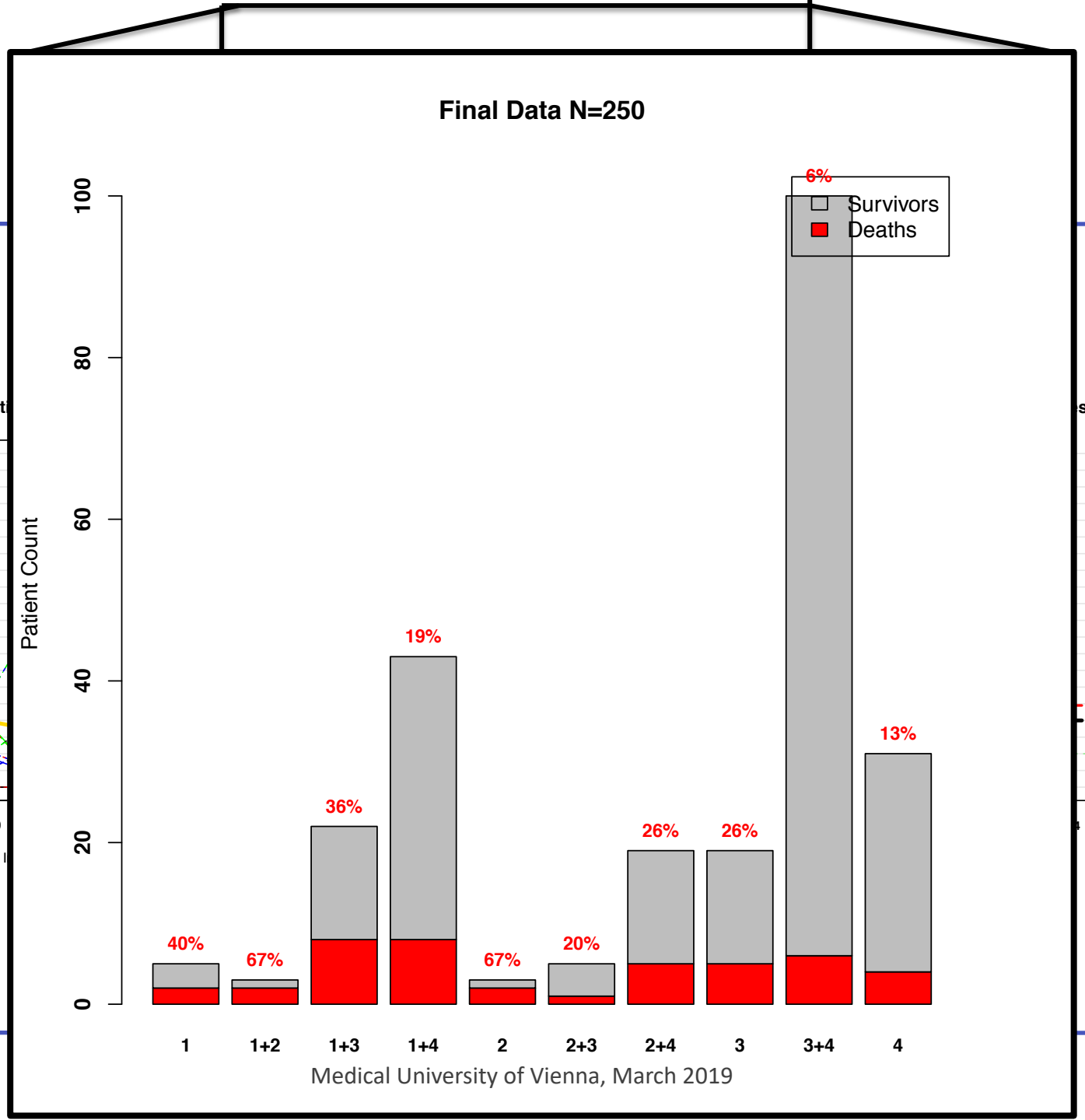
Regimens		Agents			
		1	2	3	4
Agents	1				
	2				
	3				
	4				

Example simulation








Final Data N=250
Survivors
Deaths
Patient Count
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
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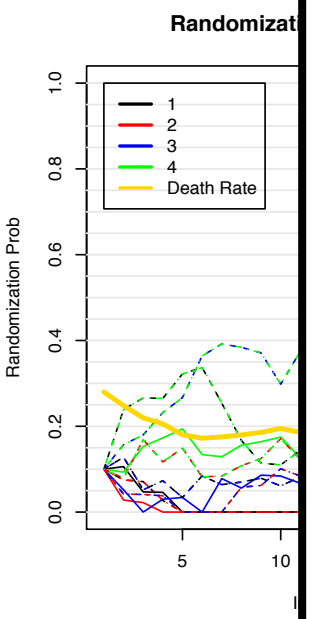
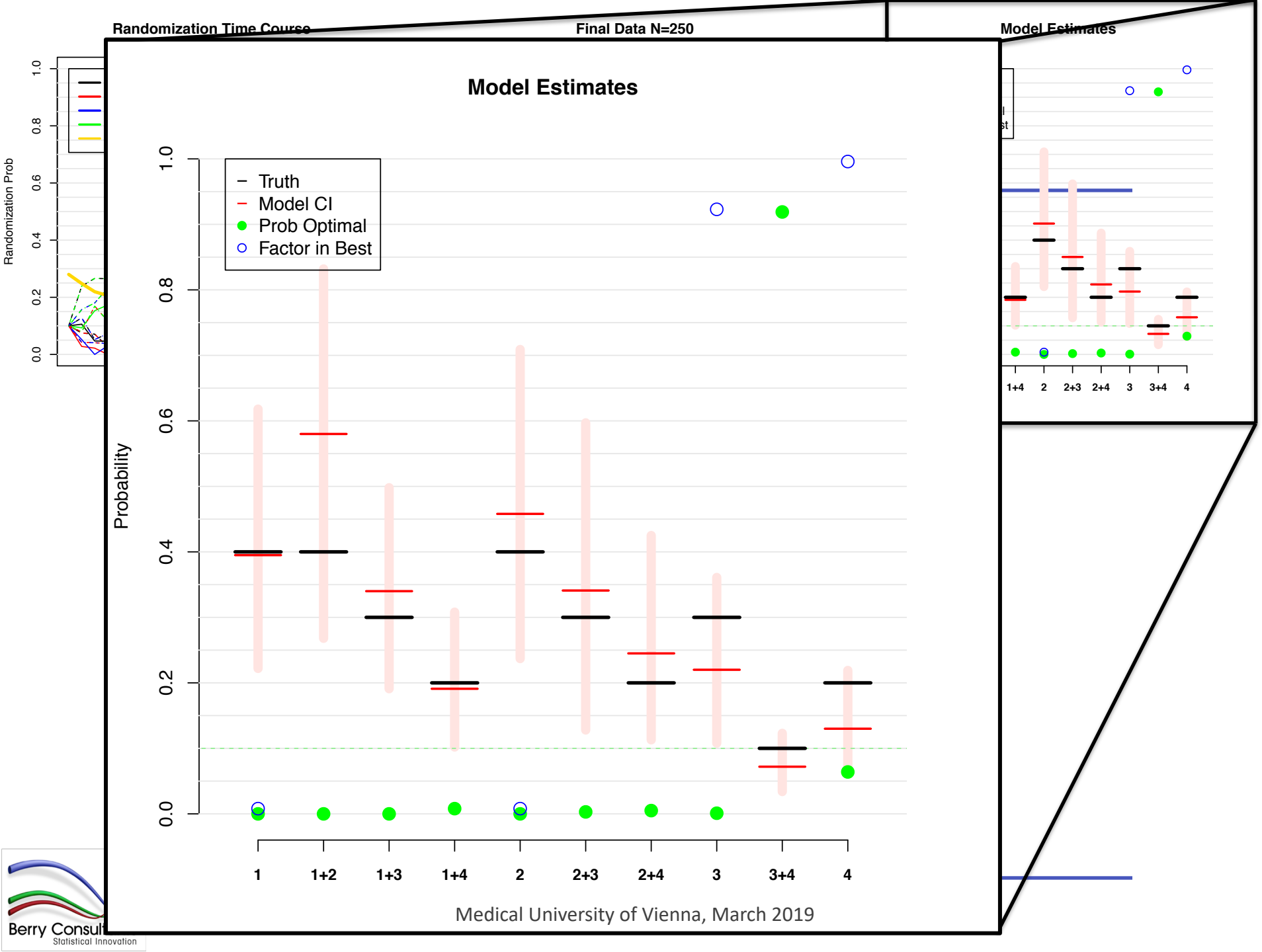
3
3+4
4
Medical University of Vienna, March 2019


Randomizat
Randomization Prob
0.0
0.2
0.4
0.6
0.8
1.0
1
2
3
4
Death Rate
5
10


s
3
3+4
4


Berry Consultants
Statistical Innovation


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
Medical University of Vienna, March 2019
Model Estimates
1+4
2
2+3
2+4
3
3+4
4
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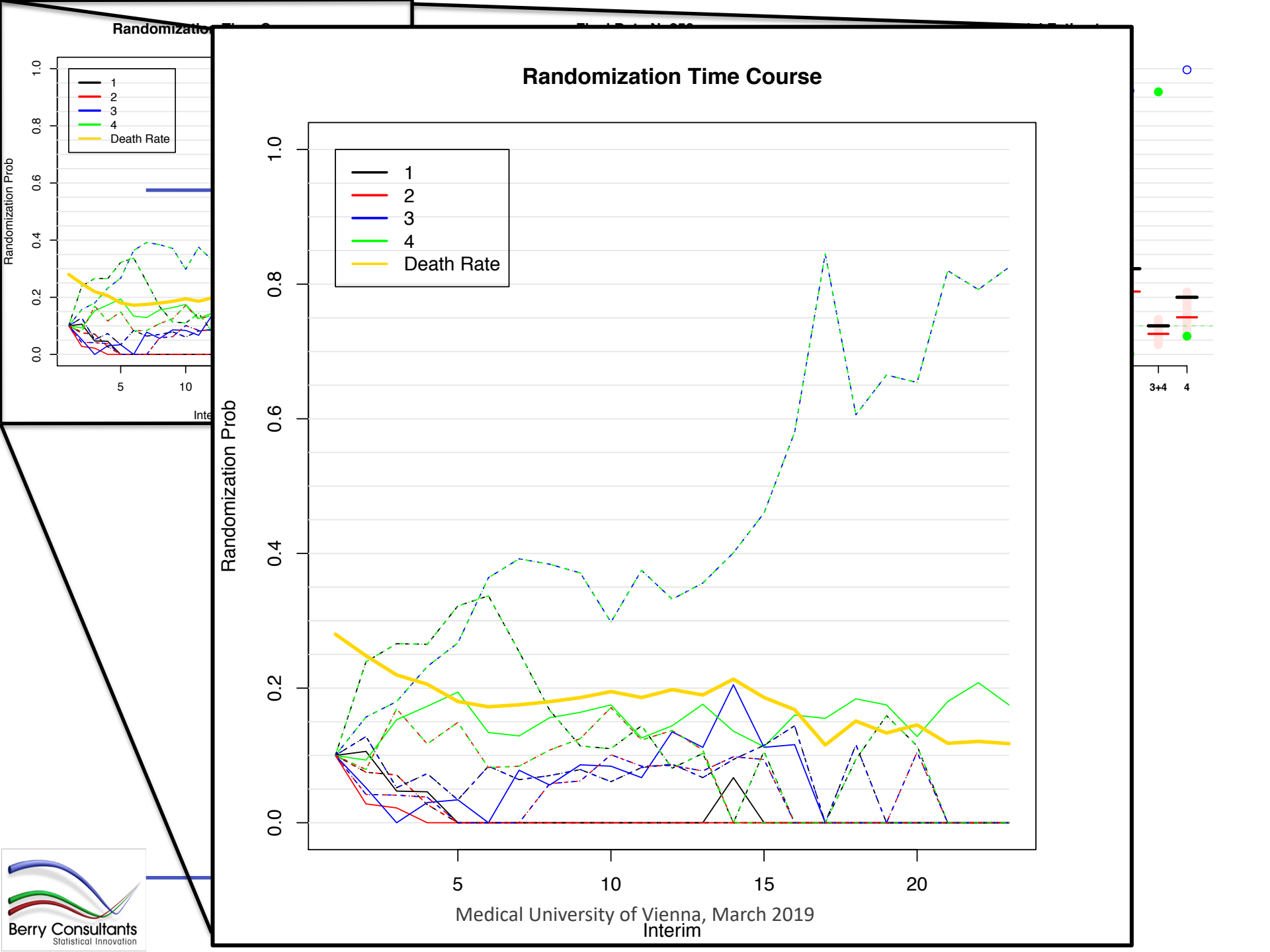
Randomization Time Course
1
2
3
4
Death Rate
Randomization Prob
0.0
0.2
0.4
0.6
0.8
1.0
5
10
15
20
Interim
Medical University of Vienna, March 2019
3+4
4
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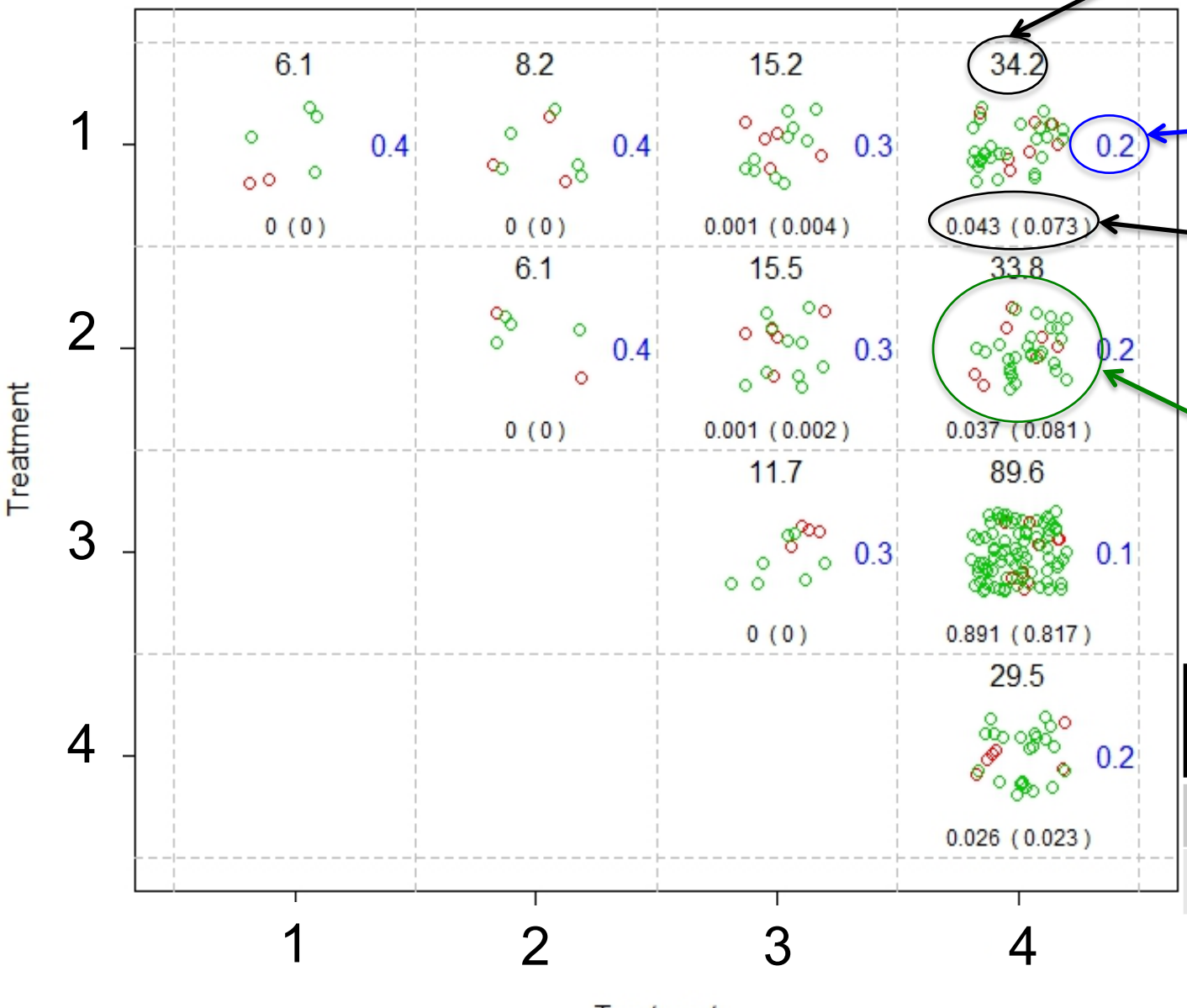
Scenario 3



Design	Mean Deaths
Adapt	49.4
Fixed	69.9

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

STATISTICAL MODELS

Ebola Statistical Model

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

- Priors:

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

- Time:
  - Incorporate time "buckets"

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

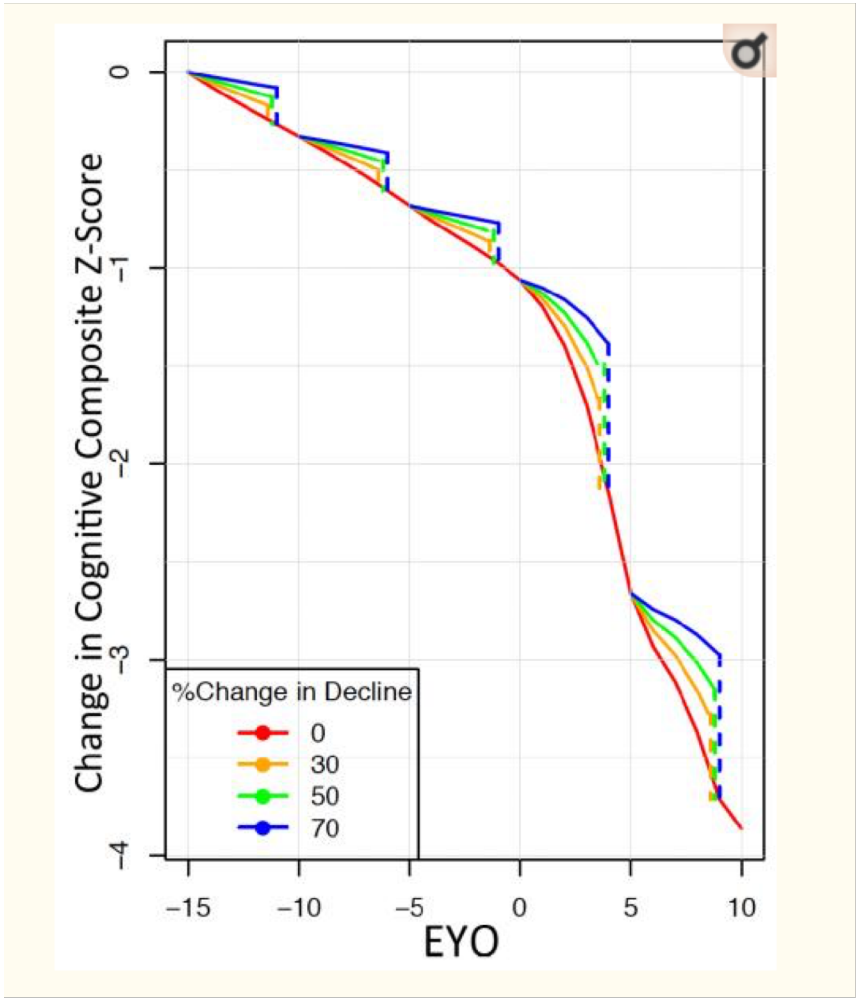
The main model

- Usually a Bayesian linear model
- This allows a great deal of flexibility, especially
  - Adding new treatments
  - Adding new treatment combinations
  - Adding subgroups
- Often combined with Bayesian hierarchical modelling across some of the terms
- See:
  - "Bayesian hierarchical modeling of patient subpopulations: Efficient designs of Phase II oncology clinical trials https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4319656/
  - "Data Analysis Using Regression and Multilevel/Hierarchical Models" - Andrew Gelman and Jennifer Hill

DIAN-TU Disease Progression Model

From: “The DIAN-TU Next Generation Alzheimer’s prevention trial: adaptive design and disease progression model” by Bateman et al.
EYO: Estimated Years to symptoms Onset

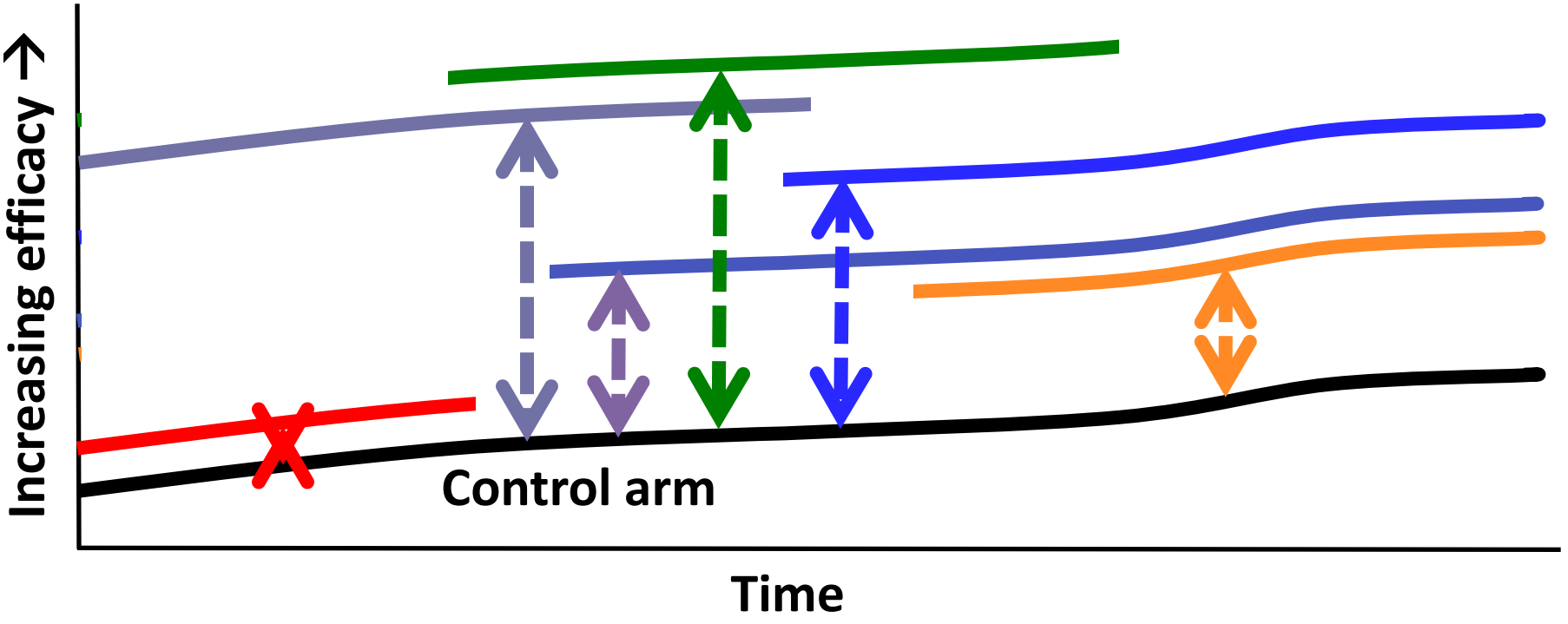
Proportional hypothetical treatment effects yield different absolute changes depending on EYO.
The red line represents the natural (i.e. placebo) rate of cognitive decline across EYO.
The colored lines illustrate different levels of slowing disease progression based on drug effect across EYO.



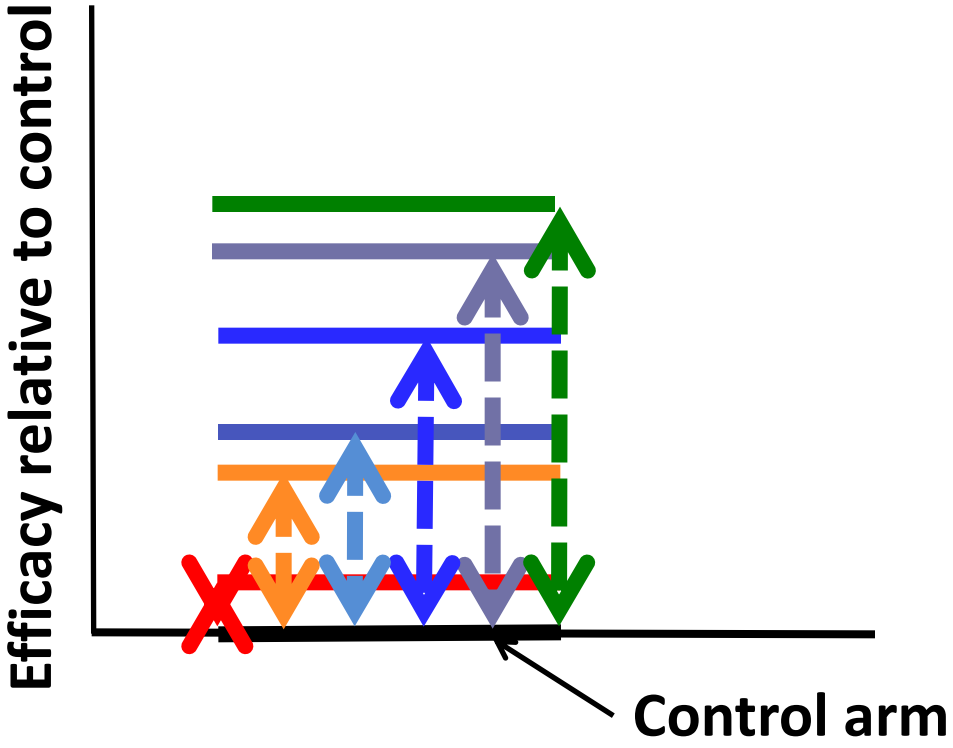
Platform Trials & “Time Machine”

- There has always been a concern about adaptive trials – what if the control response changes over time?
- In a platform trial this is much more likely, indeed the SOC may change to include a successful treatment from the trial!
- Multi-arm randomized platform trials enable solid links for bridging time periods
- These links preserve randomized comparisons for all controls, not just concurrent controls
- Not possible for a single experimental arm compared with historical controls
- All 2-armed comparisons have greater precision when using all results from all arms

Estimated efficacy relative to control and adjusted for each arm's time period



Estimated efficacy relative to control and adjusted for each arm's time period



Summary

- Simulation of Platform trials is more complex than even response adaptive trials
  - More ‘nuisance’ factors to simulate such as accrual, number of treatments, effectiveness of other treatment – size and signature, biomarkers, predictiveness of longitudinal models, effect in which signature: more scenarios
  - More OCs to analyze
  - Need agreement on acceptable error rates for different types of error

To conclude

- I hope that I have given a hint of
  - How important
  - Varied
  - Complex

  Platform Trials can be.
- They can be career defining, which is just as well because
  - They are a challenge to “get off the ground” requiring patience, determination, stamina and politics

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