ECONOMIC EVALUATION OF PLATFORM TRIAL DESIGNS

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McMaster University

JAMA Network | Open™

Original Investigation | Statistics and Research Methods

Economic Evaluation of Cost and Time Required for a Platform Trial vs Conventional Trials

Jay J. H. Park, PhD; Behnam Sharif, PhD; Ofir Harari, PhD; Louis Dron, MSc; Anna Heath, PhD; Maureen Meade, MD, MSc; Ryan Zarychanski, MD, MSc; Raymond Lee, MSc; Gabriel Tremblay, DBA; Edward J. Mills, PhD; Yannis Jemiai, PhD; Cyrus Mehta, PhD; J. Kyle Wathen, PhD

Park JJH et al. JAMA Network Open. 2022 Jul 1;5(7):e2221140-.
https://jamanetwork.com/journals/jamanetworkopen/article-abstract/2794156

PRESENTATION OBJECTIVES

01

Establish common terminologies

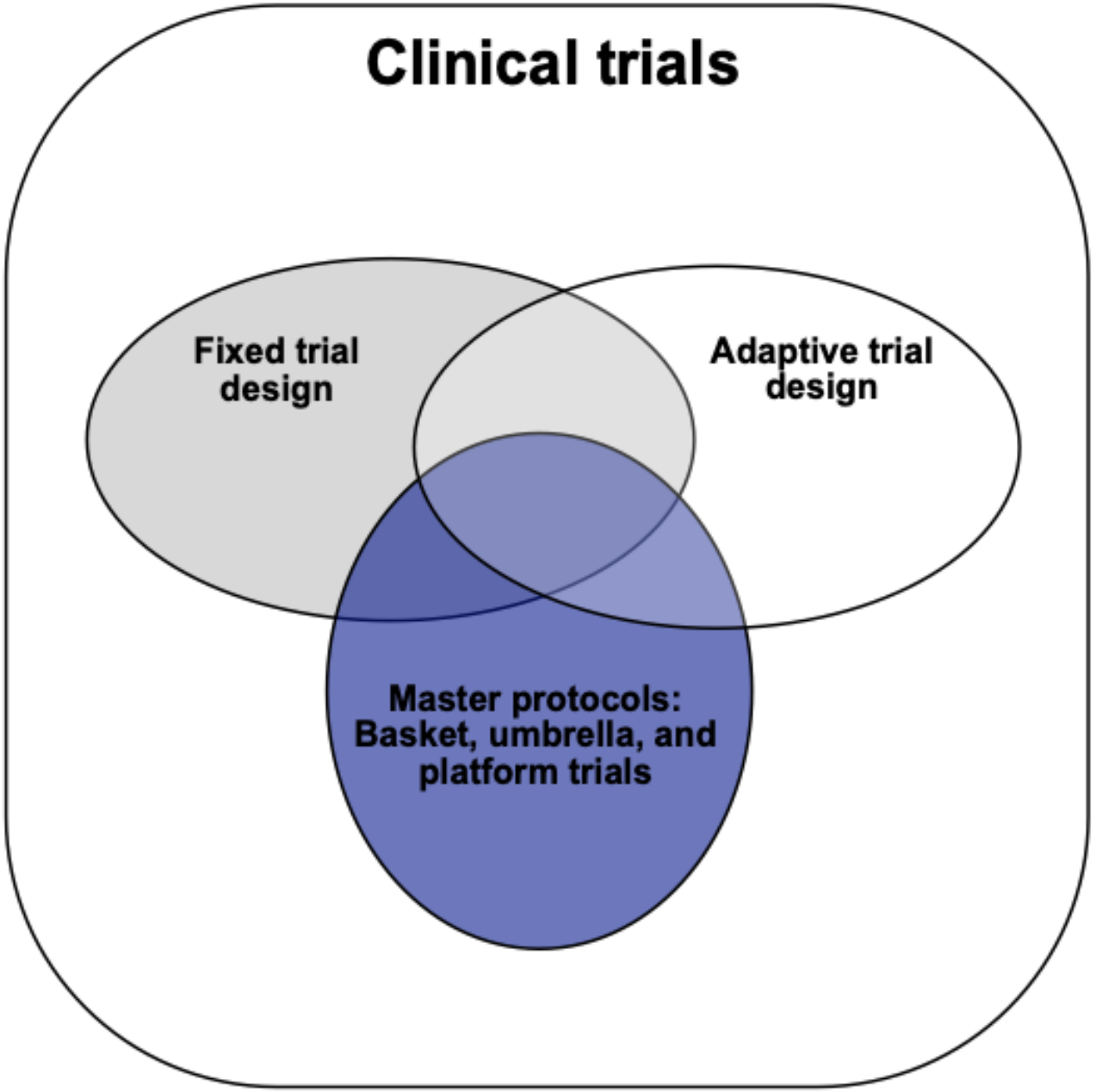
- Adaptive trial designs
- Master protocols
- Platform trials

02

Provide an overview of methods and key findings from our economic evaluation

03

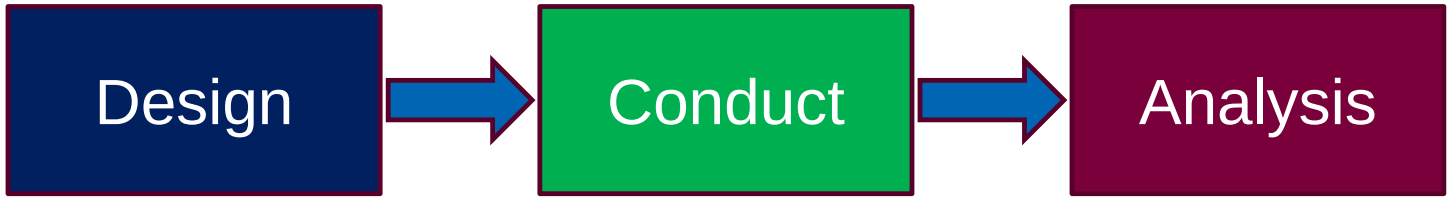
To leave the audience with some recommendations


Clinical trials
Fixed trial design
Adaptive trial design
Master protocols: Basket, umbrella, and platform trials

CONVENTIONAL APPROACH: FIXED SAMPLE DESIGNS

- When we think of clinical trials, we mostly imagine *"one-shot"* trials
  - 2-arm trial with a fixed sample size and one final analysis

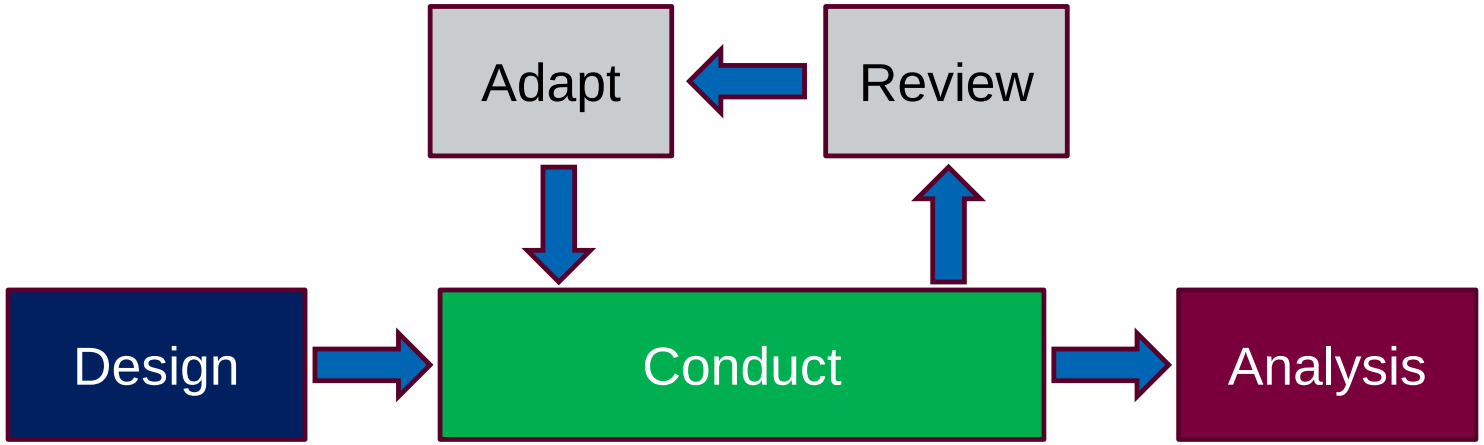
- If we can predict the future, no problem
  - Predicting the future is hard and uncomfortable in reality



The figure adapted from Pallmann et al., BMC medicine. 2018 Dec;16(1):1-5.

ADAPTIVE TRIAL DESIGNS

- An overarching terminology for trials that use accumulating data in a formal way
  - The data used as a formal guide
    - Examples: Sequential designs & response adaptive randomization



The figure adapted from Pallmann et al., BMC medicine. 2018 Dec;16(1):1-5.

ADAPTIVE TRIAL DESIGNS VS PLATFORM TRIAL DESIGNS

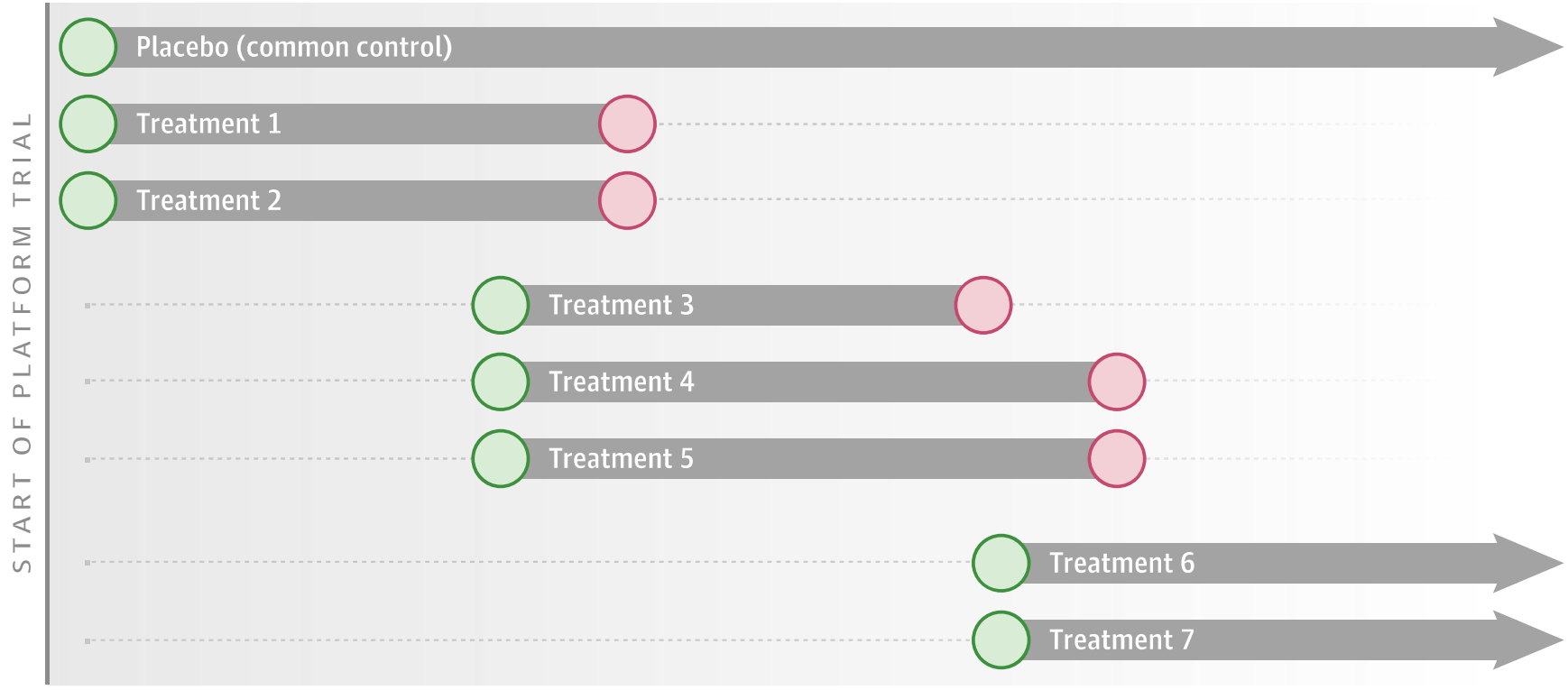
The term, ***"platform trials",*** refers to trials designed with flexibility of adding new interventions.

- Interventions can enter and leave at different time

They use a series of documents called "***master protocol"*** that outline trial plans and standard operating procedures (SOPs) for evaluation of multiple interventions

PLATFORM TRIAL DESIGNS

Figure. Illustrative Example of a Platform Trial Schema



The platform initially starts as a 3-group randomized clinical trial with placebo as a common control, and new treatments are introduced into the platform over time. Green circles indicate start of random assignment of participants to a new intervention, and red circles indicate stopping of assignment and/or testing of that intervention.

Park JJH et al. How to Use and Interpret the Results of a Platform Trial: Users' Guide to the Medical Literature. JAMA. 2022 Jan 4;327(1):67-74.

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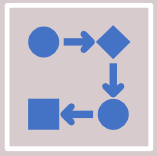


Platform trials + adaptive trial designs = Adaptive platform trials

Platform trials + fixed sample trial designs = Non-adaptive platform trials

PREVIOUS EVALUATIONS OF PLATFORM TRIAL DESIGNS

- Many published studies have described the statistical efficiencies of platform trials over conventional trial approaches
- Limited guidance on resources to establish and maintain platform trials
- Statistical efficiencies important but not everything
  - Due to large scale and perpetual nature of platform trials, the set-up is often more complex and requires more resources
    - **Cost and time considerations are important**

CHALLENGES WITH PREVIOUS EVALUATIONS

The value of platform trial as a strategy muddled with different statistical strategies that were considered

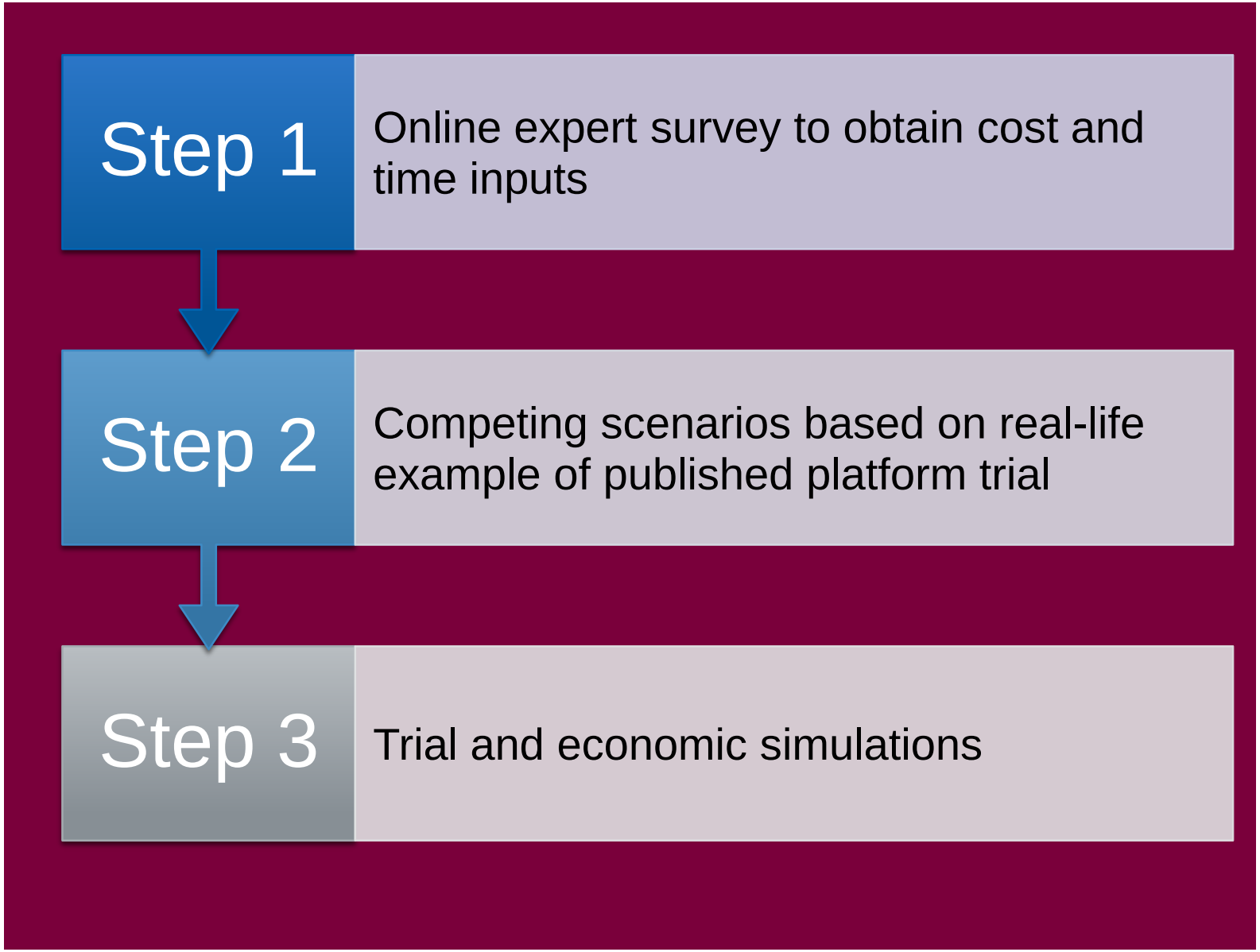
- **What design do we use?**
  - *Fixed sample design* ***vs*** *sequential designs*
  - *Static allocation* ***vs*** *dynamic allocation* (response adaptive randomization)
  - *Concurrent data* ***vs*** *non-concurrent data*

- **At the design stage, it is not possible predict**
  - *The number of interventions*
  - *The timing of their clinical evaluation*

ECONOMIC EVALUATION

- What are the costs and time requirements conducting a single platform trial versus multiple independent trials?

STUDY METHODS OVERVIEW



SAMPLING FRAMEWORK

REVIEW Open Access

Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols

Jay J. H Park[1,2], Ellie Siden[2], Michael J. Zoratti[3], Louis Dron[2], Ofir Harari[2], Joel Singer[4,5], Richard T. Lester[1], Kristian Thorlund[2,3,6] and Edward J. Mills[2,3,6*]

Park et al., BMC Trials 2019 20:572

- Survey administered to international experts with publication record on platform trials and master protocols using purposive sampling
- Each record individually reviewed to extract an email list of first, last and corresponding authors for our survey

ONLINE EXPERT SURVEY RESULTS

- Unfortunately, there was a low response rate
  - 16 (10%) out of 146 responded

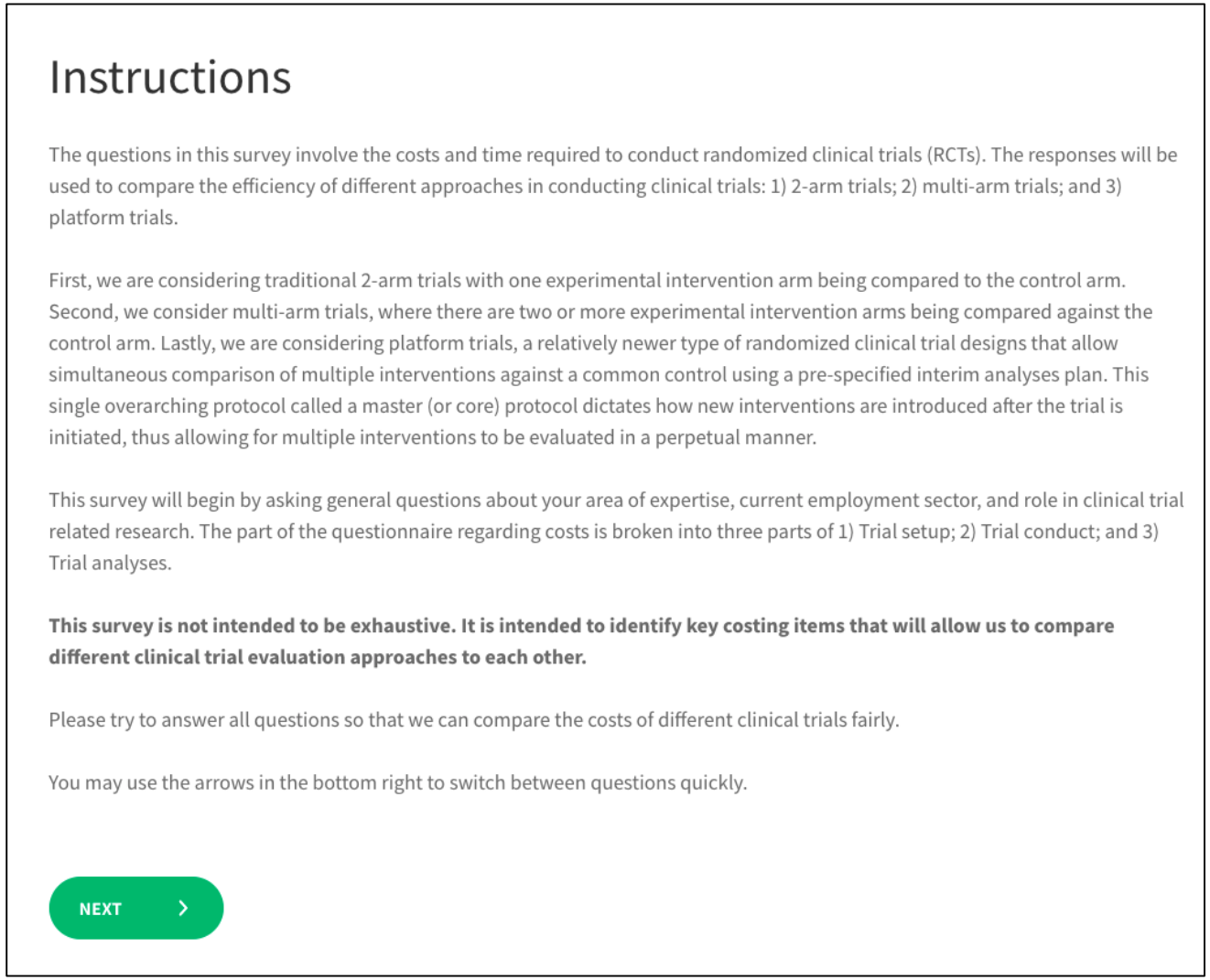
- Most respondents were from North America (69%)
  - Indicated their current employment being in the private sector (69%)
  - Had clinical trial experience in oncology (69%)

COST AND TIME PARAMETERS

1. **Trial set up (n=7)**
   - Protocol development
   - Study approval
   - Database and site set-up

2. **Trial conduct (n=6)**
   - Recruitment and follow-up cost
   - Database and site management
   - Adding a new arm

3. **Trial analysis (n=2)**
   - Interim and final analyses



Instructions

The questions in this survey involve the costs and time required to conduct randomized clinical trials (RCTs). The responses will be used to compare the efficiency of different approaches in conducting clinical trials: 1) 2-arm trials; 2) multi-arm trials; and 3) platform trials.

First, we are considering traditional 2-arm trials with one experimental intervention arm being compared to the control arm. Second, we consider multi-arm trials, where there are two or more experimental intervention arms being compared against the control arm. Lastly, we are considering platform trials, a relatively newer type of randomized clinical trial designs that allow simultaneous comparison of multiple interventions against a common control using a pre-specified interim analyses plan. This single overarching protocol called a master (or core) protocol dictates how new interventions are introduced after the trial is initiated, thus allowing for multiple interventions to be evaluated in a perpetual manner.

This survey will begin by asking general questions about your area of expertise, current employment sector, and role in clinical trial related research. The part of the questionnaire regarding costs is broken into three parts of 1) Trial setup; 2) Trial conduct; and 3) Trial analyses.

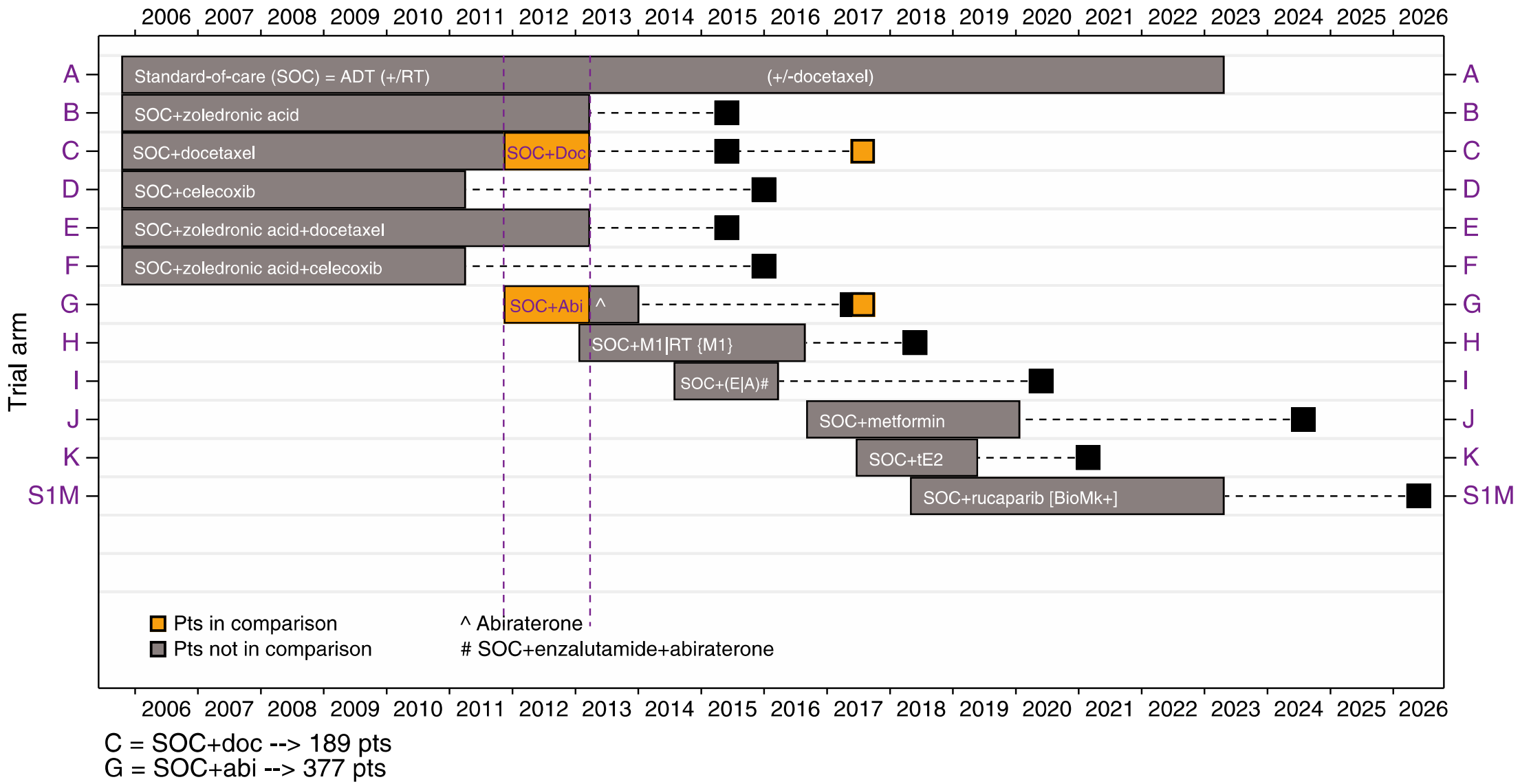
This survey is not intended to be exhaustive. It is intended to identify key costing items that will allow us to compare different clinical trial evaluation approaches to each other.

Please try to answer all questions so that we can compare the costs of different clinical trials fairly.

You may use the arrows in the bottom right to switch between questions quickly.

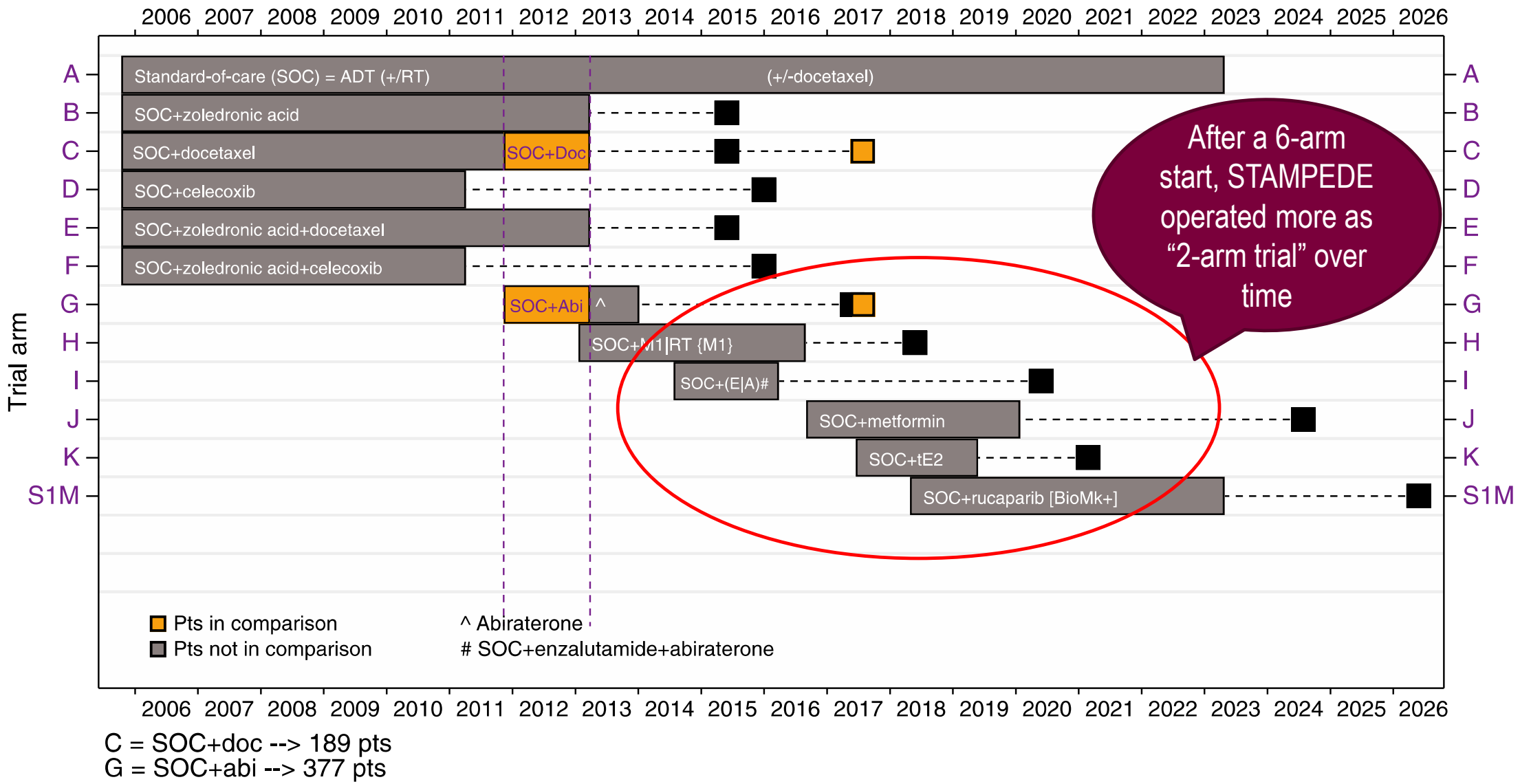
NEXT ›

- STAMPEDE is the first platform trial to be ever conducted
- Started to evaluate systematic therapies for advanced prostate cancer in 2005
  - Still ongoing!
    - Not sure when it will finish!
- 10 interventions have entered the platform trial thus far



C = SOC+doc --> 189 pts
G = SOC+abi --> 377 pts

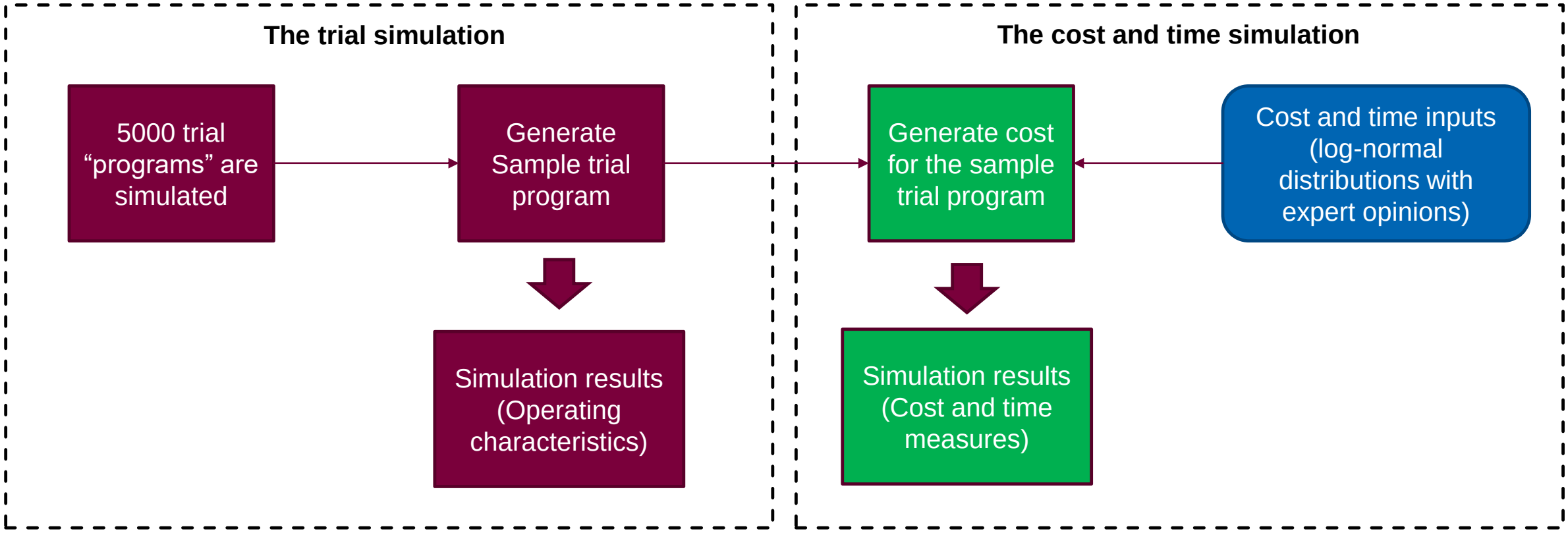
Source: Sydes MR. et al 2018 May 1;29(5):1235-48.



Source: Sydes MR. et al 2018 May 1;29(5):1235-48.

SIMULATION OVERVIEW

- Built a simulation model that used secondary literature and anonymous online survey to inform model inputs.

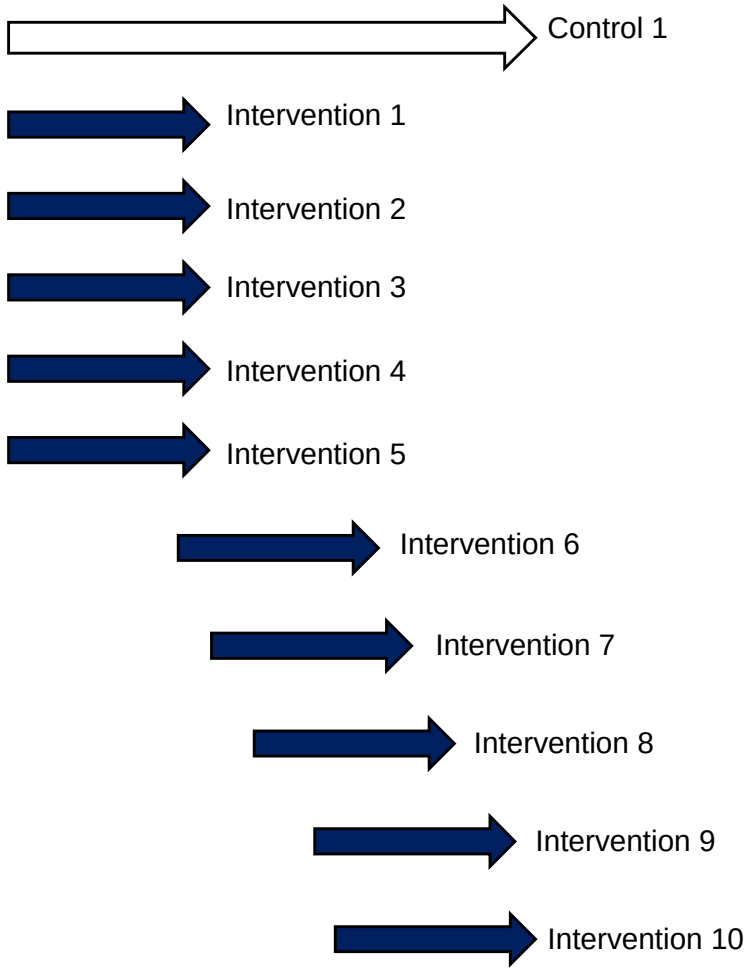


TRIAL DESIGN OF STAMPEDE

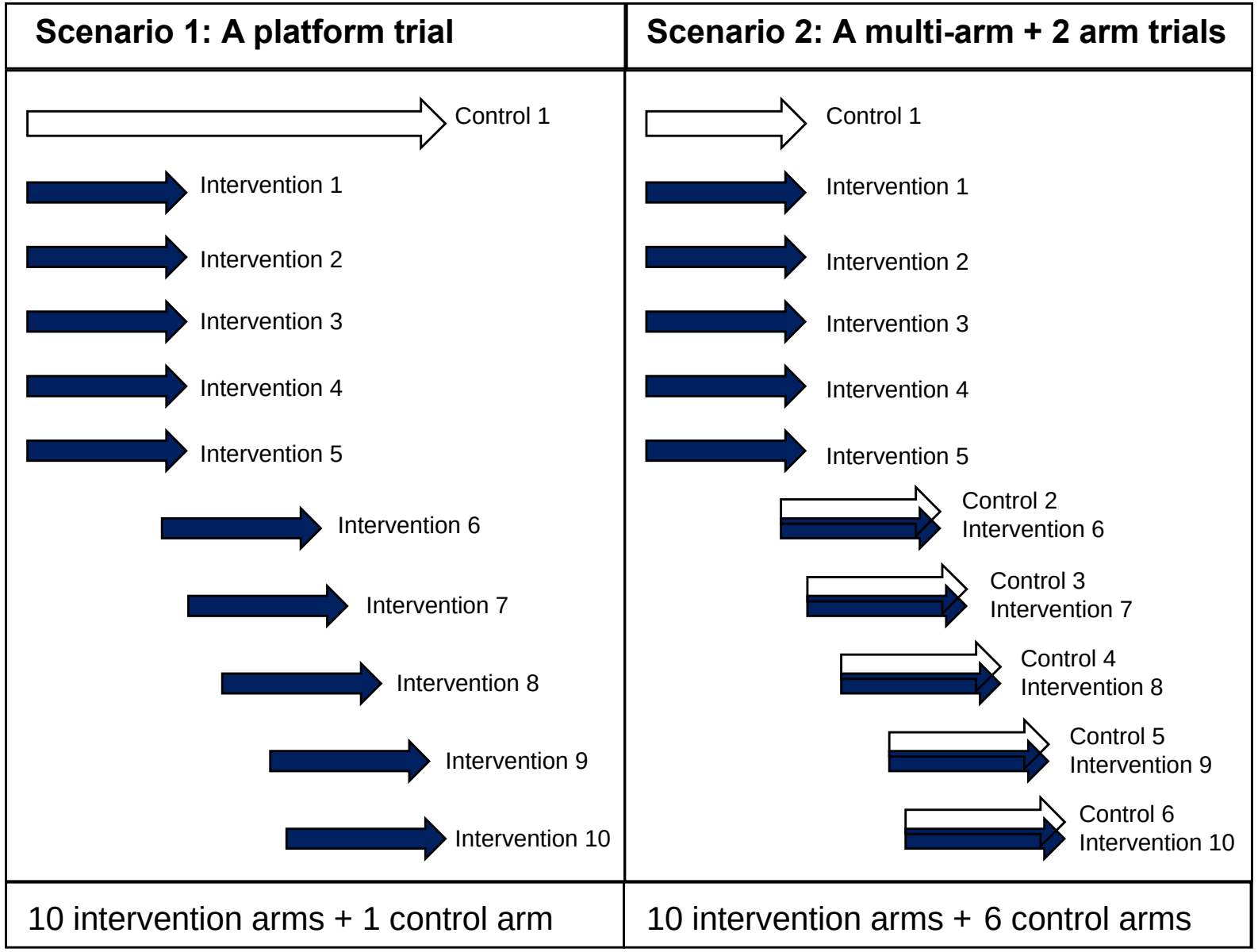
- An event-based multi-arm, multi-stage platform trial with a seamless phase IIB/III design
- Phase IIB: 3 futility interim analyses based on failure-free survival (FFS)
- Phase III: Final analysis based on overall survival (OS)

Trial stages	Accrual target
Analysis 1	113 FFS events in concurrent control
Analysis 2	215 FFS events in concurrent control
Analysis 3	334 FFS events in concurrent control
Analysis 4	405 deaths in concurrent control

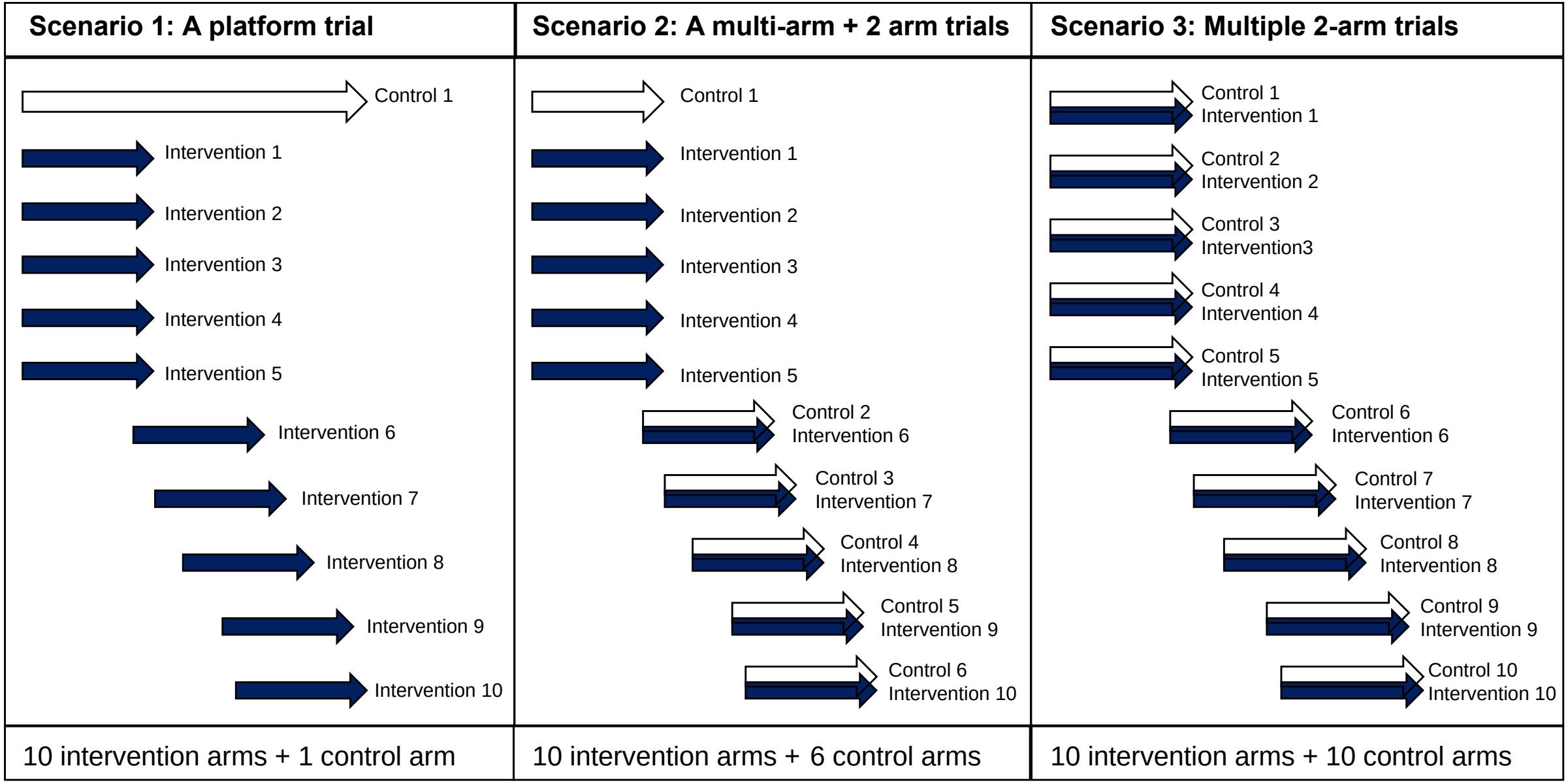
Scenario 1: A platform trial



10 intervention arms + 1 control arm



- Same trial design features used across all scenarios
- Only difference was how new interventions (6-10) would be evaluated


Scenario 1: A platform trial
Control 1
Intervention 1
Intervention 2
Intervention 3
Intervention 4
Intervention 5
Intervention 6
Intervention 7
Intervention 8
Intervention 9
Intervention 10
10 intervention arms + 1 control arm
Scenario 2: A multi-arm + 2 arm trials
Control 1
Intervention 1
Intervention 2
Intervention 3
Intervention 4
Intervention 5
Control 2
Intervention 6
Control 3
Intervention 7
Control 4
Intervention 8
Control 5
Intervention 9
Control 6
Intervention 10
10 intervention arms + 6 control arms
Scenario 3: Multiple 2-arm trials
Control 1
Intervention 1
Control 2
Intervention 2
Control 3
Intervention3
Control 4
Intervention 4
Control 5
Intervention 5
Control 6
Intervention 6
Control 7
Intervention 7
Control 8
Intervention 8
Control 9
Intervention 9
Control 10
Intervention 10
10 intervention arms + 10 control arms

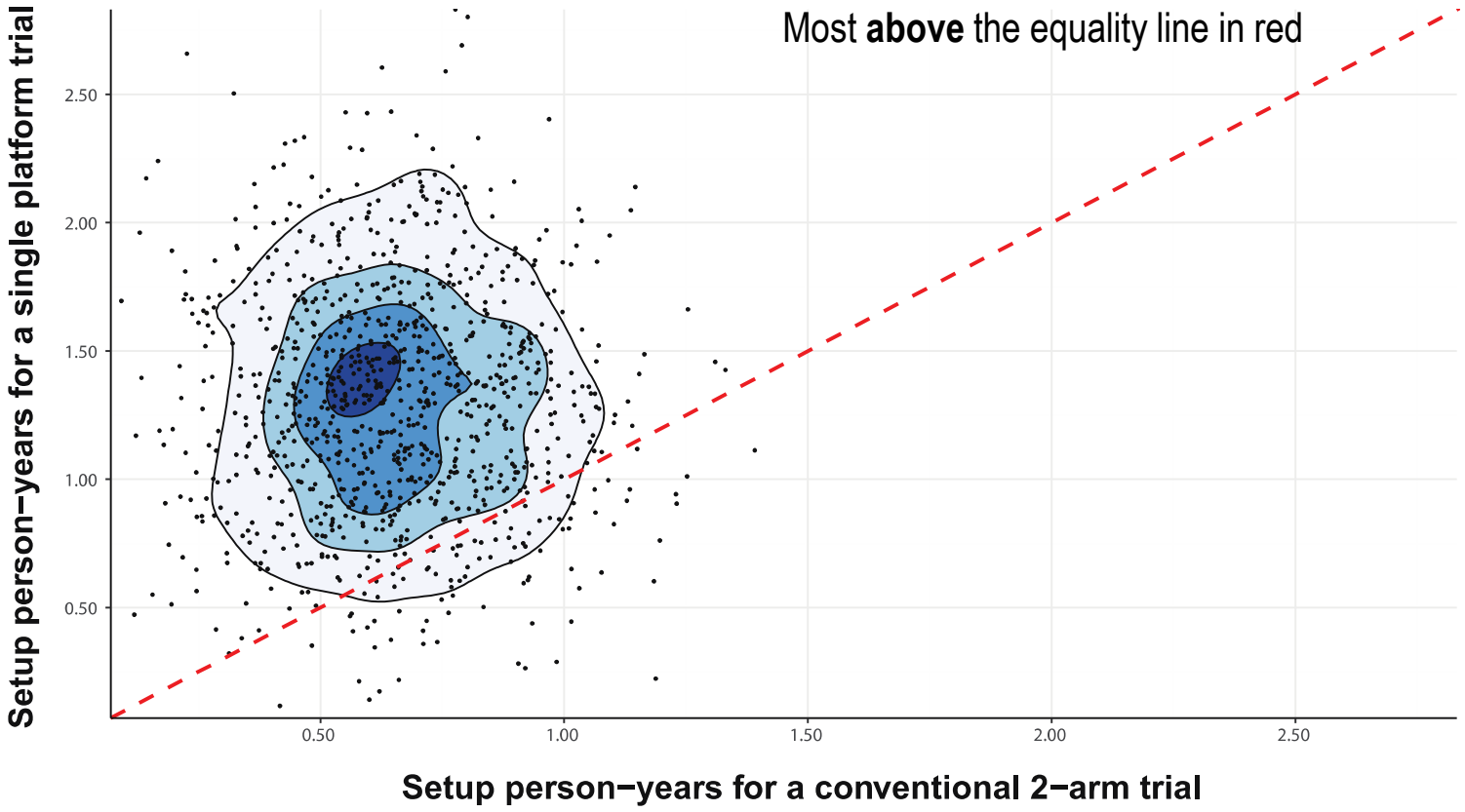
COST AND TIME OUTPUTS

- **Set-up cost and time**
  - Single study set up
  - Total set-up cost and time

- **Total cost and time** (Set-up + Conduct + Analysis)
  - 10 interventions
  - The first 5 interventions (*recall STAMPEDE started as a 6-arm trial*)
  - The last 5 interventions

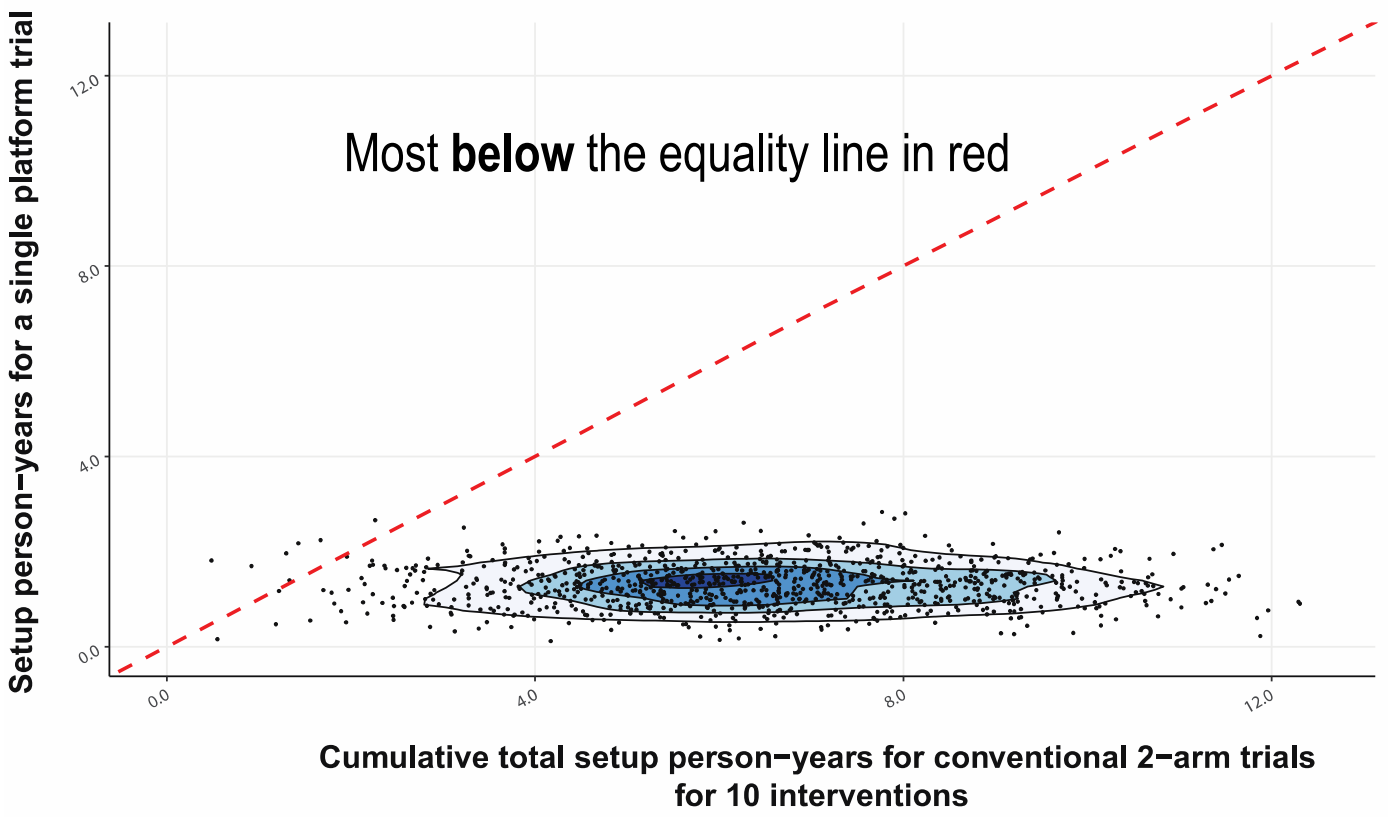
SET UP COMPARISON: A SINGLE PLATFORM TRIAL VS A SINGLE 2-ARM TRIAL

- Considerably less time and cost in setting up a single trial for conventional trials
- The median difference in set-up cost for a single 2-arm trial was -48% (IQR: -53%, -46%)



SET UP COMPARISON: A SINGLE PLATFORM TRIAL VS 10 INDEPENDENT TRIALS

- Adding a new arm much cheaper than starting a new trial
  - On average $75,626 (SD: $43,528)
- 2-arm trials had a median increase cumulative set-up cost of 391% (IQR: 365%, 438%)

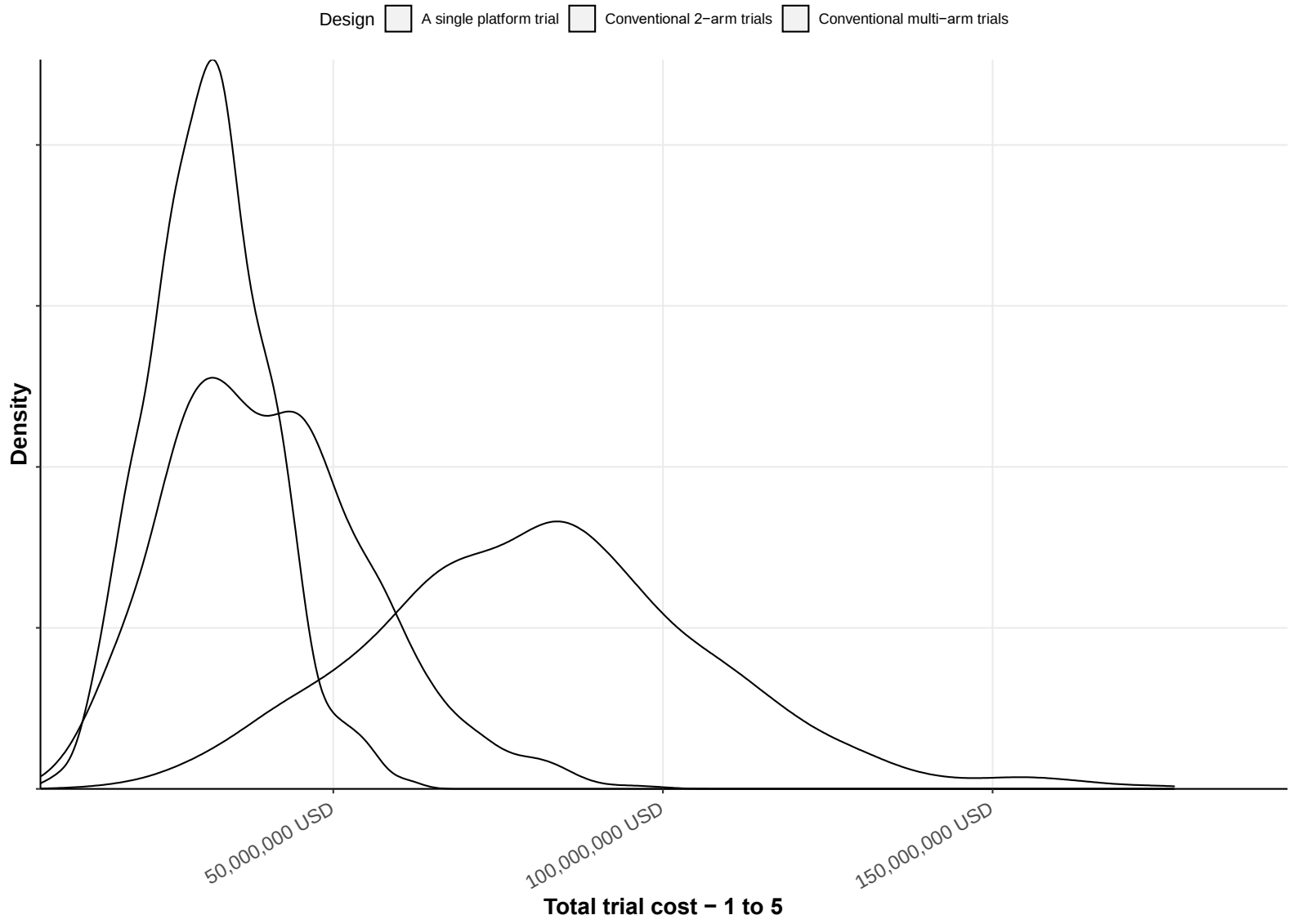


COST COMPARISON: FIRST 5 INTERVENTIONS

Scenario 2 vs platform trial
28% (5.5%; 50.1%)

Scenario 3 vs platform trial
158.4% (136.9%; 184.1%)

% difference: median (IQR)

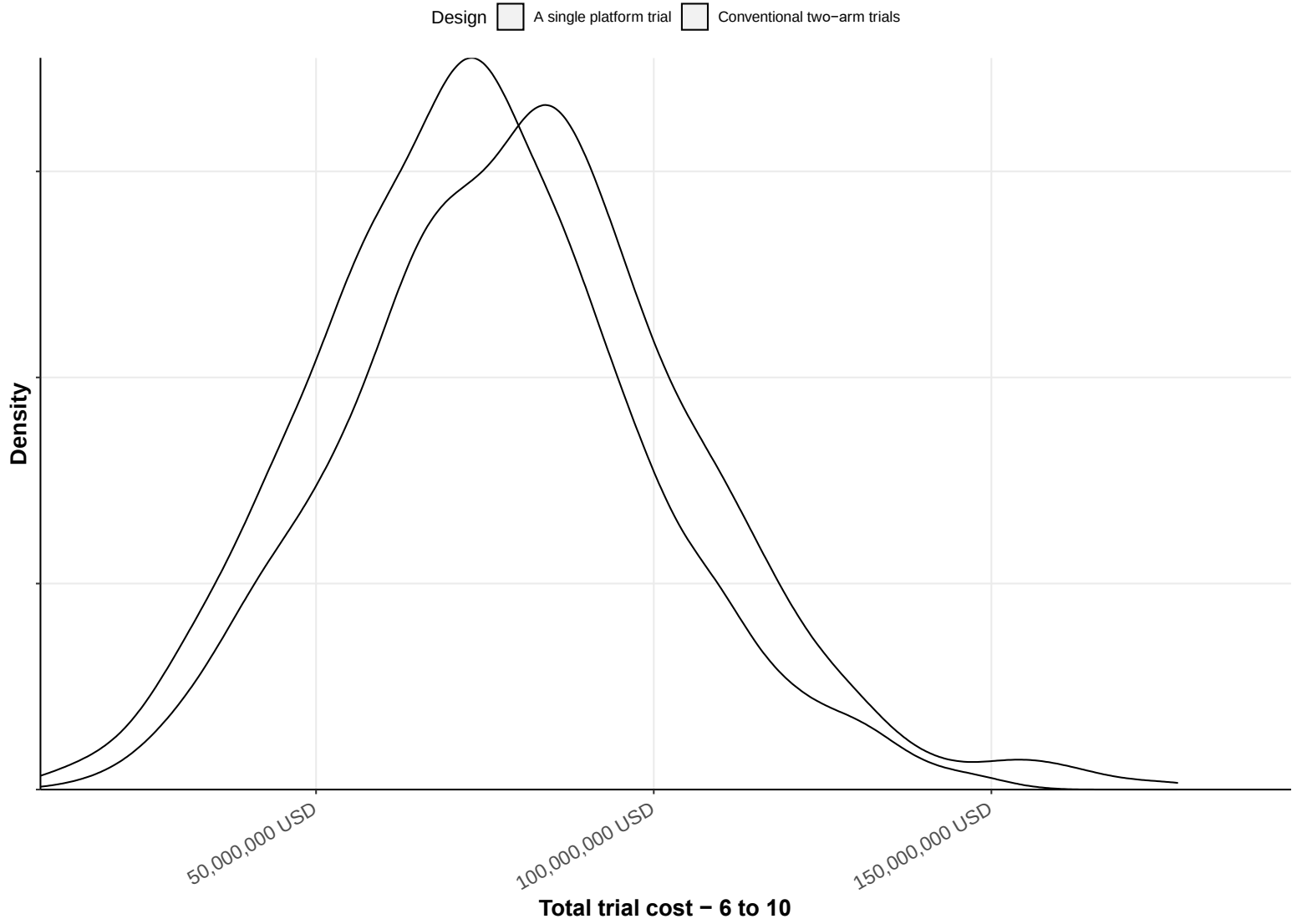


MARGINAL COST COMPARISON: LAST 5 INTERVENTIONS

Scenario 2/3 vs platform trial*
12.6% (2.1%; 22.6%)

% difference: median (IQR)

**Recall in both scenario 2 and 3, new arms were assumed to be evaluated as 2-arm trial*



TOTAL COST COMPARISON: 10 INTERVENTIONS

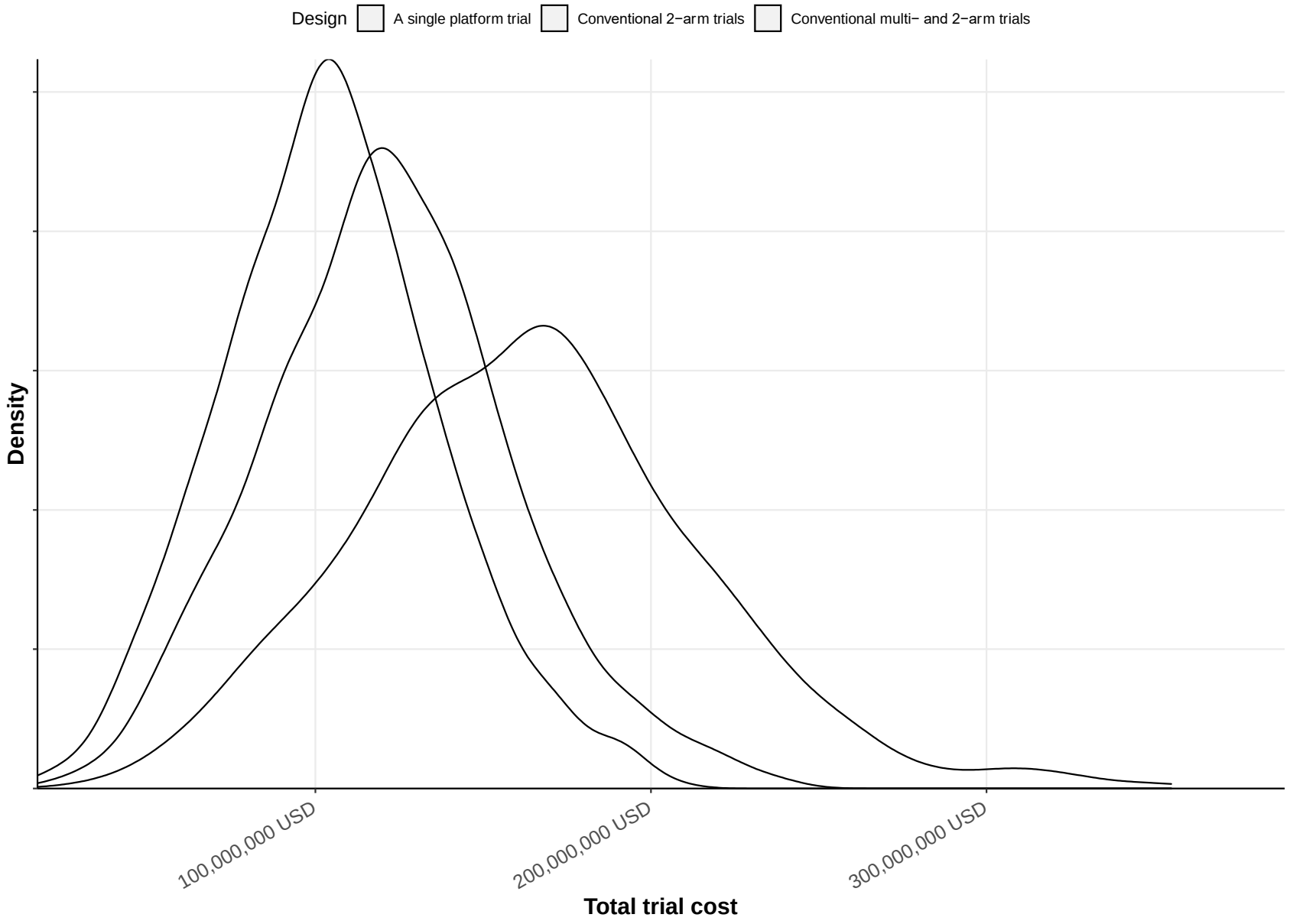
Scenario 2 vs platform trial

17.4%
(12.1%; 22.5%)

Scenario 3 vs platform trial

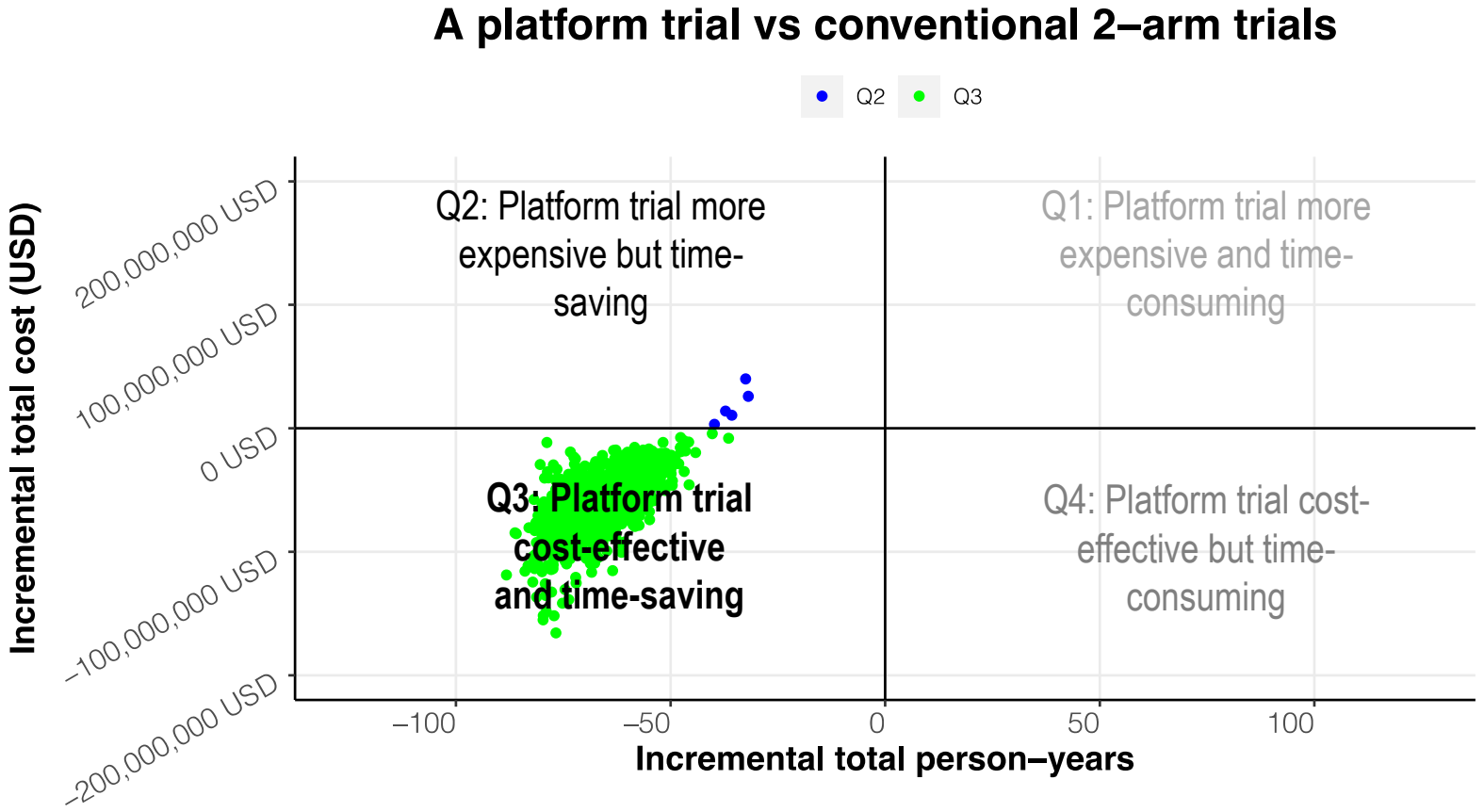
57.7%
(43.1%; 69.9%)

% difference: median (IQR)



INCREMENTAL TOTAL COST/TIME COMPARISON: A SINGLE PLATFORM TRIAL VS MULTIPLE 2-ARM TRIALS (10 INTERVENTIONS)

- Always required less time measured by total person-years
- Cost effective and time-saving (Q3) in 97.1% of all simulations (n=5000)



THE PLATFORM TRIAL MODEL

- ***Certainly not easy but also not impossible!***

- ***Longer set-up and initial cost for platform trials***
  - Trial simulation required to evaluate operating characteristics
  - Several logistical and operational considerations required

- ***In the long-run, it's more efficient and time/cost saving***
  - Sample size savings from having a common control arm
  - Redundancies in trial set-up and close out avoided, etc

Securing sustainable funding is the biggest challenge (imo)

RECOMMENDATIONS

- ***Every platform trial is different – Multiple ways to build and maintain an "airport"***
  - Perhaps that's what makes it hard
    - But there is a tendency to over-complicate things (IMO)
- ***Devil is in the detail***
  - Let's be honest about different trade-offs
- ***Need time and resources to plan***
  - Sample size calculations are easy for a reason
  - Innovation takes time and resources

RECOMMENDATIONS

- ***We don't have to complicate things because other platform trials were complicated***
  - Let's be clear about estimands and estimators
    - The main statistical efficiency comes from multi-arm aspect of platform trial

- ***We need resources and time to plan***
  - Statisticians don't grow on trees and are not free
  - Sample size calculations are quick to do. Simulations usually are not

RECOMMENDATIONS

- ***We need to work in a cross-functional team, and we need to advocate for structural changes***
  - There will be growing pains
  - Without the structural changes, I don’t think we will get there

https://evelazarus.com/yvr-fifty-years-ago/

Thank you!

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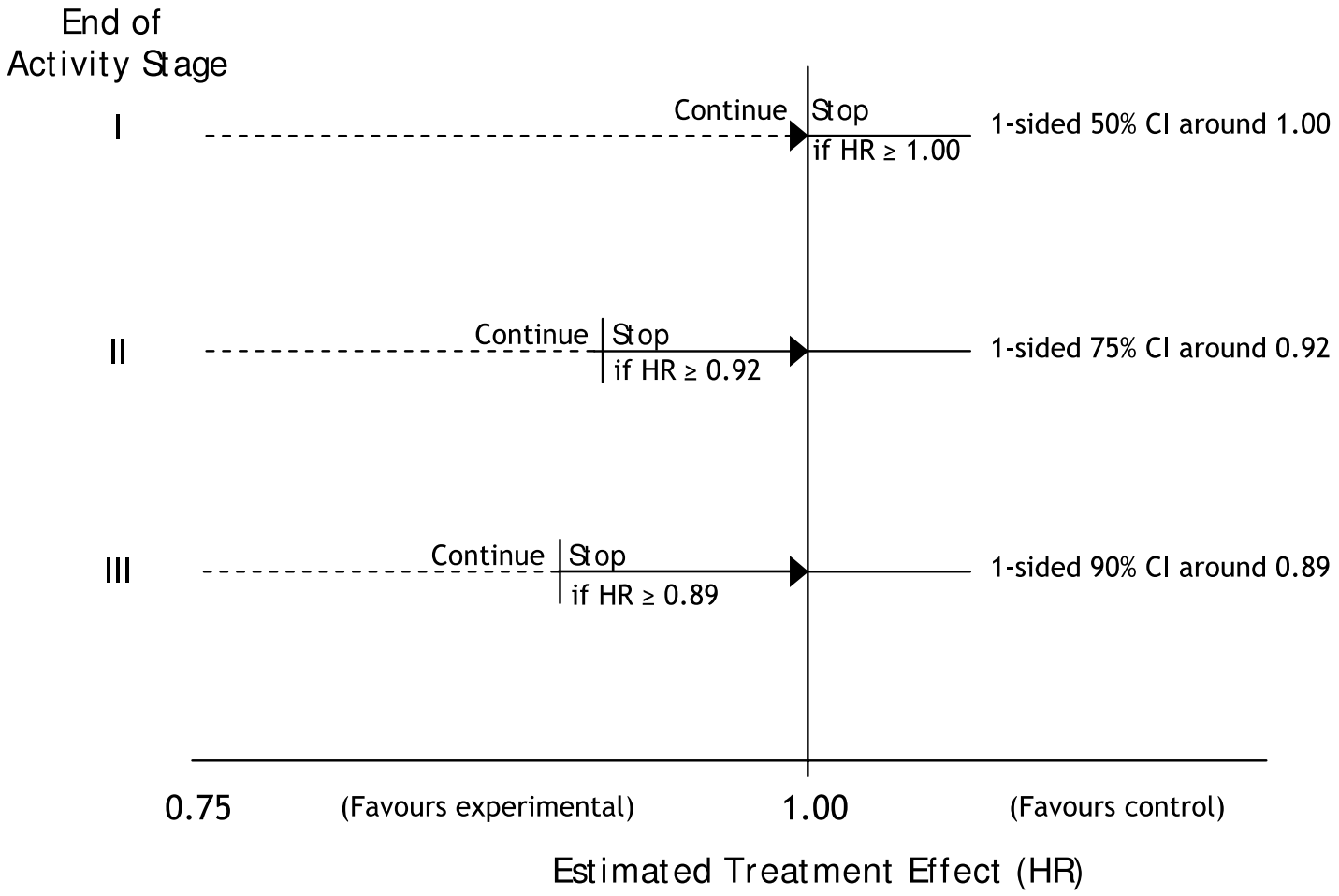
DECISION RULES FOR EACH STAGE



- Critical HR (point estimate) used to drop or graduate interventions onto the next stage
- If an intervention showed a HR that fell to the right of the cut-off, enrollment stopped for futility

Sydes et al. Trials. 2009 Dec;10(1):1-6.

Parameter	Two-arm trial: Mean (SD)	Multi-arm trial: Mean (SD)	Platform trial: Mean (SD)
Set-up cost requirements (USD 2021)			
Trial protocol development	123,333 (23,245)	136,667 (22480)	155,667 (34347)
Trial approvals	151,183 (28126)	165,367 (27200)	172,250 (38538)
Database development	32,500 (30,406)	36,667 (34763)	42,500 (30625)
Site set-up (per site)*	9440 (14086)		
Set-up time requirements (months)			
Trial protocol development	3.92 (1.98)	5.09 (2.26)	8.78 (3.83)
Trial approvals	3.67 (2.06)	4.00 (2.40)	6.50 (4.14)
Database development	2.80 (1.30)	3.20 (1.30)	5.40 (1.95)

Parameter	Two-arm trial: Mean (SD)	Multi-arm trial: Mean (SD)	Platform trial: Mean (SD)
Trial conduct cost requirements (USD 2021)*			
Recruitment (per patient)	1300 (476)		
Monthly follow-up cost per patient	313 (132)		
Monthly site management per site	5000 (3162)		
Monthly database management cost	2500 (1061)		
Trial analysis cost (USD 2021)*			
An interim analysis (per arm)	12883 (29417)		
A final analysis (per arm)	42750 (37053)		
Cost required to add a new arm (USD 2021)**			
Addition of a new arm	--	--	75626 (43528)
Time required to add a new arm (months)**			
Addition of a new arm	--	--	3.00 (1.73)

Cost (million USD) and time (years) requirements	Scenario 1: A platform trial Mean (SD)	Scenario 2 vs 1		Scenario 3 vs 1	
		Mean Difference (SD)	% difference Median (IQR)	Mean difference (SD)	% difference Median (IQR)
Total trial cost for all interventions (1-10)	104.951 (32.512)	17.154 (10.569)	17.4% (12.1%; 22.5%)	58.452 (24.942)	57.7% (43.1%; 69.9%)
Total trial cost for first five treatments (1-5)	31.356 (9.022)	9.047 (10.159)	28% (5.5%; 50.1%)	50.345 (17.957)	158.4% (136.9%; 184.1%)
Total trial cost for last five treatments (6-10)	73.594 (23.893)	8.107 (10.6)	12.6% (2.1%; 22.6%)	8.107 (10.6)	12.6% (2.1%; 22.6%)