

# Study Design Considerations for Adaptive Platform Trials

ICPE 2023 Workshop on Pragmatic Trials

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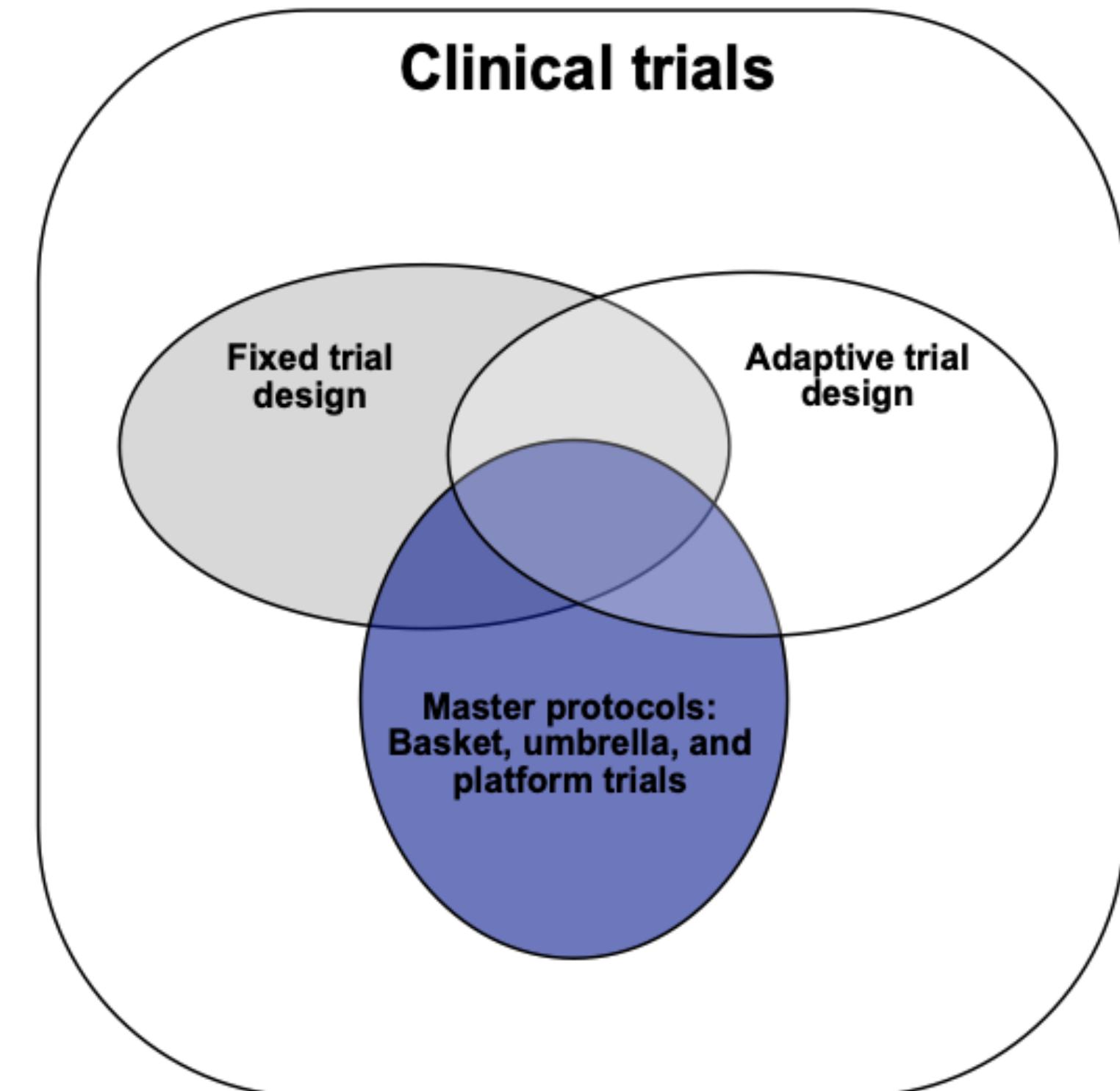
August 23, 2023

# Disclosure

- No funding was received for preparation of this course
- I am currently employed by Core Clinical Sciences that provides research consulting services in clinical trial designs and evidence synthesis

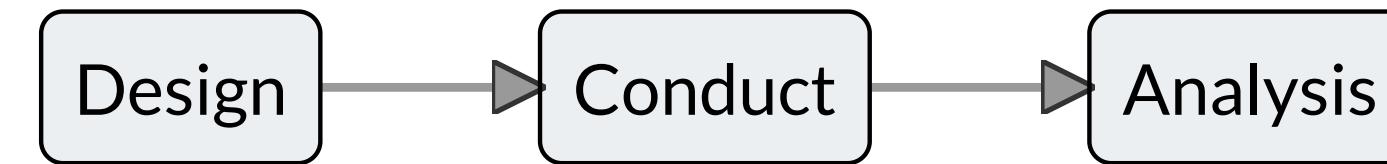
# Intended Learning Objectives

1. To establish common terminologies:
  - Adaptive trial designs
  - Master protocols
  - Platform trials
2. To discuss key design considerations of adaptive platform trials
3. To discuss a case study on adaptive platform trial for COVID-19 therapeutic outpatient research
  - The TOGETHER Trial
4. To leave the audience with some recommendations



# Conventional Trial Designs (Fixed Sample Size Designs)

- When we think of clinical trials, we mostly imagine “one-shot” trials
- A 2-arm clinical trial with a fixed sample size and one final analysis at the end



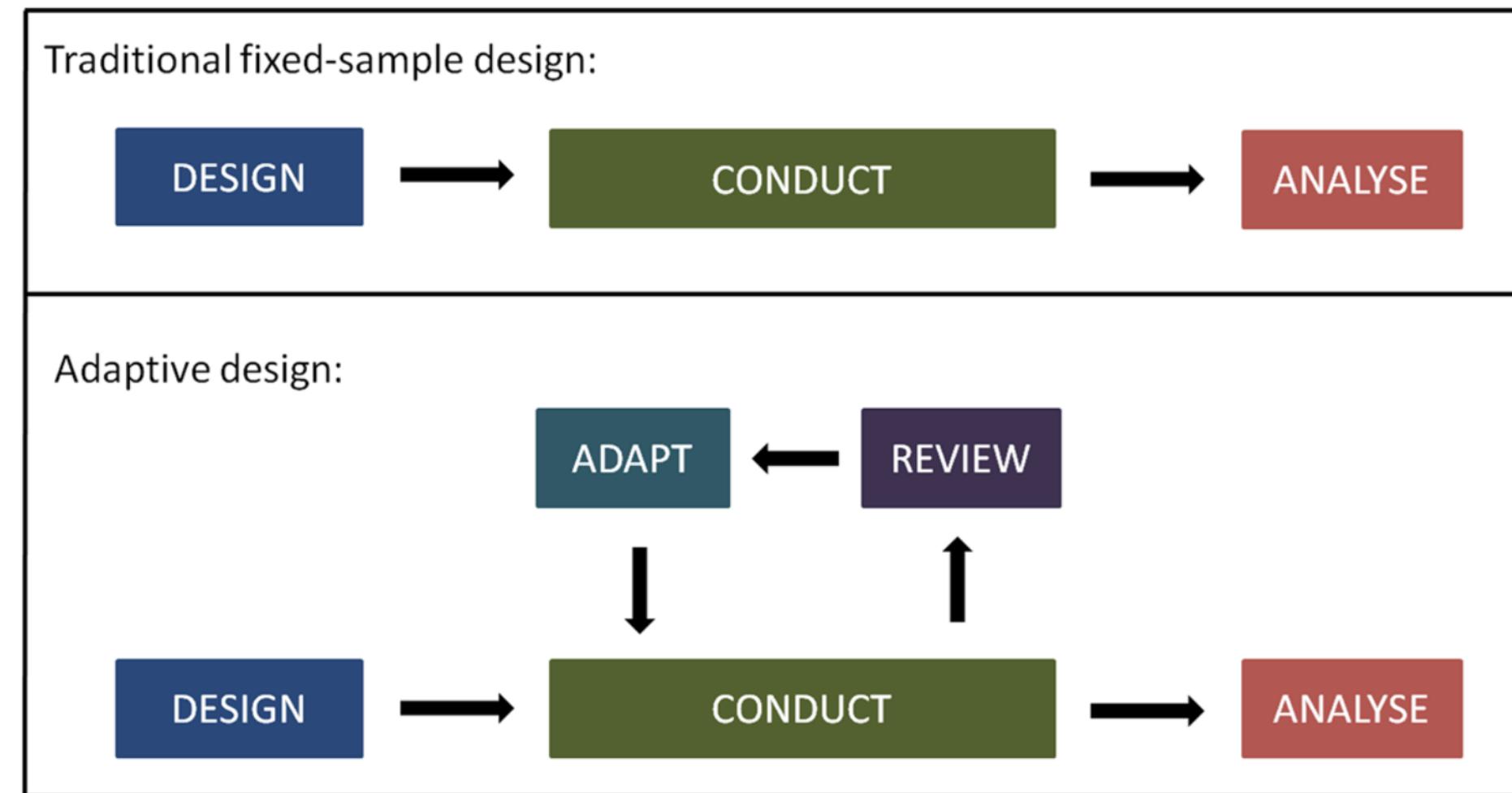
# Main Challenge with the Conventional Approach

- There are many unknowns. It is extremely difficult to **guess** right or at least uncomfortable making the guesses
- In conventional trials, we only get one guess
  - If you can predict the future, no problem with the conventional approach
- How do we plan clinical trials when we don't know much about what we are studying? (e.g., COVID-19 at the start of 2020)

# Adaptive Trial Designs

- The term, **adaptive trial designs** is an umbrella term that refers to a group of clinical trial designs that offer pre-planned opportunity to modify aspects of an ongoing trial based on accumulating trial data
- **The unifying property of adaptive trial designs:**
  - Use of accumulating interim data based on **pre-specified plans** that are developed and outlined *a priori*
- **The main motivation for adaptive trial designs is to learn from the data as they are collected during the trial and act accordingly**

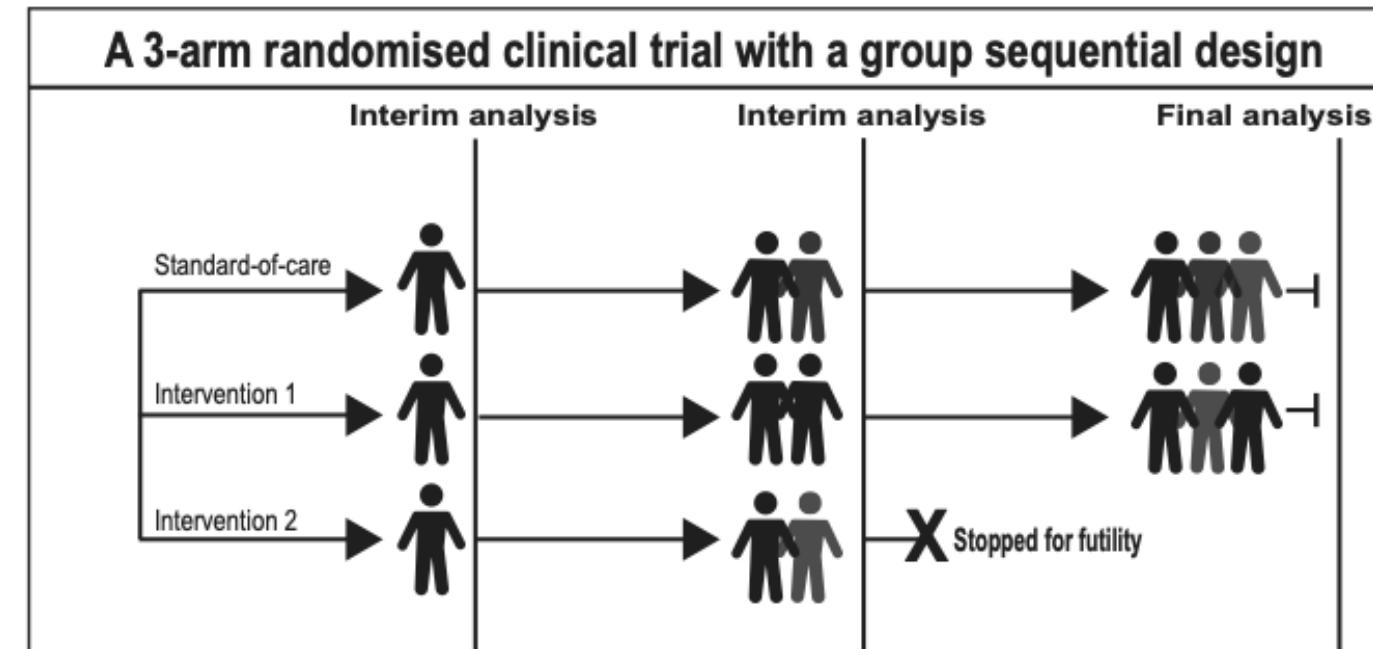
# Comparison vs Conventional Trial Designs



- We conduct one or more of the planned interim analyses according to the plan developed during the design stage

# Sequential Designs

- Refer to a type of trial designs that allow you to stop enrollment early (most common)
- You can decide to allow for early stopping based on superiority and/or futility
- **Superiority:** There is overwhelming evidence that the treatment works
- **Futility:** There is underwhelming evidence for treatment



- ## Motivation for sequential designs
- Fail faster, succeed faster

# Platform Trials

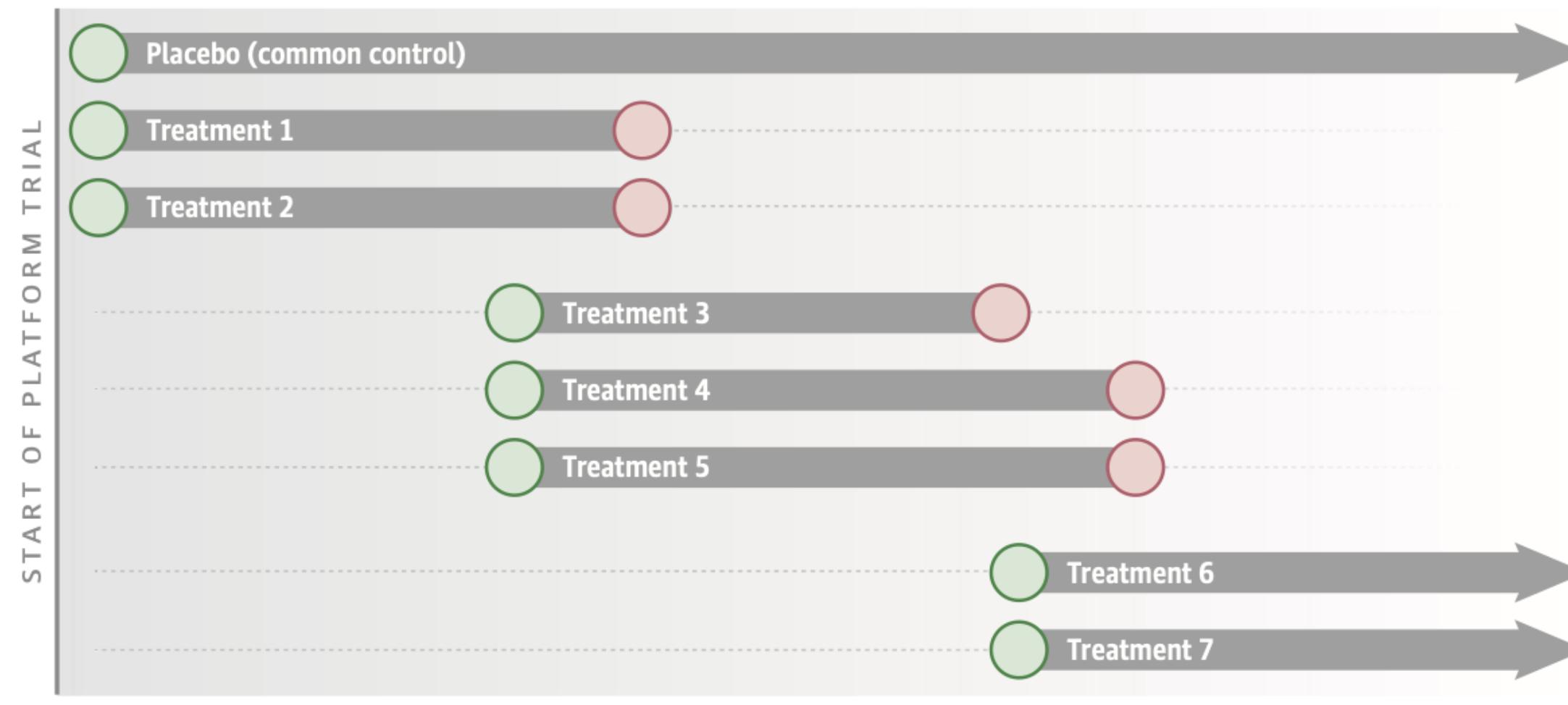
- The term refers to clinical trials designed with flexibility of adding new interventions
- Interventions can enter and leave at different times
- They use a series of documents referred to as “**master protocols**” that outline common plans for evaluation of multiple interventions

*Platform trials + adaptive trial designs = Adaptive platform trials*

*Platform trials + conventional (fixed) trial designs = Conventional (non-adaptive) platform trials*

# Illustration of Platform Trials

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.

# Airport Analogy



# Platform Trial Design Considerations

# Key Design Considerations for Platform Trials

- Active interventions and control group
- Allocation ratio
- Interim analysis plans
- Scientific merits for adding new interventions
- Control of information flow
- Timing of adding new interventions

# Active Interventions and Control Group

- While the number of active interventions will vary over time, platform trials should have a pre-determined maximum number of arms that can be active at a given time
- Operational and feasibility considerations made to determine this number. Too many arms at once makes it very difficult
- Pairwise comparisons against the common control may be preferable rather than testing for a global hypothesis testing

# Allocation Ratio

- Given the multi-arm aspects of platform trials, the probability of being randomized to the control arm can be reduced in platform trials
- It is important to consider the allocation ratio for the control vs the experimental intervention(s) using simulations
- Since we are comparing multiple treatments against the common control, we need adequate control data

# Interim Analysis Plans

Plans for interim analyses should consider:

- When will the first interim analysis occur (burn-in period)?
- How many interim analyses will we conduct? And how frequently?
- What adaptations will be allowed? What are the decision criteria?\*

In addition to these statistical rules, we specify plans to prevent operational biases

- Who will conduct the analyses? Who will be blinded and who will not be?

No one-size-fits-all solution except that

- We should use simulation-guided design to minimize anticipated regrets

# Benefits of Clinical Trial Simulations

- Useful for planning since they allow evaluation of multiple potential scenarios and candidate designs
  - We can use simulations to compare a fixed trial design option to different adaptive trial designs
- With many unknowns and assumptions that need to be made at the trial planning stage, clinical trial simulations can help to avoid trial design decisions that trial investigators would regret later after the trial shows negative findings (areas of **anticipated regret**)

# Scientific Merits for Adding New Interventions

- In addition to statistical considerations, scientific considerations that need to be made for adding new arms
- Better to pre-specify the scientific criteria that will be used to what interventions will be added before an industry partner shows interest in participating
- These scientific merits can be reviewed by an independent scientific working group that includes **patient advocacy groups** and **other scientific stakeholders** not directly involved in the trial

# Scientific Merits for Adding New Interventions

**Table 3 Criteria for potential new research arms**

- Sound rationale, including a robust biological hypothesis and compelling evidence of activity that strongly identifies a need to assess a research approach in the setting studied.
- Positive evidence of mechanisms or synergy of action (or both) in the disease area
- Investigator enthusiasm for the new research arm.
- Pharmaceutical research agents would need to be licensed or be close to being licensed at the time of activation. Without a licensed use for the drug (usually in later disease), data in the target setting are likely to be of limited value.
- Relevant industry partners willing to collaborate and contribute to the trial, if the research arm is a pharmaceutical agent.
- Successful independent peer review as for a new study.
- Recruitment to new arm must not jeopardise completion of the ongoing research arms, e.g. by diluting recruitment excessively. This means that the accrual rate must be better than predicted in the original trial or that other research arms have already stopped accrual early. STAMPEDE is presently recruiting at around 700 patients/year when 500 patients/year were targeted. This permitted capacity to consider new research agents even while all original arms remained open.
- The new comparison must still be relevant when it matures.

## Criteria used in STAMPEDE

- Biological plausibility
- Evidence of potential efficacy
- Industry partnership
- Adding a new arm would not jeopardize recruitment to the ongoing research arms

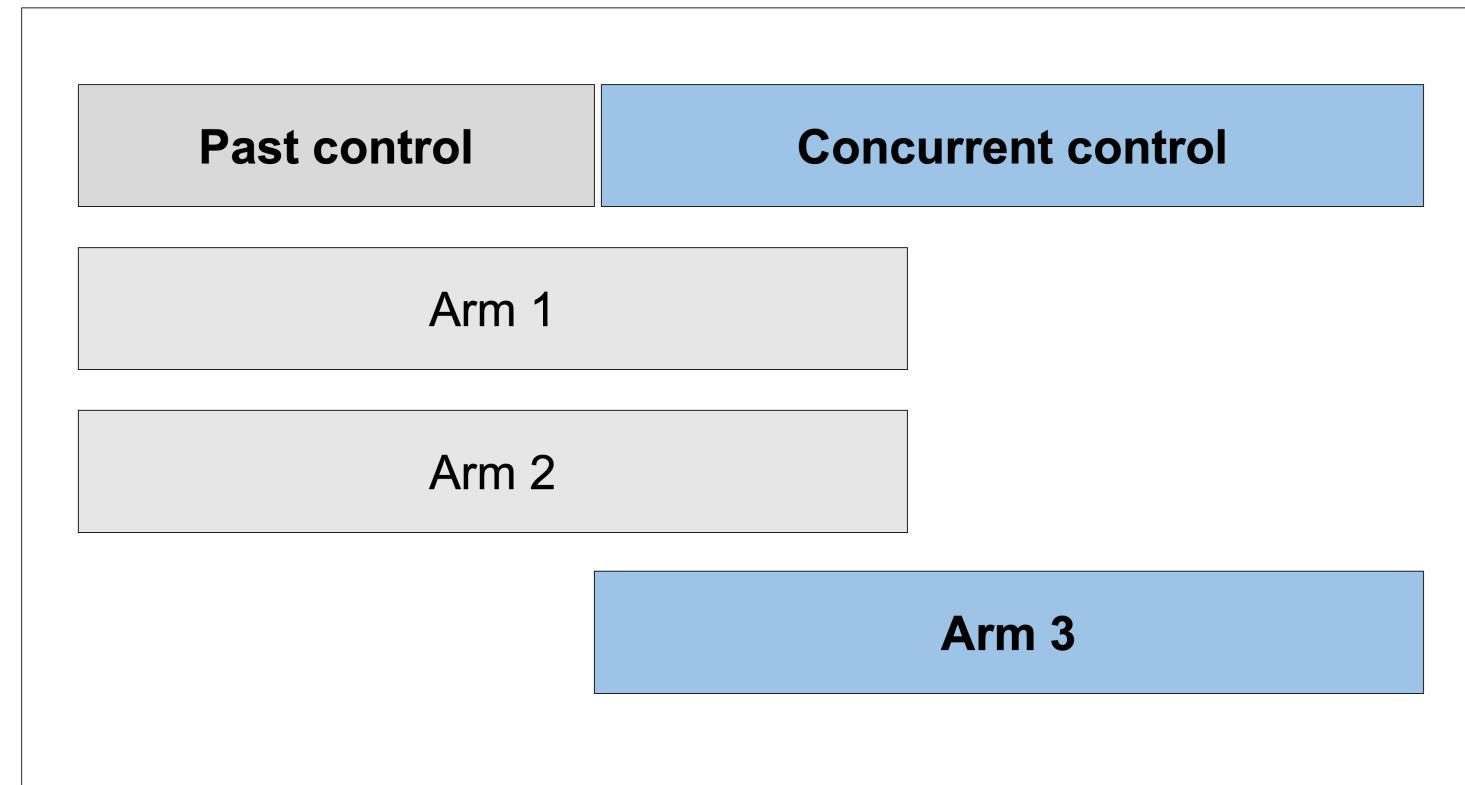
# Control of Information Flow

- Operational biases can occur if information from ongoing trial (information leakage) causes changes to participant pool, investigator behavior, and other aspects of the trial

## Not new to platform trials

- But establishing measures with strict control of communication and information flow should be implemented to prevent operational biases
- Given perpetual nature of platform trials, information leakage may be unavoidable. Conference presentations and publications will likely become available while other interventions are being evaluated.
- Rules to the trial are pre-specified. If rules need to be changed, the decision to change the rules should be driven by the science

# Timing of Adding New Interventions

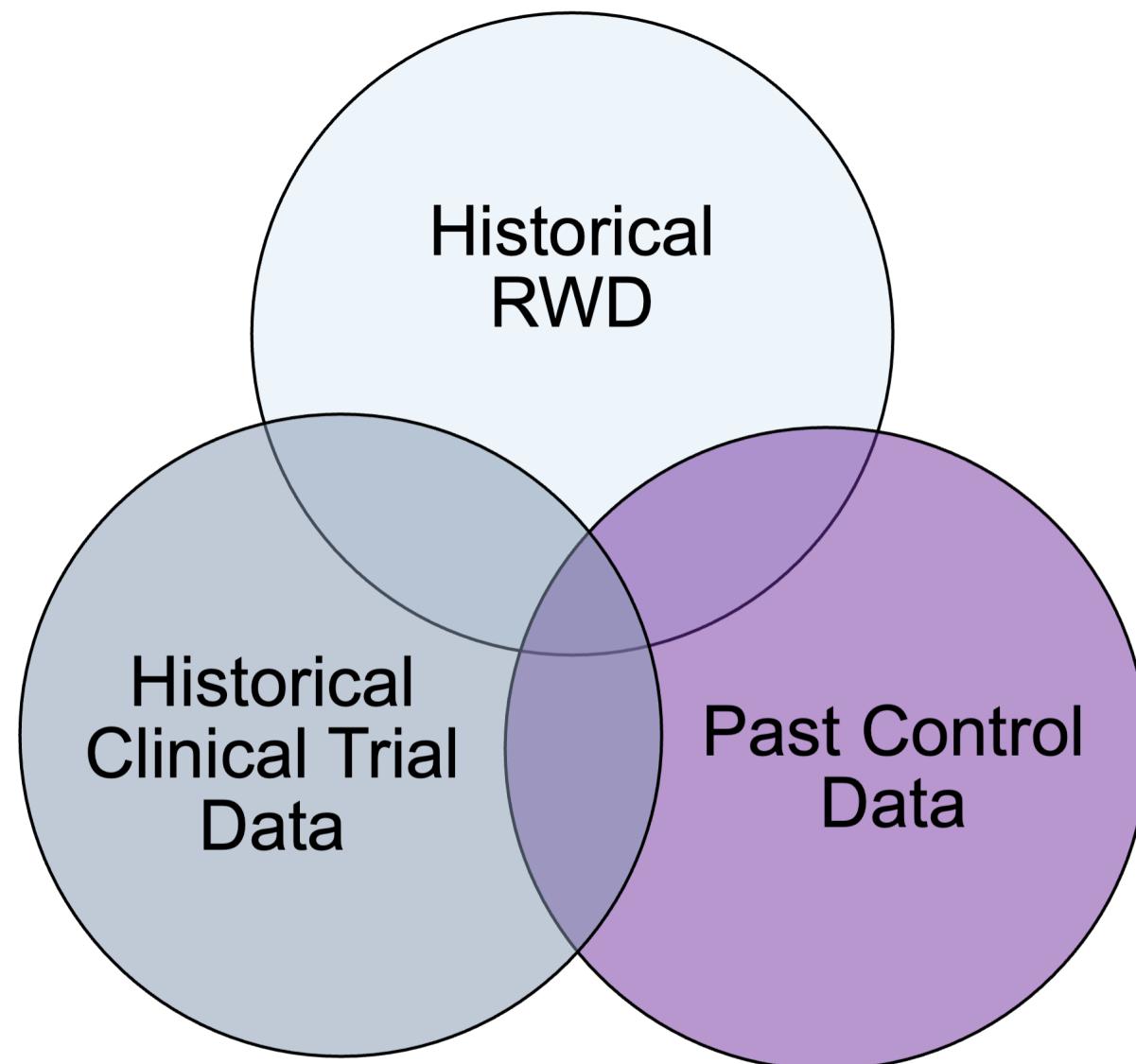


- Concurrent control data: Data from those randomized to control during the same time as the intervention
- Past control data (non-concurrent control): Data from those enrolled before the given intervention became active

## Question:

- *Should the non-concurrent control be included into the comparison of Arm 3?*
- The correct answer is **it depends**

# Past Control Data vs Other Historical Data



Important to note how non-concurrent data is different historical data

- Historical RWD are prone to systematic biases since randomization is not used in real world
- Historical randomized trial data less prone to these biases, but still study-to-study and temporal variabilities to concurrent trial
- In platform trial, temporal variabilities still exist in past control data but maybe no (or less) **study-to-study** variabilities since we are using the same master protocol

# Case Study: The TOGETHER Trial

# The TOGETHER Trial

- A Bayesian adaptive, placebo-controlled, platform trial that evaluated therapies for COVID-19 therapies in an outpatient setting for those at high risk of disease progression
- Started in June 2020 with hydroxychloroquine (HCQ) and lopinavir/ritonavir (LPV/r) vs placebo
- Has enrolled over 8,000 patients and evaluated 10+ therapies
- Each intervention was compared against the concurrent common control

INVESTIGATIONAL PRODUCTS		
INVESTIGATIONAL PRODUCT (IP)	DOSING SCHEDULE	STUDY STATUS
Hydroxychloroquine 400mg	Two tablets on Day 1, then 1 tablets for 9 days	Stopped early for futility, findings published*
Lopinavir/Ritonavir 200/50mg	Four tablets twice a day for 9 days	Stopped early for futility, findings published*
Fluvoxamine Maleate 100mg	One tablet every 12 hours for 10 days	Stopped for superiority, findings published
Ivermectin 400mcg/kg up to 90kg	3-6 6mg tablets (weight dependent) every 24 hours for 3 days	Stopped for futility, manuscript in development
Metformin Extended Release 750mg	One tablet every 12 hours for 10 days	Stopped early for futility, findings published
Doxazosin 2mg	Progressive dosing conditioned on SBP <120mmHg; 0.5 tablet Day 1-2, 1 tablet Day 3-4, 2 tablets Day 8-10, 4 tablets Day 11-14	Recruitment Paused
Peginterferon Lambda 180mcg in 0.45mL	One sub-cutaneous injection at randomization	Actively recruiting
Fluvoxamine 100mg	Twice daily for 10 days	Pending recruitment
Fluvoxamine + Molnupiravir 100mg + 800mg	Fluvoxamine twice daily for 10 days + molnupiravir twice daily for 5 days	Pending recruitment
Fluvoxamine + Inhaled corticosteroid 100mg +	Fluvoxamine twice daily for 10 days + inhaled corticosteroid	Pending recruitment

Table 1: Interventions Investigated

# The TOGETHER Trial - Continued.

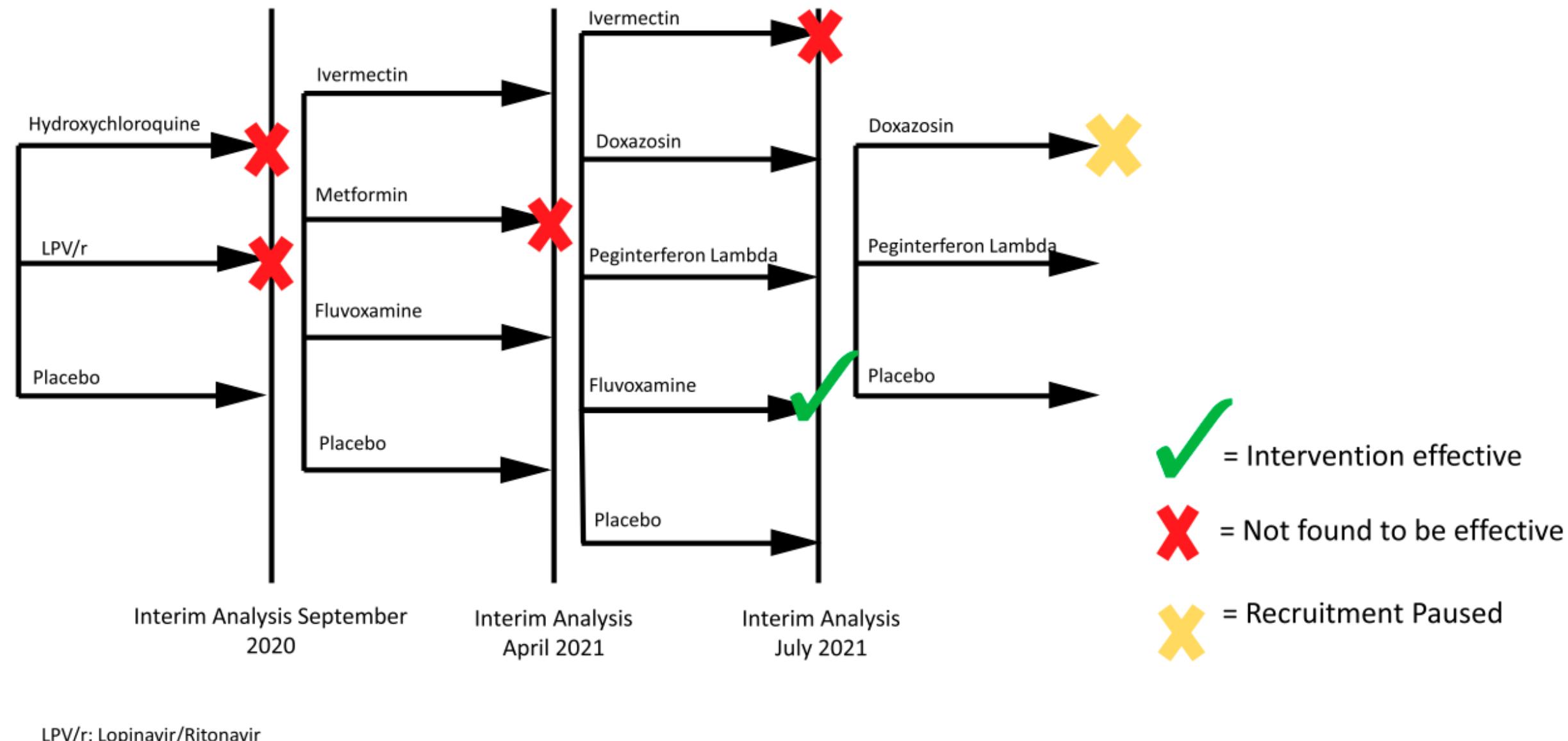
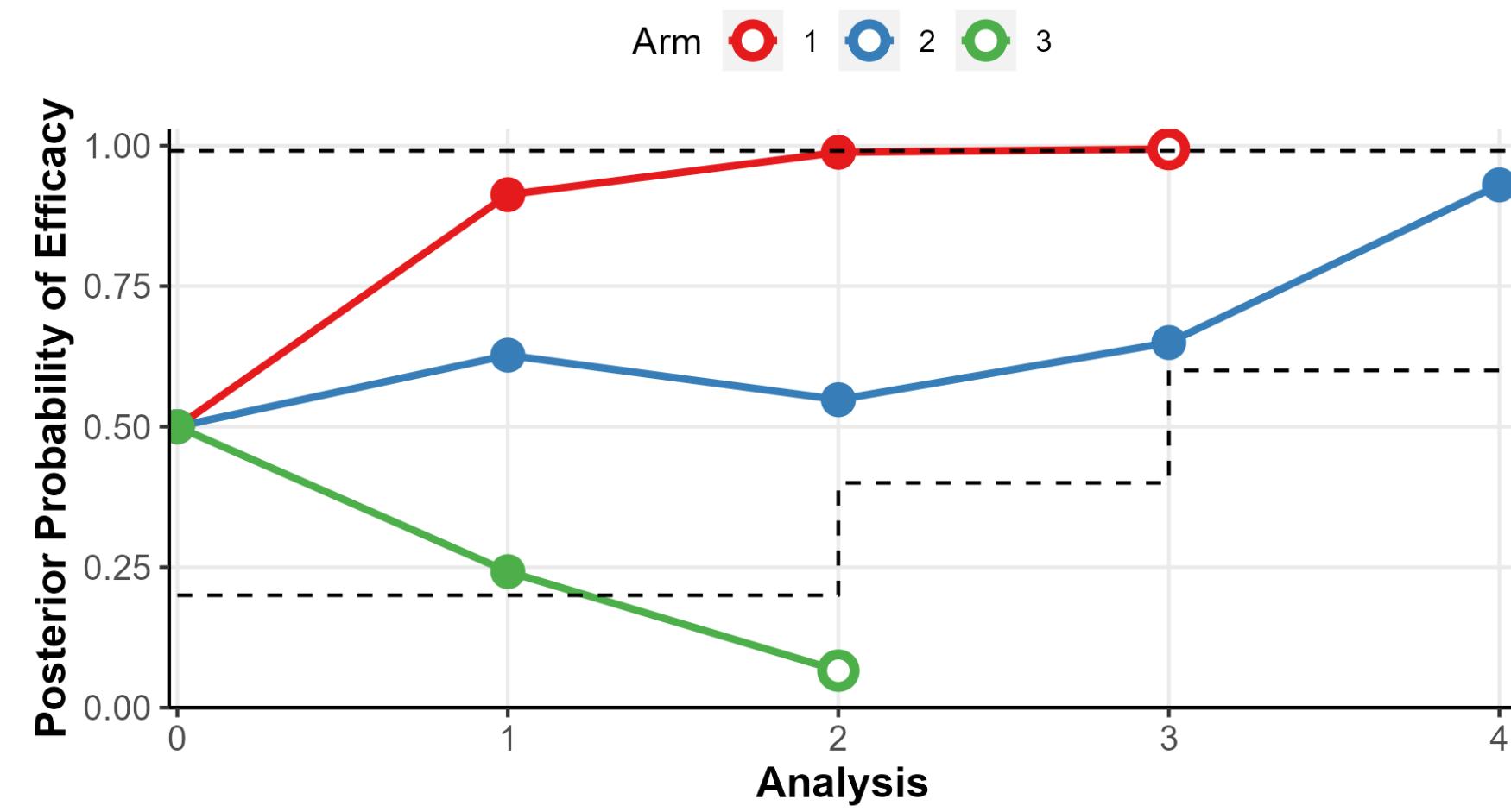


FIGURE 1. TOGETHER trial overview. LPV/r = lopinavir/ritonavir.

# Statistical Design

- It started with composite of hospitalization + mortality status at day 28
- Primary endpoint did changed over time (emergency room use added after) as the disease epidemiology changed over time
- Before new interventions were added into the platform, simulations were performed to calibrate decision rules and characterize the operating characteristics
- Simulations ( $n=200,000$ ) used to come up with stopping rules that could achieve 0.025 type I error rate (one-sided)
- We used Bayesian beta-binomial model with non-informative priors
- Analyses planned at 25%, 50%, 75%, and 100% of maximum sample N.

# Simulation Overview



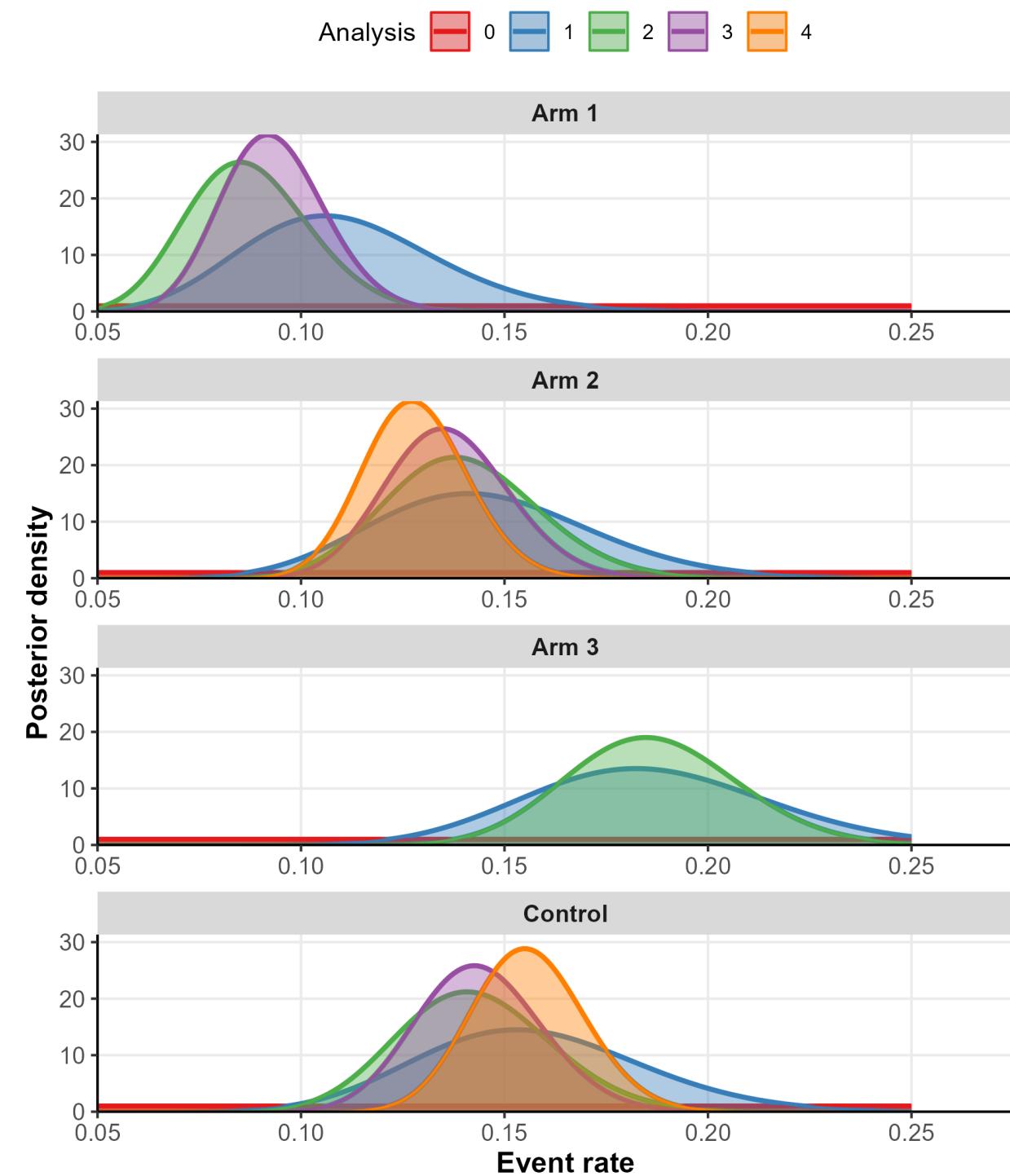
## Superiority threshold:

- $>0.99$  posterior probability of RR  $<1.00$

## Futility thresholds:

- $<0.20$ ,  $<0.40$ , and  $<0.60$
- Gradually became more stringent over time

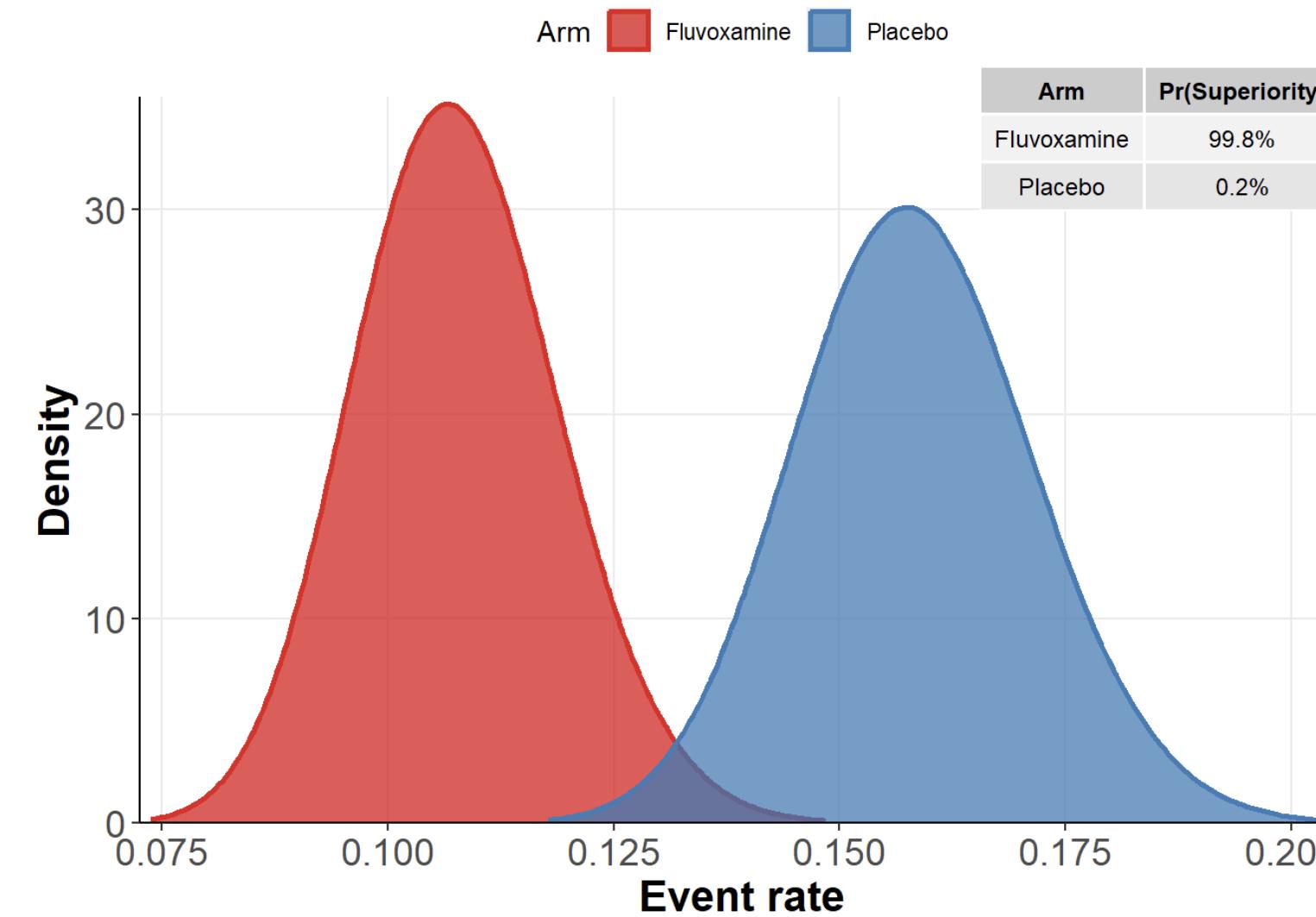
# Simulation Overview - Continued



- This figure is showing the posterior probability being updated at each interim analysis
- Red shows our specified non-informative prior
- In Arm 3, please note no Purple (3rd interim analysis) nor Orange (4th and final interim analysis), since in this virtual trial, this arm stopped for futility at Green(2nd interim analysis)

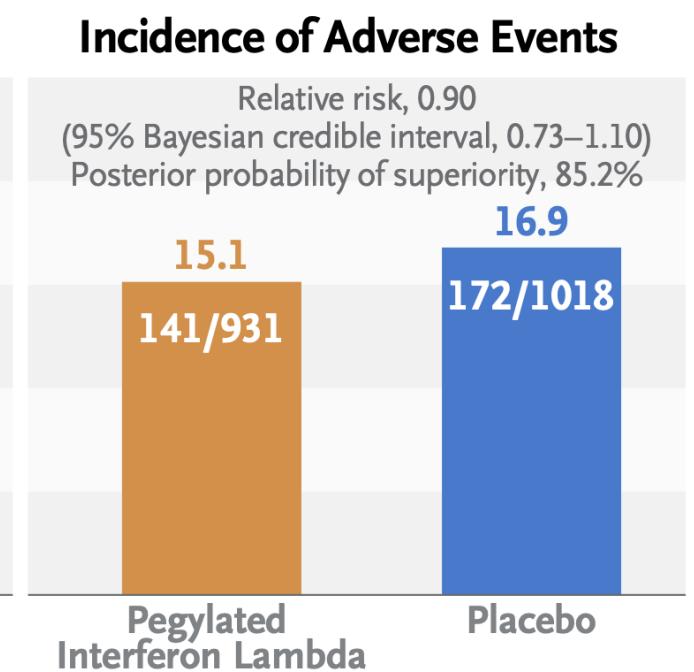
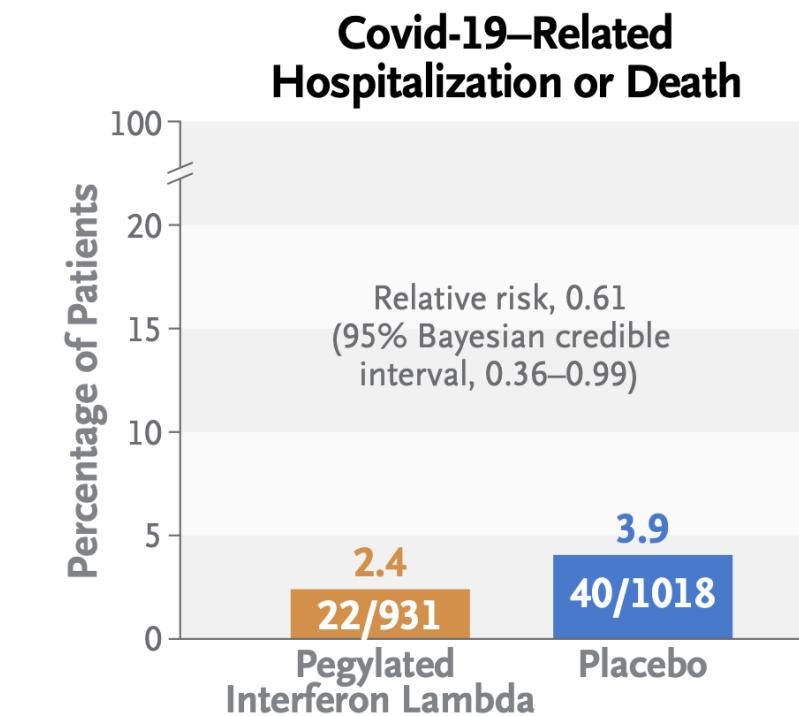
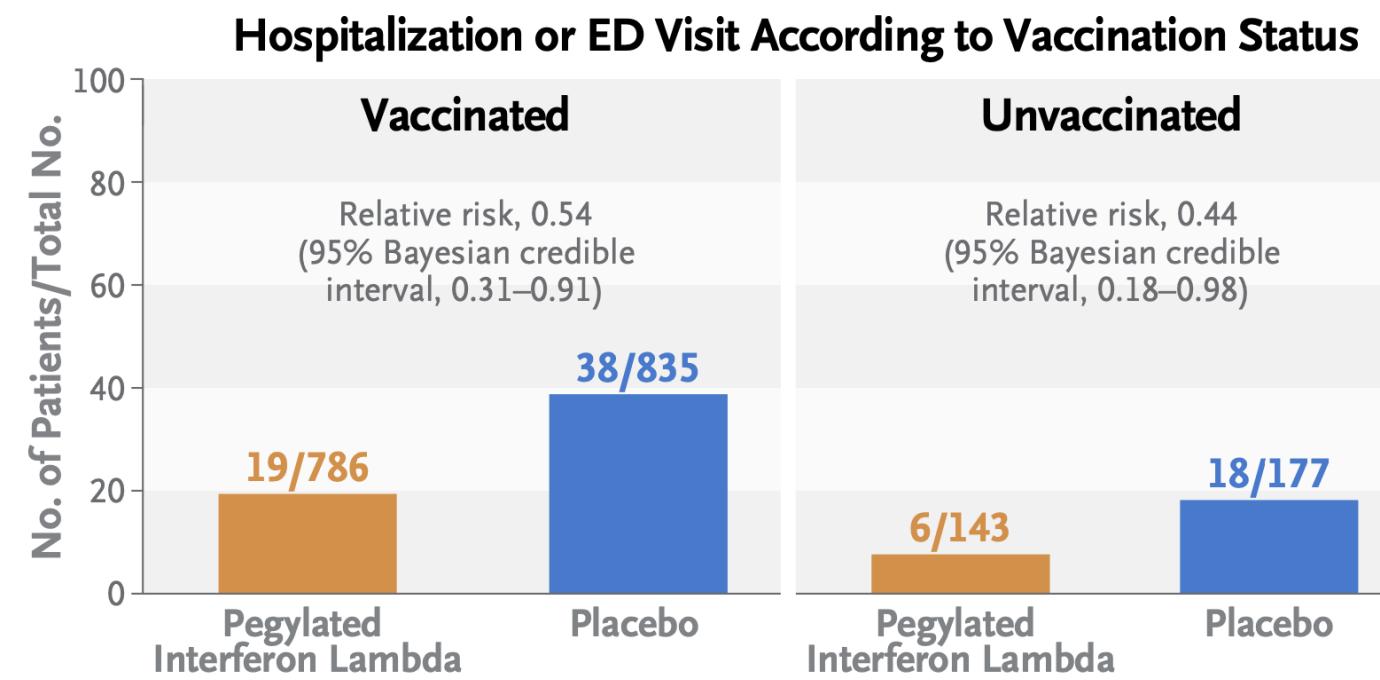
# Notable Findings from the TOGETHER Trial

## Fluvoxamine



# Notable Findings from the TOGETHER Trial

## Pegylated Interferon Lambda - A single subcutaneous injection



# Conclusion and Last Remarks

# The Model of Platform Trials

- Certainly not easy, but 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

# Recommendations

- In my opinion, there is a tendency to over-complicate things
- We don't have to complicate things because other platform trials were complicated

## Every platform trial is different

- Multiple ways to build and maintain an “airport”
- Let's be honest about different trade-offs
- The main statistical efficiency comes from multi-arm aspect of platform trial
- We need to work in a cross-functional team, and we need to advocate for structural changes

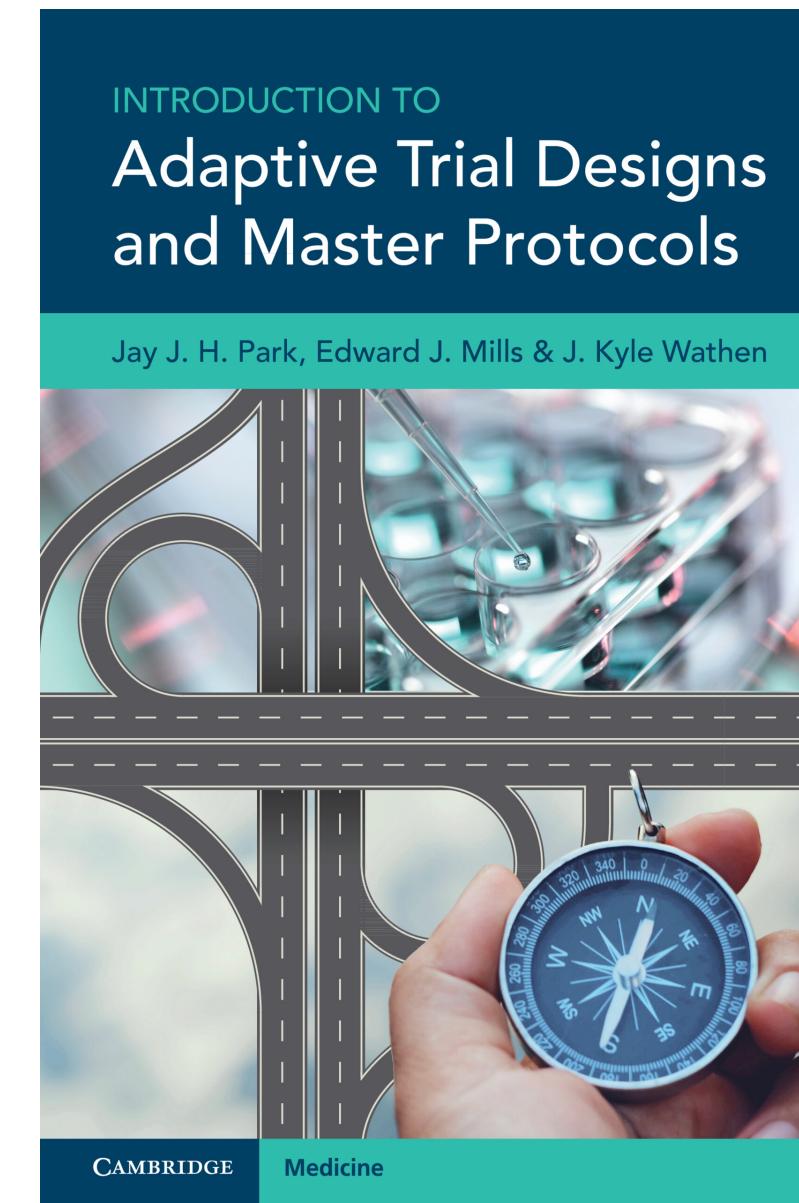
## Not easy but not impossible

- Especially not easy the first time, it does get easier (I think?)

# References

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# Book



Source: Park JJ, Mills EJ, Wathen JK. Introduction to Adaptive Trial Designs and Master Protocols. Cambridge University Press.  
ICPE 2023: Study Design Considerations for APIs | Jay Park