# Navigating the Complexities: Operational Efficiencies and Challenges in Adaptive Platform Trials

Pam Launt
Executive Director, Biostatistics and Programming
PHUSE Bengaluru SDE | 23 Nov 2024

The world leader in serving science

# Pam Launt

Executive Director, Biostatistics and Programming, PPD a division of Thermo Fisher Scientific

- 25 years of service at PPD serving in varying roles over my tenure including Lead Statistician, Senior Statistical Reviewer, People Manager, Global Resourcing Oversight, Site Head, Vaccines Business Segment Lead and Biotech Pillar Head
- Currently provide senior leadership and oversight across B&P project delivery for Biotech clients
- Senior level oversight for 20+ studies during the COVID-19 pandemic resulting in 15+ EUA or full market approvals across >100 countries.

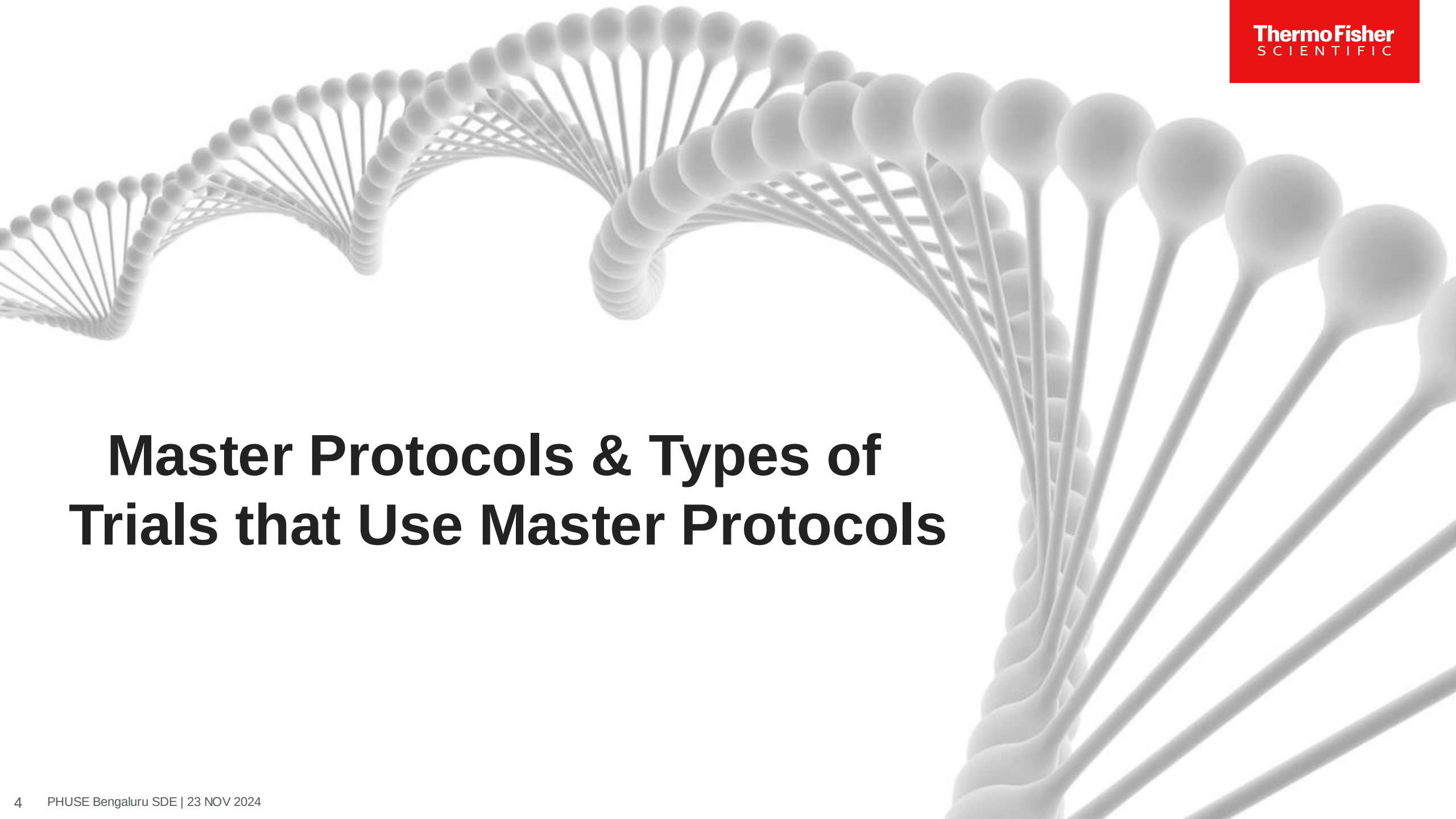
# Agenda

1. Master Protocols - Types of Trials that Use Master Protocols

2. Deeper dive into 2 Key Aspects of Platform Trials
   - Adaptive Randomization
   - Shared Control Groups

3. Case Study ACTIV-2 Platform Trial

4. Conclusions



# Master Protocols & Types of Trials that Use Master Protocols

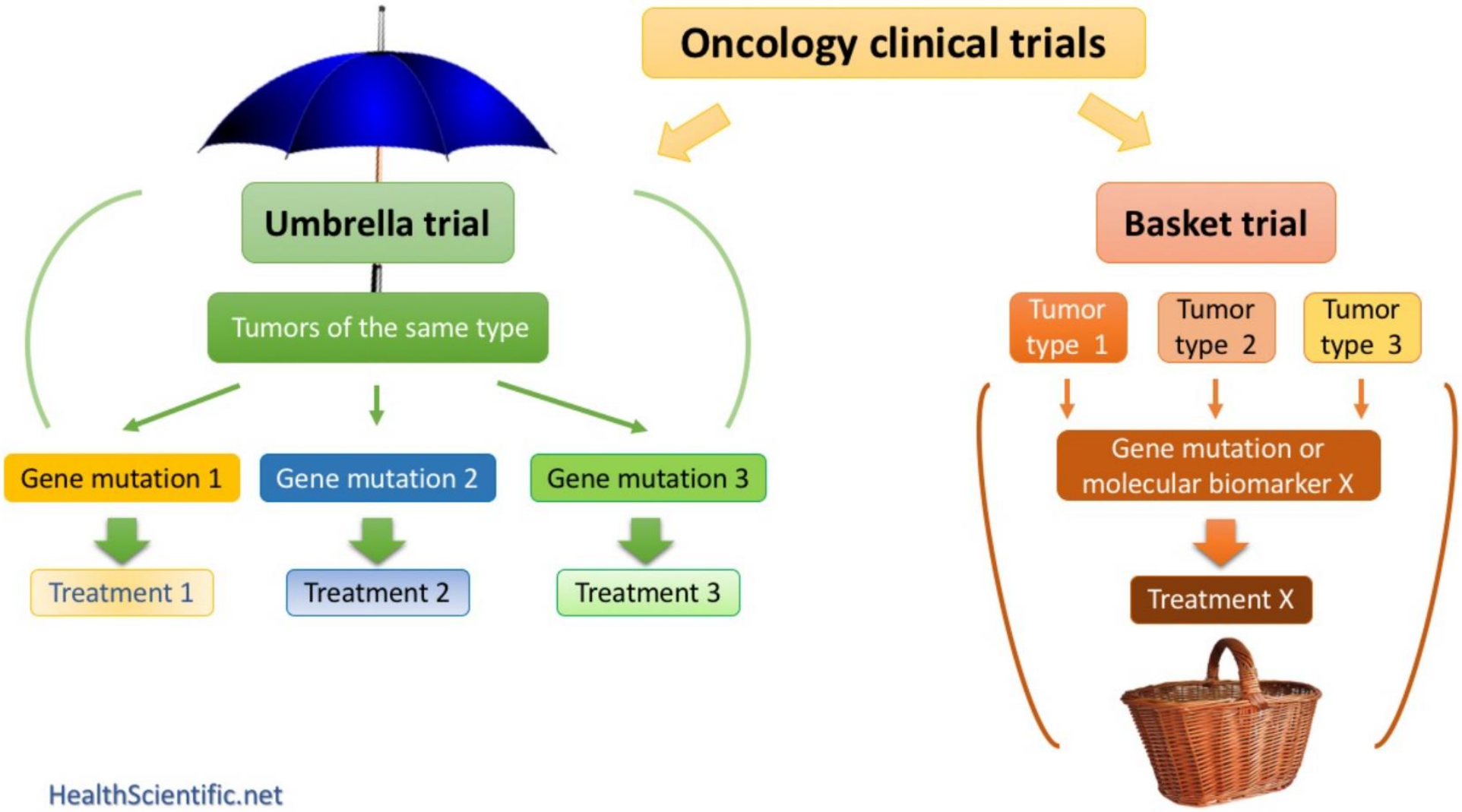
# Master Protocols

- Master protocols are **advanced clinical trial designs** that allow for the evaluation of multiple therapies, disease subtypes, or patient populations under a single overarching protocol.

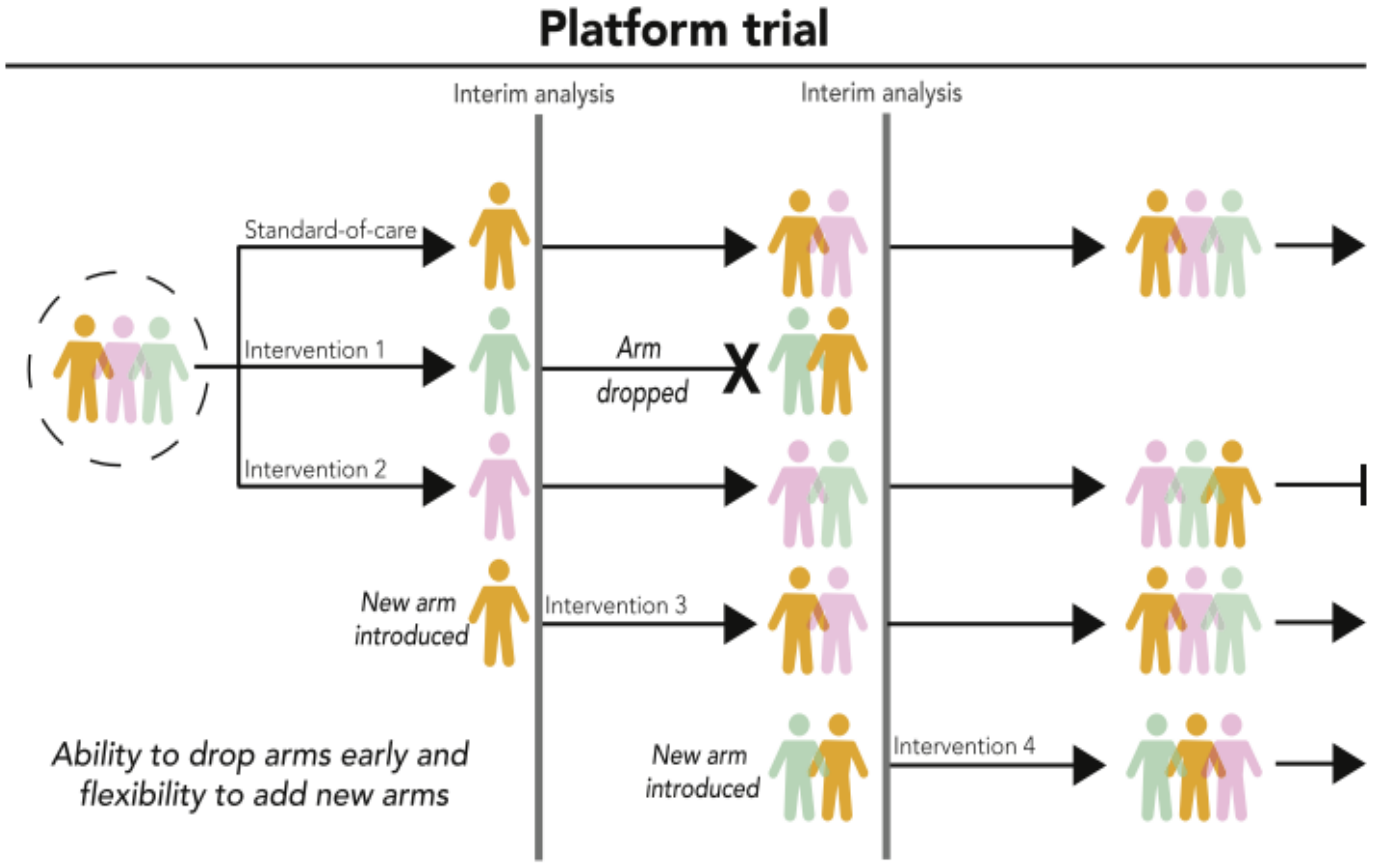
- These protocols are particularly useful in the context of complex diseases like cancer or in pandemic settings, where there are multiple potential treatments and patient subgroups to consider.

- Three main types of trial designs that use master protocols:
  1) **Basket Trials**
  2) **Umbrella Trials**
  3) **Platform Trials**

# Umbrella and Basket Trials



# Platform Trials

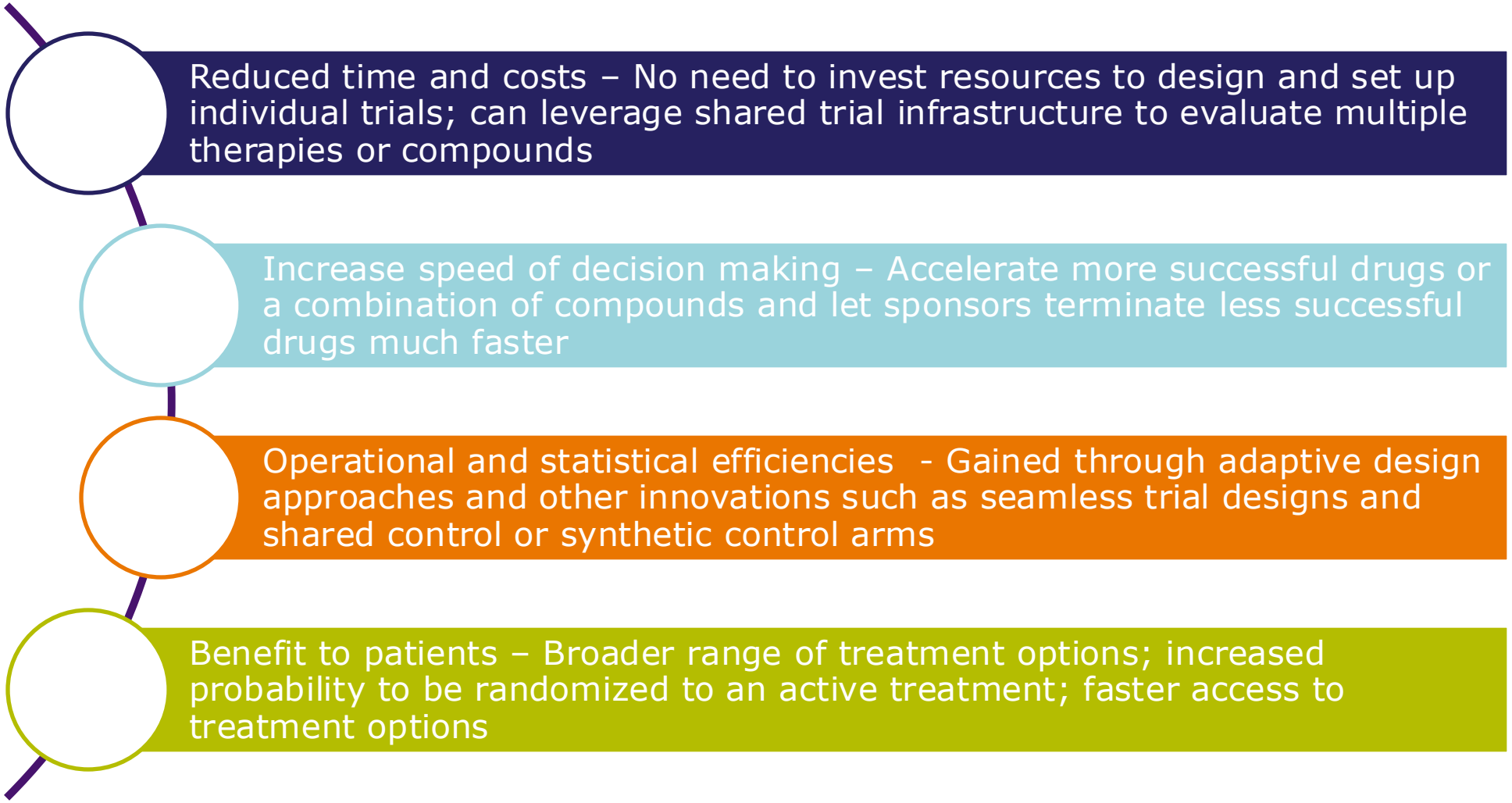



**Examples of planned adaptions:**

- Dropping arms for futility or efficacy
- Changing allocation ratios across randomized arms
- Seamless Phase 2/3 transitions
- Sample size re-estimation

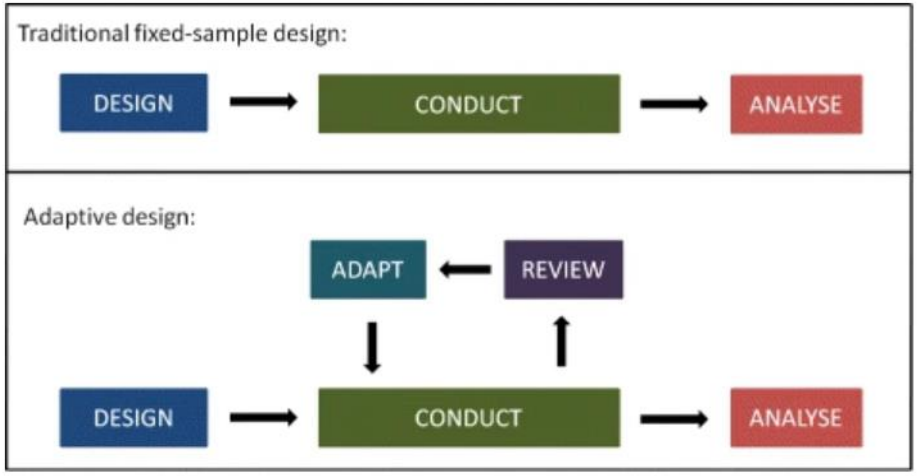
Source: An overview of platform trials with a checklist for clinical readers, *Journal of Clinical Epidemiology, Volume 125, P1-8, September 2000*

# Key Benefits of Platform Trials



# Deeper Dive into 2 Key Aspects of Platform Trials

# Adaptive (or Dynamic) Randomization




Schematic of a traditional clinical trial design with fixed sample size, and an adaptive design with pre-specified review(s) and adaptation(s)

- A flexible approach in assigning participants to different treatment arms based on accumulating data during the trial.
- New treatments may be added over time (or treatments removed) which drives the need for the probability of a participant being assigned to a particular treatment arm to change dynamically during the trial.

Adaptive designs in clinical trials: why use them, and how to run and report them | BMC Medicine | Full Text

# Adaptive Randomization Steps

1. Initial Randomization: At start of the trial, randomize to various treatment with equal or pre-set probabilities
2. Data Monitoring and Interim Analysis: As participants are treated and data accumulate, ongoing analyses evaluate the effectiveness of each treatment arm. This could include evaluating the clinical outcomes such as treatment success or adverse events.
3. Dynamic Adjustment: Based on the interim results, the randomization process can be adjusted. For example:
   - If treatment arm is showing superior efficacy or fewer side effects, more participants might be assigned to that arm.
   - If treatment is underperforming, fewer participants might be allocated to that arm or the treatment may be dropped from the trial.
   - New treatments may be added to the trial.

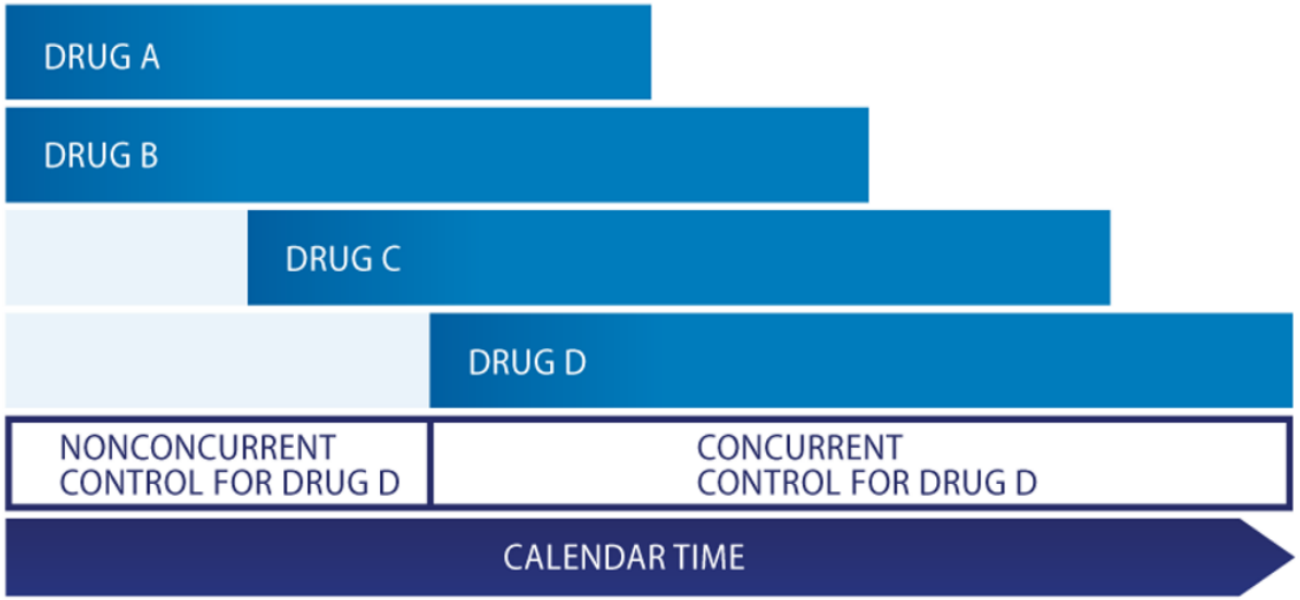
# Shared Control Group

FDA Guidance on Master Protocols (December 2023)

Guidance stresses the importance of avoiding systemic differences between groups caused by

1. Temporal shift in subject conditions
2. Changes in standard of care
3. Changes in trial conduct

**Figure 1: A Schematic to Illustrate Concurrent and Nonconcurrent Control Arm Data for Evaluating Drug D in a Hypothetical Platform Trial**




Master Protocols for Drug and Biological Product Development | FDA

# Case Study
# ACTIV-2 Platform Trial

*Acknowledgment: This project has been funded in whole or in part with Federal funds from the NIAID, National Institutes of Health, Department of Health and Human Services, under Contract No. 75N930221D00035*

# ACTIV-2 Seamless phase 2/3 adaptive, randomized, controlled platform trial designed to evaluate investigational agents for the treatment of nonhospitalized persons with COVID-19

CASE STUDY

## Background

- Study was developed by the AIDS Clinical Trials Group as one of several trials under the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) initiative
- 252 participating sites across 8 distinct countries Argentina, Brazil, Canada, Guatemala, Mexico, Philippines, South Africa and the United States
- 4044 participants enrolled
- 7 different pharma partners
- Evaluated 11 agents (including active control) with 3 agents advancing to Phase 3
- 7 Protocol Amendments

## Implementation

- Master statistical analysis plan + 7 analysis plan amendments
- Adaptive randomization
- Pooling different placebos as a control group
- Complexities with maintaining study blind in a shared placebo setting
- Adapting to address the changing therapeutic landscape
- Adjusting study design to the evolution of SARS-CoV-2 variants

## Highlights

- Unprecedented collaboration with government agencies and across public & private sectors
- Cross-functional expertise required to support planning and implementation
- Operational efficiencies gained through implementation of Master SAP, Master SDTM, Master ADaM and Master TLFs
- Specialized expertise required to design and execute an adaptive randomization plan
- Complex planning required to execute interim analyses leveraging shared placebos
- Design allowed continuous evaluation of the efficacy results and led to a reduced overall sample size

# ACTIV-2 Platform Trial : Overview of Agent Enrollment

Modes of administration and frequency of dosing differed across the agents

Number of subprotocols available for enrollment varied over time due to:

- Product availability at site
- IRB/Regulatory approval timelines
- Differences in eligibility criteria

Eligibility of participants to agents varied due to:

- Product availability at site
- Differences in eligibility criteria
- Evolving standard of care


**Figure 2.** Enrollment timelines for placebo-controlled evaluation of agents in ACTIV-2. Dashed arrow perimeters indicate agents for which phase 2 enrollment was terminated early for administrative reasons. Enrollment shown is for placebo-controlled phase 2 evaluation for all agents and placebo-controlled phase 3 evaluation of A/R (the only agent that underwent placebo-controlled phase 3 evaluation in ACTIV-2). Abbreviations: A/R, amubarvimab/romlusevimab; Bam, bamlanivimab; IM, intramuscular injection; IV, intravenous infusion; Ph, phase; T/C, tixagevimab/cilgavimab.

Source: Pooling Different Placebos as a Control Group in a Randomized Platform Trial: Benefits and Challenges from Experience in the ACTIV-2 COVID-19 Trial, *Journal of Infectious Disease, JID 2023:228 (Suppl 2)*, Moser et al

# ACTIV-2 Adaptive Randomization

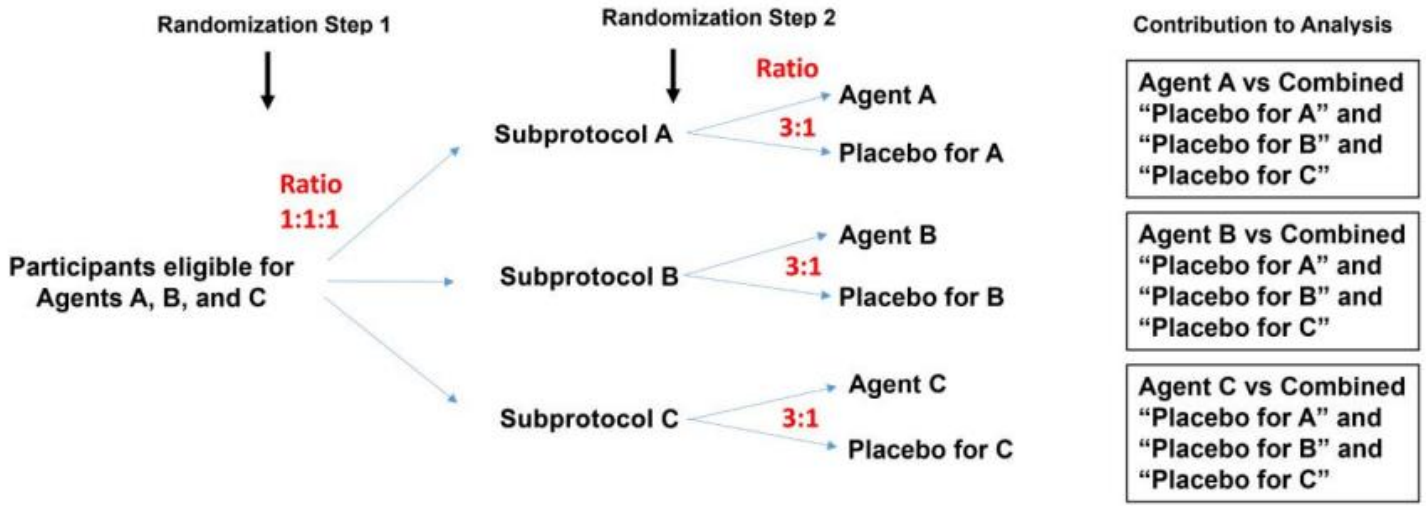



**Figure 1.** Illustrative example of randomization scheme for a stratum of participants eligible for 3 agents, A, B, and C.

**Type I error rate was controlled separately for each agent**

- Approach was considered acceptable from the US FDA

**Areas of complexity**

- Randomization step 1 was unblinded Randomization step 2 was blinded
- 7 sub protocols with new agents entering over time
- Each subject could be eligible to be randomized to a different set of sub protocols

**Benefits**

- 2-step randomization results in approximately equal size comparison groups, maximizing statistical power irrespective of number of subprotocols

Source: Pooling Different Placebos as a Control Group in a Randomized Platform Trial: Benefits and Challenges from Experience in the ACTIV-2 COVID-19 Trial, *Journal of Infectious Disease, JID 2023:228 (Suppl 2)*, Moser et al

# How is an adaptive randomization implemented?

- Static randomization schedule is generated that allows for all possible combinations
  - (2^k) – 1 possible strata where k=number of agents
- IRT system is programmed to collect from the site all stratification factors, including which agent(s) subject qualified for
- Randomization 1 is “Stratified” by agents for which a subject qualifies
- Assigned agent, including the ratio designation, becomes strata in Randomization 2

Randomization 1

| Strata | Possible Intervention “Assignment” |
|---|---|
| A | A1 |
| B | B1 |
| C | C1 |
| AB | A2 |
| | B2 |
| AC | A2 |
| | C2 |
| BC | B2 |
| | C2 |
| ABC | A3 |
| | B3 |
| | C3 |

# How is an adaptive randomization implemented?

- Randomization 2 is “Stratified” by assigned agent and ratio from Randomization 1
- After being randomized to an agent in Randomization 1 in an ***unblinded*** fashion, subject is randomized in a ***blinded*** fashion k:1 ratio of active:control where k is the number of agents to which the subject could have been randomized
- Block size is dynamic based on randomization ratio

Note: December 2023 FDA Guidance released a revised recommendation for the ratio of active:control -> sqrt(k):1

Randomization 2

| Strata | Example Block for Treatment Assignment |
|---|---|
| A1 | A |
| | Placebo for A |
| A2 | A |
| | A |
| | Placebo for A |
| A3 | A |
| | A |
| | A |
| | Placebo for A |

# Shared Placebo Control Group – Impact to Analysis

- Possible that a subject may not qualify for all treatments available, should only share placebo control from agents a subject ***could*** have received
- Example below shows subjects in analysis of Treatment A to the ***Concurrent Shared Control***

| Treatments Subject Could Receive | Assigned Intervention | Treatment | |
|---|---|---|---|
| | | Active | Control |
| A | A | A | PA |
| B | B | B | PB |
| C | C | C | PC |
| A or B | A | A | PA |
| | B | B | PB |
| A or C | A | A | PA |
| | C | C | PC |
| B or C | B | B | PB |
| | C | C | PC |
| A or B or C | A | A | PA |
| | B | B | PB |
| | C | C | PC |

A = Active A

PA = matching placebo for A

B = Active B

PB = matching placebo for B

C = Active C

PC = matching placebo for C

# Shared Placebo Approach in ACTIV-2 Platform Trial

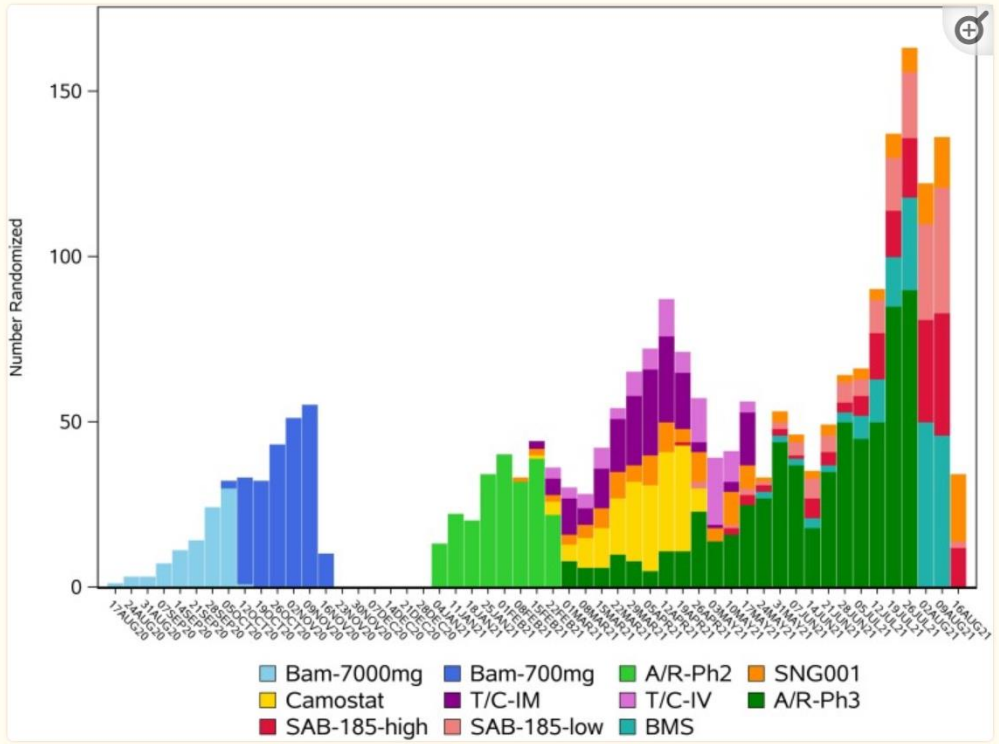



Figure 3.

Enrollment over time for the placebo-controlled evaluation of agents in ACTIV-2. Abbreviations: A/R-Ph2, amubarvimab/romlusevimab phase 2; A/R-Ph3, amubarvimab/romlusevimab phase 3; Bam-700 mg, bamlanivimab 700 mg; Bam-7000 mg, bamlanivimab 7000 mg; BMS, BMS-986414 + BMS-986413; SAB-185-high, SAB-185 high dose; SAB-185-low, SAB-185 low dose; T/C IV, tixagevimab/cilgavimab by intravenous infusion; T/C-IM, tixagevimab/cilgavimab by intramuscular injection.

## Efficiency of the pooled placebo control in terms of sample size

- Not fully realized due to the early term of 2 subprotocols for administrative purposes (Bam-7000mg, T/C IV)

- Focusing on the other 9 subprotocols that fully accrued.
  - ✓ If each subprotocol had enrolled their own distinct placebo group, total sample size would have been 2382 participants (220 per agent in phase 2, plus 622 for agent graduated to phase 3).
  - ✓ Actual total of 2231 participants achieved a 6% reduction.
  - ✓ Minimal gain is primarily due to 57% of participants who could only be randomized to 1 subprotocol

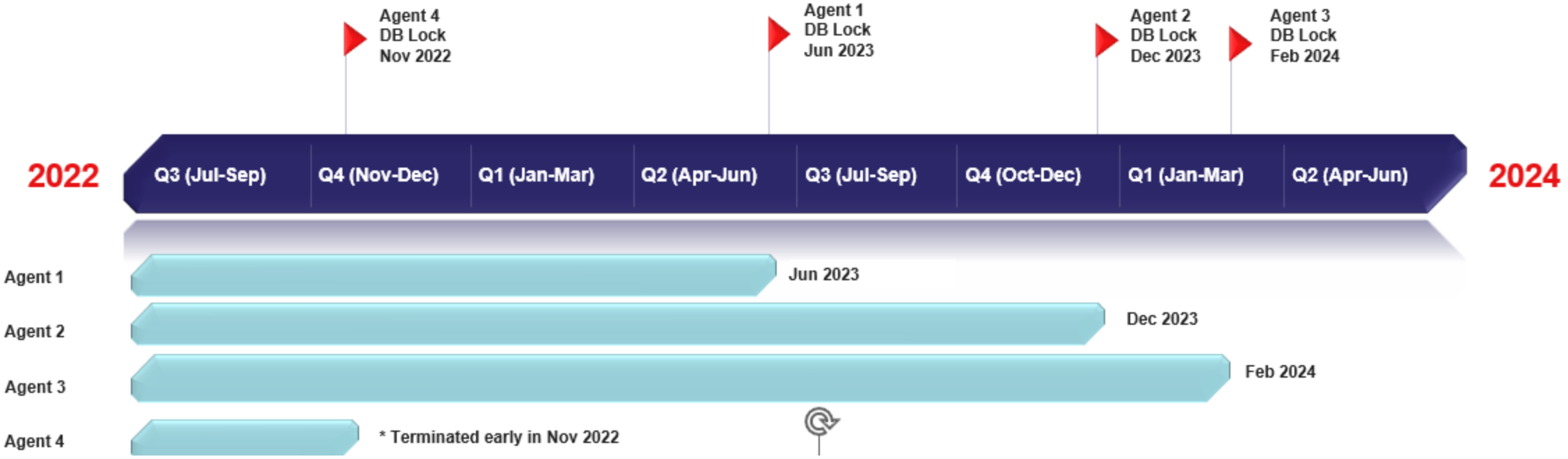
- Focusing on agents in phase 2 enrolled 10 Feb 2021 onwards, using pooled placebo achieves 26% reduction in sample size (from 1320 subjects required if had distinct placebo groups down to 972).

- If all agents and enrollment occurred concurrently, could have achieved a 42% reduction in sample size for placebo controls.

Source: Pooling Different Placebos as a Control Group in a Randomized Platform Trial: Benefits and Challenges from Experience in the ACTIV-2 COVID-19 Trial, *Journal of Infectious Disease, JID 2023:228 (Suppl 2)*, Moser et al

# Logistical Challenges with Shared Controls

## Example Scenario (not ACTIV-2)




- Multiple Data Release Points – The different timing of interim analyses and database locks for different agents makes it challenging to maintain the blind and requires controlling when the shared placebo data is released
- Complexity of Information Flow - Flow of information must be tightly controlled at points in time to avoid unintentional unblinding, making the negotiation of delivery timelines for DSMBs or at the point of Database Locks of utmost importance

# CONCLUSIONS

Platform Trials

**01** Platform trial execution require highly experienced clinical trial teams and careful planning to ensure a successful execution

**02** Despite the challenges, significant gains in operational efficiencies and cost savings can be realized with platform trials

**03** The ability to make rapid, data-driven decisions in platform trials ensures that patients gain faster access to effective treatments, ultimately improving outcomes and saving lives.

# Dhanyavaad & Thank you

# References


1. Master Protocols for Drug and Biological Product Development Guidance for Industry Master Protocols for Drug and Biological Product Development
2. COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention Guidance for Industry COVID-19-Master-Protocols-Evaulating-Drugs-and-Biological-Products.pdf
3. An overview of platform trials with a checklist for clinical readers Overview of Platform Trials Journal of Clinical EpidemiologyPIIS0895435619309874.pdf
4. Platform trials –GIENS WORKSHOPS 2022 Platform Trials main.pdf
5. Pooling Different Placebos as a Control Group in a Randomized Platform Trial: Benefits and Challenges From Experience in the ACTIV-2 COVID-19 Trial Pooling Different Placebos as a Control Group in a Randomized Platform Trial (jiad209).pdf
6. Adaptive designs in clinical trials: why use them, and how to run and report them | BMC Medicine | Full Text

# Disclaimer

The views and opinions expressed in this presentation and the accompanying paper are those of the Author only and not reflective of PPD/Thermo Fisher Scientific.