IMPERIAL

Session: Harnessing the Potential of Platform Trials in Chronic Diseases

Utilizing real world evidence to characterize target populations and define clinical outcomes

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20/05/2025

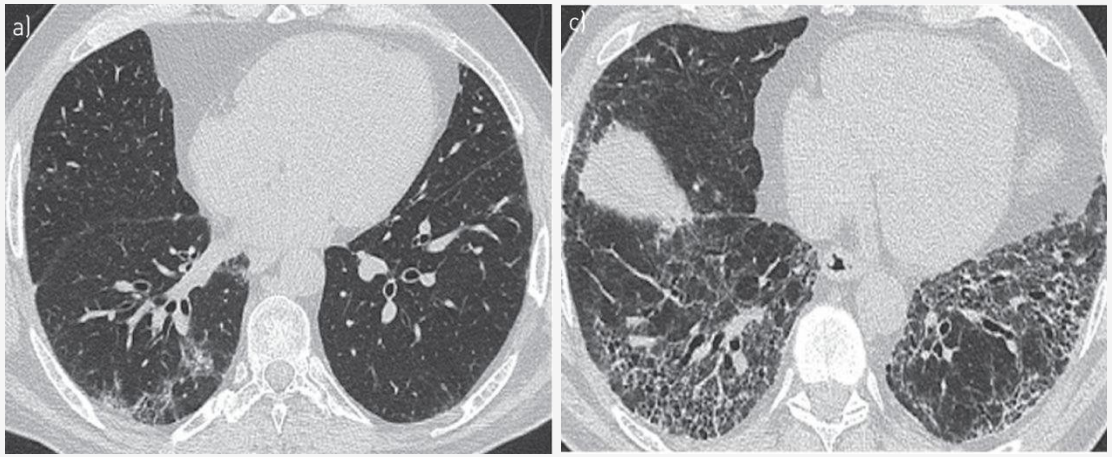
MTW Centre for Fibrosing Lung Disease

Relevant disclosures

1. Scientific Advisory Board Member of patientMpower

Utilizing real world evidence to characterize target populations and define clinical outcomes

<12 months >



DOI: 10.1183/16000617.0073-2018

1. Why do we need trials in **pulmonary fibrosis**?
   - Chronic: rare progressive disease
2. Challenges of traditional clinical trials
   - A brief history of PF trials
3. The value of observational studies
   - Natural history of fibrotic lung disease
4. Setting expectation for future trial design
   - Learning from real world evidence

1. Why do we need trials in Pulmonary Fibrosis

Setting the scene

70,000
in the UK are living with PF

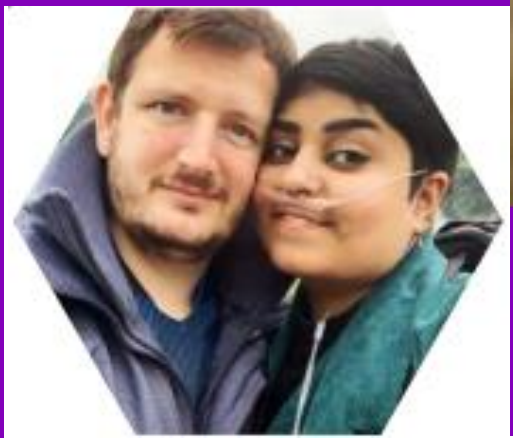
1 in 100
of all deaths are from IPF

3-5 years
life expectancy for IPF

1 in 3
people in the UK have never heard of PF

46%
of people with IPF survive 5 years

"It's an awful thing to say but I wish it was cancer. There would be more support if I had cancer."



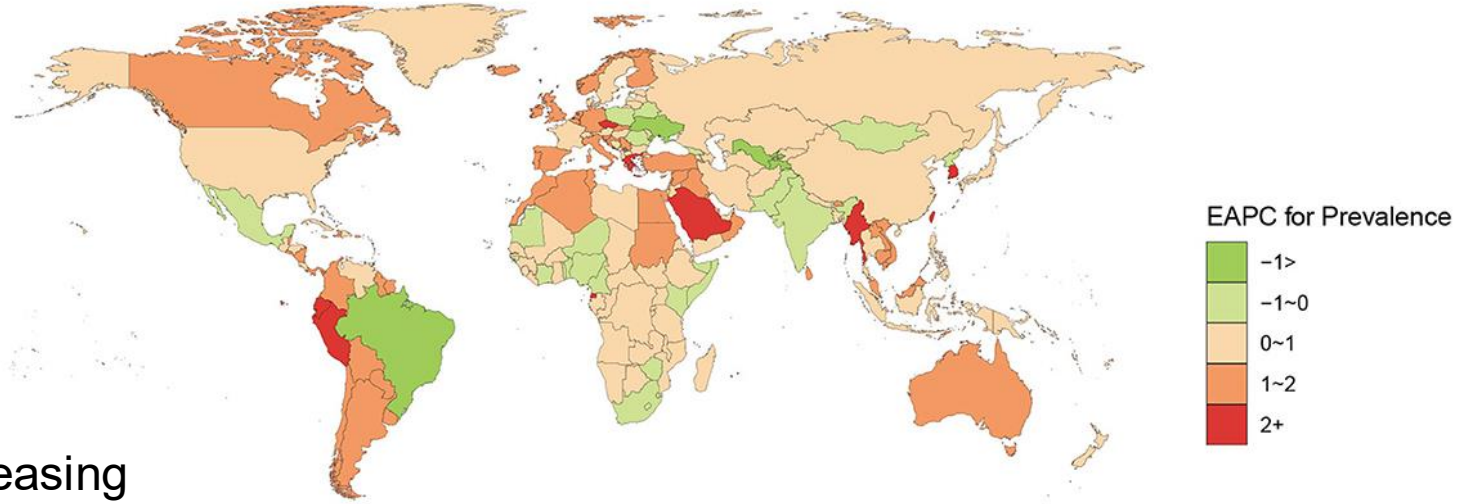
Action for Pulmonary Fibrosis

1. Why do we need trials in Pulmonary Fibrosis

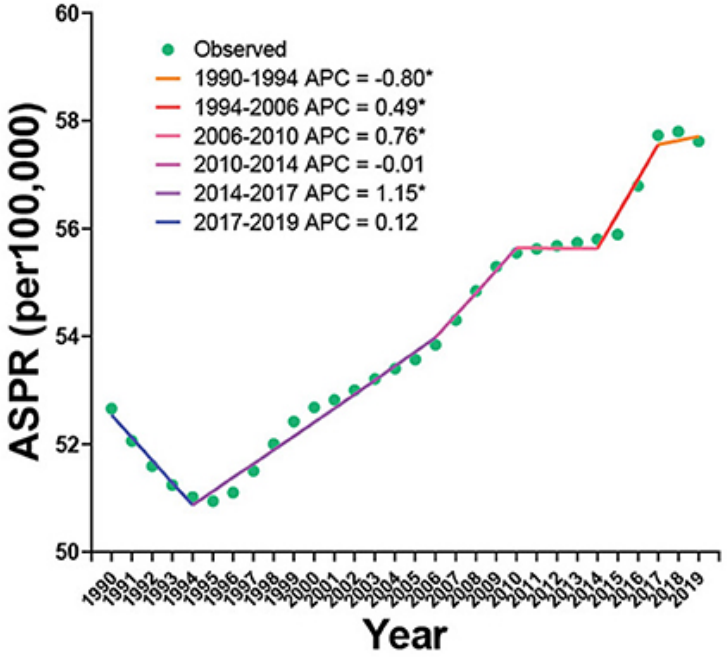
Setting the scene

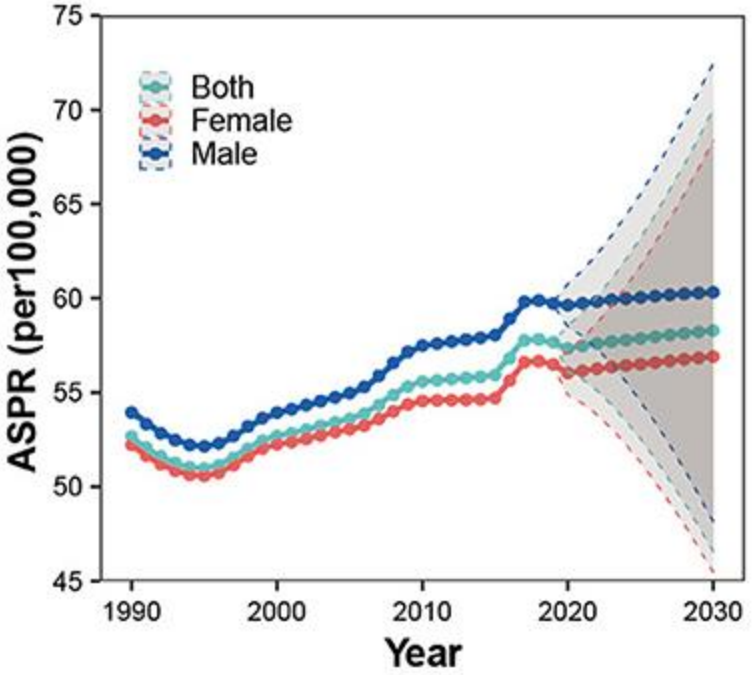
Global Burden of Disease

- Interstitial lung disease
- Change in prevalence 1990-2019
- Age-standardized prevalence increasing



DOI: 10.3389/fmed.2023.1141372





2. Challenges of traditional clinical trials in rare disease

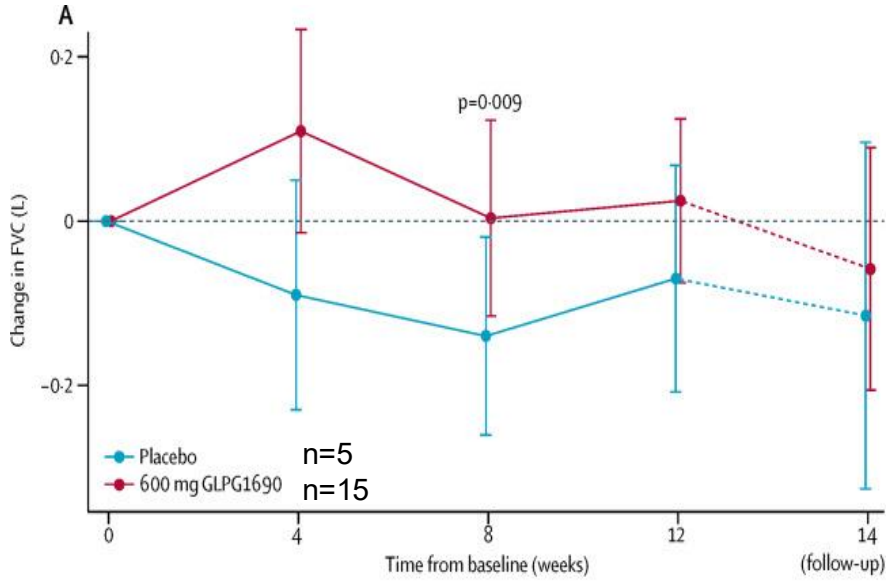
Underpowered Phase II evidence

LPA = fibrogenic; Ziritaxestat: inhibits LPA production

Short follow up and small sample size

FLORA

PHASE II

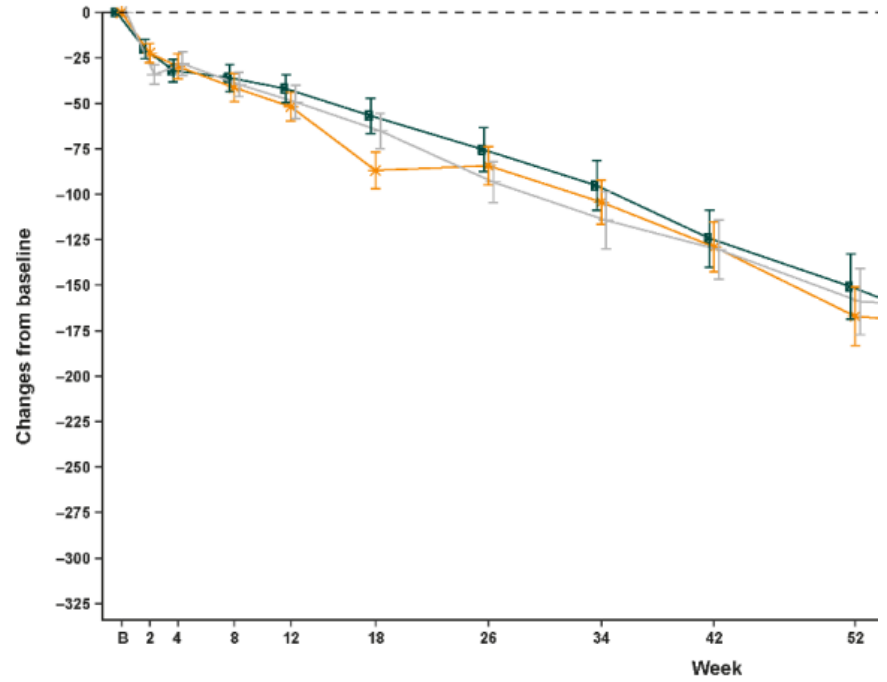


Early termination: Futility

>1200 recruited

ISABELA 1&2

Phase III



Number of patients

Ziritaxestat 600 mg q.d.	428	403	391	371	352	309	264	246	217	209
Ziritaxestat 200 mg q.d.	431	409	392	367	351	322	283	249	229	234
Placebo	420	398	390	363	354	322	277	235	219	225

2. Challenges of traditional clinical trials in rare disease

Outliers suggesting efficacy

Pentraxin-2 antifibrotic preclinical; Zinpentraxin alfa

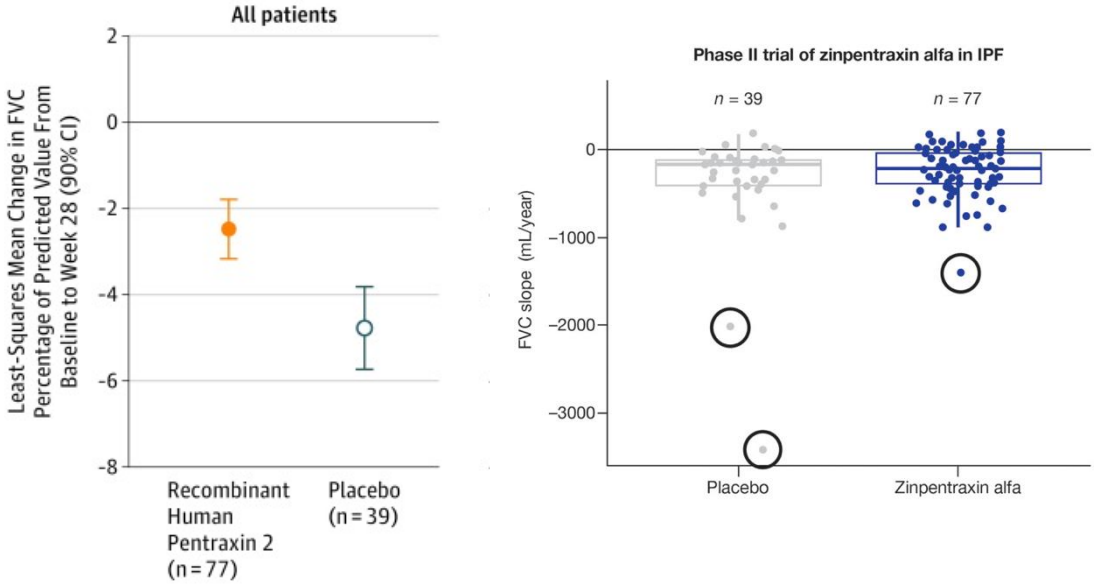
Outliers can have big effects in small samples

Early termination: Futility

>650 recruited

NCT02550873

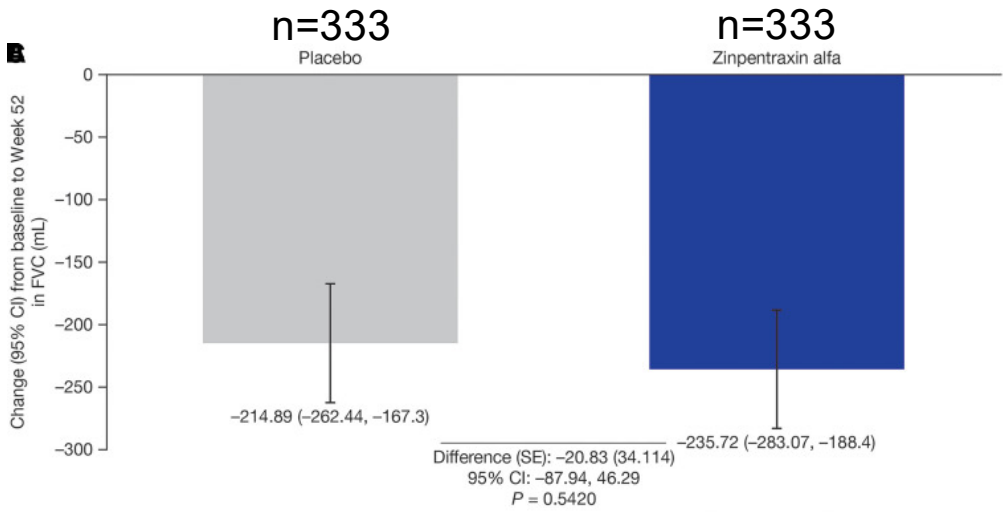
Phase II



DOI: 10.1001/jama.2018.6129

STARSCAPE

Phase III



DOI: 10.1164/rccm.202401-0116OC

2. Challenges of traditional clinical trials in rare disease

‘Trends’ in post-hoc subset analyses

Endothelin-1 profibrotic; Bosentan, receptor antagonist

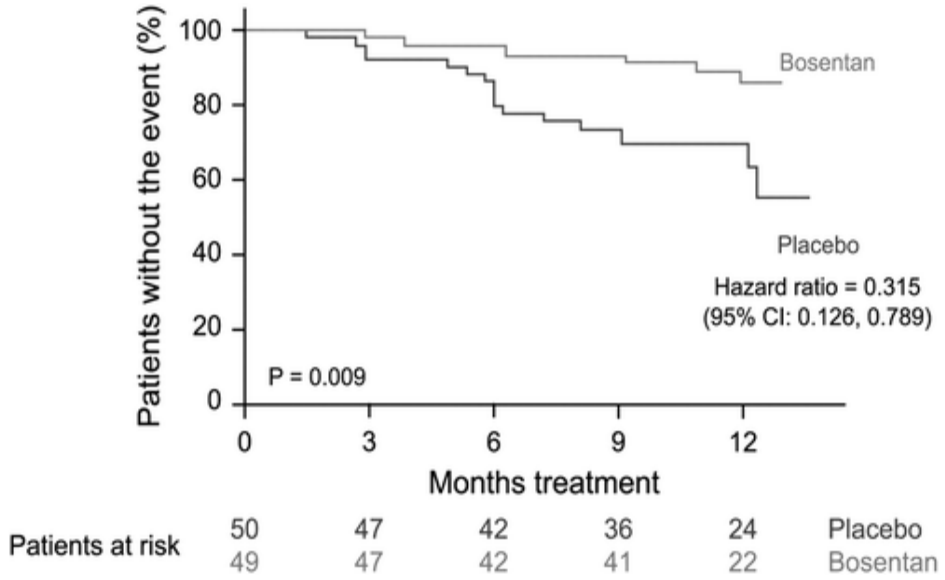
Post-hoc based restrictive inclusion criteria

No efficacy on endpoint

>600 recruited

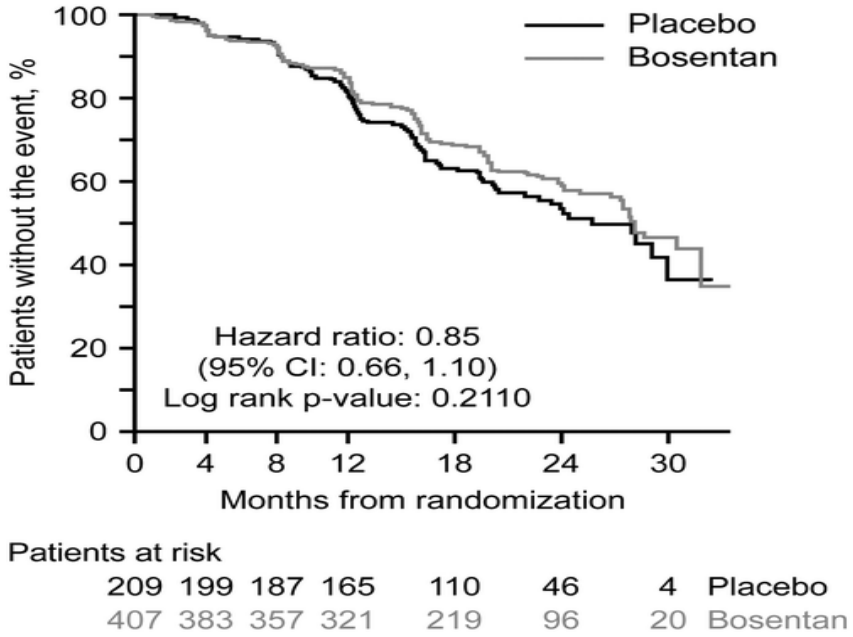
BUILD-1

non–pre-defined post hoc analysis: biopsy



DOI: 10.1164/rccm.200705-732OC

BUILD-3



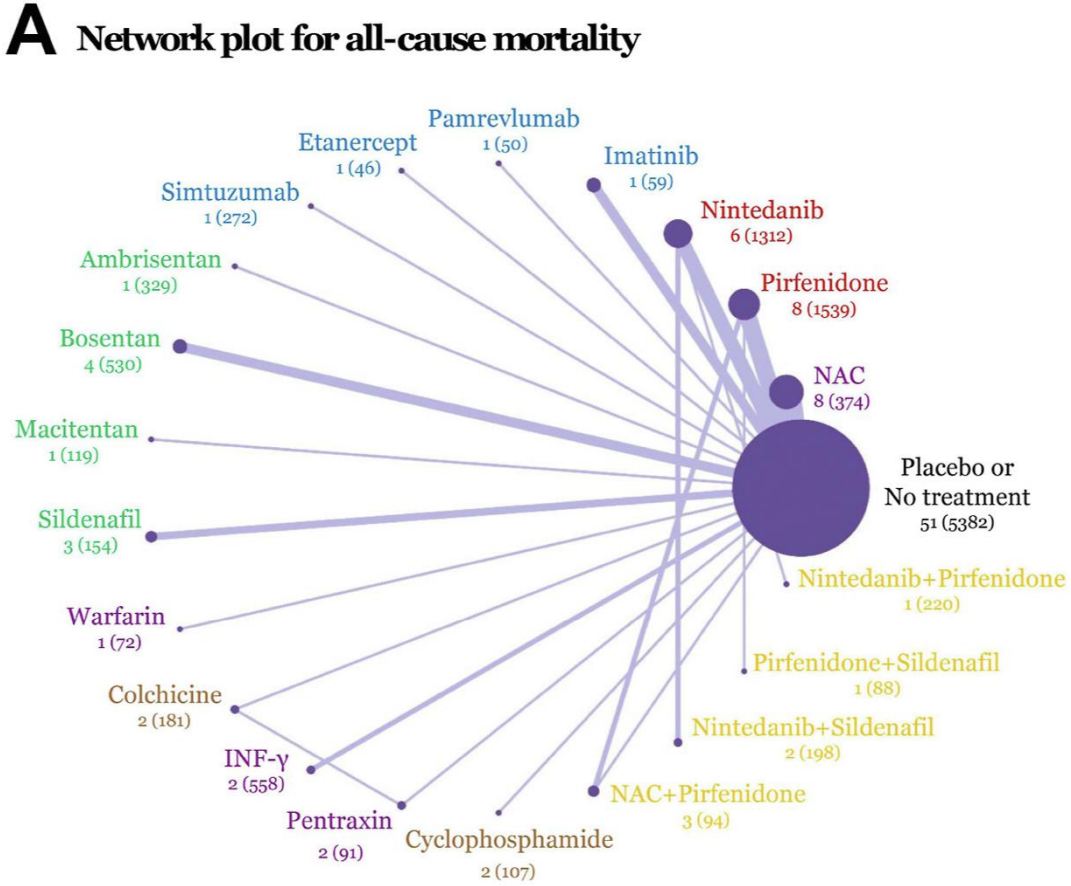
DOI: 10.1164/rccm.201011-1874OC

2. Challenges of traditional clinical trials in rare disease

Lessons from IPF trial history

- **Traditional**
  - Phase 2 small sample, underpowered
  - Outliers have a big effect in small studies
  - Post hoc ‘trends’ not generalisable, restrictive

- **Large number of participants with no benefit**
  - Rare progressive disease
  - Only two licensed antifibrotics reduce decline
  - 25% of all randomisations to antifibrotic
  - 75% of all randomisations placebo or ineffective



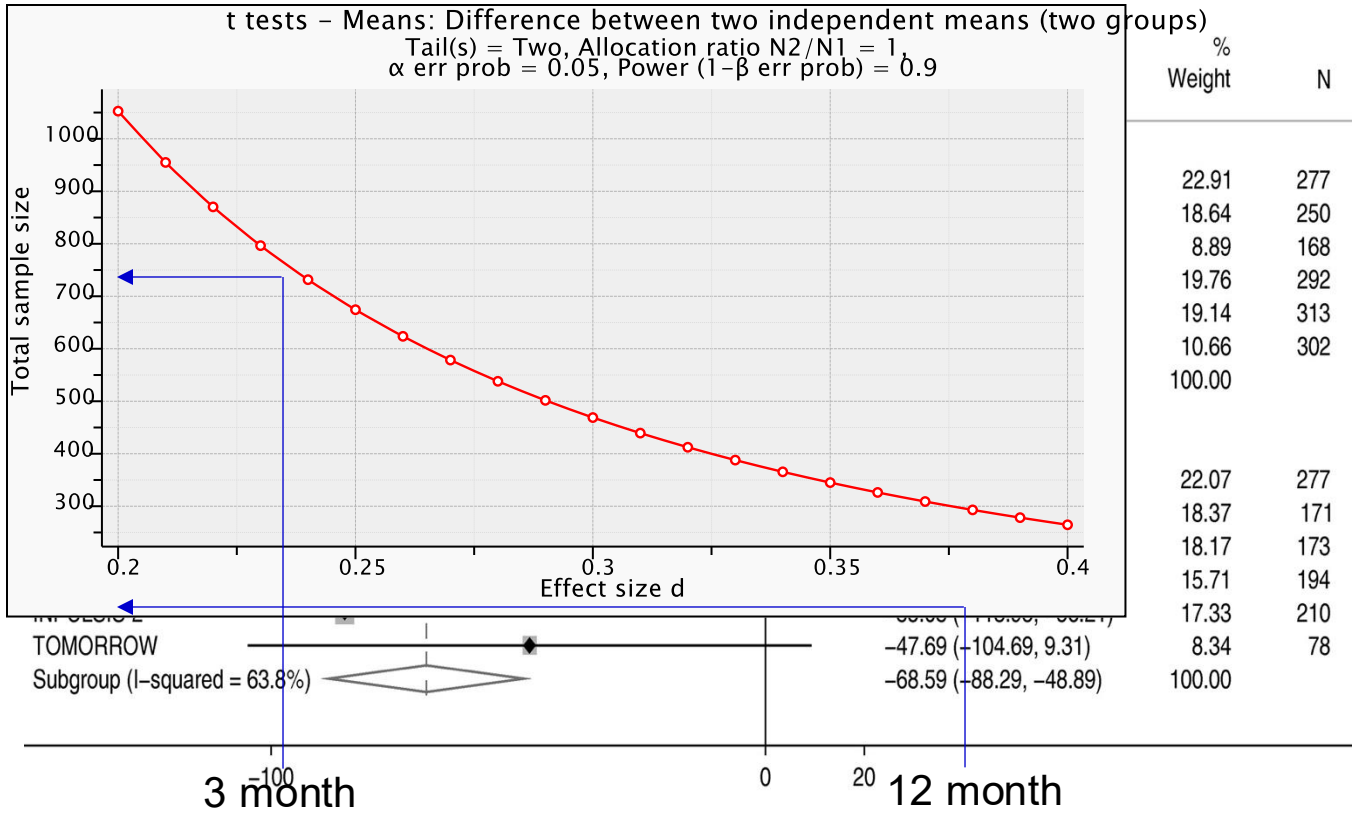
53 trials:12,551 participants (2023)

DOI: 10.1016/j.eclinm.2023.102071

2. Challenges of traditional clinical trials in rare disease

FVC endpoints and sample size

Individual participant data meta-analysis of FVC decline in antifibrotic trials



12 months
- Difference 83.2ml (23.4; 142.9)
- Standardised effect size = 0.328

3 months
- Difference 42.9ml (24.0; 61.8)
- Standardised effect size = 0.220

3 months N=872

12 months N=394

Traditional design with earlier FVC endpoints not practical in rare disease

DOI: 10.1164/rccm.202109-2091OC

3. The value of observational studies in modelling endpoints

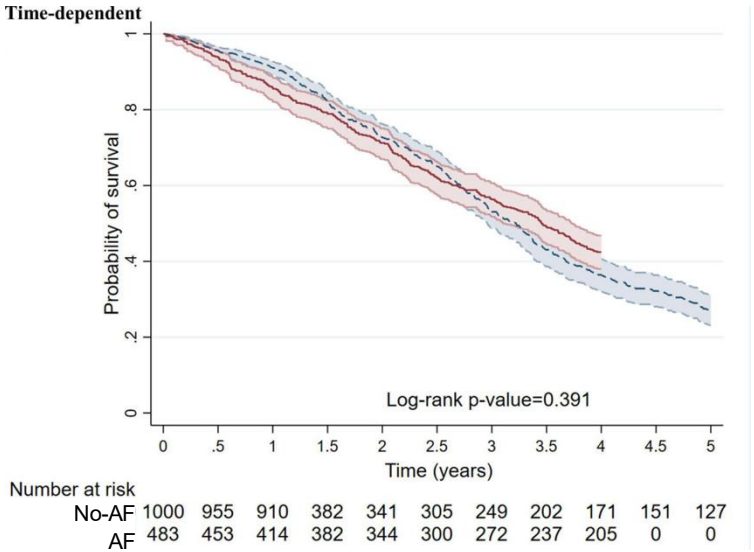
Missing data and survival bias in registry studies

Registry benefit

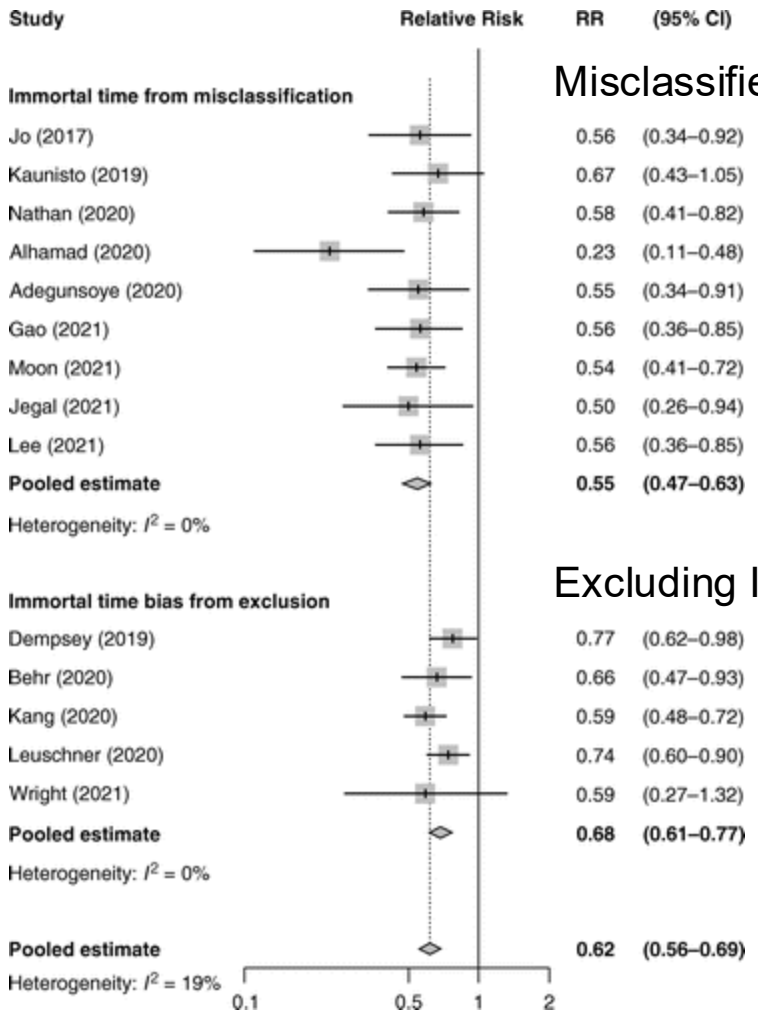
- Large cohorts
- Real world: no restrictive inclusion criteria

Registry problem

- Outcome may be biased by practices
- Prevalent cases, inconsistent ‘start’
- Immortal time bias with antifibrotics



DOI: 10.3389/fmed.2023.1157706



Misclassified as exposed

Excluding IT for cases only

DOI: 10.1164/rccm.202207-1301LE

3. The value of observational studies in modelling endpoints

Natural history of pulmonary fibrosis

Longitudinal disease behaviour

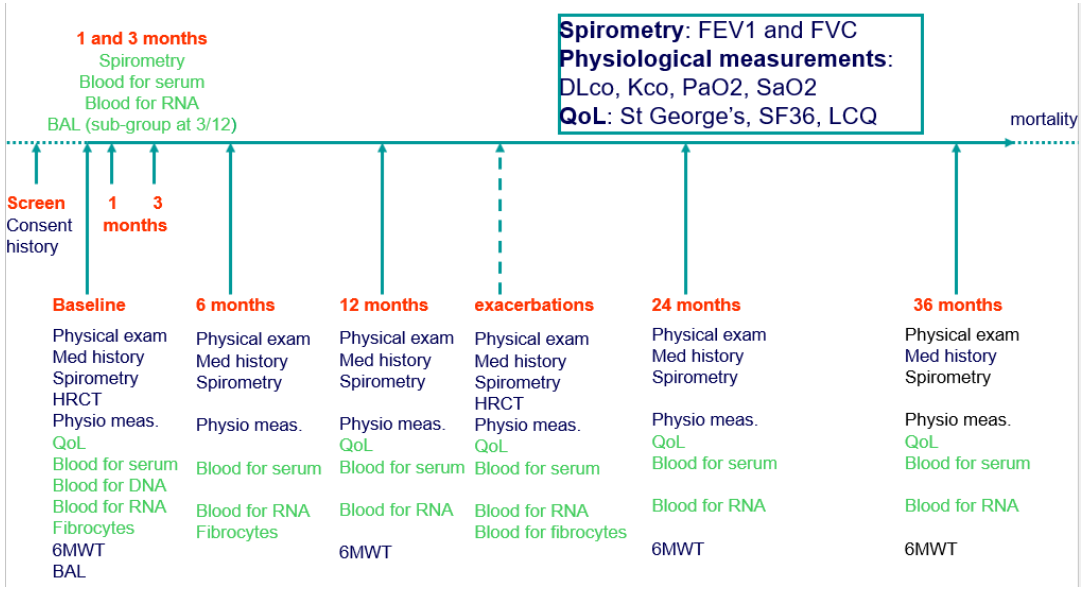
- IPF (PROFILE study)
- Fibrotic ILD (INJUSTIS study)

- Incident cases
- Protocolised follow-up timepoints/sampling
- *Natural history – similarities across fILD*

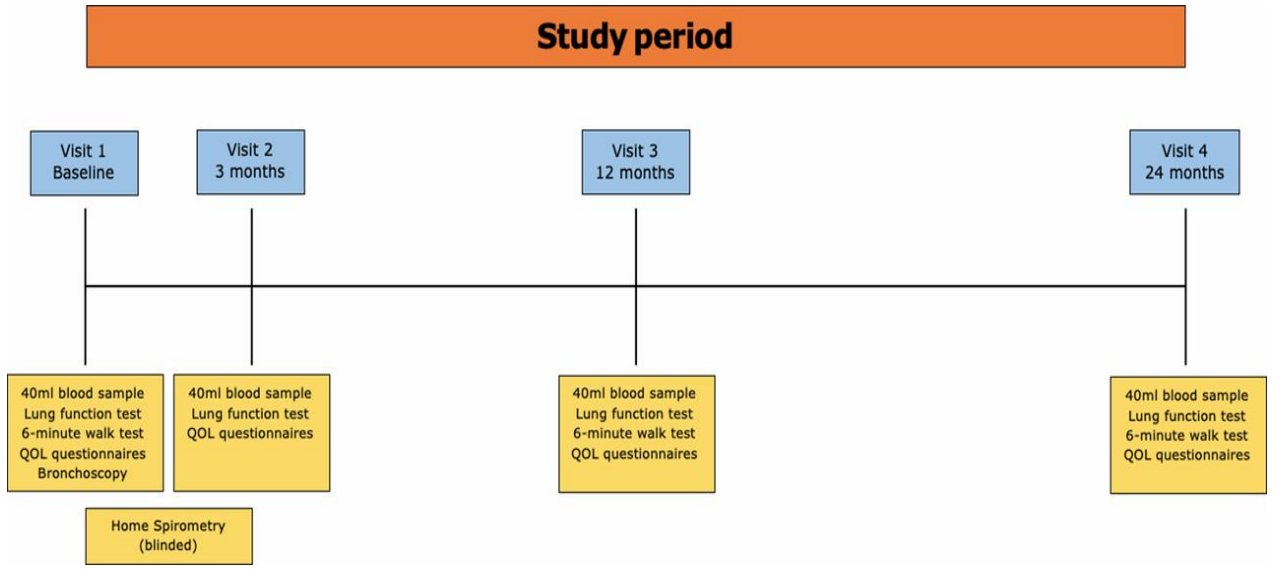
Fibrotic ILD severity

	Overall	IPF	non-IPF
Lung physiology			
FEV1 (% predicted)	86.8 (23)	87.6 (21.6)	86.6 (23.5)
FVC, L	2.85 (0.86)	3.00 (0.89)	2.80 (0.84)
FVC (% predicted)	84.4 (21.1)	84.6 (18.9)	84.4 (21.8)
DL_{CO} (% predicted)	57.5 (17.6)	58.7 (16.0)	57.1 (18.1)

PROFILE – idiopathic pulmonary fibrosis



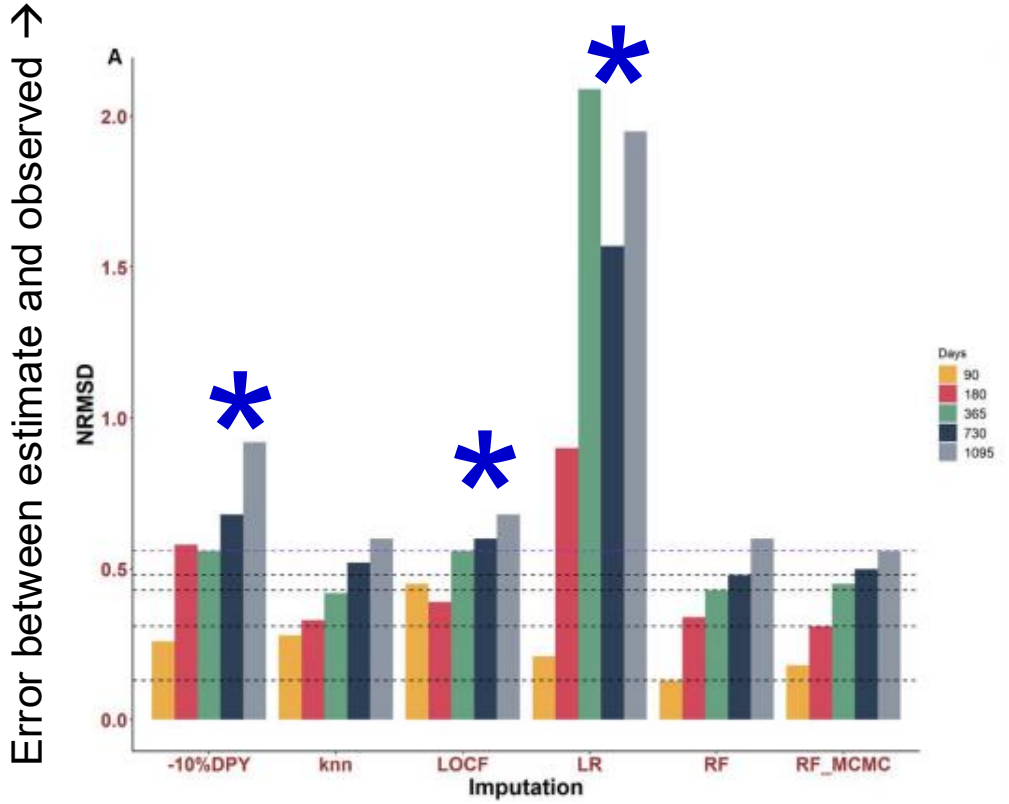
INJUSTIS – fibrotic interstitial lung disease

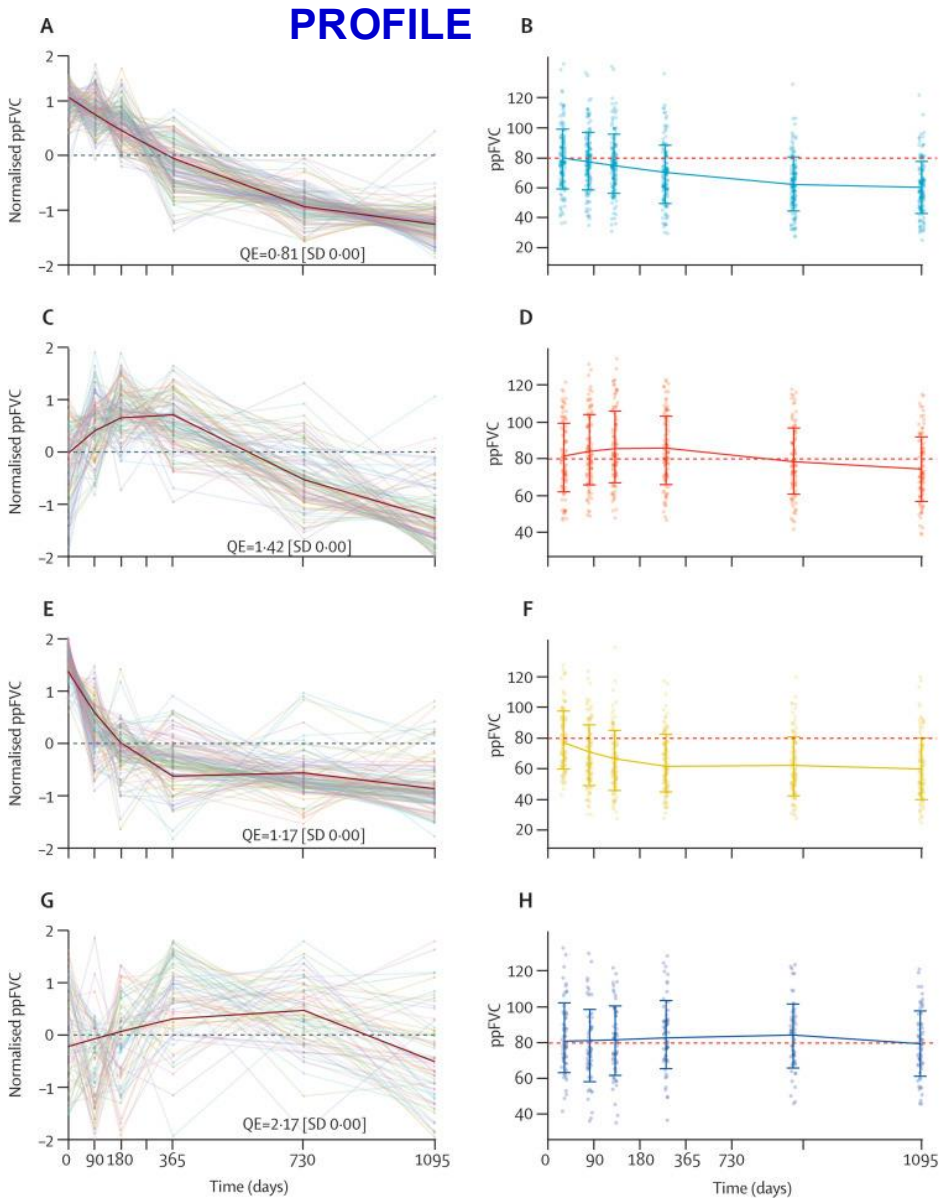


3. The value of observational studies in modelling endpoints

Understanding heterogeneity in trajectory

- Disease severity linked to missingness
- Traditional imputation leads to error
- Discrete trajectories of lung function change





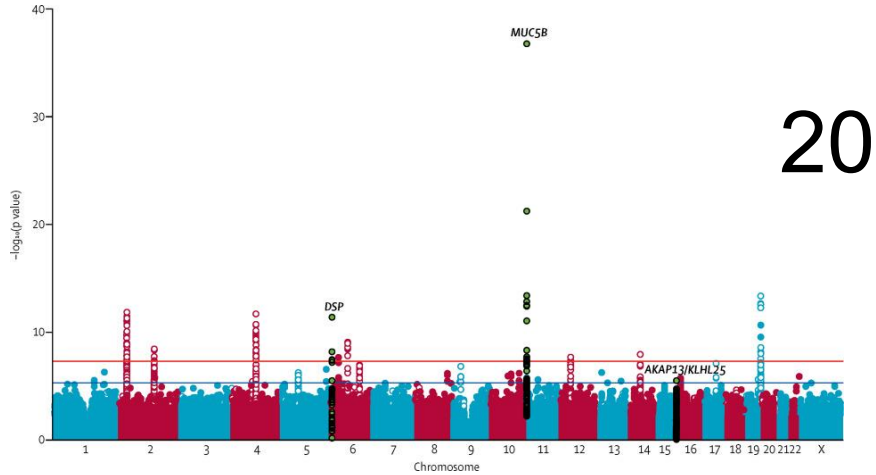
DOI: 10.1016/S2589-7500(22)00173-X

3. The value of observational studies in modelling endpoints

Novel strata and endpoints from real-world populations

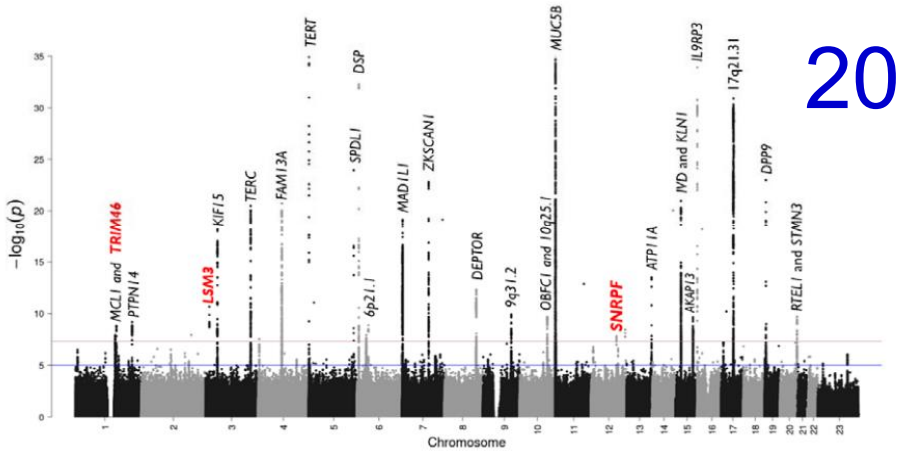
Clinically curated contribution to GWAS

PROFILE



2017

DOI: 10.1016/S2213-2600(17)30387-9

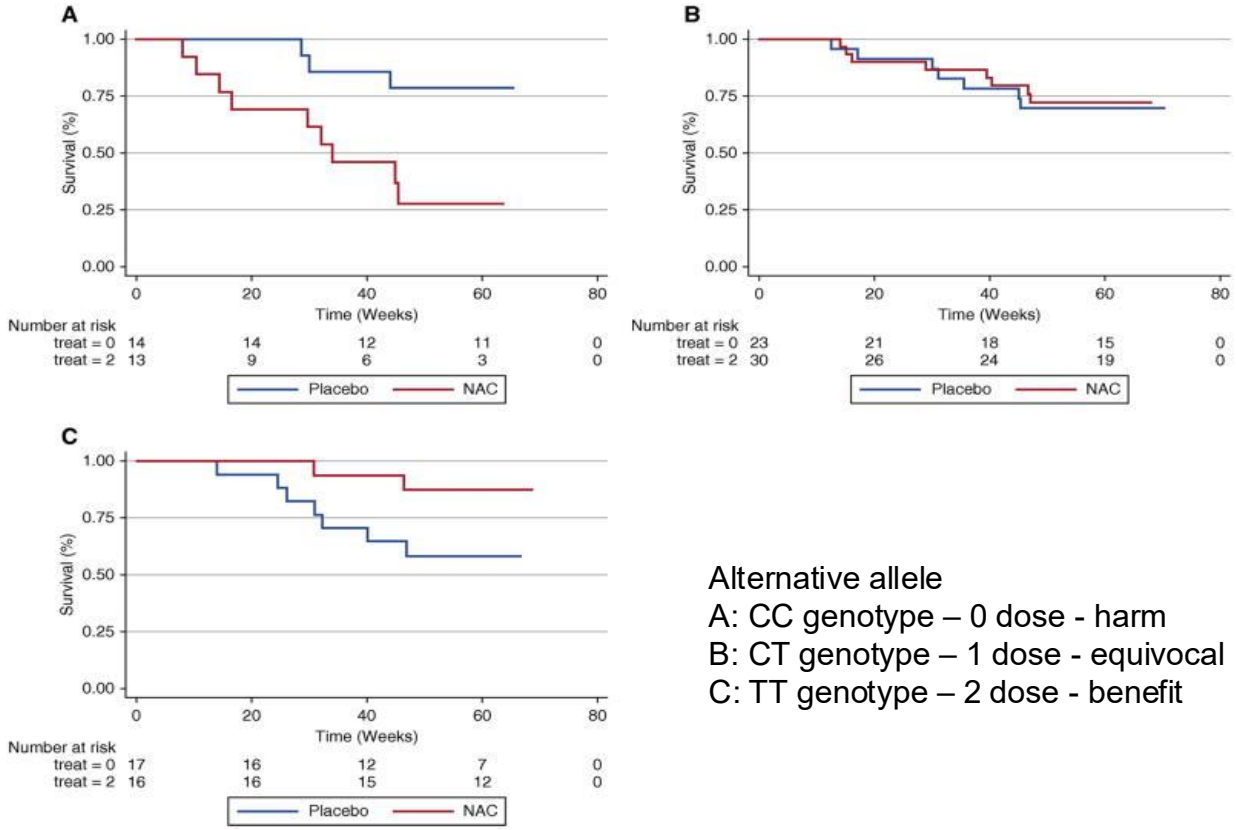


2025

DOI: 10.1101/2025.01.30.25321017

Pharmacogenetic design – *novel strata*

TOLLIP rs3750920 and survival after NAC anti-inflammatory therapy (PANTHER)



Alternative allele
A: CC genotype – 0 dose - harm
B: CT genotype – 1 dose - equivocal
C: TT genotype – 2 dose - benefit

DOI: 10.1164/rccm.201505-1010OC

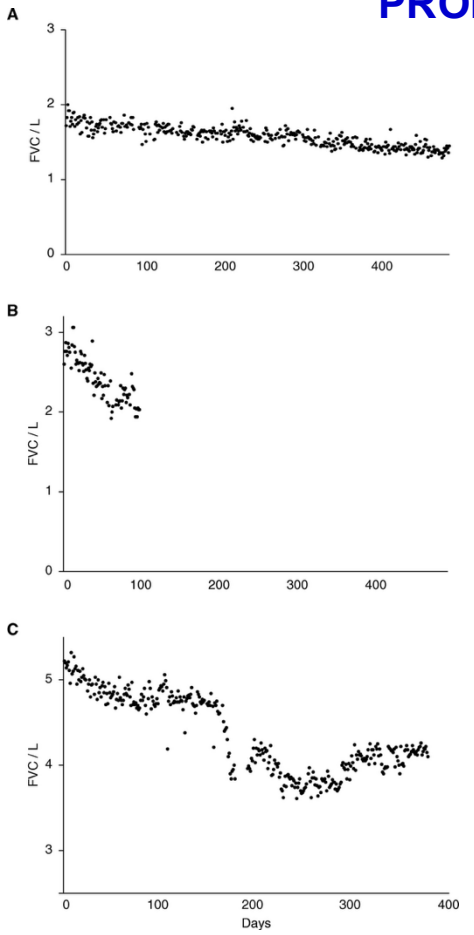
3. The value of observational studies in modelling endpoints

Novel strata and endpoints from real-world populations

Home spirometry

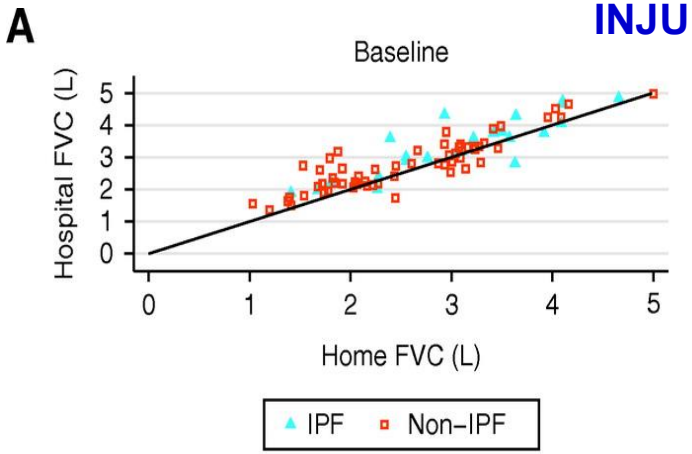
Trajectories

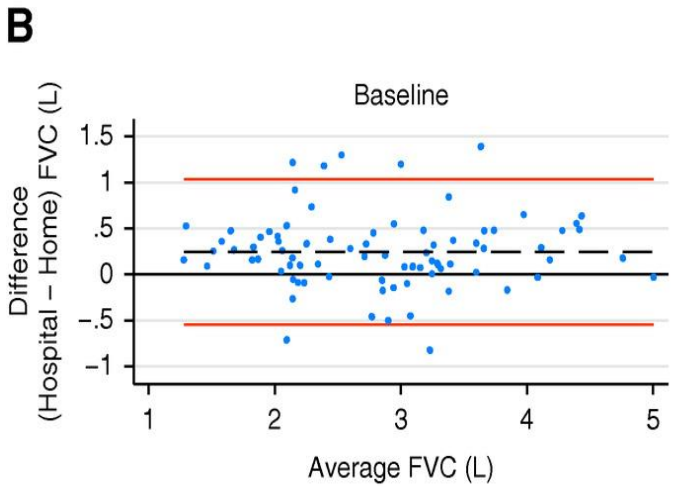
PROFILE



Agreement

INJUSTIS

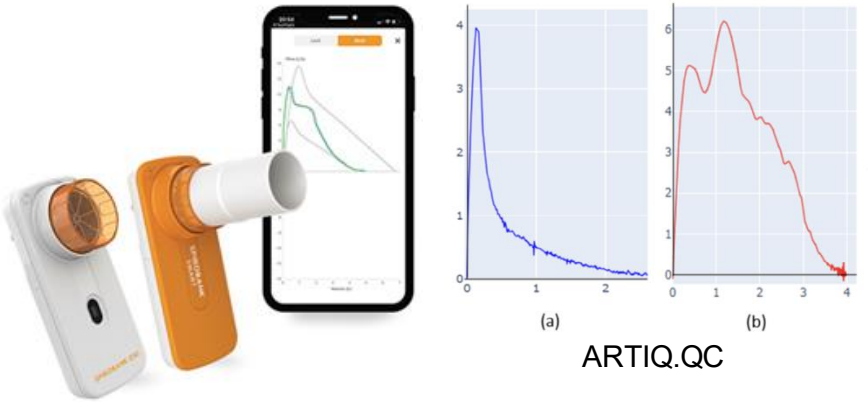




Novel endpoints

Spiro	Placebo	Antifib
Clinic	-113.0 ml	-17.8 ml
Home	-157.1 ml	-87.7 ml

DOI: 10.1016/S2213-2600(19)30341-8



ARTIQ.QC

DOI: 10.1164/rccm.201511-2152OC

DOI: 10.1513/AnnalsATS.202105-612RL

4. Setting expectation for future trial design

Learning from prospective observational studies

Characterising target populations

- Inclusive trials with real-word cases
- Increased opportunity to benefit
- Opportunity to stratify upon mechanism

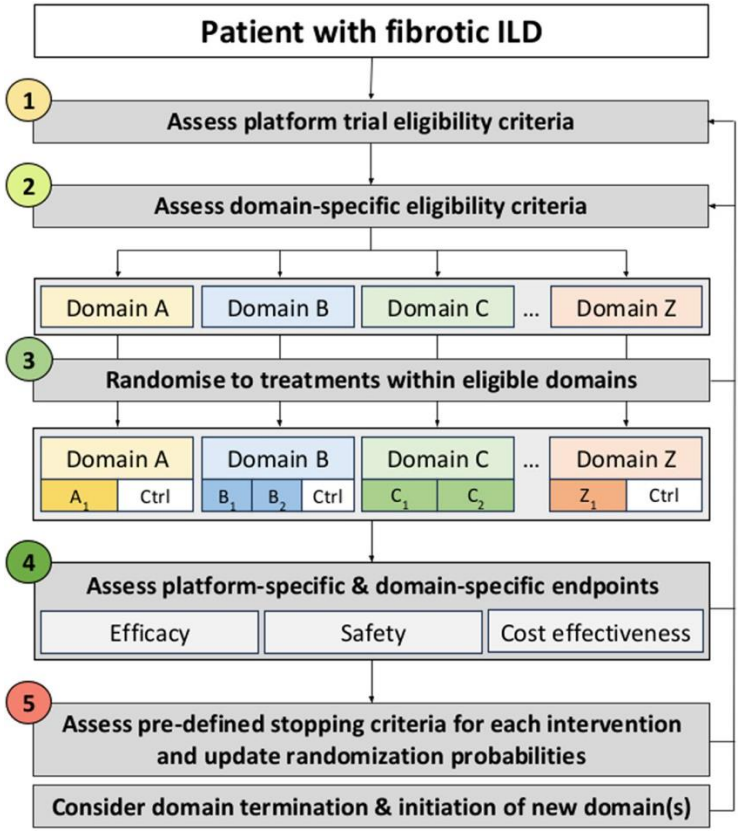
- Embedded
- Adaptive
- Multifactorial

Defining clinical outcomes

- Natural history to inform power calculations
- Techniques to address missing data
- Decisions based on early changes

- Simulations
- SAP
- Response

Platform trial?



DOI: 10.1136/thorax-2023-221148

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Logistical and Statistical Considerations of a Shared Control in Platform Trials

Harnessing the Potential of Platform Trials in Chronic Diseases

Society for Clinical Trials Annual Meeting

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May 20, 2025

Disclosure

- No relevant disclosures

Outline of Presentation

- Introduction to Master Protocols & Platform Trials
- Features of Platform Trials
- Considerations Related to the Shared Control Arm
- Summary & Conclusion

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Introduction to Master Protocols & Platform Trials

Master Protocols

- **Master protocol**: study protocol designed to answer multiple research questions within single trial infrastructure
  - Evaluate multiple interventions and/or disease populations, with “sub-protocols” for each evaluation within master protocol
- Originated in oncology, but use has expanded to other disease areas
- FDA guidance on master protocols
  - COVID-19 (May 2021)
  - Oncology Drugs and Biologics (March 2022)
  - Drugs and Biological Products (DRAFT, December 2023)
- Can be complex but allow for flexibility and increased efficiency, if implemented appropriately

Master Protocols

- Three major trial design types which use a master protocol

Trial Type	Treatments	Disease Groups/Subtypes	Timing of Multiple Evaluations
Basket	Single	Multiple	Simultaneous
Umbrella	Multiple	Single	Simultaneous
Platform	Multiple	Single or Multiple	Flexible, can enter/exit throughout

- Some variation/inconsistency in terminology used
  - Design types (above)
  - Multiple evaluations lead to “sub-protocols” or “appendices” to the master protocol
    - Will use intervention specific sub-protocol (ISSP) here
  - “Disease cohorts”
  - “Treatment domains”

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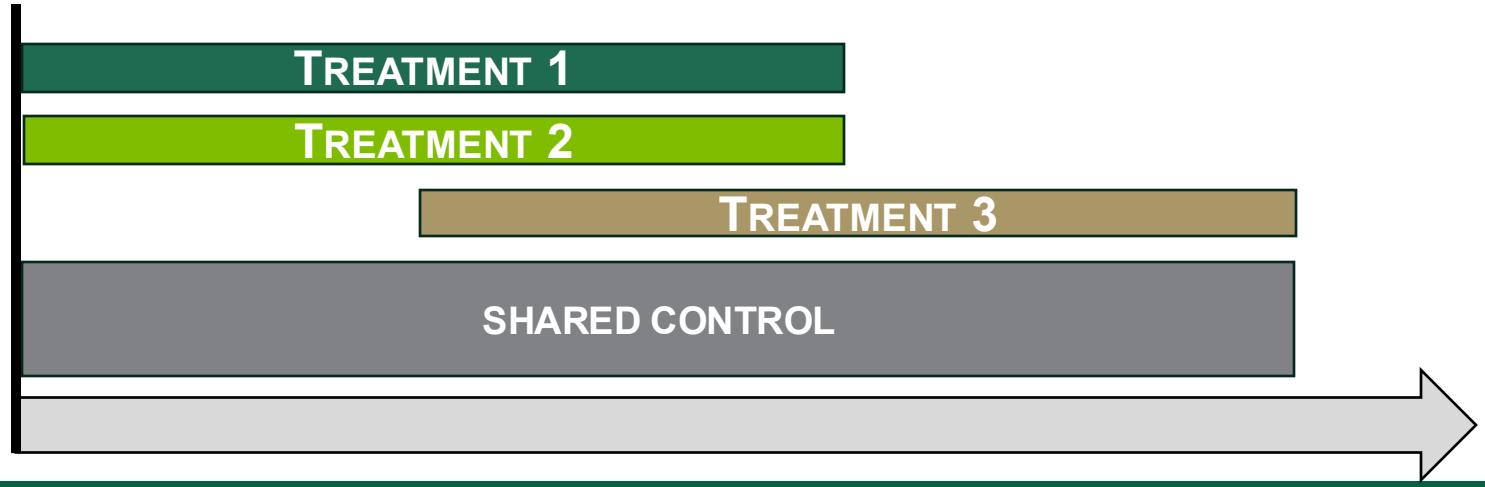
Features of Platform Trials

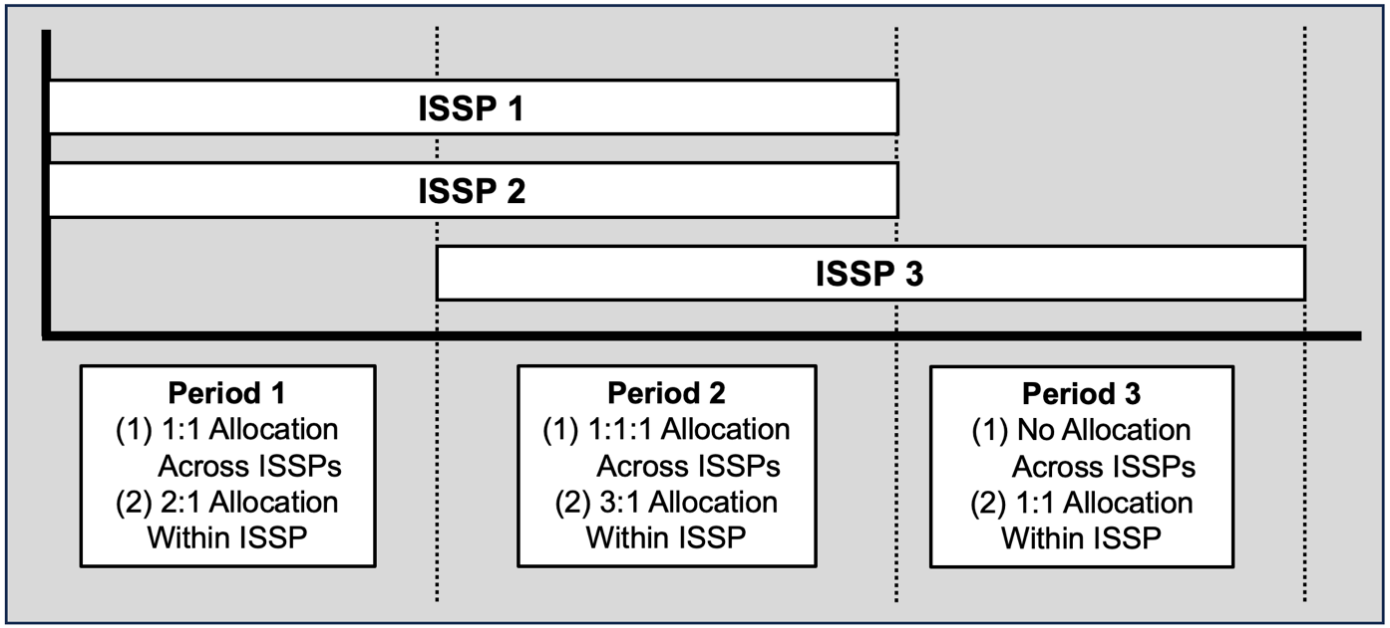
Key Features of Platform Trials

- **Answer multiple research questions**
  - Multiple interventions and/or multiple disease populations
- **Adaptive**
  - Allow interventions to enter/exit throughout
- **Shared control arm**
  - Combined control group



Randomization in Platform Trials

- Randomization often done in a two-stage procedure
  1. Randomized to a sub-protocol, with equal allocation
  2. Randomized to active treatment or control, with k:1 allocation (active:control), where k is number of ISSPs currently enrolling



- Advantages and disadvantages to this strategy

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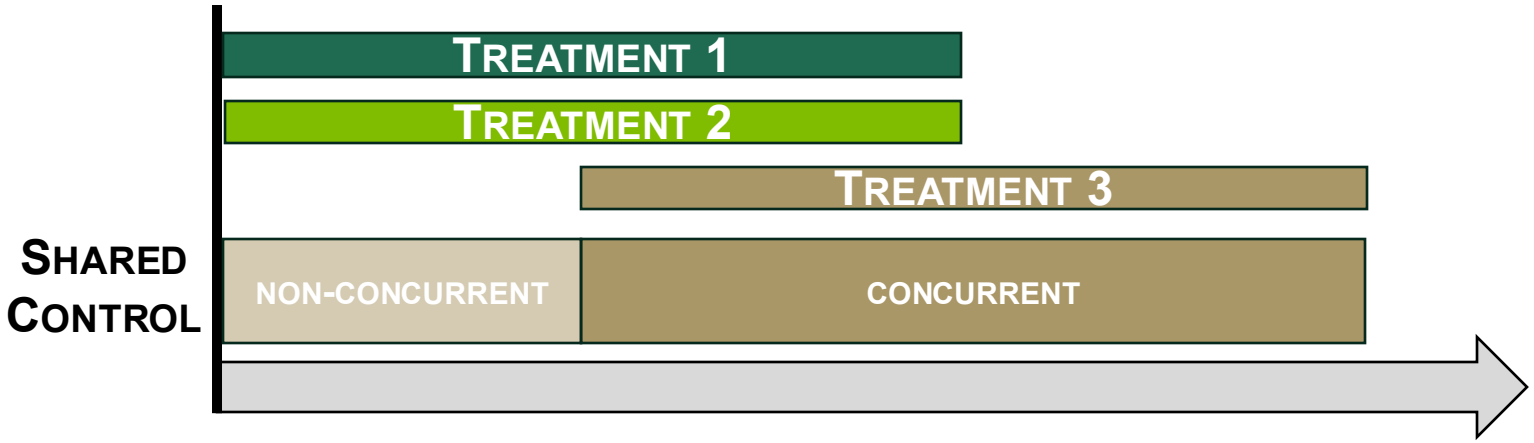
Considerations Related to the Shared Control Arm

Shared Control Arm

- Shared control group often defined according to timing in the platform trial



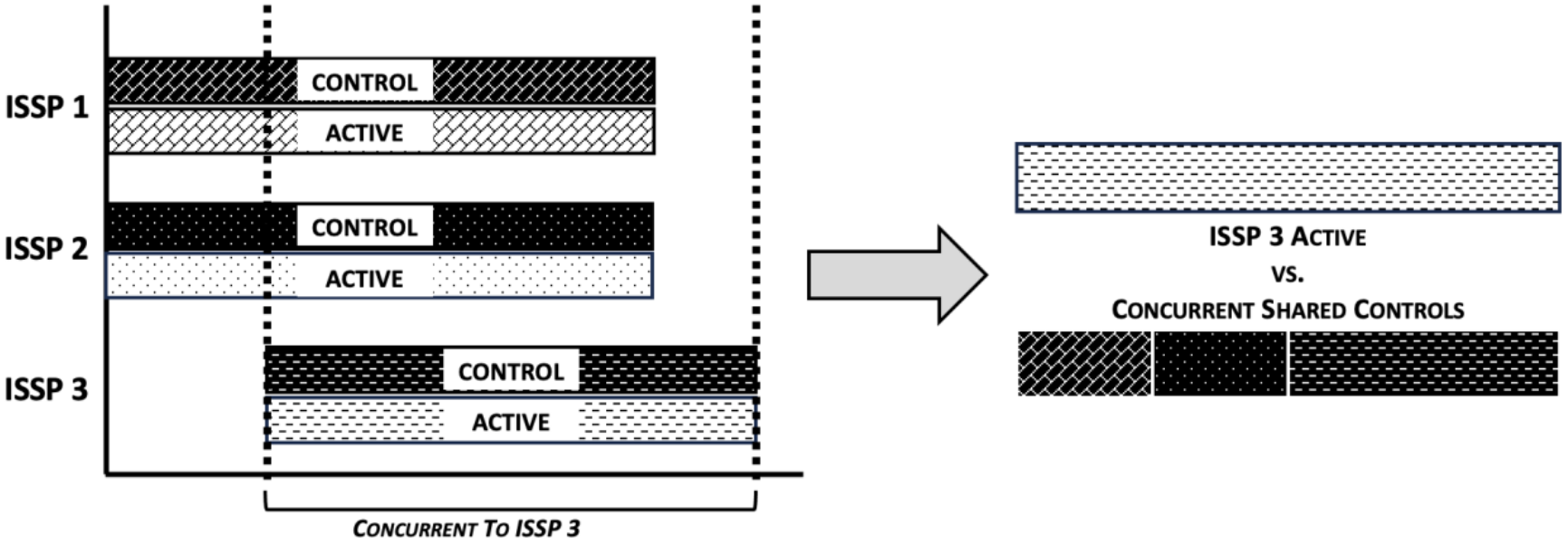
- Can also be defined according to other characteristics (e.g., eligibility to be randomized to certain ISSP)
- There could be factors which lead to systematic differences between controls
  - According to time (e.g., “placebo drift”)
  - According to ISSP
- FDA draft guidance (Dec. 2023) highlights selection of control group as major design and analysis considerations

Differences in Controls Over Time

- **Key Questions**:
  - Can we use non-concurrent control data?
  - And if so, how should we do this?
- Regulatory perspective
  - Guidance to date focuses on primary analyses of efficacy using only concurrent controls
  - Secondary or exploratory analyses may involve nonconcurrent controls
- Various analytical approaches for incorporating non-concurrent controls and literature supporting their utility
  - Consider evidence from other related, well-established research areas (e.g., historical data, real-world evidence, meta-analyses)

Differences in Controls by ISSP

- Even with concurrent only, we could have systematic differences between controls (e.g., according to ISSP)
  - Try to prevent this by ensuring ISSPs share as much as possible through the central master protocol
- For example, different modes of administration across ISSPs
  - To maintain blinding within ISSP, require different placebo for different ISSPs
  - What if different form of placebo elicits different placebo effects?



General Analytic Considerations

- Given these potential challenges, careful consideration is required in developing an analysis plan
- Defining the shared control group
  - Which control participants should be used in any given analysis?
  - Are the controls concurrent? Are they “co-eligible”?
  - Is there concern of differential placebo effects by ISSP?
- Modeling approaches (e.g., dynamic borrowing) to account for potential time period effects and/or differences by ISSP
- Sensitivity analyses to verify findings
  - For example, using only controls from the analysis ISSP

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Summary & Conclusion

Considerations are Not Limited to Shared Control

- Considerations across the lifecycle of a trial

Design	Decision rules for arm-dropping (efficacy and futility), study procedures, and inclusion/exclusion for an overarching protocol Simulations for sample size calculations
Conduct	Randomization procedures, consenting, blinding (and all may need adjustments any time an arm enters/exits) Funding and potentially undefined timeline
Analysis	Use of shared control data in analyses for a specific arm – which controls should be included in a given analysis?
Dissemination	Reporting and data sharing while platform may be ongoing

Summary & Conclusion

- Master protocols, and platforms in particular, have distinct advantages, including a great deal of flexibility
- Flexibility comes with unique challenges and considerations that span the lifecycle of the trial
  - These include ones related to a key feature of the platform trial, the shared control arm
- Strategies exist to address both logistical and statistical considerations, including those related to the shared control
- Many examples of successful platform trials when implemented in appropriate settings with thoughtful design elements and analytic plans (at this session!)

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- Path To Prevention (P2P) Platform Trial Teams, especially P2P Stats Group

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Thank you!

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DATA coordinating and Collaborative Research Unit (DATA CRU)

https://www.uab.edu/datacru/

Innovating & Adapting in Platform Trials for Chronic Diseases

Barbara Wendelberger, PhD

The Annual Meeting of the Society for Clinical Trials
20 May 2025

BERRY

Shaping the Future
of Trial Design in Chronic Diseases

Definition

Chronic diseases are defined broadly as conditions that last 1 year or more and require ongoing medical attention or limit activities of daily living or both.

https://www.cdc.gov/chronic-disease/about/index.html

BERRY

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- **The right questions**

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  - Are we leveraging natural history study (NHS) data?

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  - Disease progression modeling

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  - Embedded, multifactorial designs

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  - Embedded, multifactorial designs
  - Evidence-based simulation assumptions, run-in data, and borrowing from NHS

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The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES

ATTENTION: Due to global market conditions, you may experience a delivery delay for your print issue of the New England website. We regret any print delays and are working to ensure all issues are delivered as

REVIEW ARTICLE | THE CHANGING FACE OF CLINICAL TRIALS

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Authors: Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D. Author Info & Affiliations

Published July 6, 2017 | N Engl J Med 2017;377:62-70 | DOI: 10.1056/NEJMra1510062 | VOL. 377 NO. 1

High-quality evidence is what we use to guide medical practice. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

BERRY

Platform Trial Innovation

REMAP-ILD

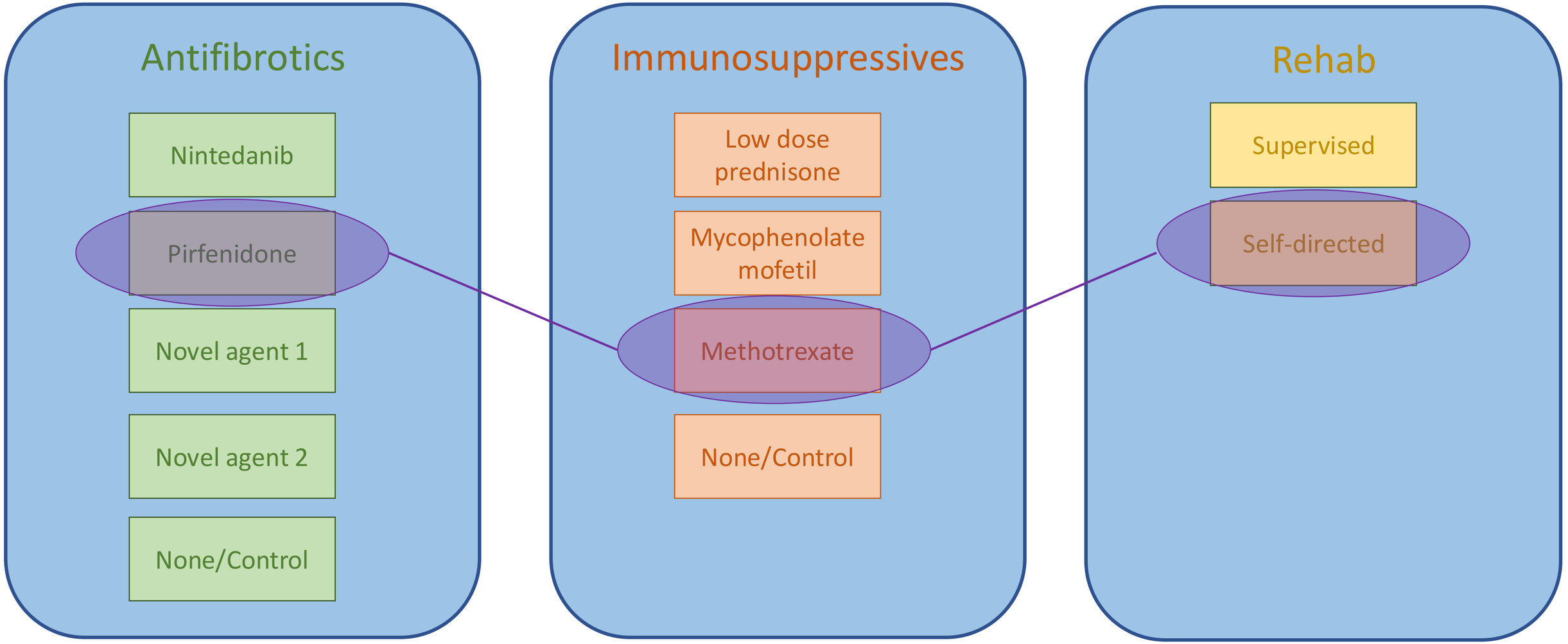
Randomized Embedded Multifactorial Adaptive Platform Trial in Interstitial Lung Disease

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

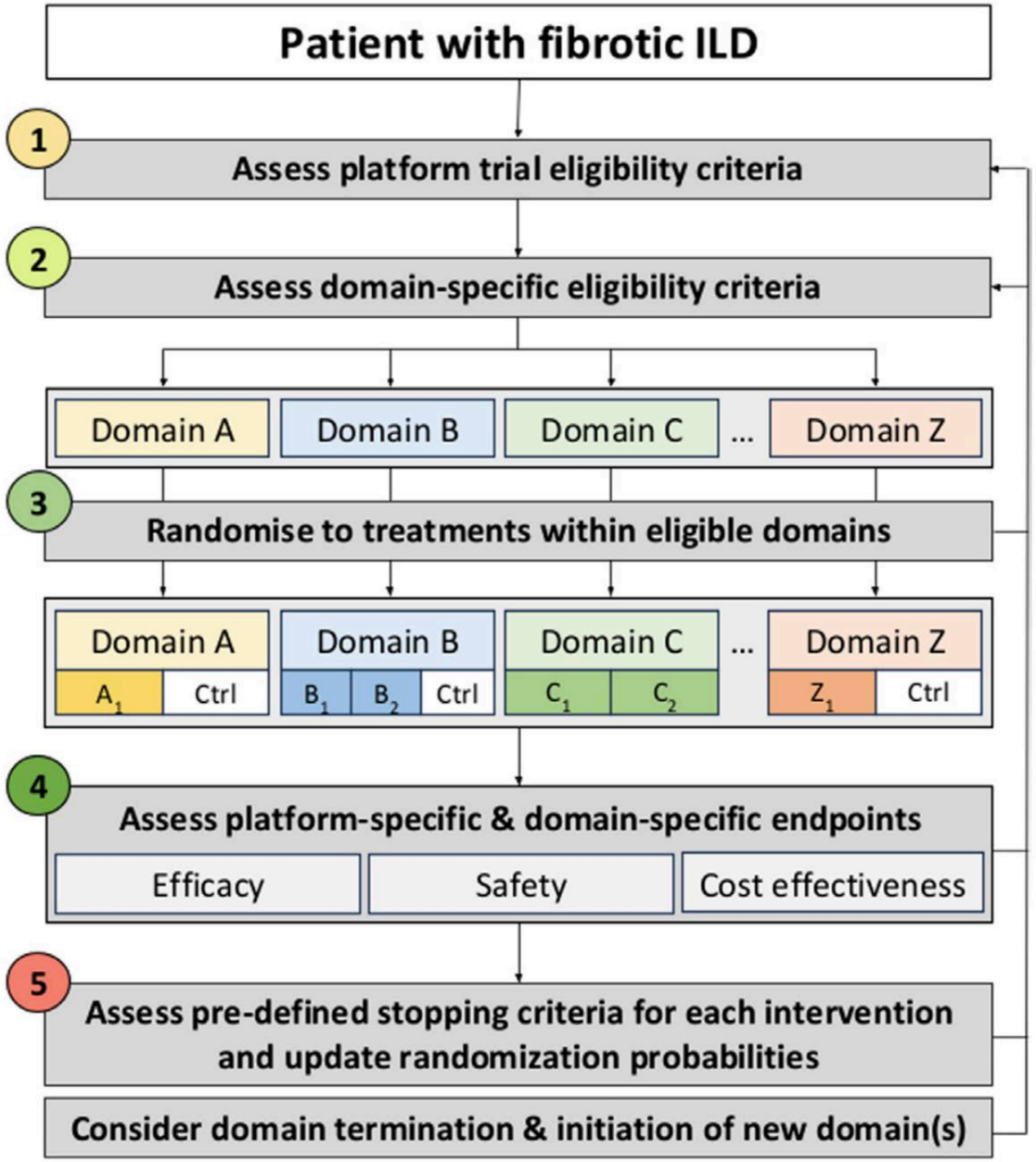
Randomized Embedded Platform Trial in Stage 2B Neuronal α-Synuclein Disease (NSD)

Randomized Embedded Multifactorial Adaptive Platform Trial in Interstitial Lung Disease

REMAP-ILD



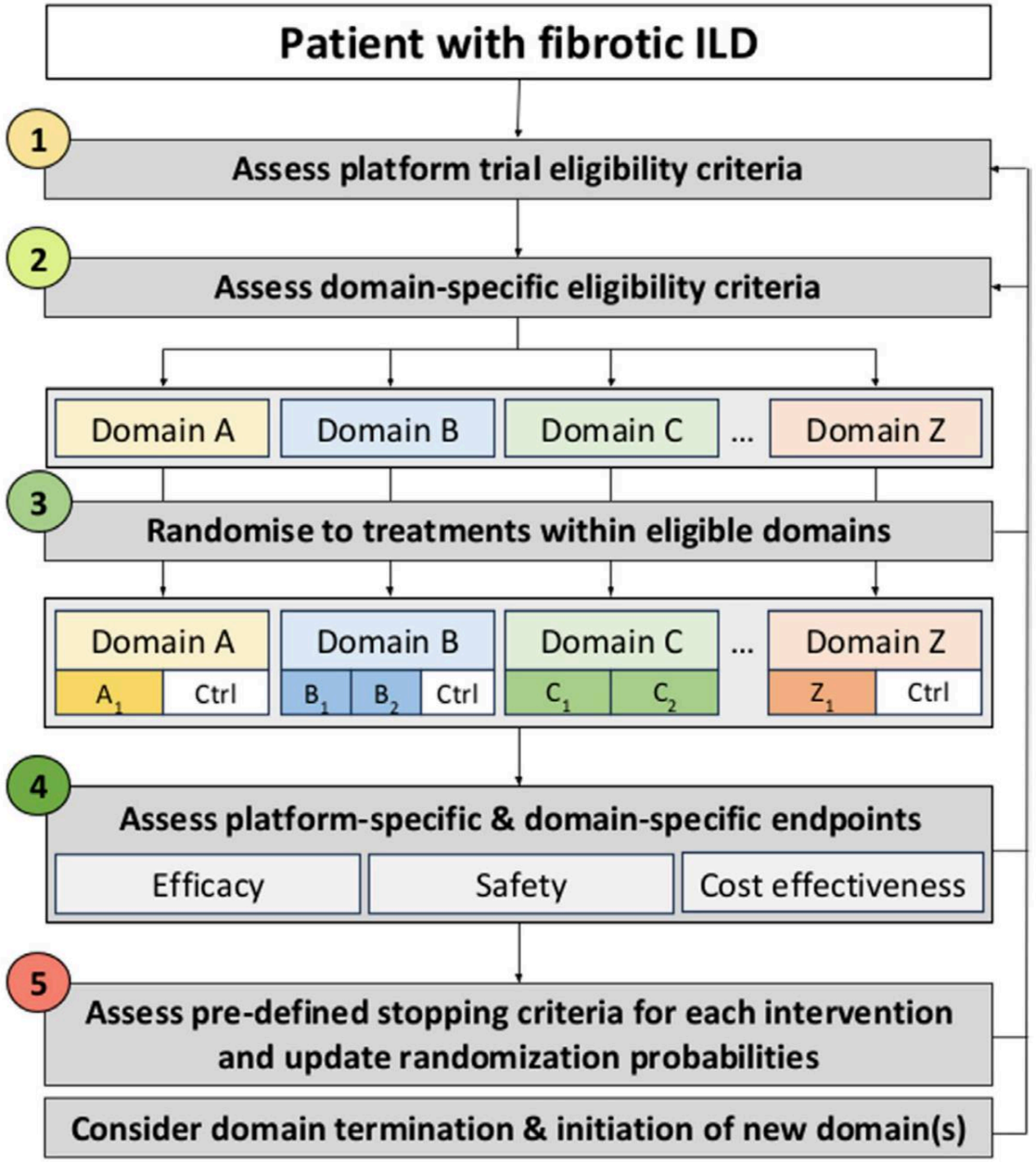
BERRY Multiple factors from different domains create a regimen.



REMAP-ILD

BERRY

Kawano-Dourado L, Kulkarni T, Ryerson CJ REMAP-ILD consortium, *et al* Adaptive multi-interventional trial platform to improve patient care for fibrotic interstitial lung diseases *Thorax* 2024;**79:**788-795.



REMAP-ILD

Trial Adaptations

- Early success
- Futility

Analysis Triggers

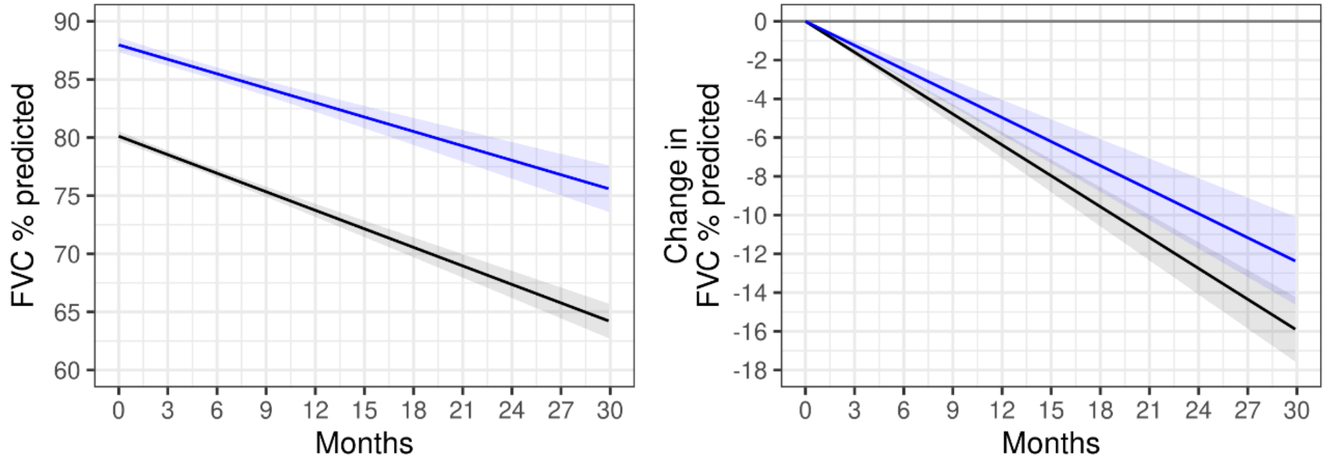
- # patients with 1 year of follow up
- Calendar based thereafter

BERRY

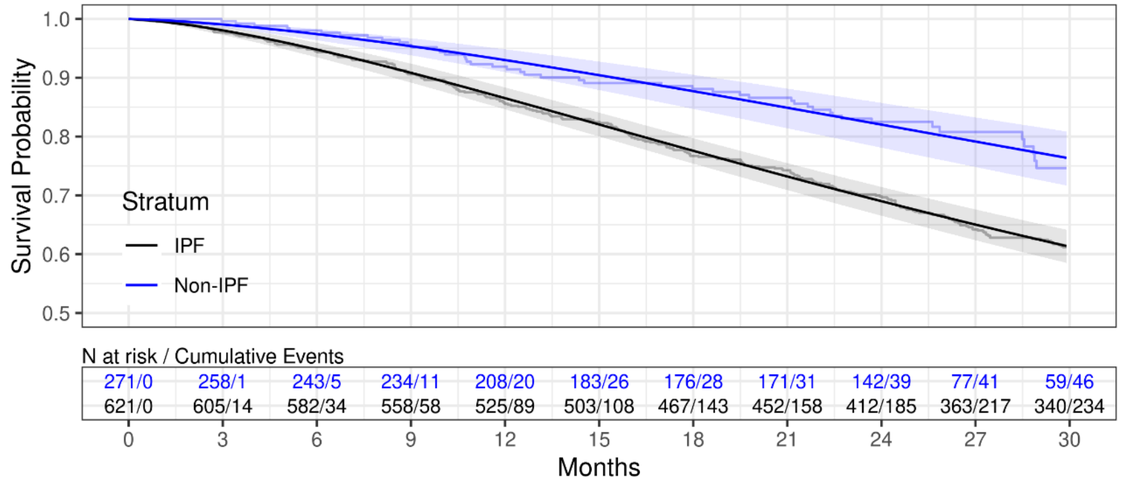
Kawano-Dourado L, Kulkarni T, Ryerson CJ REMAP-ILD consortium, *et al* Adaptive multi-interventional trial platform to improve patient care for fibrotic interstitial lung diseases *Thorax* 2024;**79:**788-795.

Joint Bayesian Disease Progression Model

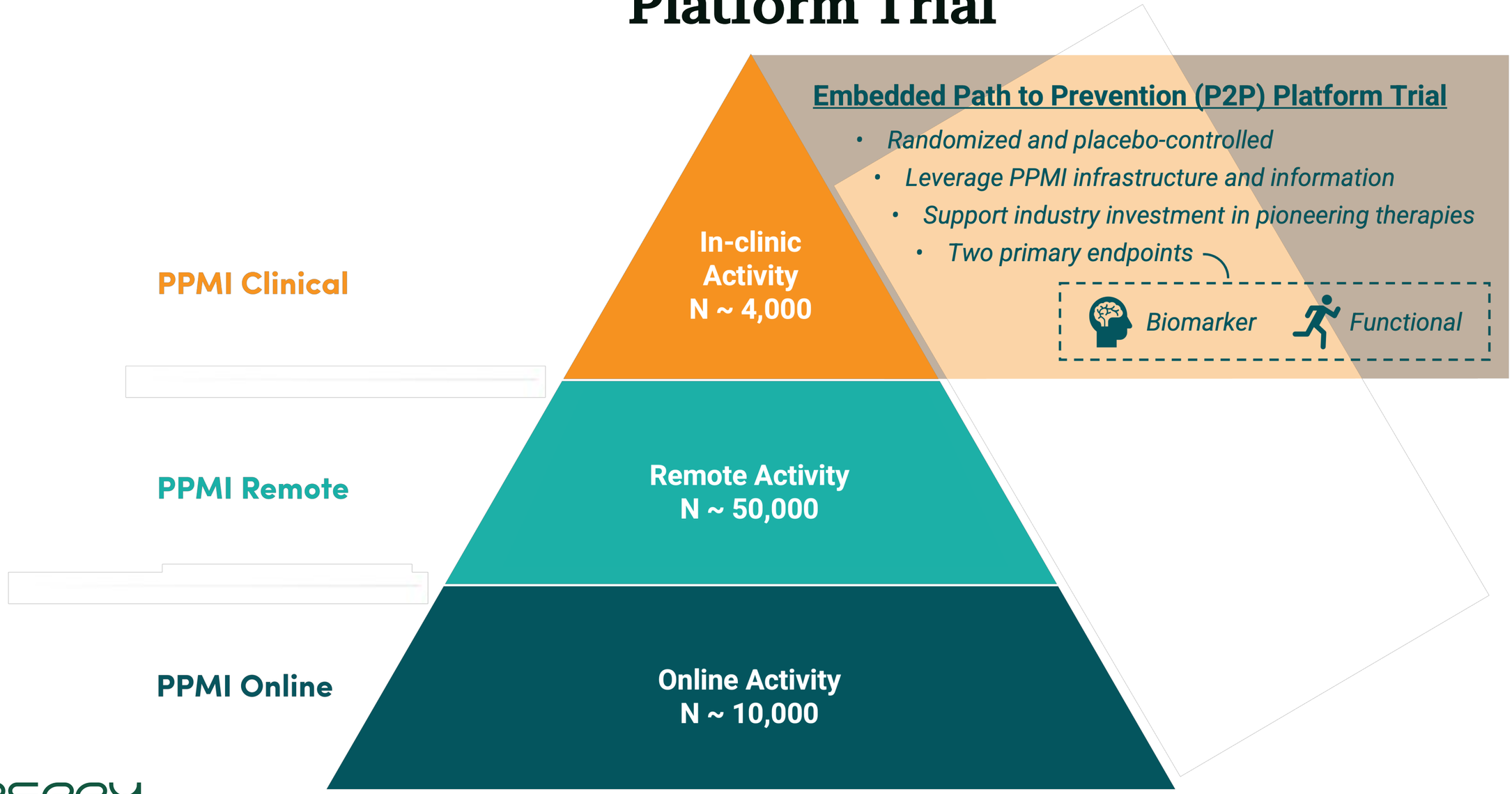
Lung function



Survival

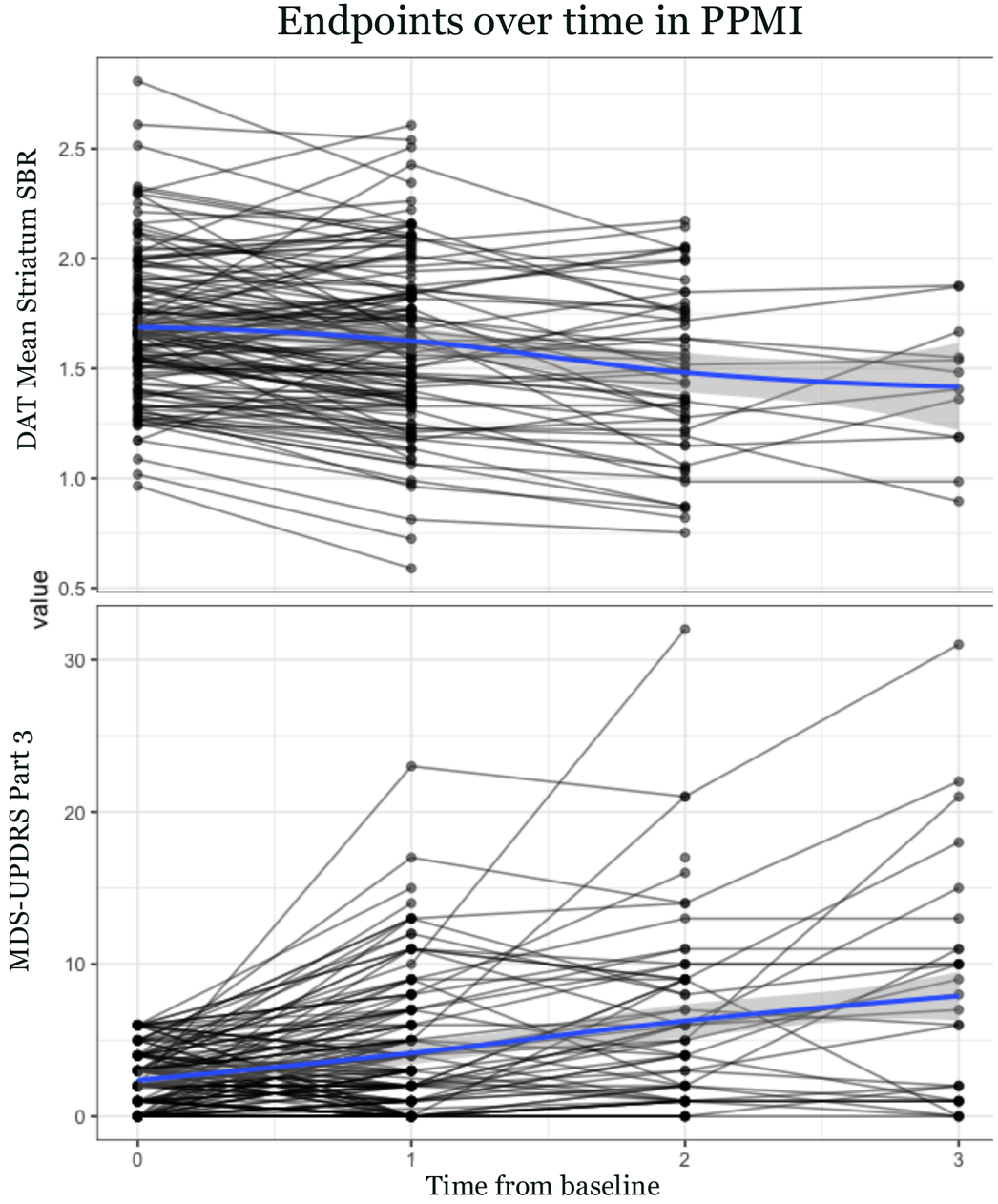


Path to Prevention (P2P) Platform Trial



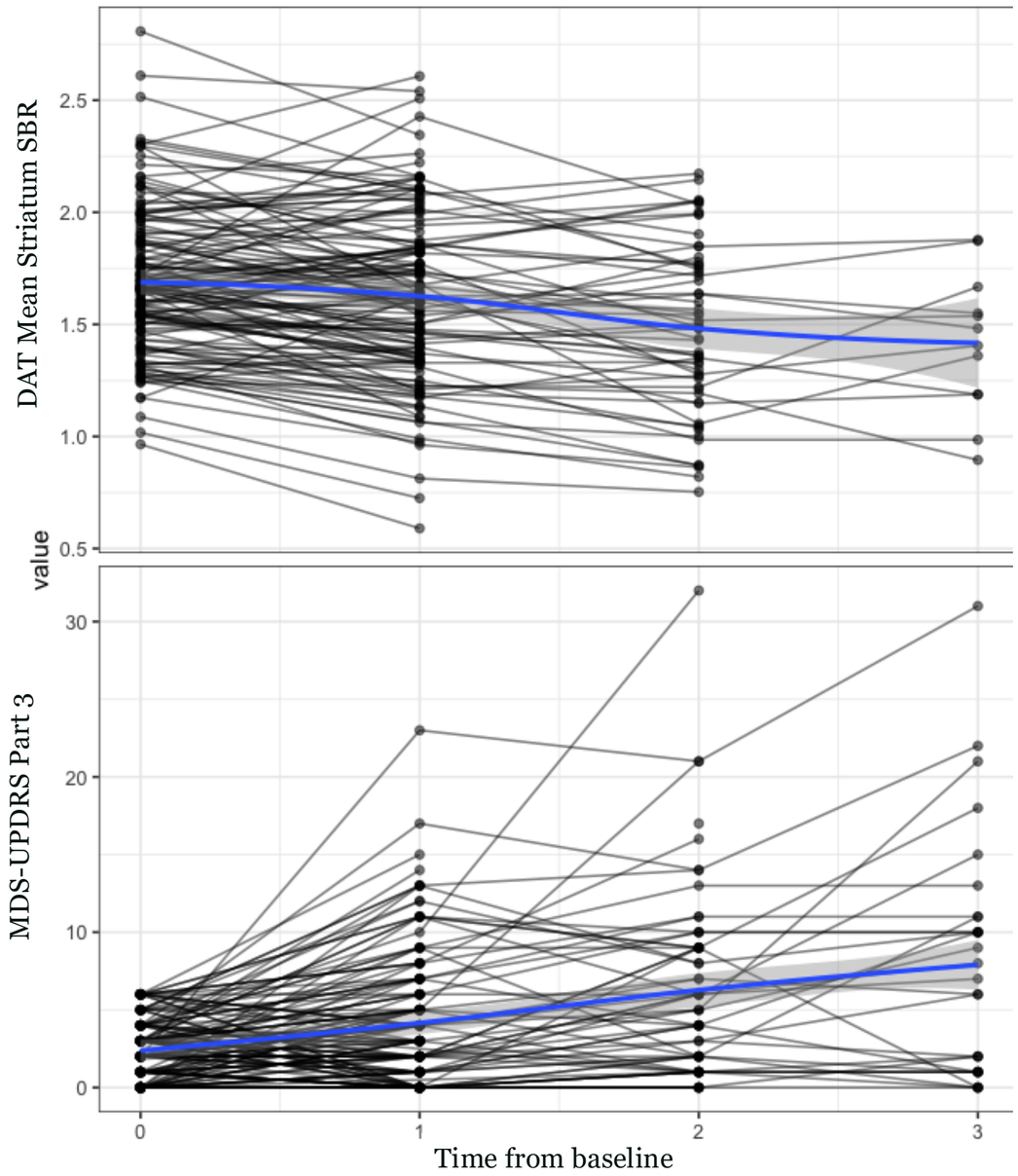
Adapted with permission from https://www.ppmi-info.org/study-design (accessed on April 16, 2025).

Two Primary Endpoints



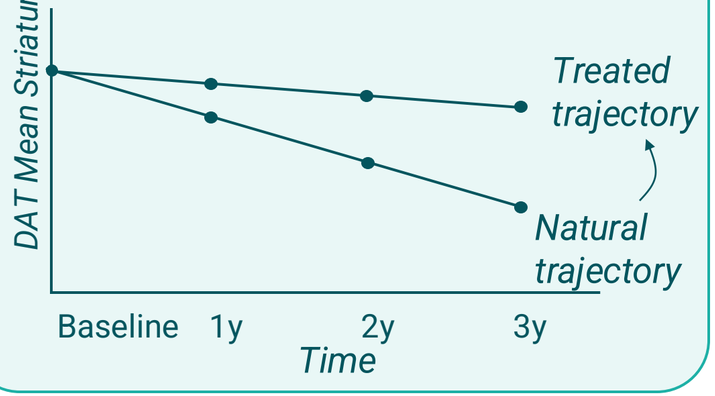
Two Primary Endpoints

Endpoints over time in PPMI



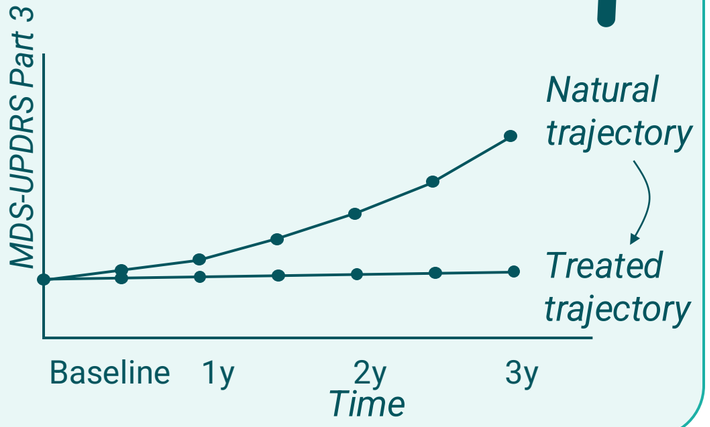
BIOMARKER

DAT Mean Striatum SBR

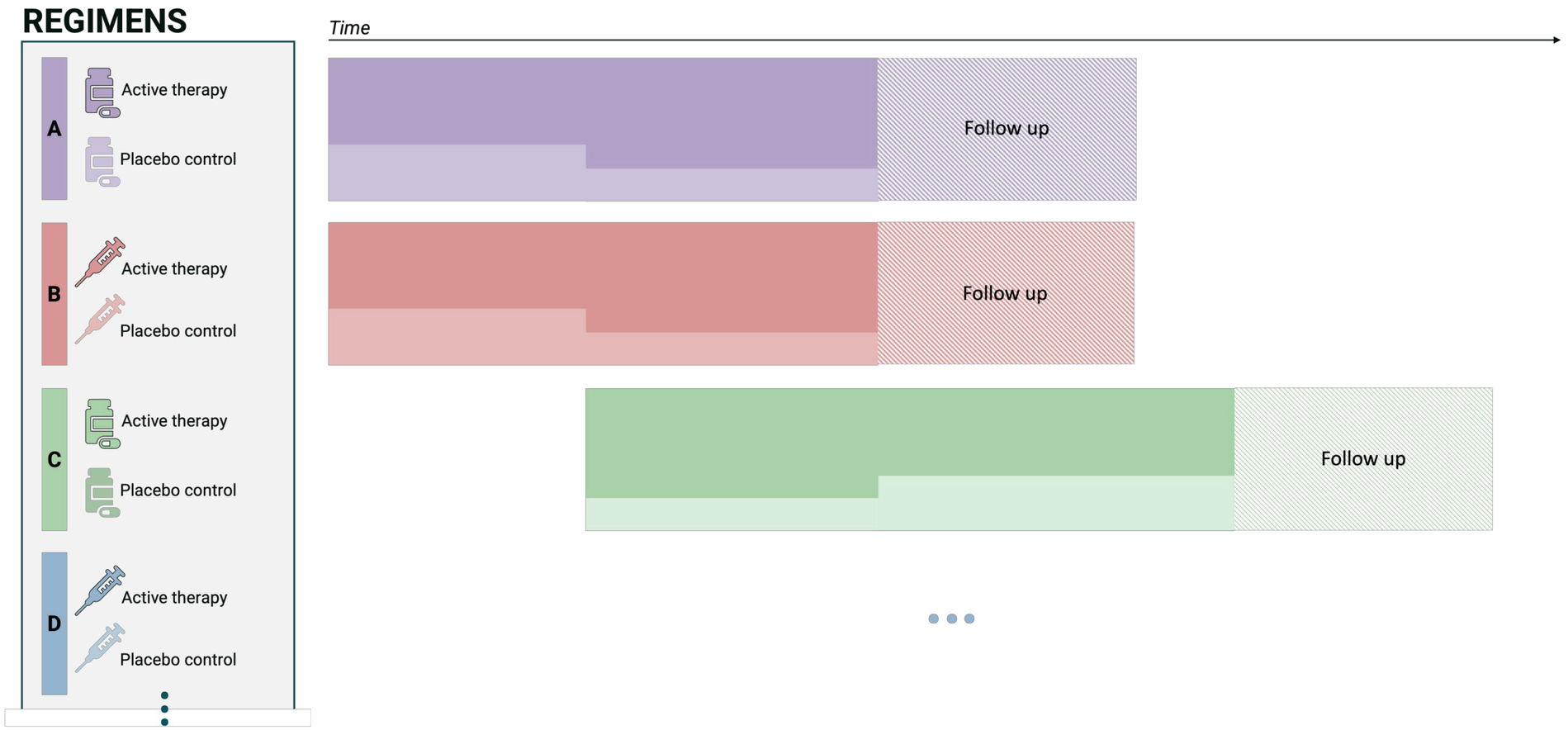


FUNCTIONAL

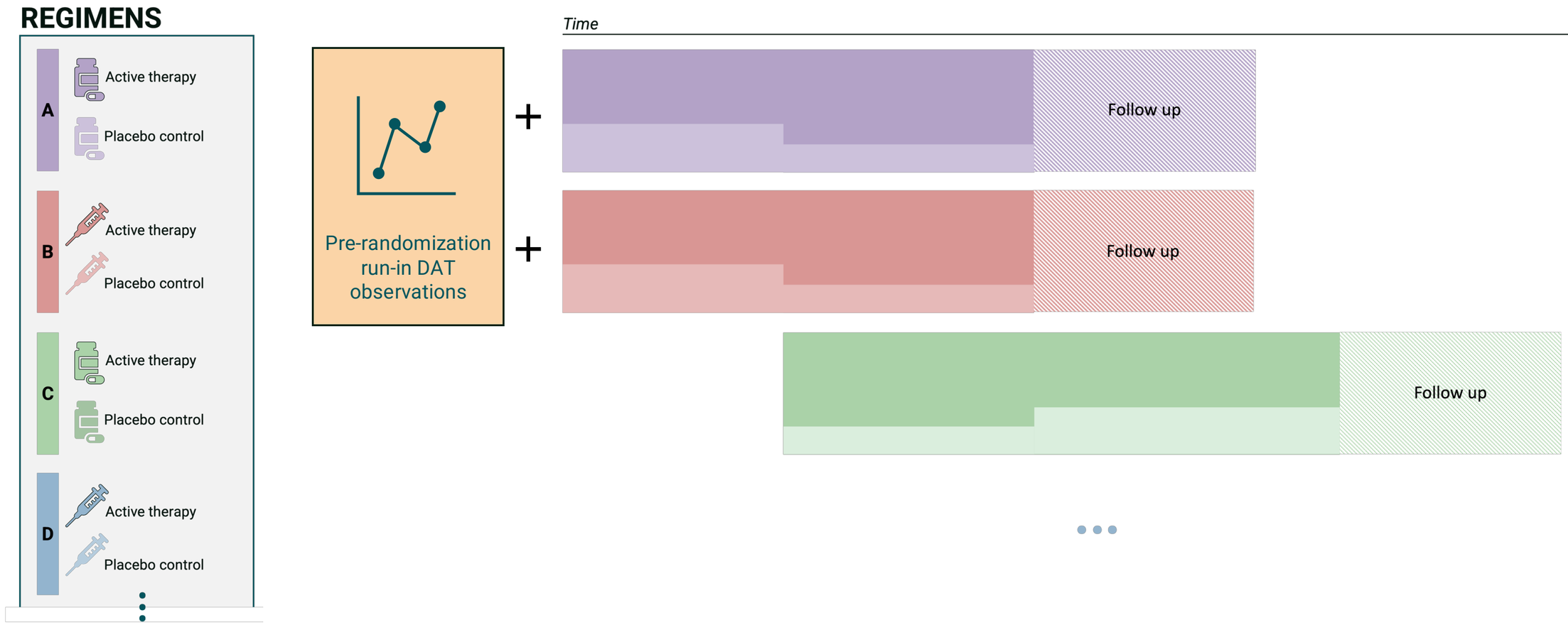
MDS-UPDRS Part 3



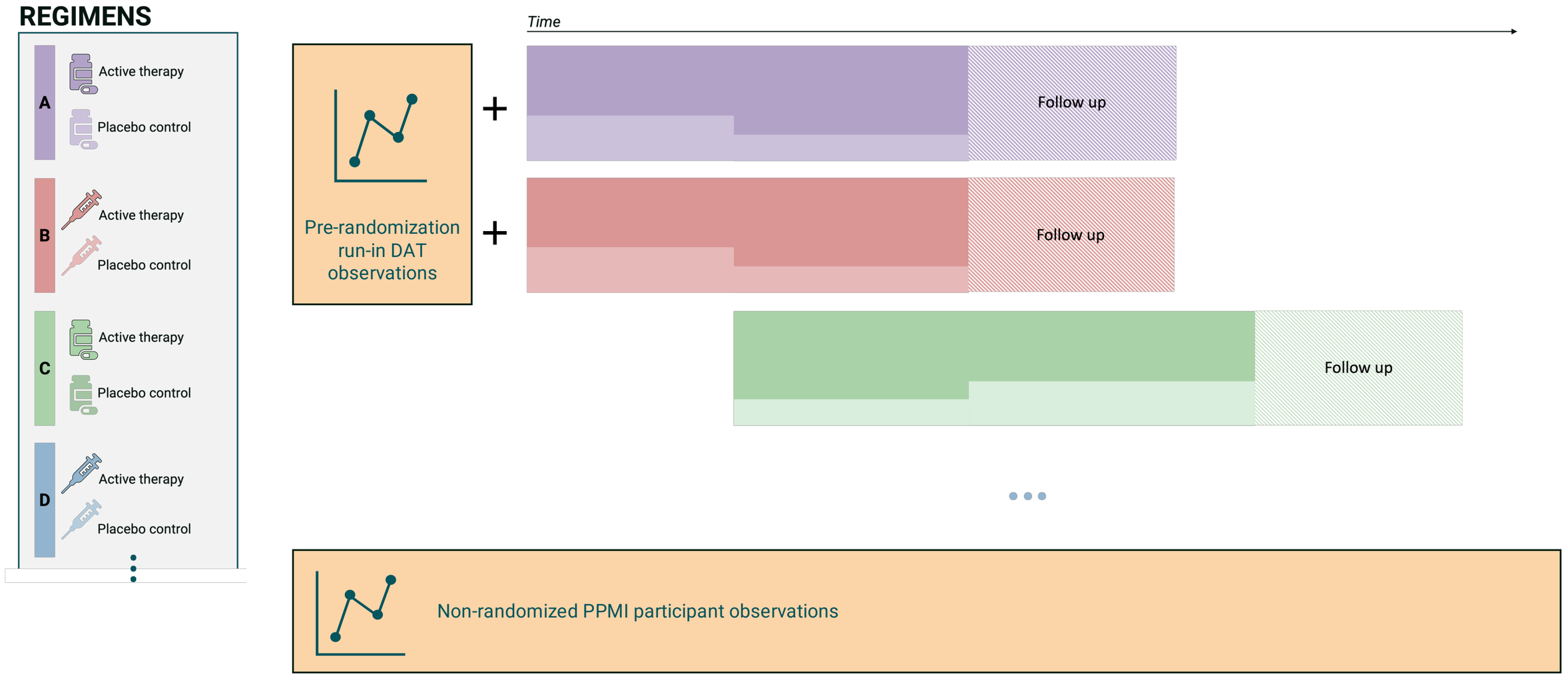
P2P Platform Trial Innovations
Multiple Therapies, Shared Control



P2P Platform Trial Innovations
Pre-randomization Run-in Data from PPMI



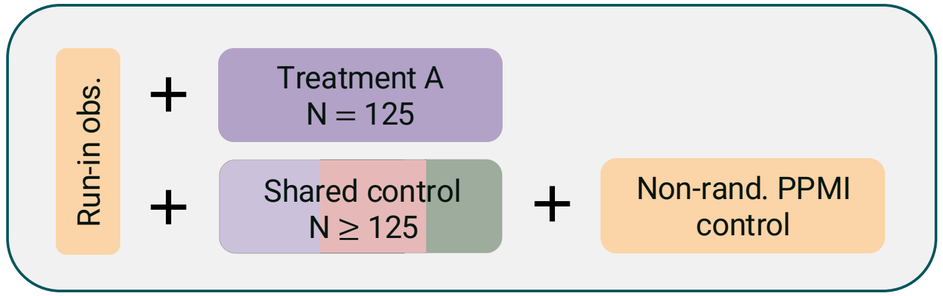
P2P Platform Trial Innovations
Supplement Control Observations with Non-randomized PPMI Data



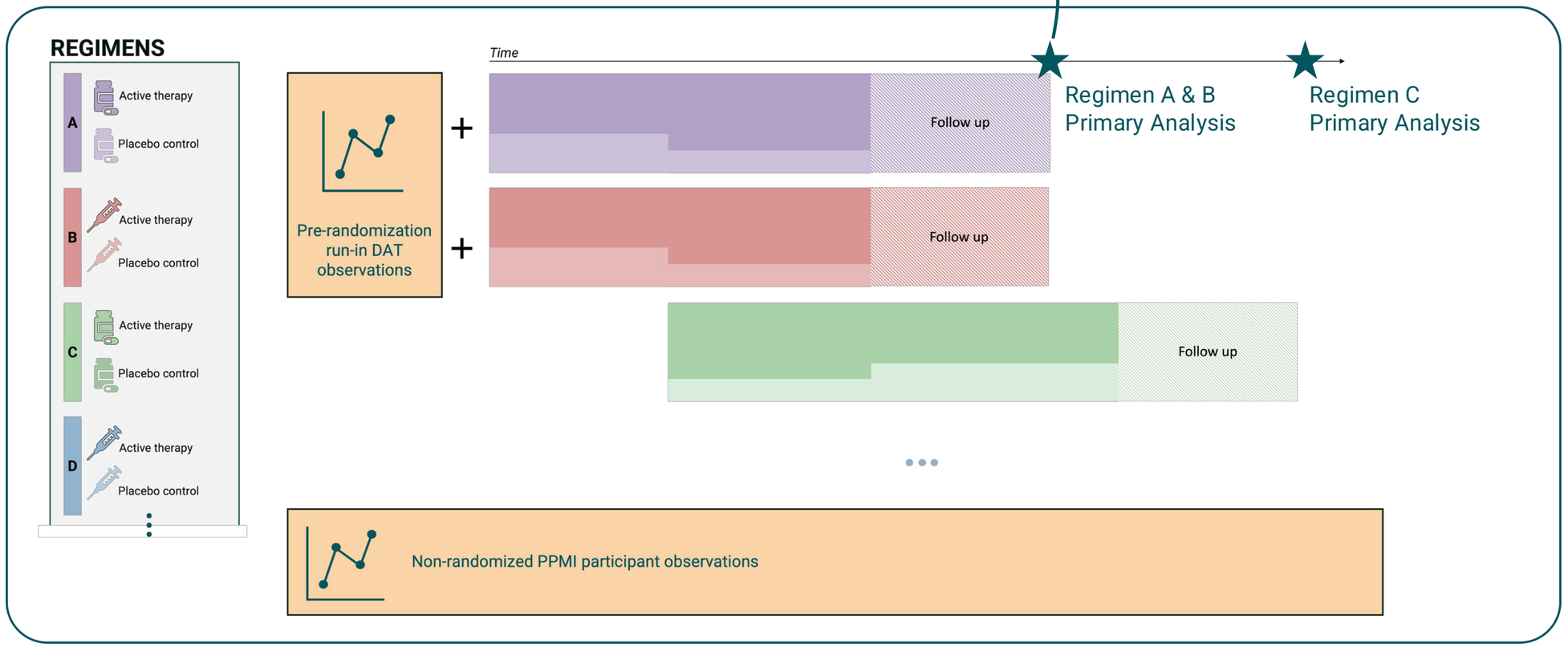
Evaluating a Therapy
Analysis Dataset

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

REGIMEN A Primary Analysis Dataset



- **125 active therapy participants** randomized per regimen.
- Use **all available information** to characterize:
  - Natural worsening of a control patient
  - Slowed worsening of a treated patient
- Non-rand. observations supplement rand. controls.

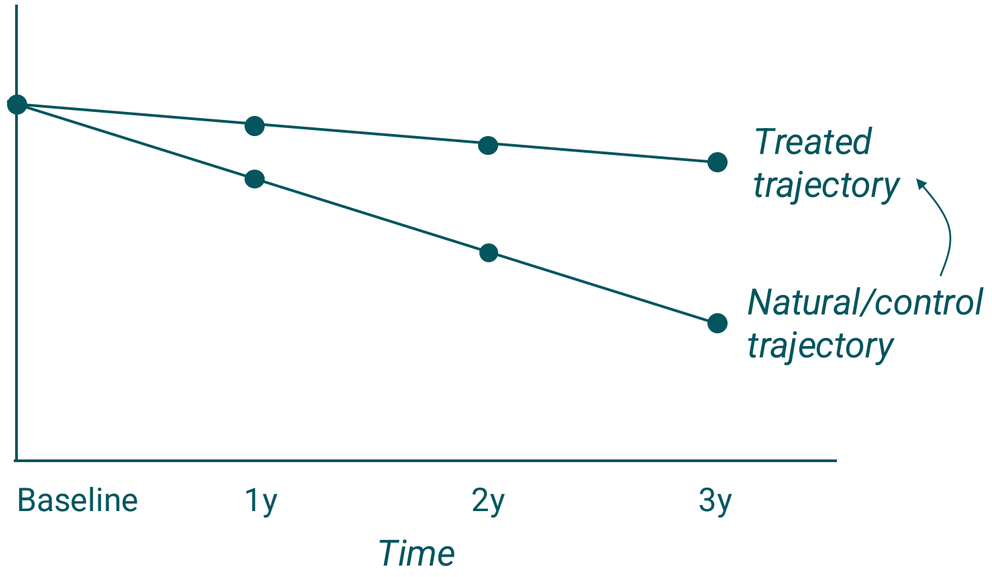


Evaluating a Therapy
Bayesian Primary Analysis Model Highlights

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

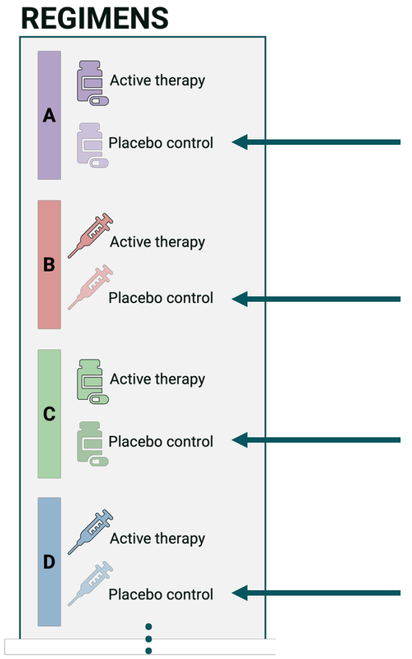
Longitudinal

*Leveraging all information from a participant over time to characterize **disease progression**.*



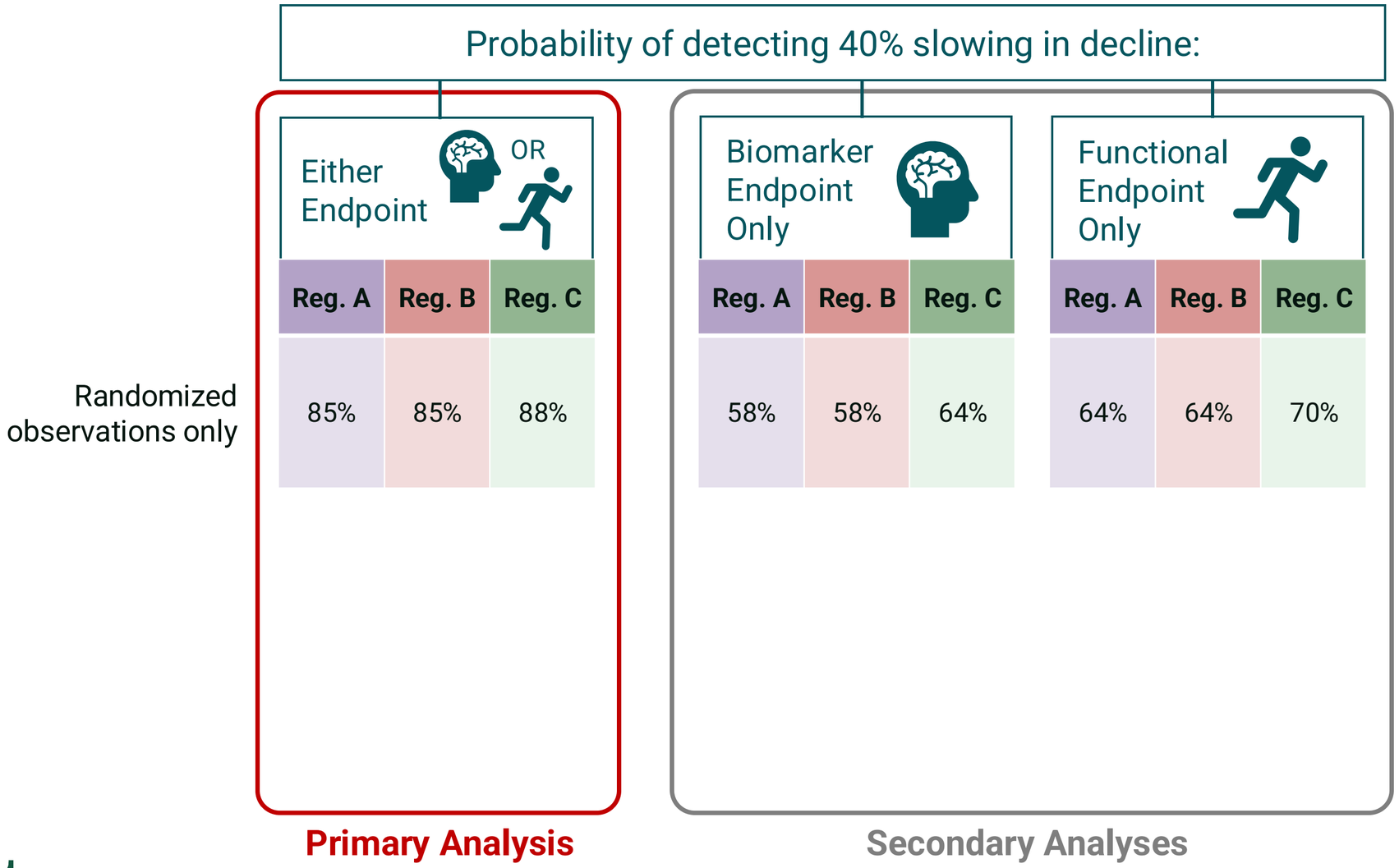
Robust to Differences in Control

*Dynamic adjustments to amount of sharing among **randomized** and **non-randomized control** observations.*



BERRY

Power to Detect an Effective Treatmer
Primary and Secondary Analyses



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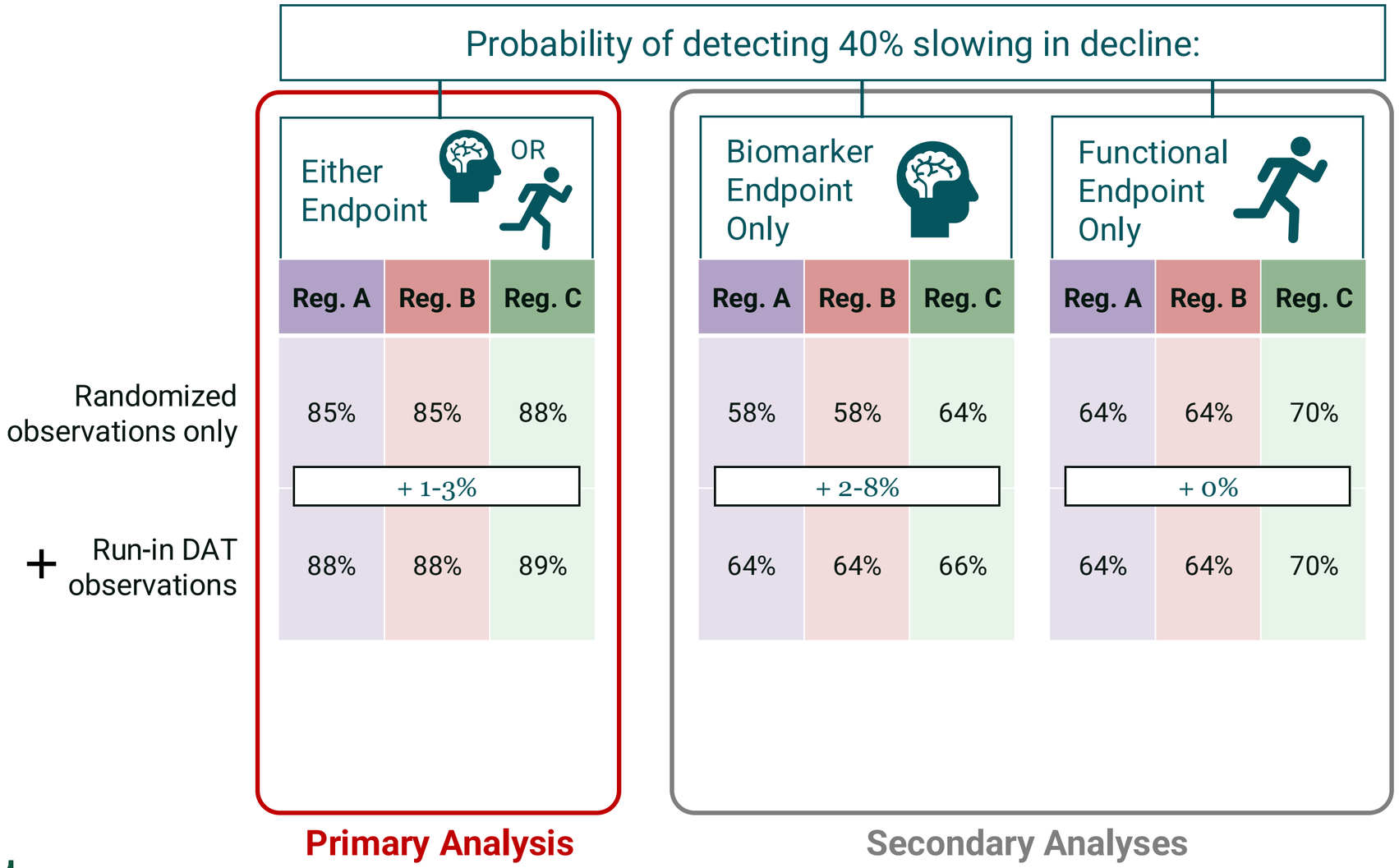

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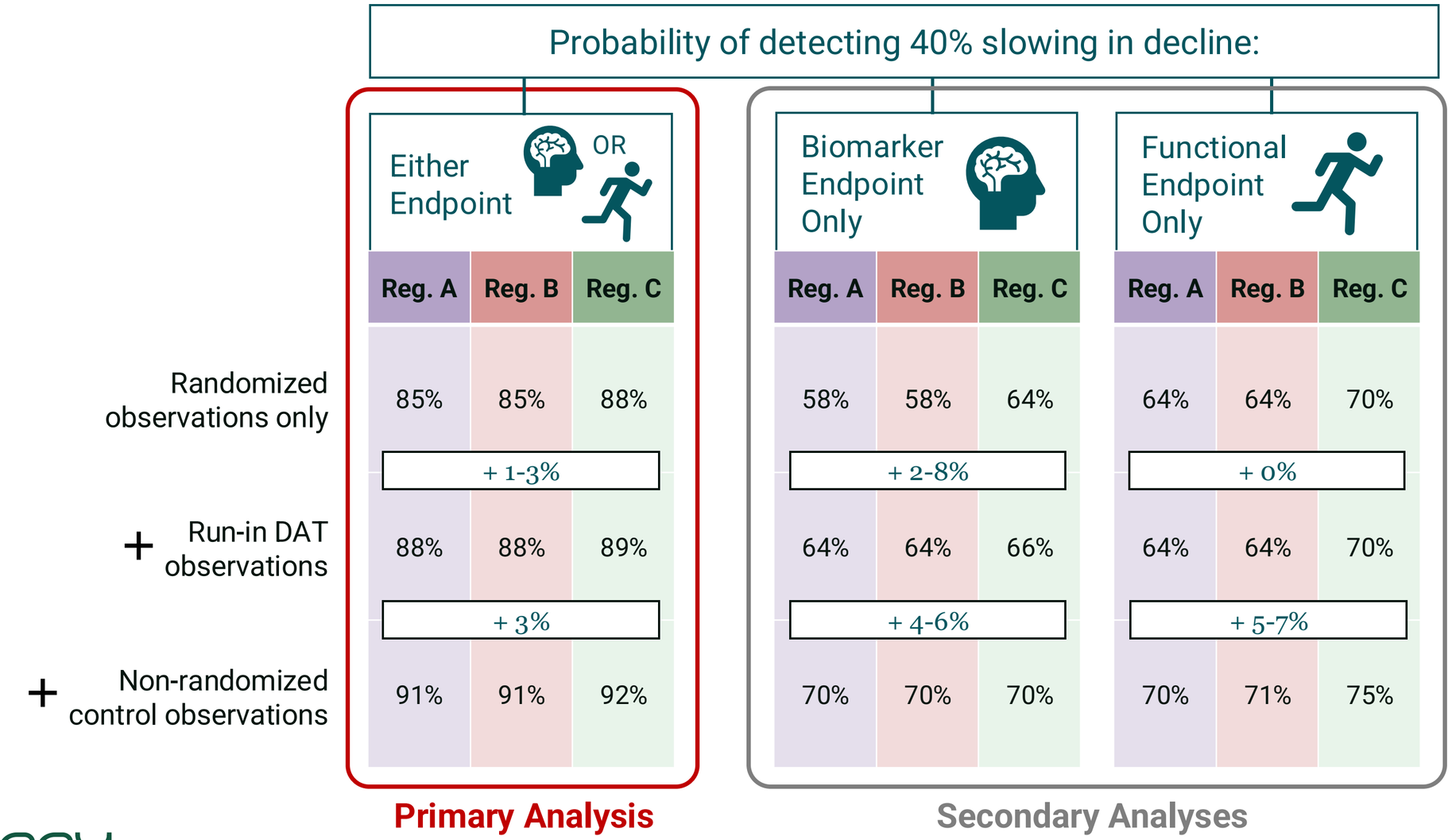


When will we find the first effective therapy?*

Platform Trial Development Pathway

- Perpetually enroll 3 regimens at a time
- N = 125 active therapy participants per regimen
- N ~ 42 control participants per regimen (shared)
- Participants followed for 2 years

5 Treatments Tested

9.8 Years

Participants

835 Up to and including the effective regimen

216 Already enrolled to answer new research questions

75% Treated, 25% Control

Traditional Development Pathway

- Sequence of fixed trials with equal randomization
- N = 125 active therapy participants per trial
- N = 125 control participants per trial
- Participants followed for 2 years

5 Treatments Tested

16.1 Years

Participants

1250

50% Treated

50% Control

** Assumes 20% of therapies tested are effective. Both designs have 90% power to detect a truly effective therapy. Assumes accrual rate of 15 patients per month. All numbers presented are averages.*

Success in the Chronic Disease Space

- **Embedded trials** to leverage existing infrastructure, with operational and statistical benefits
- **Innovative analyses** to quantify treatment effect, maximize power, and improve interpretability of results
- Rigorously collected NHS data to **supplement and inform clinical trial design and analysis**
- **Adaptive platform trials** to produce expedited, robust, and patient-centric evidence on efficacy for multiple therapeutic options

Acknowledgements

- **REMAP-ILD team**: Tom Jensen, Melanie Quintana, Roger Lewis
- **P2P team**: Amy Crawford, Cora Allen-Savietta
- Mike Krams

Especially: Gisli Jenkins, Iain Stewart, Chris Ryerson, Leticia Kawano-Dourado, Wendy Adams, Pilar Rivera Ortega

Especially: Tanya Simuni, Chris Coffey, Ken Marek, Katie Kopil, Michael Brumm, Charlie Choi

COORDINATING THE SET UP AND OPERATIONS OF PLATFORM TRIAL IMPLEMENTATION IN CHRONIC DISEASE SETTINGS

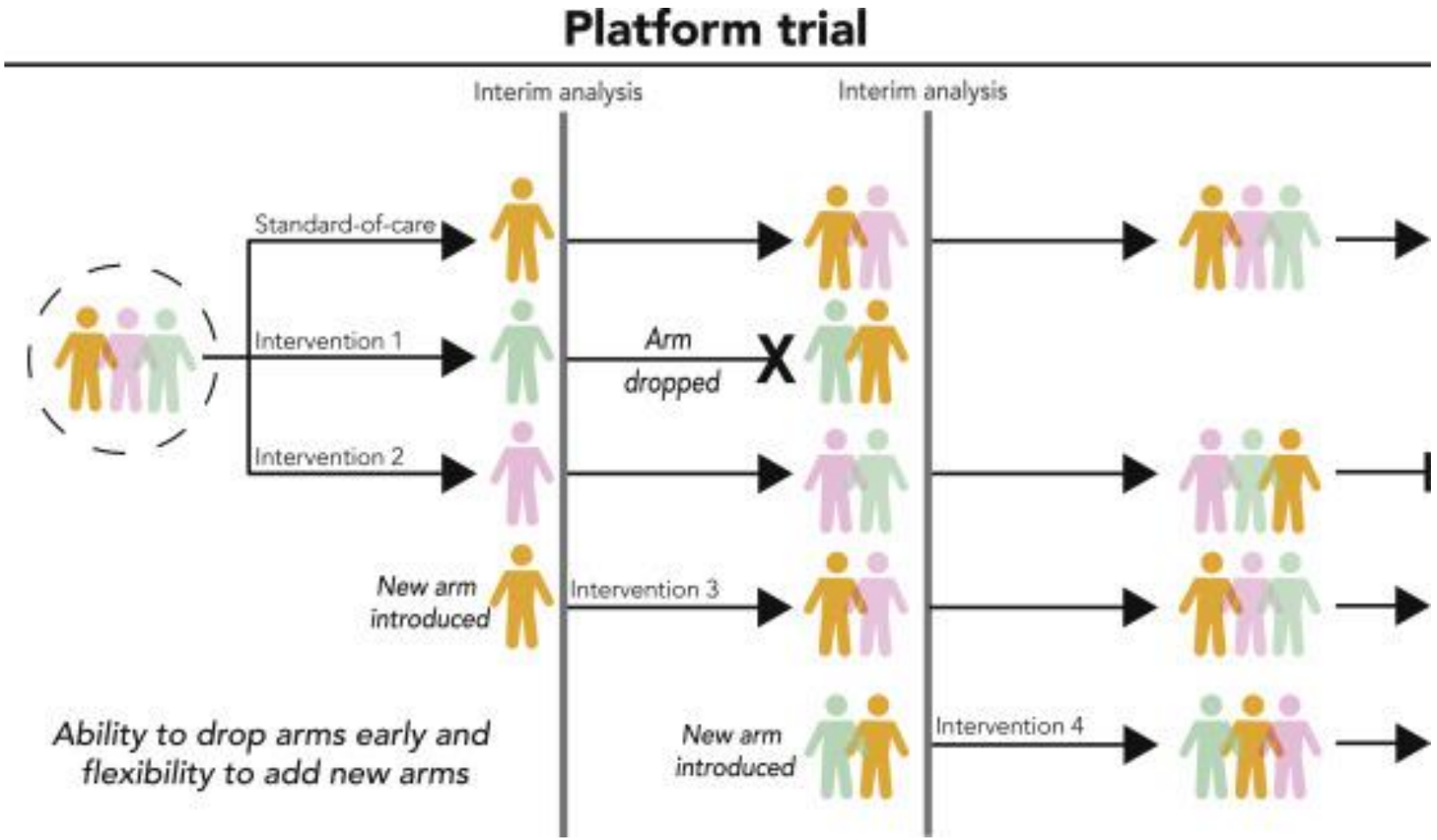
JOHN VANBUREN, PHD

UNIVERSITY OF UTAH DATA COORDINATING CENTER

HEALTH
UNIVERSITY OF UTAH

UTAH DCC
DATA COORDINATING CENTER

OPERATIONALIZING CHANGES



Park et. Al. 2020. An overview of platform trials with a checklist for clinical readers. *Journal of Clinical Epidemiology*. 125 (1-8). https://doi.org/10.1016/j.jclinepi.2020.04.025

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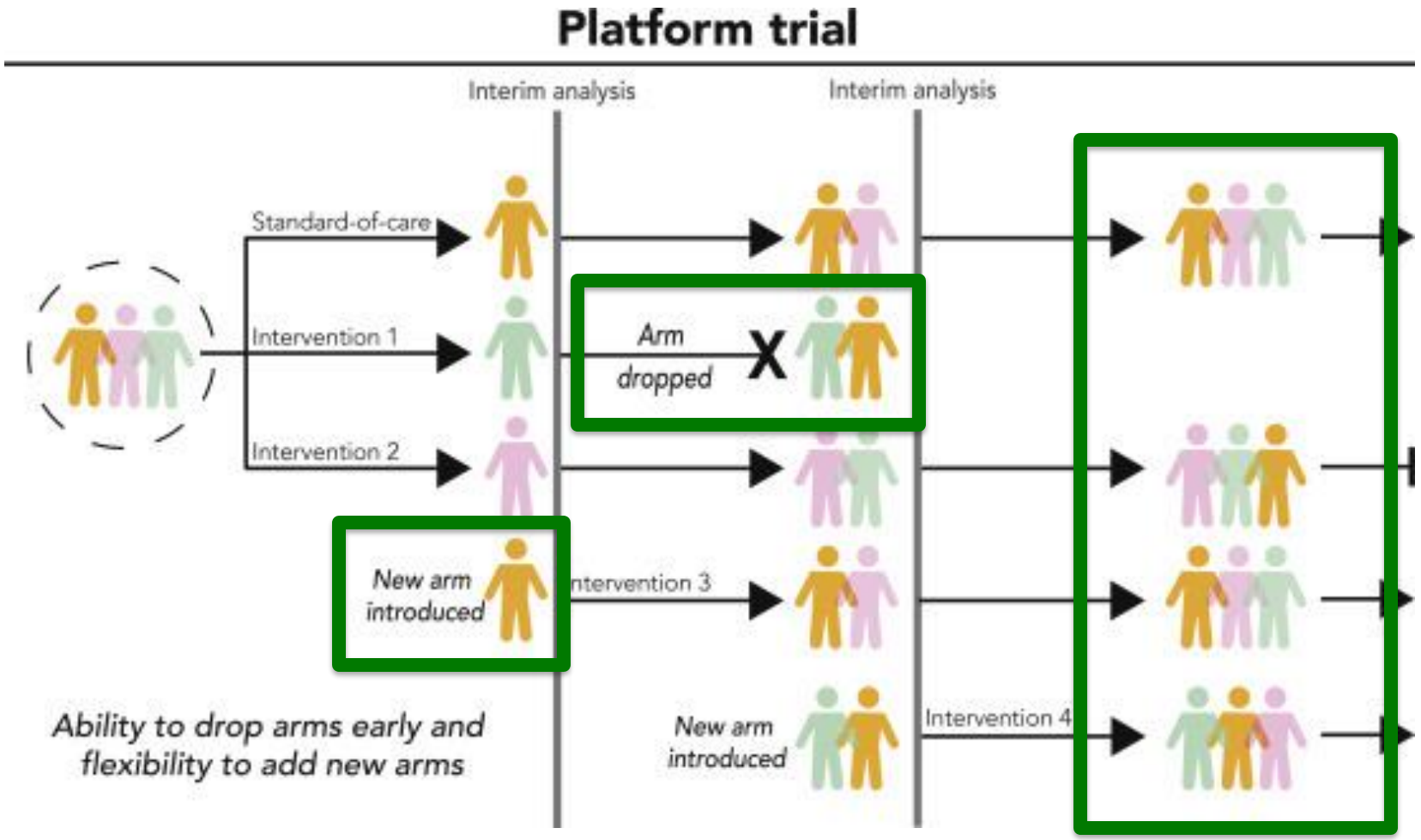

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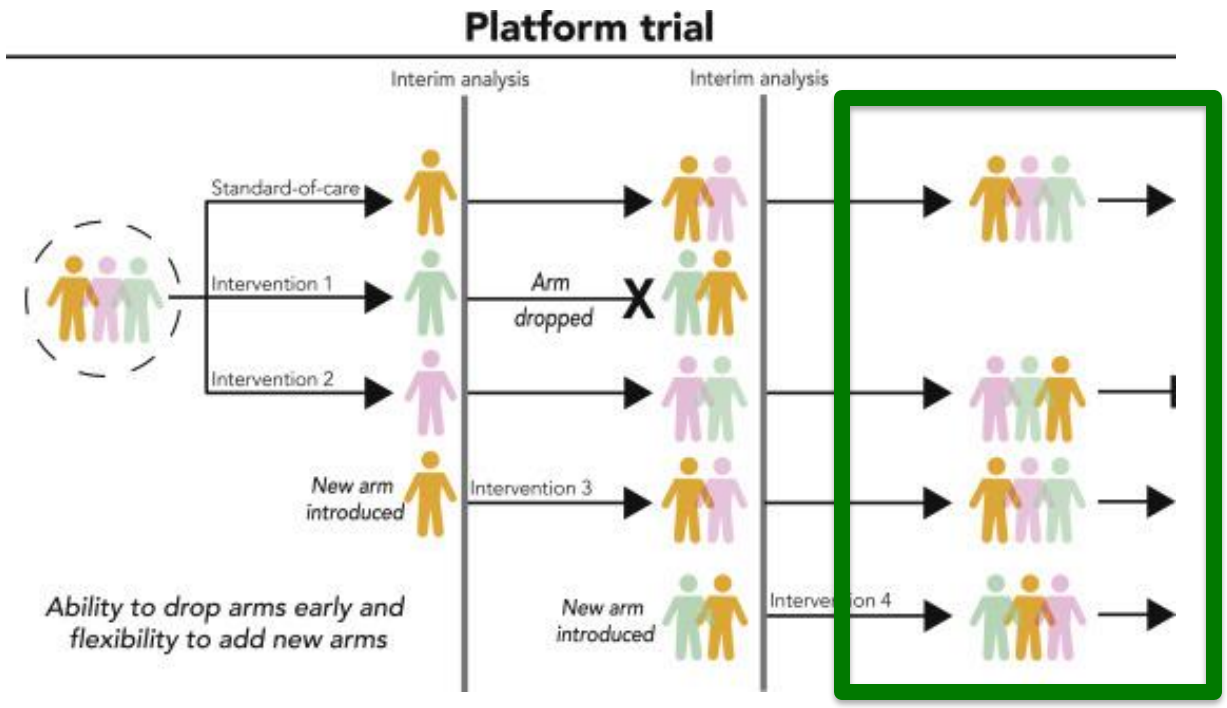

Ongoing Trial

- Monitor participant data
- Communicate with sites
- Data cleaning activities
- Safety DSMB meetings
- Regular submissions to ethical boards (e.g., IRB continuing review) and regulatory agencies

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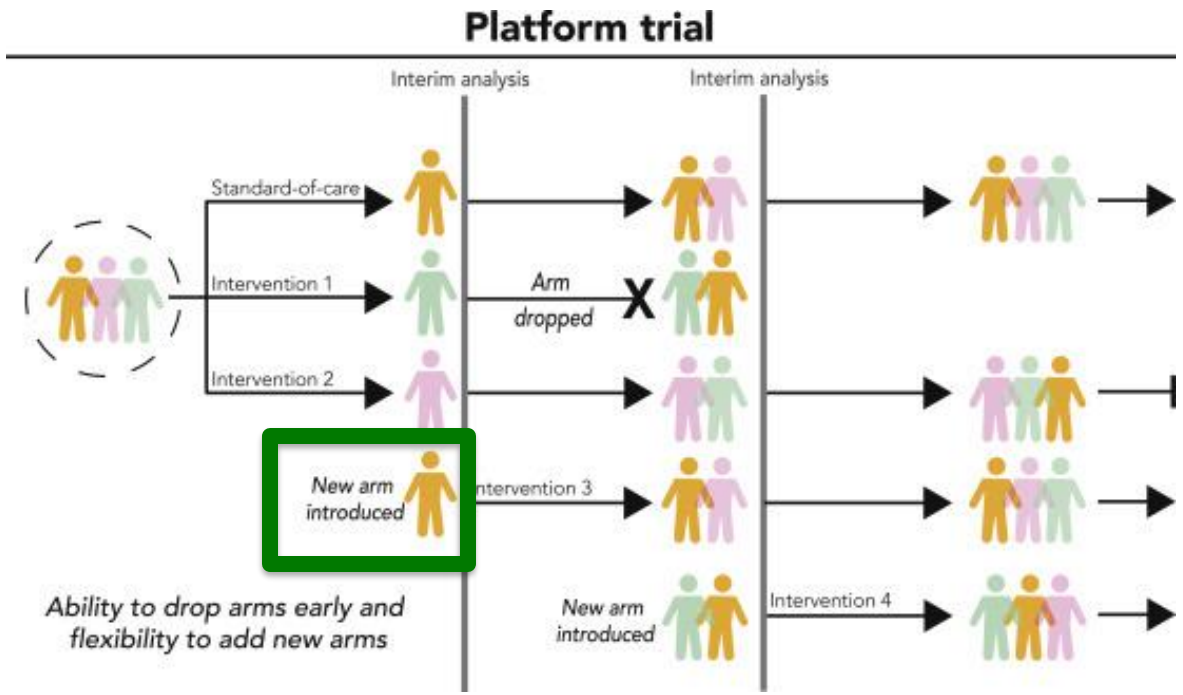
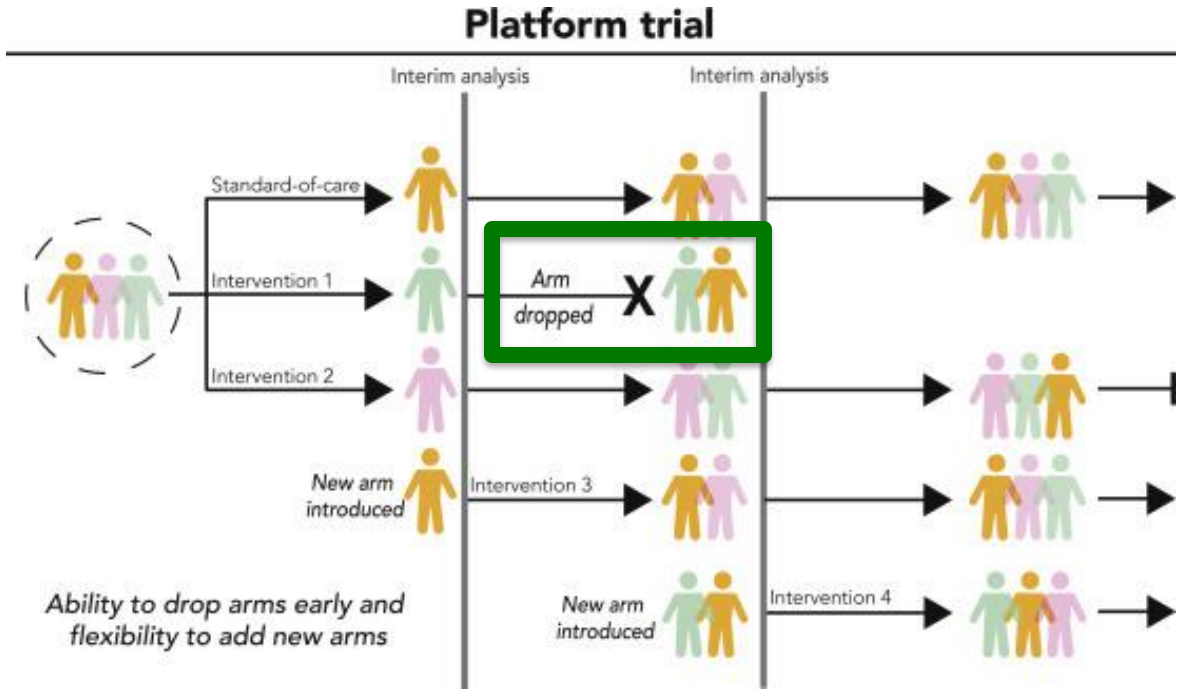


Before Adding an Intervention

- Monitor current enrollment and project when a 'slot' will open
- Create protocol-specific material (appendix information for intervention)
- Prepare database change to incorporate any intervention-specific elements
- Submit IND/IDE material (if required) to FDA and non-US regulatory agencies
- Submit material such as protocol and consent forms to ethical boards (e.g., IRB) for review
- Update Interactive Response Technology (IRT – randomization system) with new information and change allocations
- Inform monitoring board (e.g., DSMB) of addition

Park et. Al. 2020. An overview of platform trials with a checklist for clinical readers. *Journal of Clinical Epidemiology*. 125 (1-8). https://doi.org/10.1016/j.jclinepi.2020.04.025

OPERATIONALIZING CHANGES



<u>After Intervention Closure</u>

- Remove protocol-specific material (appendix information for intervention)
- Update database remove any intervention-specific elements (once data entry complete)
- Prepare submission of IND/IDE material (if required or going for indication) to FDA and non-US regulatory agencies
- Submit material such as protocol and consent forms to ethical boards (e.g., IRB) for review
- Update Interactive Response Technology (IRT – randomization system) to stop allocating to arm and change allocations
- Inform monitoring board (e.g., DSMB) of completion
- Complete final monitoring of participants in intervention so data can be locked and provided to sponsor

Park et. Al. 2020. An overview of platform trials with a checklist for clinical readers. *Journal of Clinical Epidemiology*. 125 (1-8). https://doi.org/10.1016/j.jclinepi.2020.04.025

DURATION OF THE STUDY

- Platform trials are designed to recruit and follow participants for several years
  - Documentation of historic knowledge and decisions
  - Staff turnover
  - Trial fatigue

https://summitlife.org/passing-the-baton-summit-life-today-2/

TRIAL REQUIREMENTS – PAUSING SITES

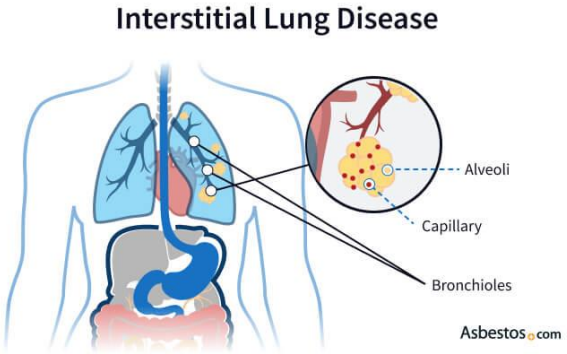
- Some trials might require >1 active intervention to proceed
- If no interventions are in the pipeline, study may need to go on enrollment pause
- Challenges for sites
  - RIF staff members
  - Take on other studies to bridge funding effort
  - Stay knowledgeable of study without retraining efforts required

FUNDING

- Large sources of academic funding (e.g., NIH) not willing to commit indefinitely to a study
- Rare diseases higher ‘risk’ for recruitment
- Funding likely needs to be driven by industry of philanthropy

CONQUER

- Registry for systemic sclerosis patients
  - Multi-organ disease (e.g., skin, lung)
  - <5 years disease duration since first non-Raynaud symptom
- Funded by the Scleroderma Research Foundation
- >1,100 enrolled participants since 2018 across 18 sites
- Participants return for standard of care visits. Data up to every 6 months are collected



HEALTH
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https://www.aocd.org/page/SystemicSclerosis
https://www.asbestos.com/mesothelioma/interstitial-lung-disease/

CONQUEST

- Competition in systemic sclerosis community to enroll in clinical trials
- CONQUER registry data used to identify potentially eligible CONQUEST participants
- Eligibility include:
  - Interstitial lung disease AND < 7 years disease duration, OR
  - Limited disease on MMF

Potential CONQUEST subjects at [redacted]

Site	Subject ID
[redacted]	164-32
	164-34
	164-44
	164-46
	164-52
	164-55
	164-58
	164-60
	164-68

HEALTH
UNIVERSITY OF UTAH

UTAH DCC
DATA COORDINATING CENTER

RARE DISEASE STUDY DESIGN CHALLENGES

- The setup of rare disease registries will drive the applicability to being able to quantify expected progressions for an RCT
  - CONQUER follow-up: every 6 months based on the original baseline date
  - Another rare disease registry: every 12 months based on when your last follow-up visit was
- Important to determine what types of data will be collected in rare disease registries

Learnings from Chronic Pain Master Protocol (CPMP): FDA Complex Innovative Designs Pilot Program

SCT 2025

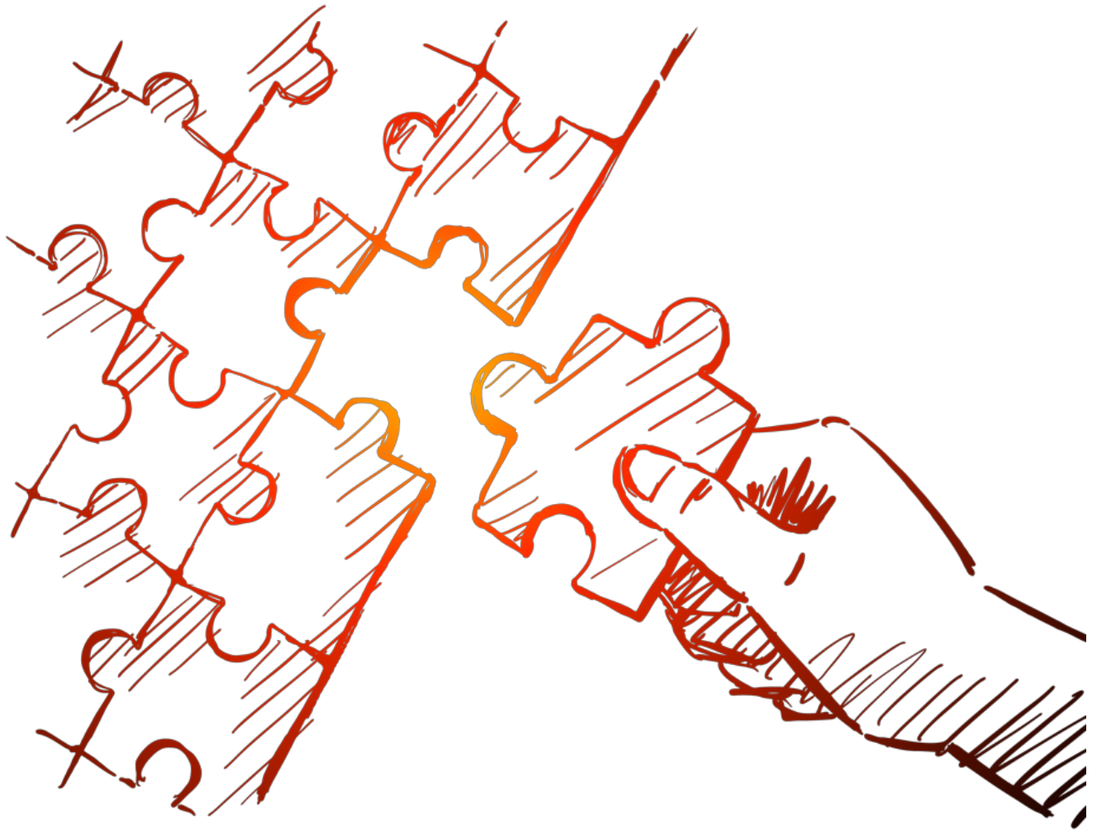
Phebe Kemmer, PhD
Eli Lilly and Company

Acknowledgements:
Saptarshi Chatterjee, PhD
Will Landau, PhD
JonDavid Sparks, PhD

Motivation

Significant Unmet Need:
1 in 4 American adults experiences chronic pain*

Challenge in investigating novel mechanisms to treat chronic pain:
How can we develop a clinical approach to quickly evaluate multiple assets in multiple pain indications without *a priori* differentiation information?

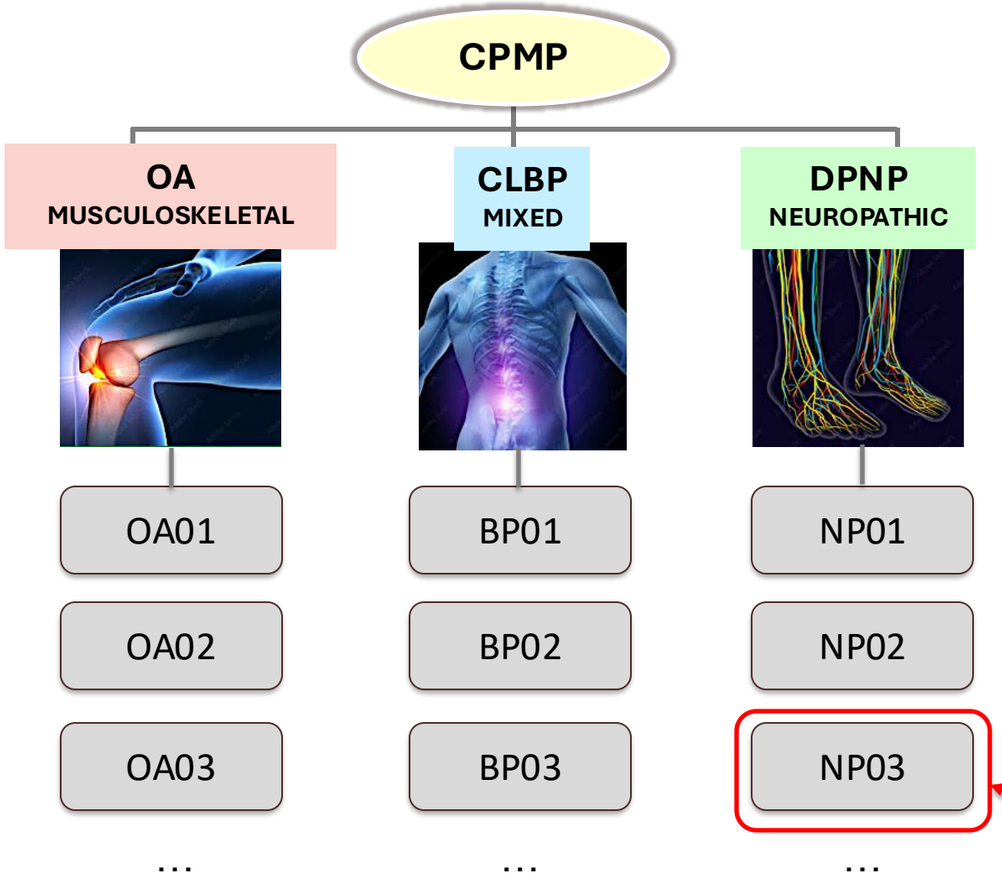


*NCHS Data Brief, Nov 2024, https://www.cdc.gov/nchs/data/databriefs/db518.pdf

Chronic Pain Master Protocol Framework

Each pain type is a **DSA** (Disease State Addendum) to the Master Protocol

Each asset is tested in an **ISA** (Intervention-Specific Appendix)



Goal:
lean, efficient signal identification for multiple assets across multiple pain types

Each ISA is its own clinical trial: a parallel randomized controlled phase 2a (proof of concept) design with 1 active LY arm and its own placebo arm.

OA=osteoarthritis
CLBP=chronic low back pain
DPNP=diabetic peripheral neuropathic pain

Trial Selected for FDA Complex Innovative Design Pilot Program

Who We Are | Caring | Discovery | Products | Careers | Investors | Partners

Lilly's Pain Clinical Trial Protocol Selected for FDA Complex Innovative Trial Designs Pilot Meeting Program

09/05/2019

INDIANAPOLIS, Sept. 5, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced the U.S. Food and Drug Administration (FDA) has accepted its application to enter the Complex Innovative Trial Designs (CID) Pilot Meeting Program, an initiative which aims to further modernize drug development, improve efficiency, and promote innovation. Lilly's proposed program involves a master protocol for the development of novel approaches to the treatment of multiple types of chronic pain, one of the largest unmet medical needs in the United States.

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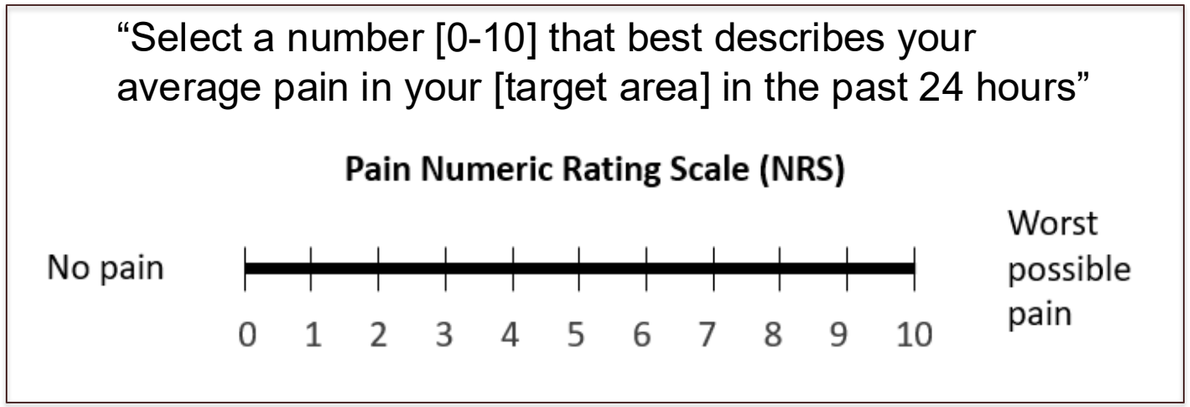
Key Features of the CPMP

Standardized scales and common visit schedule across studies:

- Pain: Numerical Rating Scale (primary)
- Physical functioning
- Emotional functioning
- Patient global assessment of improvement



Other features:

- 2:1 randomization to active and placebo arms within a study
- 8-week trial duration
- Studies (ISAs) may be enrolling patients simultaneously

5

Benefits of Master Protocol framework

Operational Efficiencies

- Common clinical site footprint (~30 US sites) reduces need for re-training
- Same monitoring team and single database across multiple disease states and assets → data and site readiness
- Consistent collection of safety and biomarker data collection.
- Ability to integrate safety data across chronic pain states earlier in development

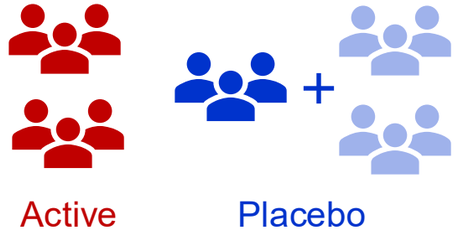
Statistical Efficiencies

- Standardized data collection allows direct comparisons of study results within and between pain types
- **Statistical exchangeability: Patients are randomized under the same set of experimental conditions** → opportunity to borrow placebo data between studies to boost study power.
- Each study prespecifies the borrowing strategy and the analysis method that will be used.

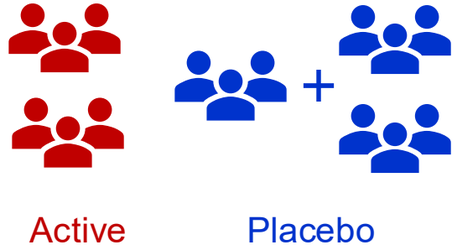
Placebo Borrowing Approaches in the CPMP setting

No borrowing:
Use current study data only for primary analysis

Dynamic borrowing:
Borrow placebo data based on similarity to current study

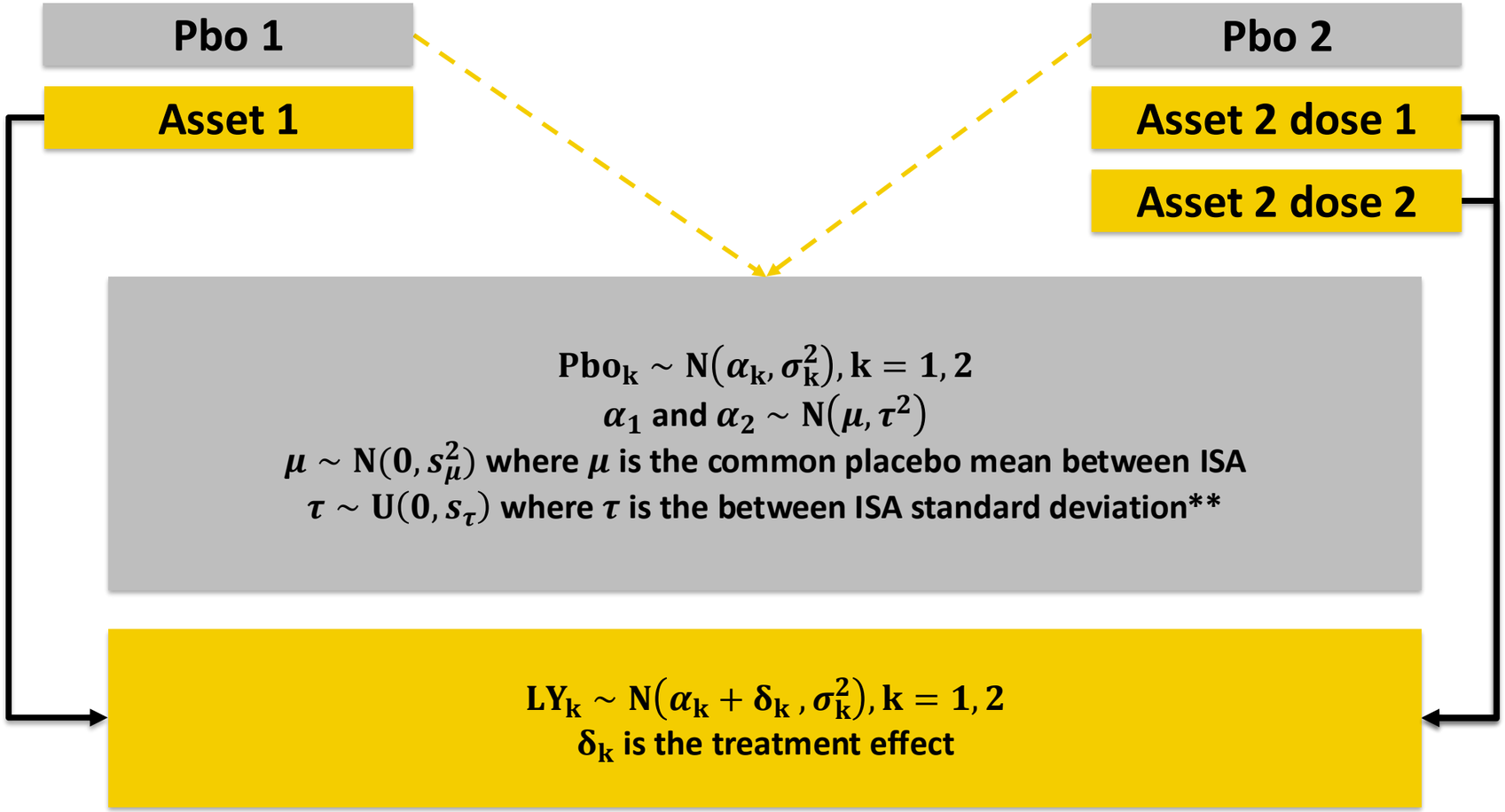


Full borrowing:
Pool placebo data from other CPMP studies for primary analysis.



- **Dynamic approach** adapts the level of borrowing based on the similarity of the placebo response, and protects against “over-borrowing”. In CID discussions, FDA was supportive of this approach.
- Simulations demonstrated that dynamic borrowing can control type I error and **increase study power**, under certain conditions.
- **Hierarchical modeling** is the most stable and robust dynamic borrowing option. It can use an informative prior to force a certain amount of borrowing, or a non-informative prior that can borrow any amount depending on commensurability of historical placebo data.
- Note: It may not always be appropriate to borrow, e.g. evidence of placebo drift.

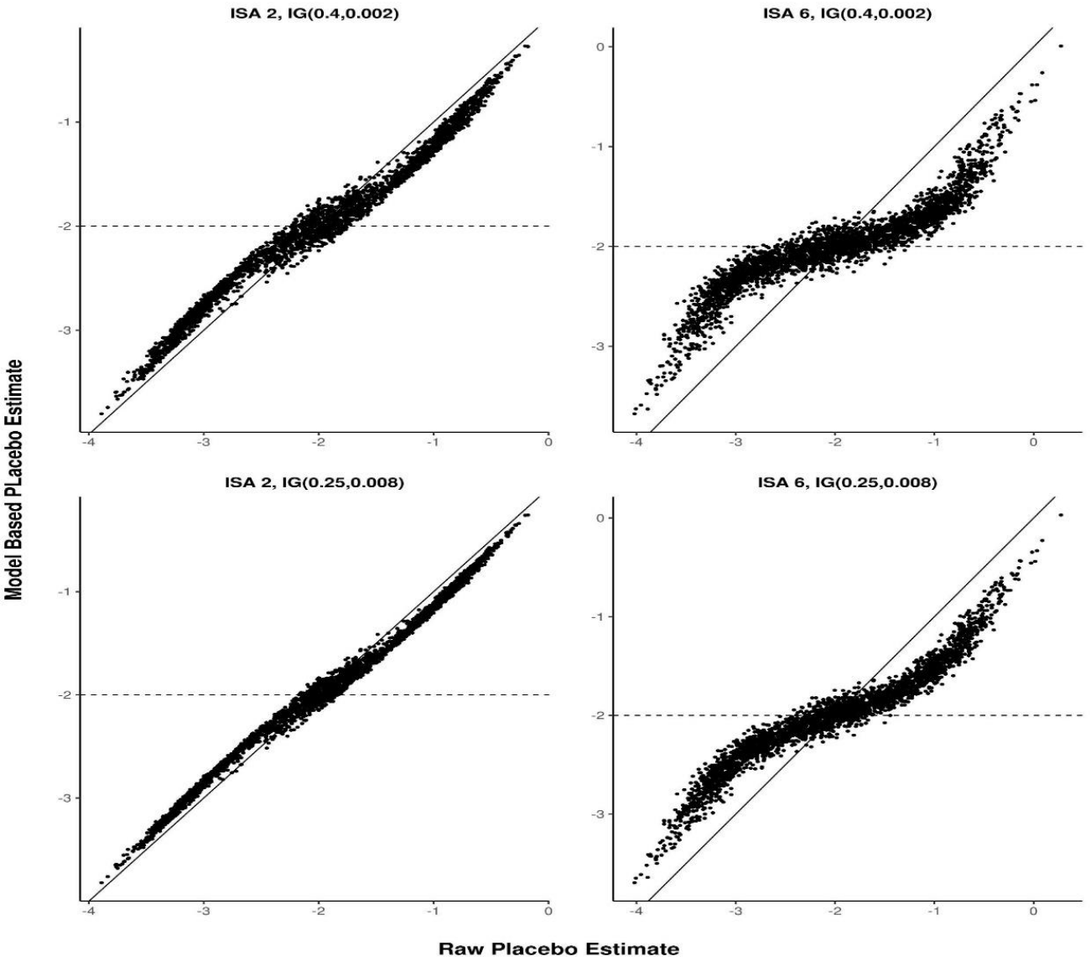
Bayesian Hierarchical Model



- Example: 2 ISAs
- α_k is the placebo mean from ISA k
- The placebo patients are assumed to come from a common population characterized by grand mean μ and between-study standard deviation τ
- τ is the key parameter that defines the amount of borrowing. (Large s_τ = no borrowing, small s_τ = more borrowing).
- The hierarchical structure borrows information across studies to shrink the placebo group mean toward a common grand mean.
- Intuitive and interpretable in the setting of multiple historical ISAs.

**An inverse gamma prior can also be used.

Dynamic Placebo Borrowing with the Hierarchical Model



Simulation Details:

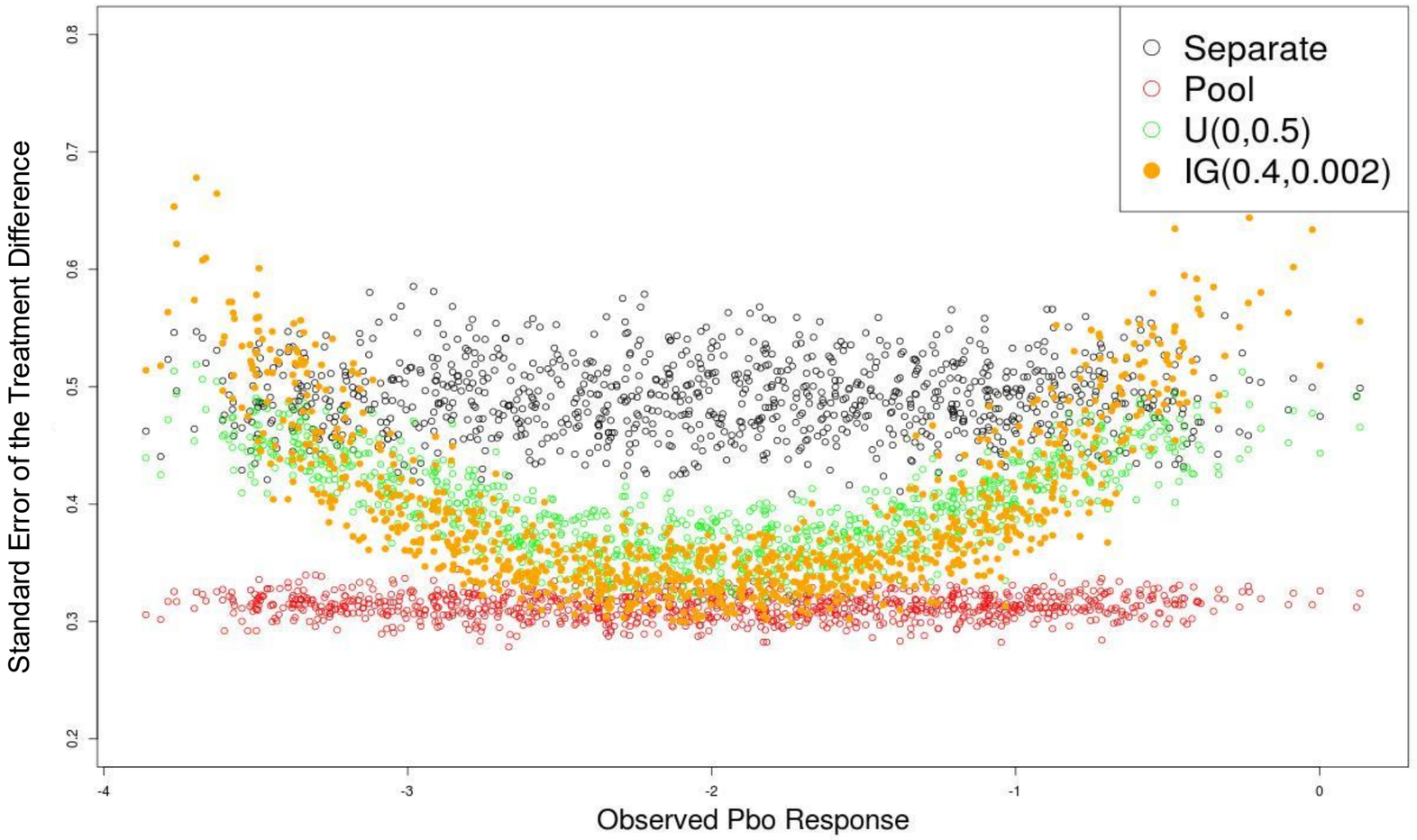
- 2 or 6 ISAs simulated with a true mean of -2 placebo response
- The model-based placebo estimates from the final ISA (y-axis) are illustrated against the raw placebo observations (x-axis)

Key points:

- Illustrates the dynamic nature of hierarchical borrowing.
- The model-based estimates are gravitated towards -2 when the raw placebo estimates are around -2
- With observed placebo means far from -2, model based estimates gradually shift towards the diagonal

Credit: Saptarshi Chatterjee

Dynamic Placebo Borrowing with the Hierarchical Model



Simulation Details:

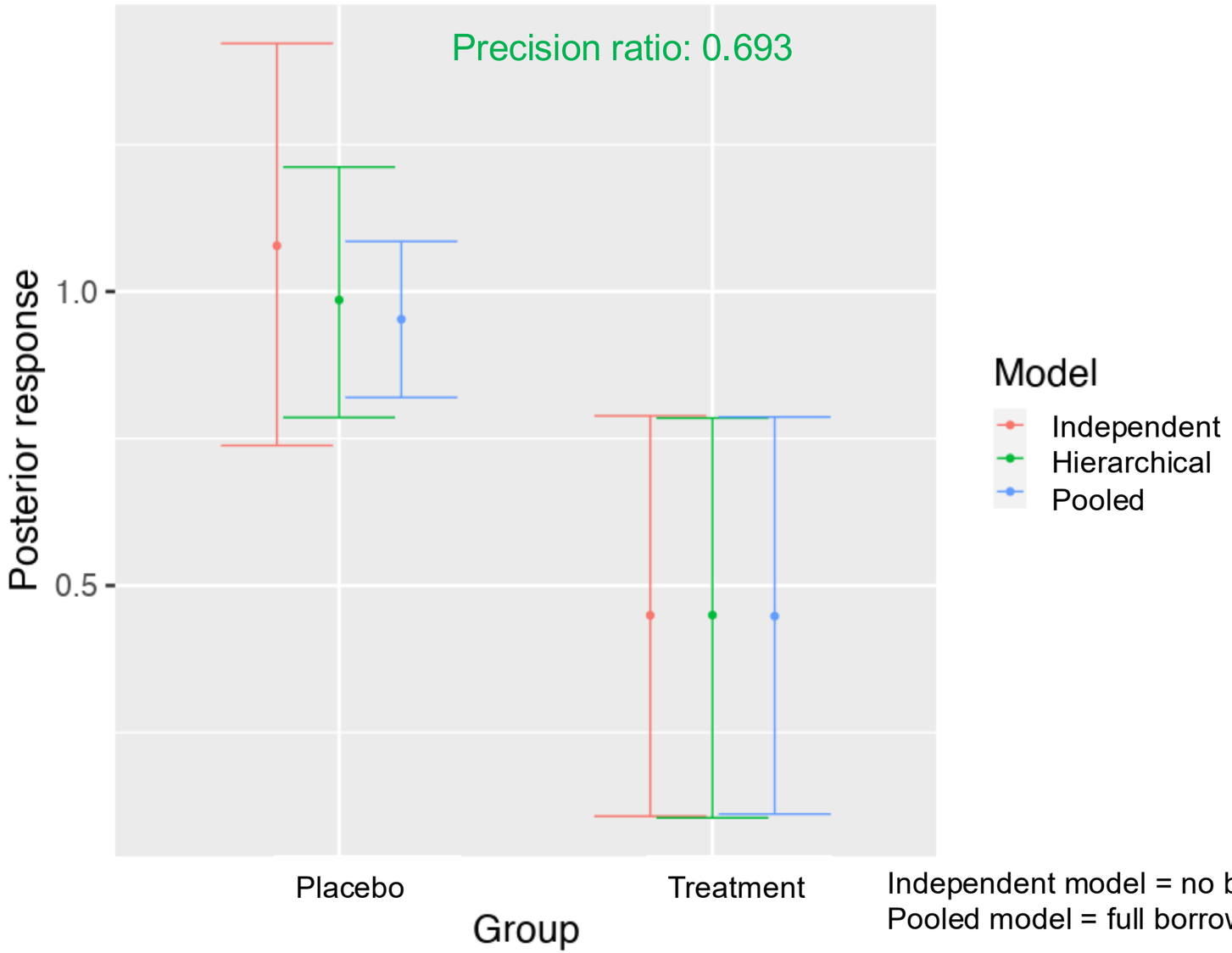
- Multiple ISAs simulated with a true mean of -2 placebo response
- The placebo estimates from the final ISA are represented in the graphic

Key points:

- Lower points in the graphic represent a reduction in the standard error of the treatment difference (good)
- The closer the observed mean to -2, the dynamic borrowing emulates pooling
- As the observed mean gets further from -2, less borrowing occurs and emulates a separate analysis

Credit: Saptarshi Chatterjee

Example results: placebo borrowing at a single time point (simulated data)



- Placebo response estimate varies based on the amount of borrowing. The variability is smaller when we do more borrowing.
- The precision ratio quantifies the amount of borrowing (i.e. contribution of the variance of the grand mean relative to the contribution of the posterior variances after hierarchical modeling)

R packages (published on CRAN):

- **{historicalborrowlong}:** longitudinal hierarchical, independent, and pooled models.
- **{historicalborrow}:** non-longitudinal hierarchical, mixture, independent, pooled models.

Independent model = no borrowing
Pooled model = full borrowing

Credit: Will Landau

Key Learnings from 4 Years of CPMP: Challenges

- **Master protocol concept requires a balance of standardization vs. flexibility**
  - Trade-offs between optimizing operational efficiency and scientific goals
  - High standardization limits the ability to address asset-specific needs

- **Heterogenous Ph3-like population** increases enrollment speed and translatability of results, but small sample sizes could decrease magnitude of treatment effect and potential responder identification
- **2:1 randomization ratio** has risk of increasing placebo response.
- **Integrated dataset** requires external unblinded support to maintain blinding while ISAs are ongoing.
- **Study differences** (e.g. route of administration) may commensurability of placebo data
- **Repeat enrollers**: consider potential bias and impact to placebo borrowing.
- **In practice, not everyone loves statistical borrowing!?**

Key Learnings from 4 Years of CPMP: Benefits

Operational efficiencies realized (by 3rd asset):

- 30% Cost Reduction versus a standalone trial
- 50% less time from Design Lock to First Patient Dosed
- Enrollment duration reduced 30%

CPMP in Summary

In 4 years (2020-2023):

- 12 studies completed across 4 assets
- 30+ clinical sites across the US & PR
- 1700+ participants enrolled in the program

- CPMP design introduces numerous statistical challenges, opportunities, and data analysis borrowing decisions
- Tremendous operational benefits have been realized. Ultimately, a master protocol will enable better medicines to get to patients sooner!

More about CPMP: 2 recent scientific disclosures

General Section
Research Protocol

OPEN

PAIN REPORTS

An innovative phase 2 chronic pain master protocol design to assess novel mechanisms in multiple pain types

Kelly L. Knopp*, AnnCatherine M. Downing, Leslie Anthony, Saptarshi Chaterjee, Karen Price, JonDavid Sparks

Abstract

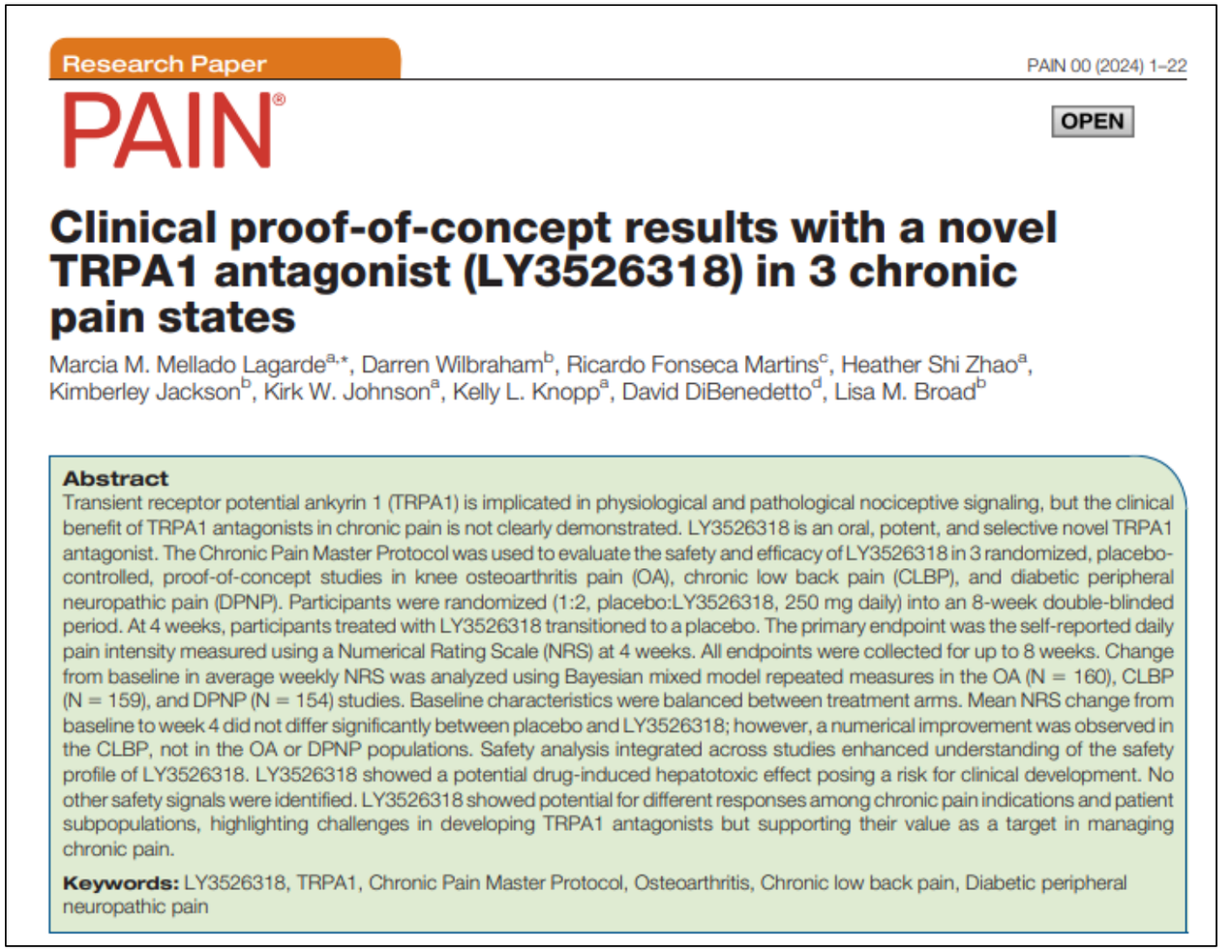
Introduction: The phase 2 chronic pain master protocol (CPMP) presented here provides a construct to accelerate the investigation of novel analgesics, broadly referred to here as mechanisms. Designed to address historical challenges in analgesic research and development, such as the choice of indication, this protocol enables the efficient evaluation of potential therapeutics with different mechanisms of action in 3 pain types: nociceptive pain (osteoarthritis), neuropathic pain (diabetic peripheral neuropathic pain), and mixed pain (chronic low back pain).

Methods: The study design was determined before the identification of any specific molecule. Statistical simulations were conducted to optimize the methodology and design, the culmination of which were submitted to and accepted by the Complex Innovative Trial Design Pilot Meeting Program, a unique collaboration with the United States Food and Drug Administration. Benefits of the CPMP include limiting the number of study participants exposed to placebo and reducing the total sample size over time by leveraging placebo data across studies within a pain type and efficacy data across pain types for a specific molecule. The CPMP design enables: (1) efficient evaluation of multiple novel mechanisms of action; (2) the study of multiple molecules simultaneously or serially; (3) direct statistical comparison of molecules within a pain type; and (4) efficient planning and conduct of clinical studies. ClinicalTrials.gov ID NCT05986292.

Perspective: By evaluating novel mechanisms across different pain types, therapeutic potential can be assessed more efficiently compared with traditional individual clinical studies.

Keywords: Analgesics, Clinical study, Master protocol, Pain

Oct 2024: https://pmc.ncbi.nlm.nih.gov/articles/PMC11487222/



Research Paper

PAIN 00 (2024) 1–22

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Clinical proof-of-concept results with a novel TRPA1 antagonist (LY3526318) in 3 chronic pain states

Marcia M. Mellado Lagarde[a,*], Darren Wilbraham[b], Ricardo Fonseca Martins[c], Heather Shi Zhao[a], Kimberley Jackson[b], Kirk W. Johnson[a], Kelly L. Knopp[a], David DiBenedetto[d], Lisa M. Broad[b]

Abstract

Transient receptor potential ankyrin 1 (TRPA1) is implicated in physiological and pathological nociceptive signaling, but the clinical benefit of TRPA1 antagonists in chronic pain is not clearly demonstrated. LY3526318 is an oral, potent, and selective novel TRPA1 antagonist. The Chronic Pain Master Protocol was used to evaluate the safety and efficacy of LY3526318 in 3 randomized, placebo-controlled, proof-of-concept studies in knee osteoarthritis pain (OA), chronic low back pain (CLBP), and diabetic peripheral neuropathic pain (DPNP). Participants were randomized (1:2, placebo:LY3526318, 250 mg daily) into an 8-week double-blinded period. At 4 weeks, participants treated with LY3526318 transitioned to a placebo. The primary endpoint was the self-reported daily pain intensity measured using a Numerical Rating Scale (NRS) at 4 weeks. All endpoints were collected for up to 8 weeks. Change from baseline in average weekly NRS was analyzed using Bayesian mixed model repeated measures in the OA (N = 160), CLBP (N = 159), and DPNP (N = 154) studies. Baseline characteristics were balanced between treatment arms. Mean NRS change from baseline to week 4 did not differ significantly between placebo and LY3526318; however, a numerical improvement was observed in the CLBP, not in the OA or DPNP populations. Safety analysis integrated across studies enhanced understanding of the safety profile of LY3526318. LY3526318 showed a potential drug-induced hepatotoxic effect posing a risk for clinical development. No other safety signals were identified. LY3526318 showed potential for different responses among chronic pain indications and patient subpopulations, highlighting challenges in developing TRPA1 antagonists but supporting their value as a target in managing chronic pain.

Keywords: LY3526318, TRPA1, Chronic Pain Master Protocol, Osteoarthritis, Chronic low back pain, Diabetic peripheral neuropathic pain

Dec 2024: https://pubmed.ncbi.nlm.nih.gov/39679712/