



# THE EU-PEARL INTEGRATED PLATFORM TRIAL FOR MAJOR DEPRESSION

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# EU-PEARL CONSORTIUM



## HOSPITALS



## UNIVERSITIES



## PATIENT ORGANISATION



## DATA, STATISTICS



## REGULATORY



## PROJECT MANAGEMENT



## EUROPEAN RESEARCH INFRASTRUCTURES



## BIOPHARMACEUTICAL COMPANIES





# MISSION

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Strategic **alliance** between the **public** and **private** sectors to:

Transform  
the way  
**clinical trials**  
are conducted

Engage lived  
experience  
in IRP design

Improve and  
accelerate **drug**  
**development**  
processes

by developing a collaborative clinical trial framework  
for platform clinical trials/Integrated Research Platforms (IRPs)



# EU-PEARL JOURNEY



Project closure – FINAL  
EVENT

2<sup>nd</sup> Stakeholder Event

2023

April 2023



1<sup>st</sup> Stakeholder  
Workshop

Accelerating Clinical Trials in the EU (ACT EU)  
Delivering an EU clinical trials transformation initiative

Application CTR & launch CTIS on 31 Jan 2022

COVID-19  
Pandemic

Project Kick Off meeting

November 2019



# INTEGRATED RESEARCH PLATFORMS (IRP<sub>s</sub>)

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A framework to carry out a patient-centric platform trial which includes:



Shared master protocol and methodology.



Scientific, legal, regulatory and ethical requirements.



Network of hospitals, clinicians and researchers.



Data governance policies and procedures.



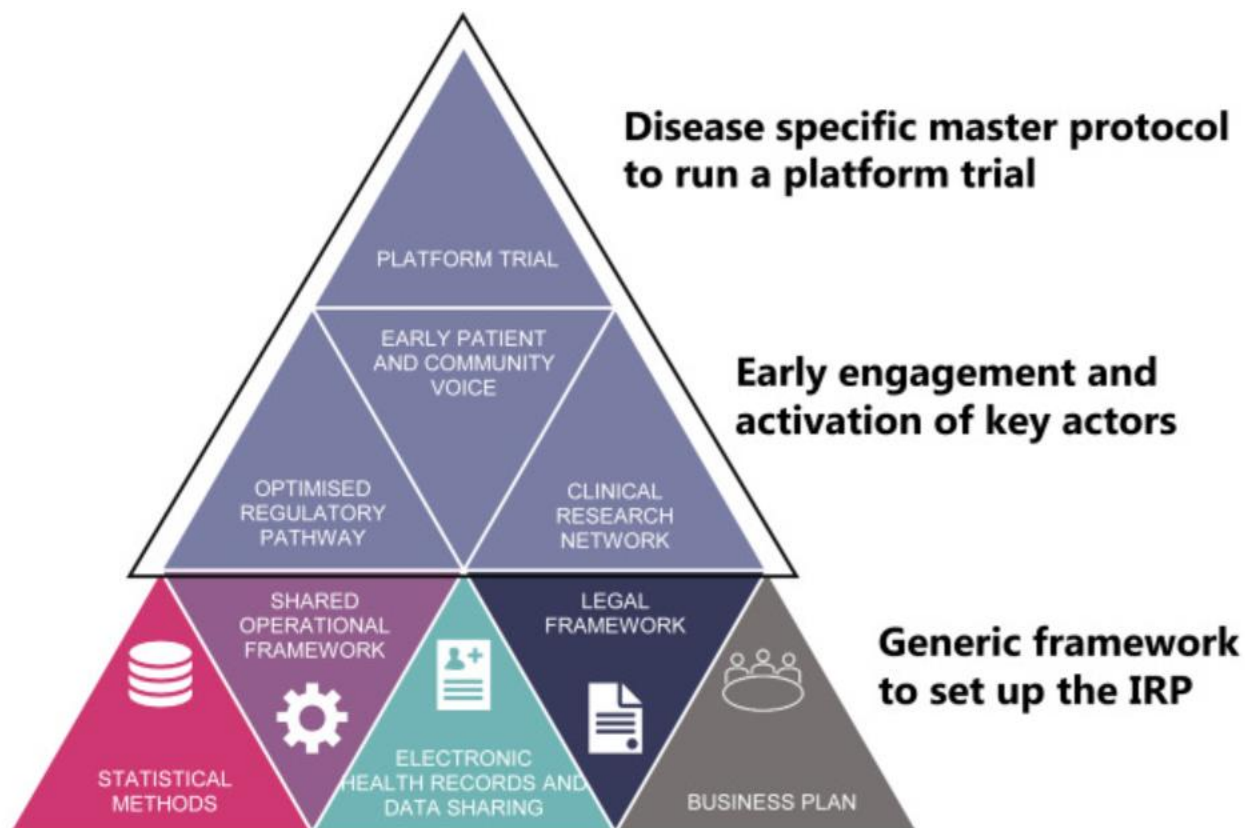
Regulated access to patient electronic health records and patient cohorts.



Pathway for patients' participation in trials design.



# EU PEARL APPROACH



## ELEMENTS OF AN INTEGRATED RESEARCH PLATFORM

Koenig et al., eClinMed 2024 DOI:<https://doi.org/10.1016/j.eclinm.2023.102384>



# SUMMARY OF OUTCOMES

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**Build master protocol capabilities and drive efficiency**

**The reference on the INTEGRATED RESEARCH PLATFORM setup**

## Methods and tools for platform trials

Templates for master protocols and appendices

Patient and community engagement platform

Simulation and visualization tools

Platform trials best practices tool

## IRP Framework

Regulatory & legal frameworks

Data privacy and security governance

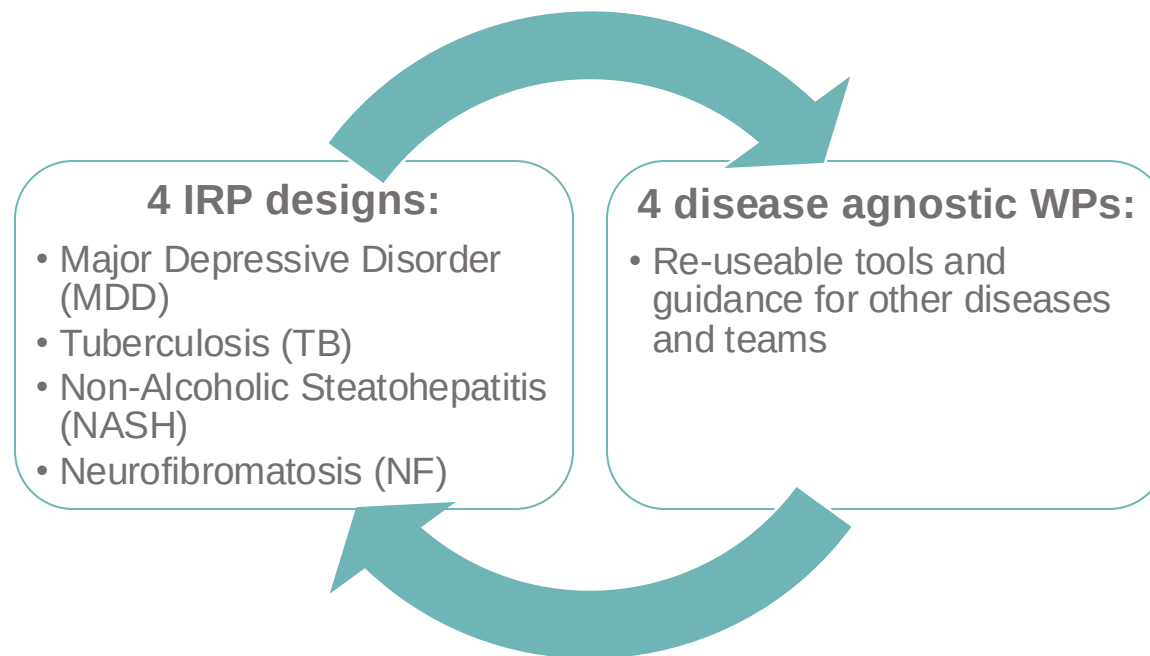
EHR-enabled site networks

Harmonization across the field



# PROJECT SET UP

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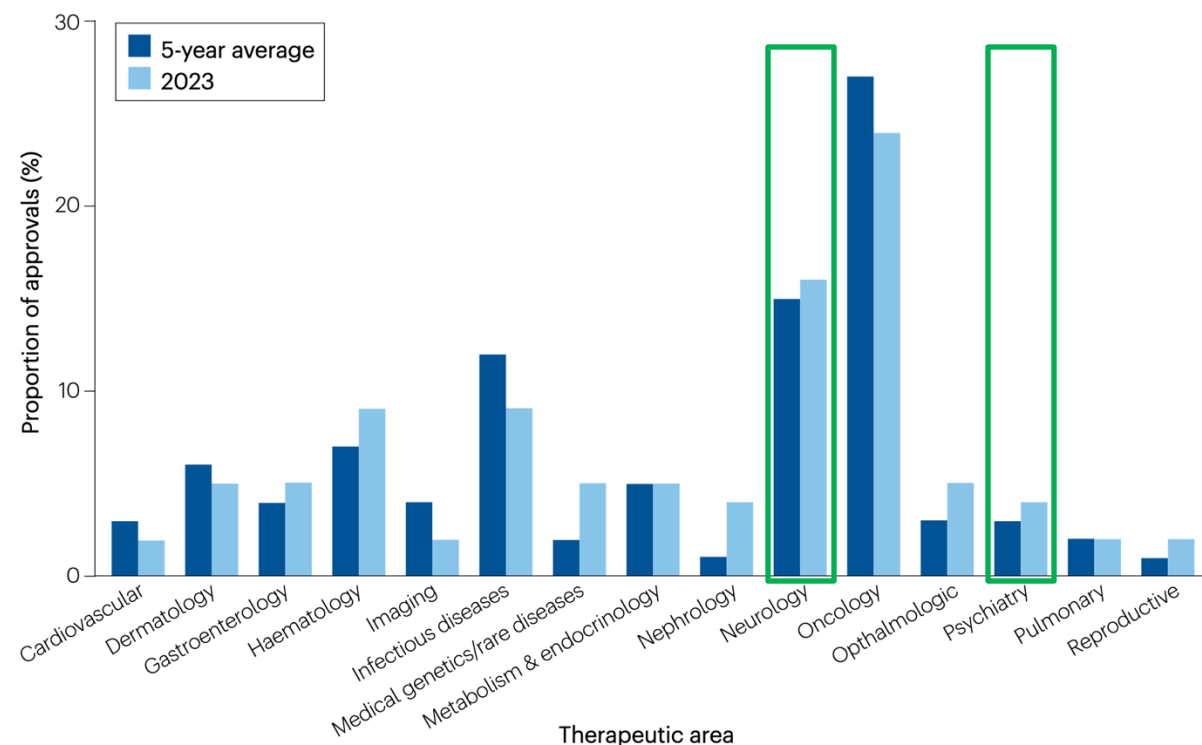


Set up 8 work packages  
Design only



# THE NEED FOR TRIAL INNOVATIONS IN PSYCHIATRY

- New drug approvals in psychiatry have lagged behind other areas of medicine
- Evidence for comparative effectiveness is lacking for many of the available treatments
- Classical “one drug, one trial” approaches are slow and ineffective
- Trials need to be better designed to generate better evidence, faster

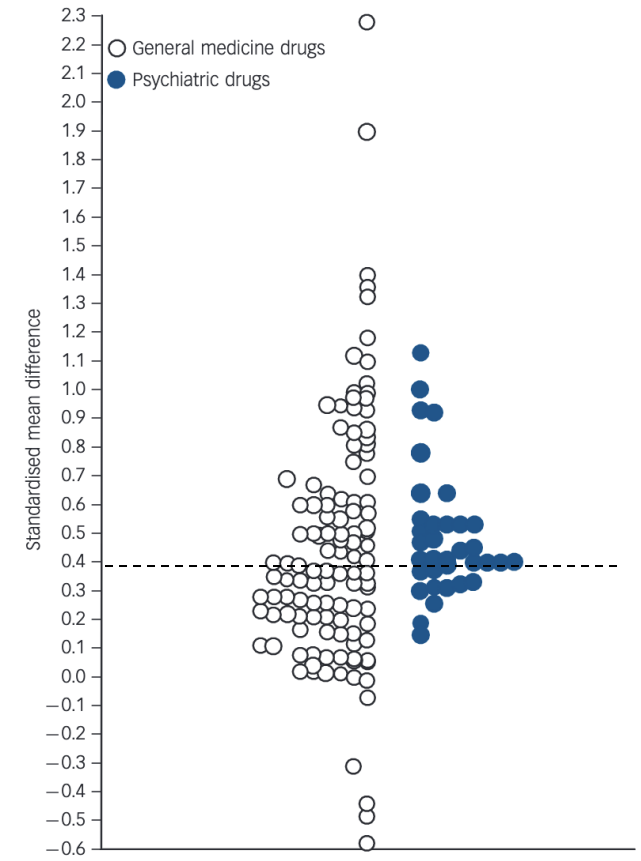
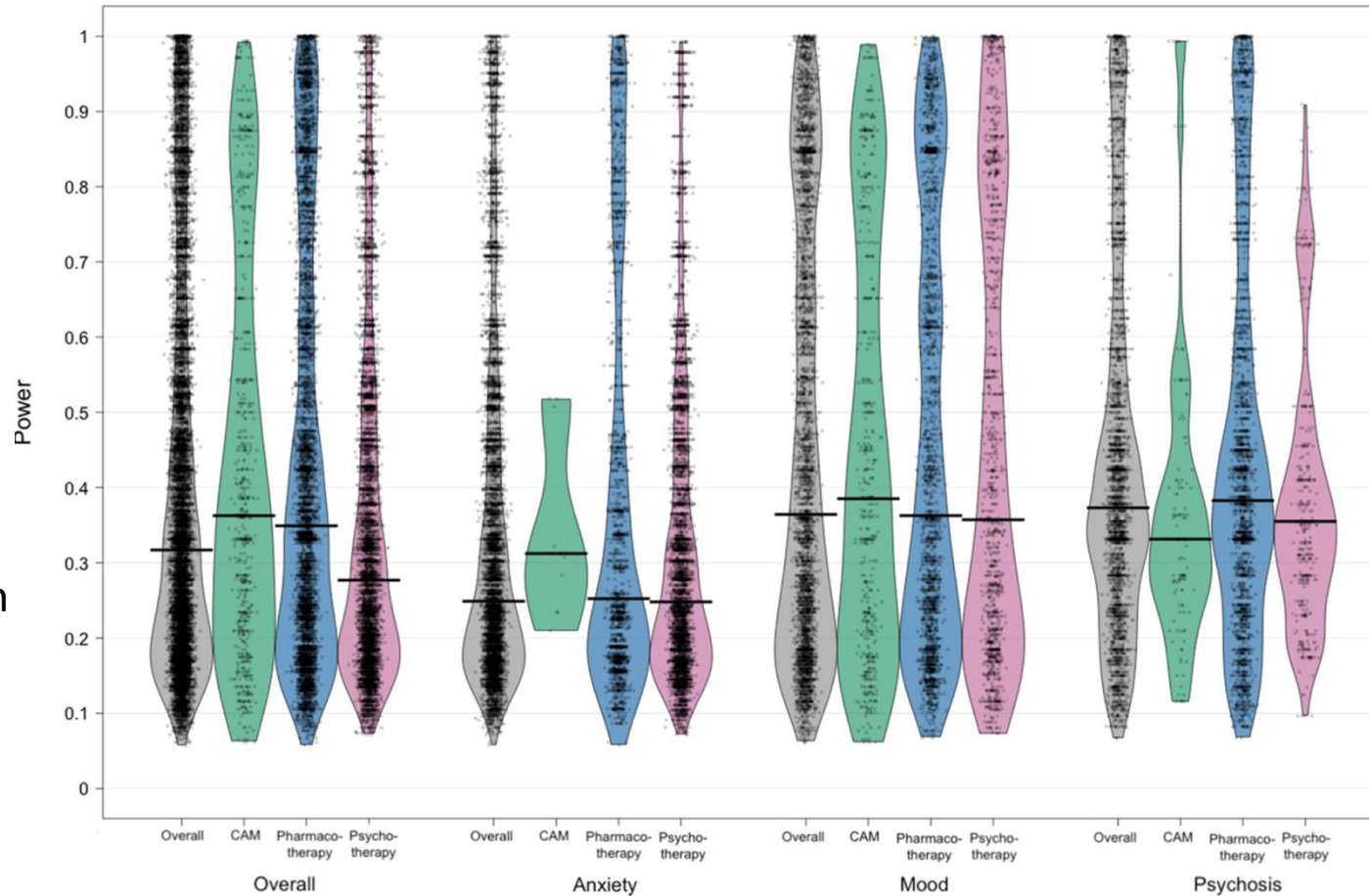




# A LANDSCAPE OF UNDERPOWERED TRIALS

Power to detect  
SMD=0.40  
256 reviews with  
10.686 meta-  
analyses and  
47.384 studies

De Vries et al.,  
*Psychol Med* (2022)



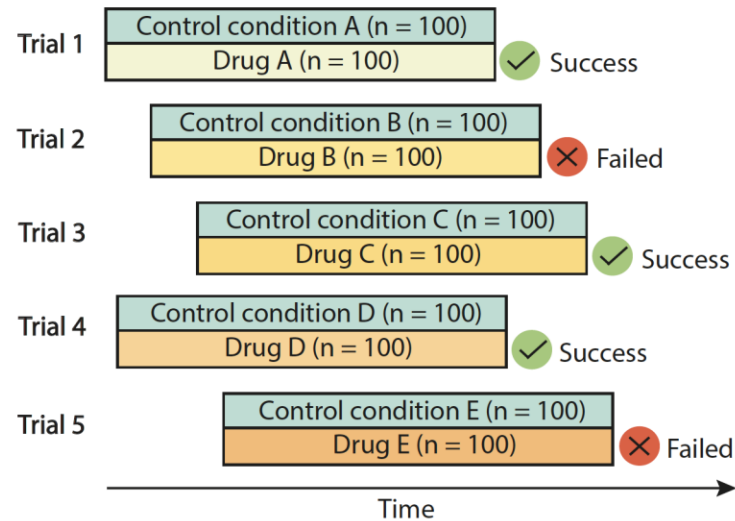
Leucht et al., *Br J Psych* (2012)



# PLATFORM TRIALS: IMPROVED SPEED AND EFFICIENCY

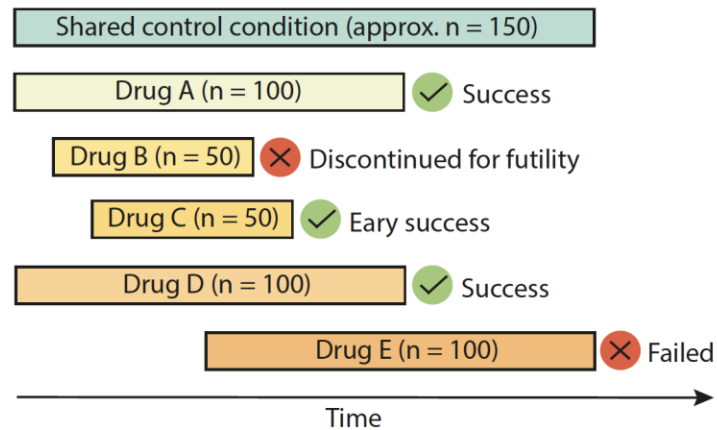
## Individual randomized controlled trials

Overall sample size: N = 1000



## Platform trial

Overall sample size: approx. N = 550

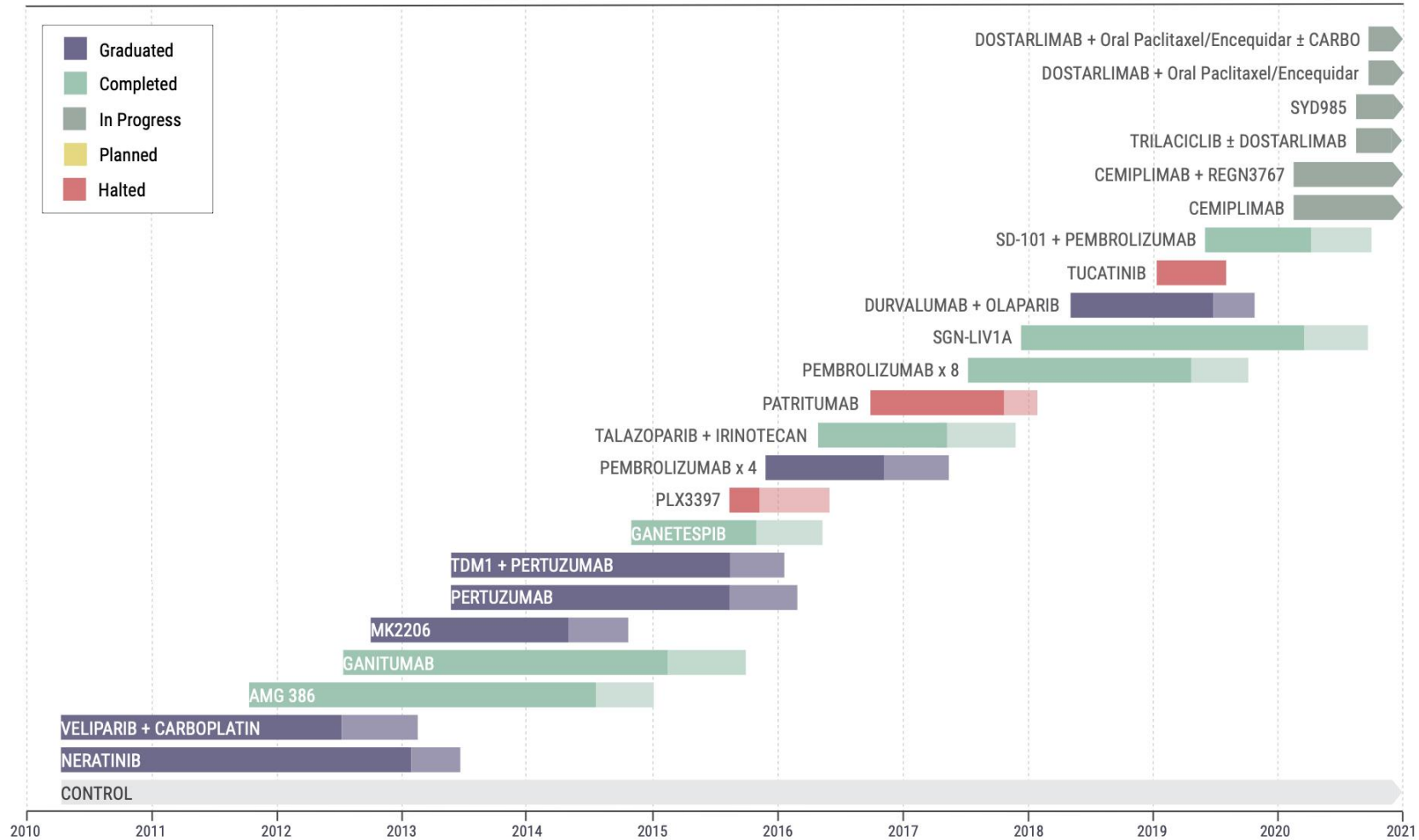


Gold et al., *Nat Rev Psych* (2022)

| "One treatment, one trial"                                                                                                                                                                                                                                                                                                    | Platform Trial                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Inefficient (infrastructure built from scratch for each trial)</li> <li>• Limited in the questions they address</li> <li>• Typically 50% of participants assigned to control group</li> <li>• Limited power to detect smaller (but potentially relevant) clinical effects</li> </ul> | <ul style="list-style-type: none"> <li>• Shared infrastructure -&gt; faster recruitment</li> <li>• Comparative efficacy / effectiveness</li> <li>• Fewer participants on control / placebo</li> <li>• Shared controls -&gt; increased power</li> <li>• Increased flexibility (adding and dropping of arms)</li> <li>• Can accommodate different types of treatments</li> </ul> |



# PLATFORM TRIALS: IMPROVED SPEED AND EFFICIENCY



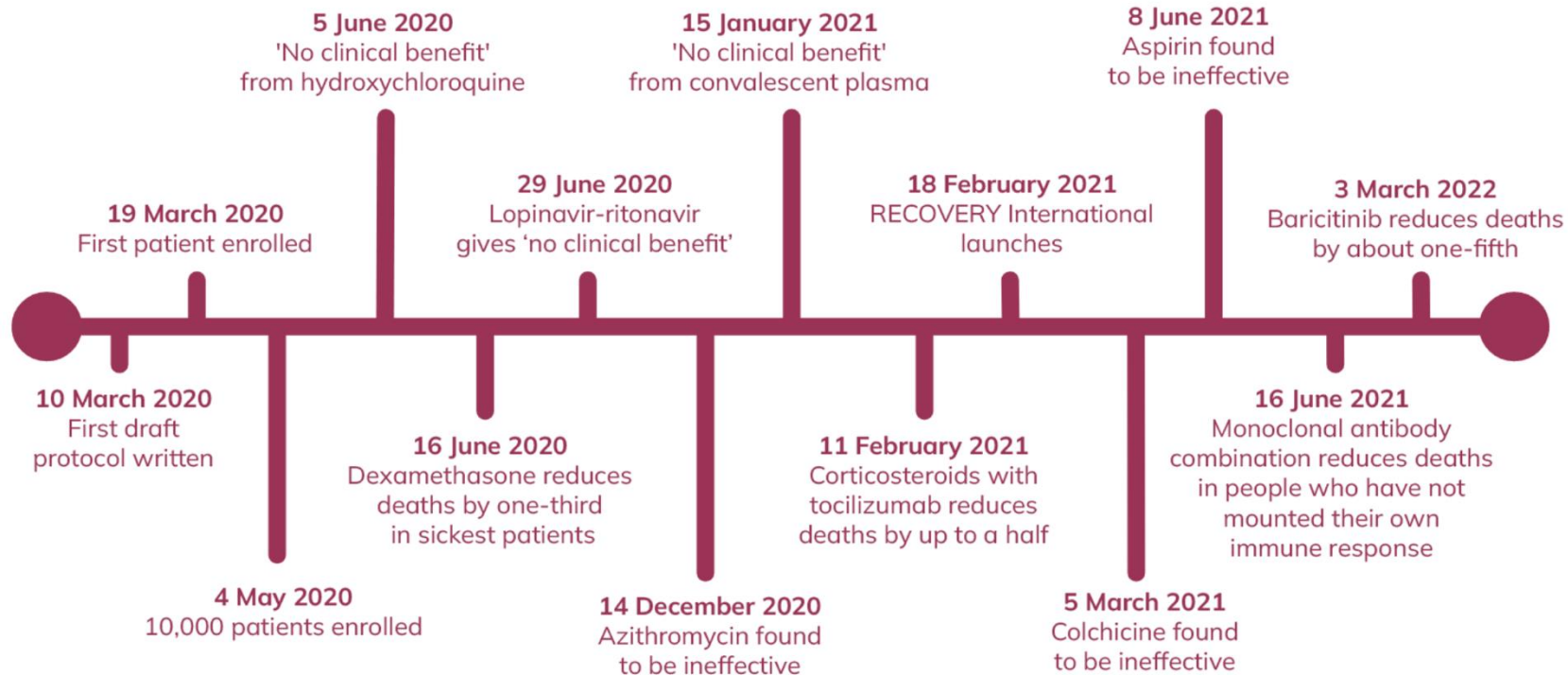


# PLATFORM TRIALS: IMPROVED SPEED AND EFFICIENCY



**RECOVERY**  
Randomised Evaluation of COVID-19 Therapy

**2 years on**



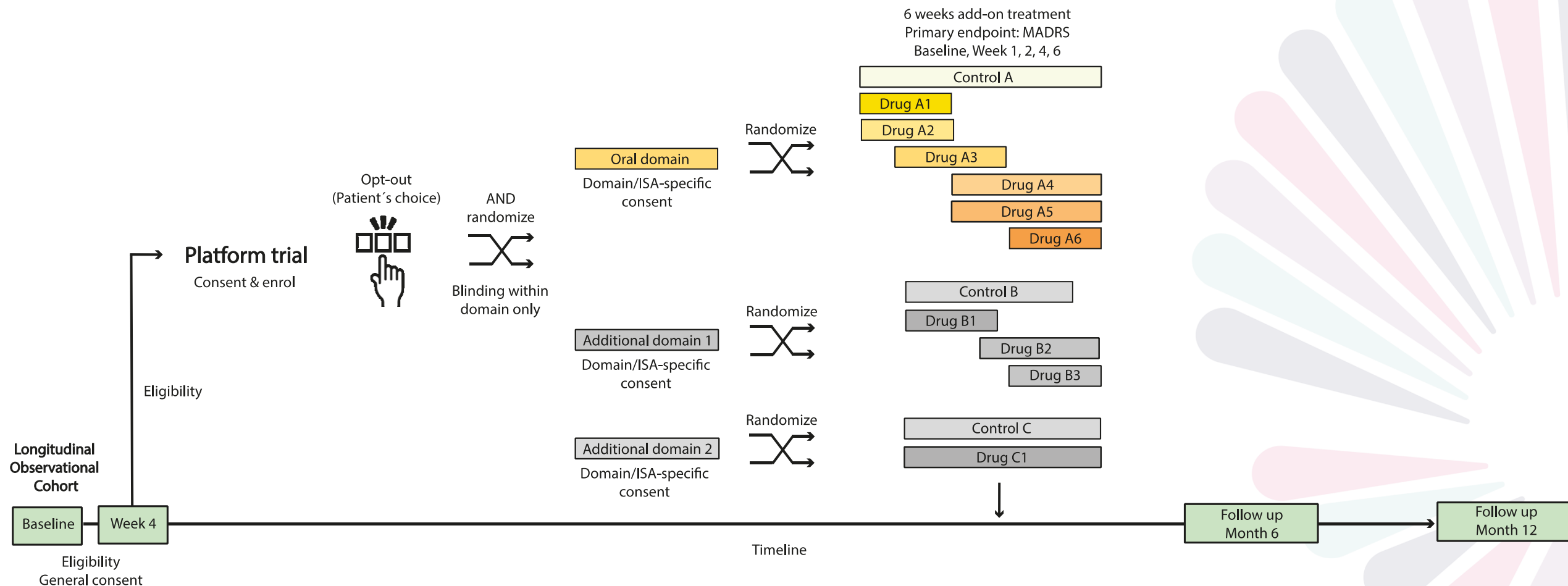


# EU-PEARL: PROJECT GOAL FOR MDD

## DESIGN A PATIENT-CENTRIC PLATFORM TRIAL FOR TREATMENT-RESISTANT DEPRESSION

|                            |                                                                                                                                                                                                                                                                                     |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Treatment Duration         | 6 weeks plus long-term follow-up                                                                                                                                                                                                                                                    |
| Endpoints                  | Primary: <b>MADRS (Clinician-based Rating scale)</b> at week 6<br>Secondary: a “menu” of outcomes to include symptom burden (anhedonia, sleep, cognitive function etc) as well as psychological, physical, and social health<br>Allow testing for fast-acting <1-2 weeks            |
| Treatments and Comparators | Allow for <b>different routes of administration</b> (domains)<br><b>Augmentation/combination approaches (add on)</b> to existing antidepressant, with placebo add-on as the comparison<br>Suitable for <b>new and repurposed drugs</b><br><b>Blinding <u>only within</u> domain</b> |
| Trial arms                 | Customizable sample size: <b>40-120 participants per experimental arm</b> (phase II/PoC) but also allow larger arms for comparative effectiveness                                                                                                                                   |

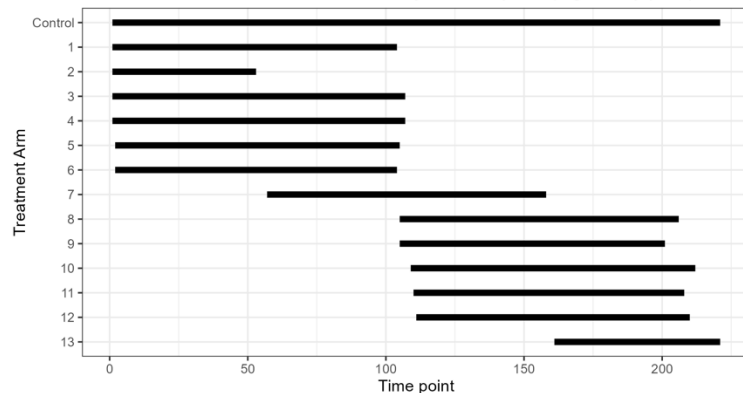
# AN INTEGRATED PLATFORM TRIAL FOR MDD



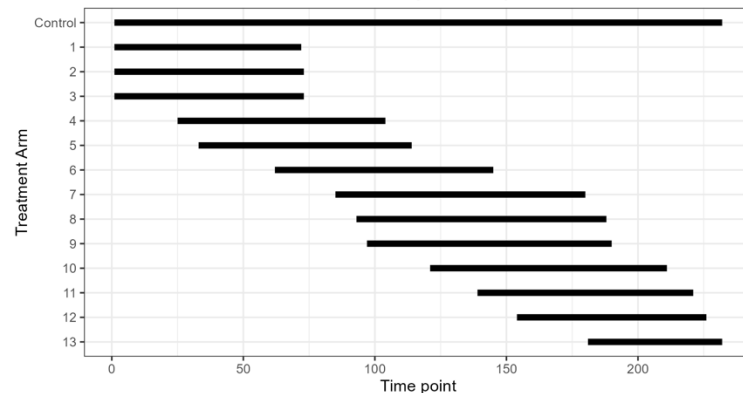
# TRIAL SIMULATIONS

## Examples

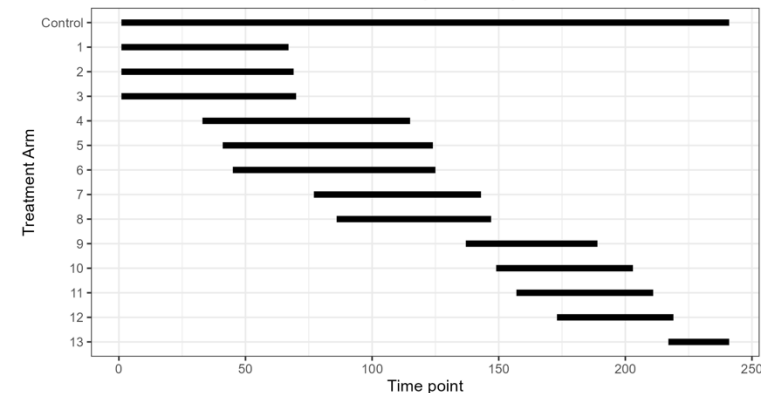
One selected simulation, N = 80, futility boundary 0.5 (high entry prob)



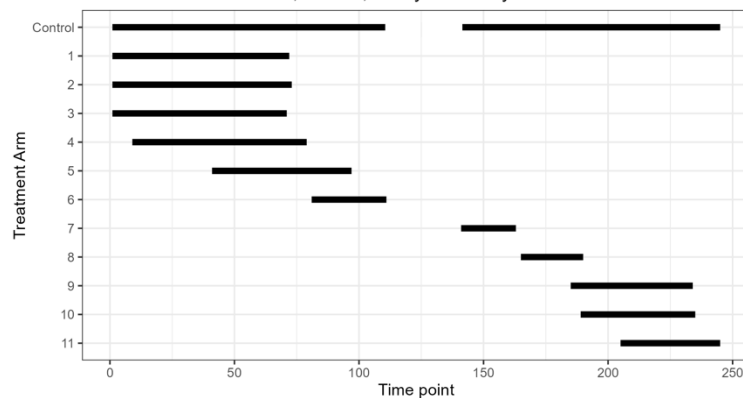
One selected simulation, N = 80, futility boundary 0.5



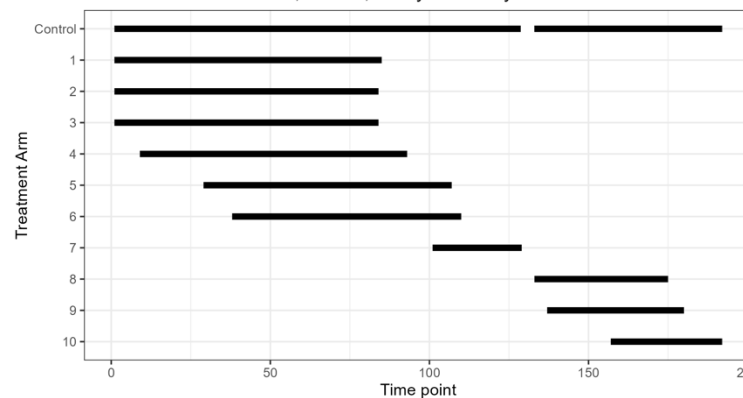
One selected simulation, N = 80, futility boundary 0.5



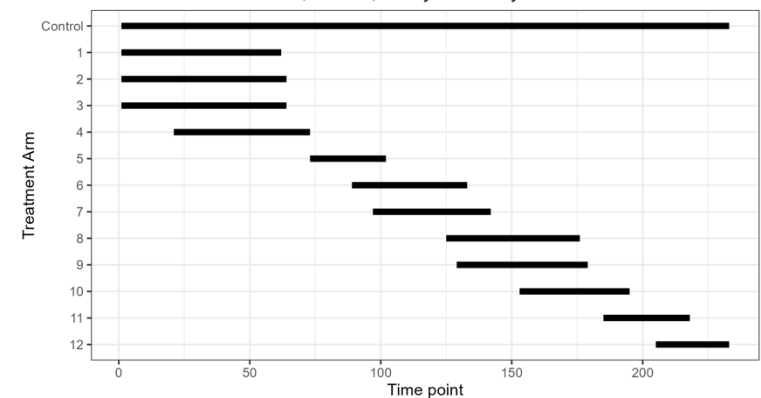
One selected simulation, N = 80, futility boundary 0.5



One selected simulation, N = 80, futility boundary 0.5



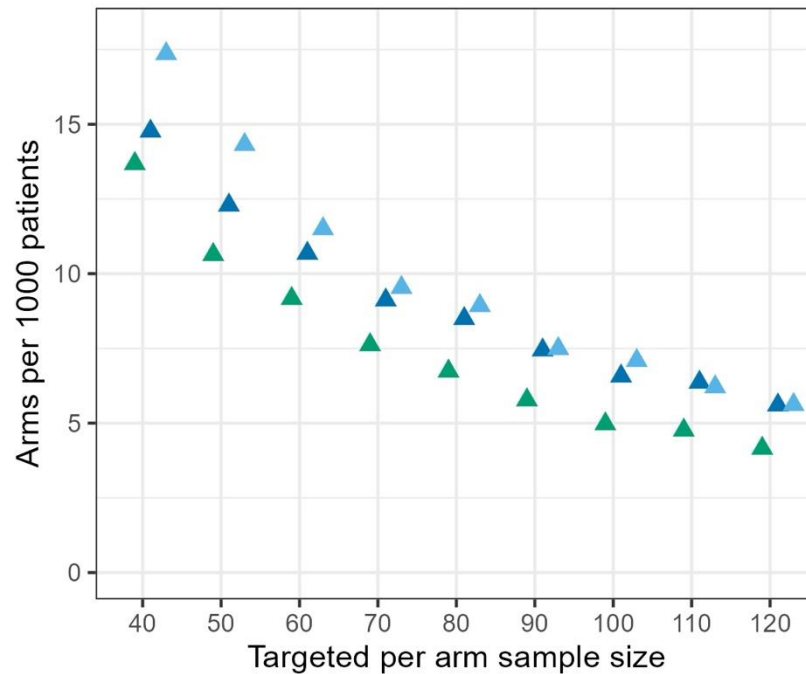
One selected simulation, N = 80, futility boundary 0.5



# SIMULATION RESULTS

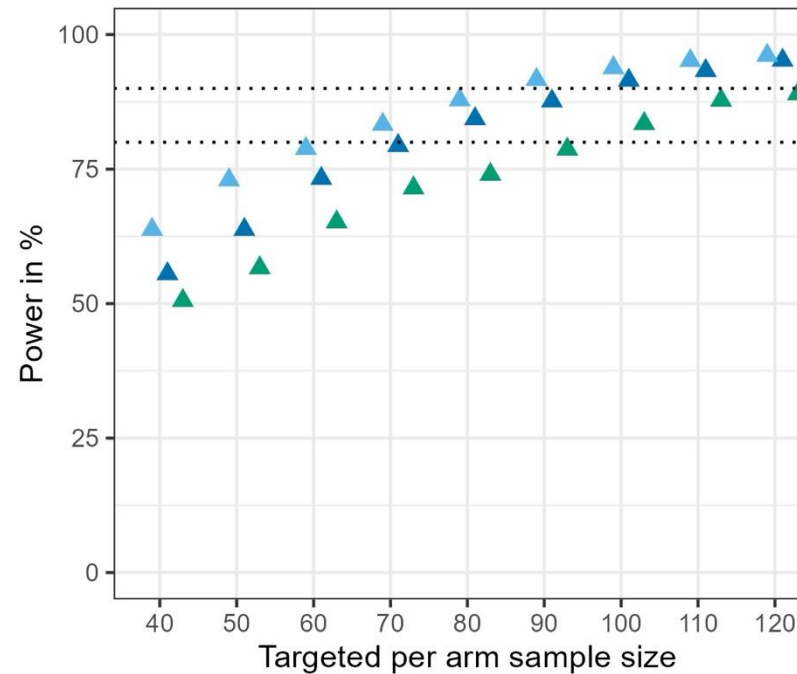
- **Higher power** and **more arms read-out** per 1000 patients for a platform trial compared to the "classic" approach with individual 2-arm trials

**A** Arms in different trial types



Trial type: ▲ platform trial [max] ▲ platform trial [exp] ▲ 2-arm RCTs

**B** Power for  $d=0.35$  in different trial types



- 10.000 simulation runs per combination of simulation parameters
- more than 1 million simulated trials overall
- 38 scenarios explored in detail

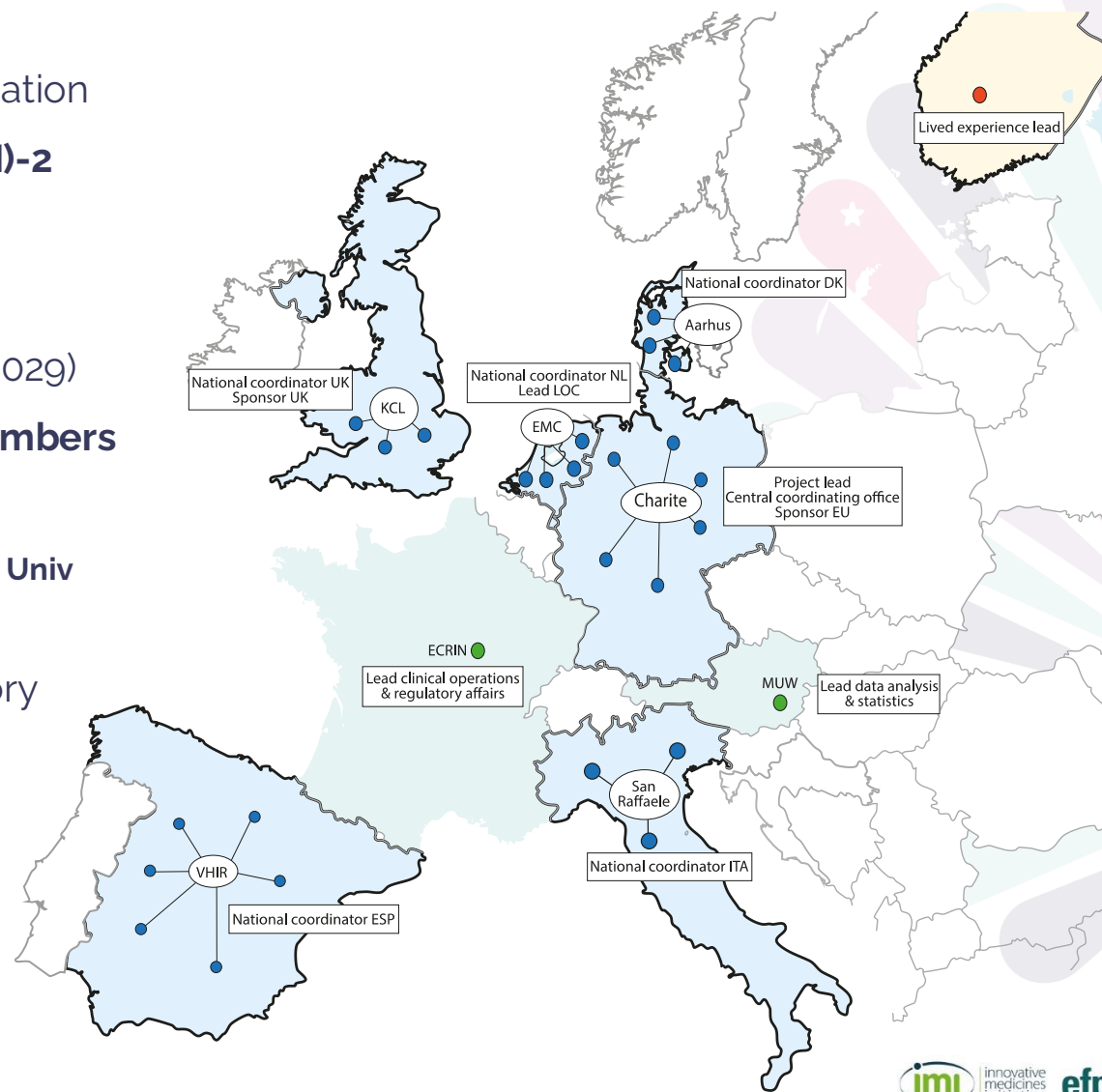
Freitag et al., *in revision*

# PAN-EUROPEAN SITE NETWORK

- Consortium funded for a planning & conceptualization phase by the **Innovative Medicines Initiative (IMI)-2** (2019-2023)
- Implementation phase and first two trial arms of repurposed oral drugs (+ shared placebo) (2025-2029)
- **Site network** (30 sites), coordinated by **EUHA members** in six European countries

**Charité** (GER), **EMC** (NL), **VHIR** (ESP), **San Raffaele** (ITA), **Univ Aarhus** (DK), **KCL** (UK)

- **ECRIN** to support clinical operations and regulatory affairs (co-sponsor)
- **MUW** to lead data analysis and statistics
- **Lived experience experts** as collaborators



# CHALLENGES & BARRIERS

|              | Challenge                                                                                                                                                                                                                                                   | Mitigation strategy                                                                                                                                                      |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Regulatory   | Difficulties with obtaining regulatory approval due to novel trial design                                                                                                                                                                                   | Early engagement with regulatory authorities and ethics commissions during the planning stage<br>Continued communication throughout the life cycle of the platform trial |
| Trial design | Blinding can be challenging in platform trials that accommodate different types of treatments (routes of administration, etc.)                                                                                                                              | Split the platform trial into “domains” (e.g. drugs with same route of administration and dosing paradigm etc) that can be fully blinded and thus share a placebo arm    |
|              | Blinding issues could be exacerbated given the importance of expectancy effects in mental health and the subjective nature of many commonly used outcome measures.<br>Lower probability to be assigned to placebo may increase responses in placebo groups. | Set a lower limit of placebo allocation<br>Consider communicating range of allocation likelihood rather than exact numbers                                               |
|              | Time trends in treatment responses (incl placebo responses) are likely, e.g. when a particularly “attractive” treatment enters or leaves the trial                                                                                                          | To avoid bias by time trends, restrict primary analyses to using only concurrent controls and/or keep the allocation ratio fixed / use stratified analyses               |
|              | Need for understanding the trial’s operating characteristics under different scenarios prior to launch                                                                                                                                                      | In-depth pre-trial simulations to inform design choices                                                                                                                  |
|              | Frequent interim analyses needed                                                                                                                                                                                                                            | Establish infrastructure for efficient dataflow and appropriately staffed / experienced statistics team                                                                  |

# CHALLENGES & BARRIERS

|                    | Challenge                                                                                                                                                   | Mitigation strategy                                                                                                                                                                                                                                                                                                                                 |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Acceptability      | Potential participants may be reluctant to join because of the complexity of the trial                                                                      | Involvement of LE experts from the very beginning of the design process<br>Outreach campaigns co-designed                                                                                                                                                                                                                                           |
|                    | Trial can contain vastly different treatment forms which may not all be equally attractive and participants may thus be reluctant to agree to be randomized | LE experts as collaborators in key roles (including choice of treatments to be tested)<br>Consider opt-out or opt-in features for domains of the trial<br>Consider adding the opportunity to re-randomize to subsequent cohort/domain, if participant does not benefit from initial treatment                                                       |
| Treatment Pipeline | Depth of the treatment / drug development pipeline to sustain a platform trial may not be known or potentially insufficient for certain indications         | Build the platform trial so that it can also accommodate candidates for repurposing as well as comparative effectiveness<br>These will be in addition to running newly developed treatments / drugs                                                                                                                                                 |
|                    | Industry / compound owners may be reluctant to run their drugs in a platform trial, where they have limited control over design and conduct                 | Establish “proof of platform” by launching, recruiting, and reading out arms of repurposed drugs to demonstrate feasibility<br>“Neutral” ownership of infrastructure<br>Initiate collaborative discussions with industry early and maintain throughout<br>Consider offering incentives for early buy-in (discounted user fees / case payments etc.) |



# THE PEARLDIVER PLATFORM TRIAL FOR MDD

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- Increased efficiency (infrastructure, resources)
  - increased statistical power
  - more compounds tested
  - fewer participants on placebo
- Collaborative design including lived experience, industry etc
- Early regulatory input (Innovation Task Force, EMA)
- “Customizable” to different preferences and risk tolerance
- Can provide comparative efficacy (if desired)
- Not owned by a commercial entity, funded by Wellcome & led by an open collaborative consortium
- Can later accommodate other “domains” (incl non-pharmacological) and serve as a model for other indications (e.g. anxiety, psychosis etc)



# ACKNOWLEDGEMENTS

IMI2 EU-PEARL consortium work package for MDD:

Charité Universitätsmedizin Berlin (GER), Erasmus Medical Center (NL), Janssen (BE), King's College London (UK), Novartis (CH), Medizinische Universität Wien (AT), San Raffaele, Milan (IT), Vall d'Hebron Institut de Recerca (VHIR), Barcelona (ES)

