3° ENCONTRO NACIONAL DE INVESTIGAÇÃO CLÍNICA & INOVAÇÃO BIOMÉDICA

New designs and methodologies in clinical trials

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AICIB AGÊNCIA DE INVESTIGAÇÃO CLÍNICA E INOVAÇÃO BIOMÉDICA

Discloser - *Bias and confounding factors*

ERA4Health Partnership

Co-funded by the European Union

To establish a dedicated funding mechanism supporting multinational Investigator-Initiated Clinical Studies (IICS) across Europe

- **Task 2B1.2 Challenges for new trial methodologies (PtCRIN-ECRIN)**

- PtCRIN, Portuguese Clinical Research Infrastructures network, member of ECRIN-ERIC
- Academic clinical research organizations/units, NOVACRU
- Academic, Pharmacologist
- CEIC, National Clinical Research Ethics Committee

Clinical trial phases and designs

Different Phases = Different purposes

Dose selection
Pharmacokinetics
Drug Interactions
Short term safety
Long term safety
Efficacy
Pilot vs Pivotal
Etc..

Different Designs= Different internal and external validity and feasibility

Bias,
Confounding,
Representative population,
Implementation time,
Etc..

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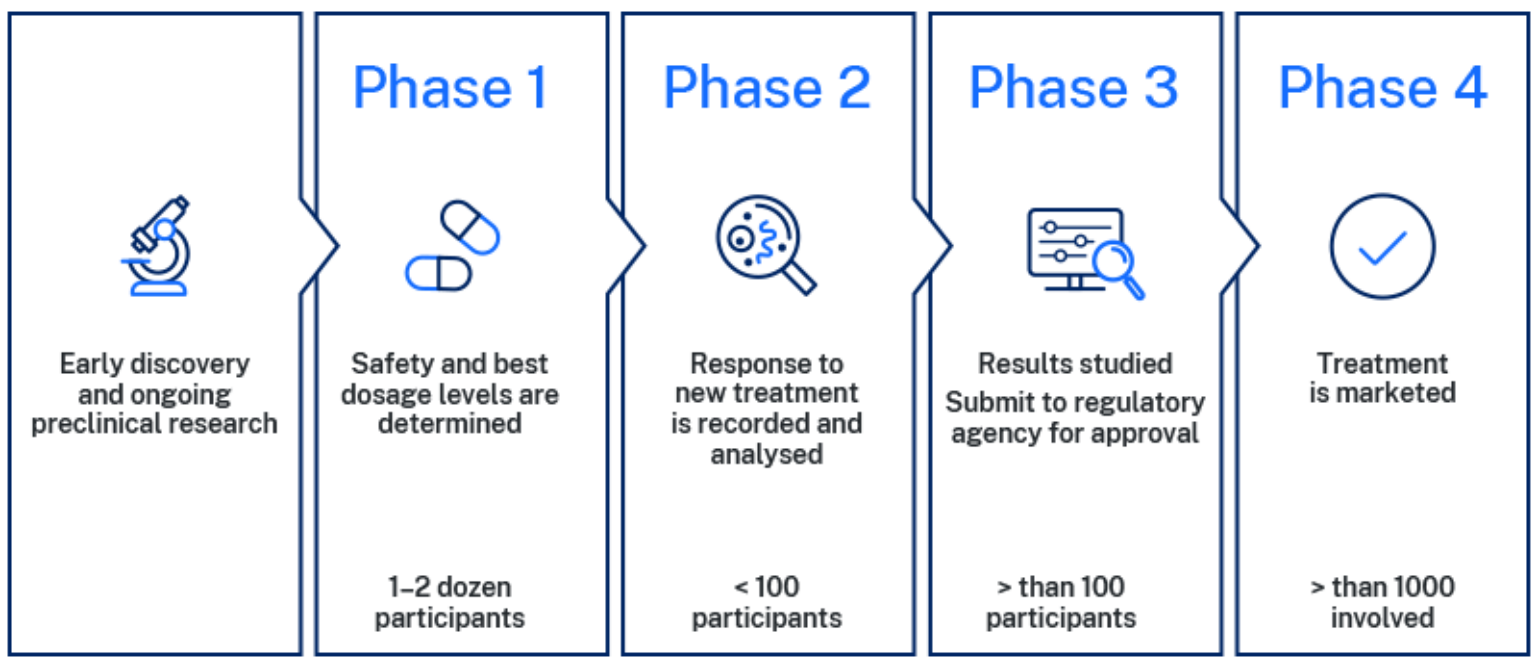
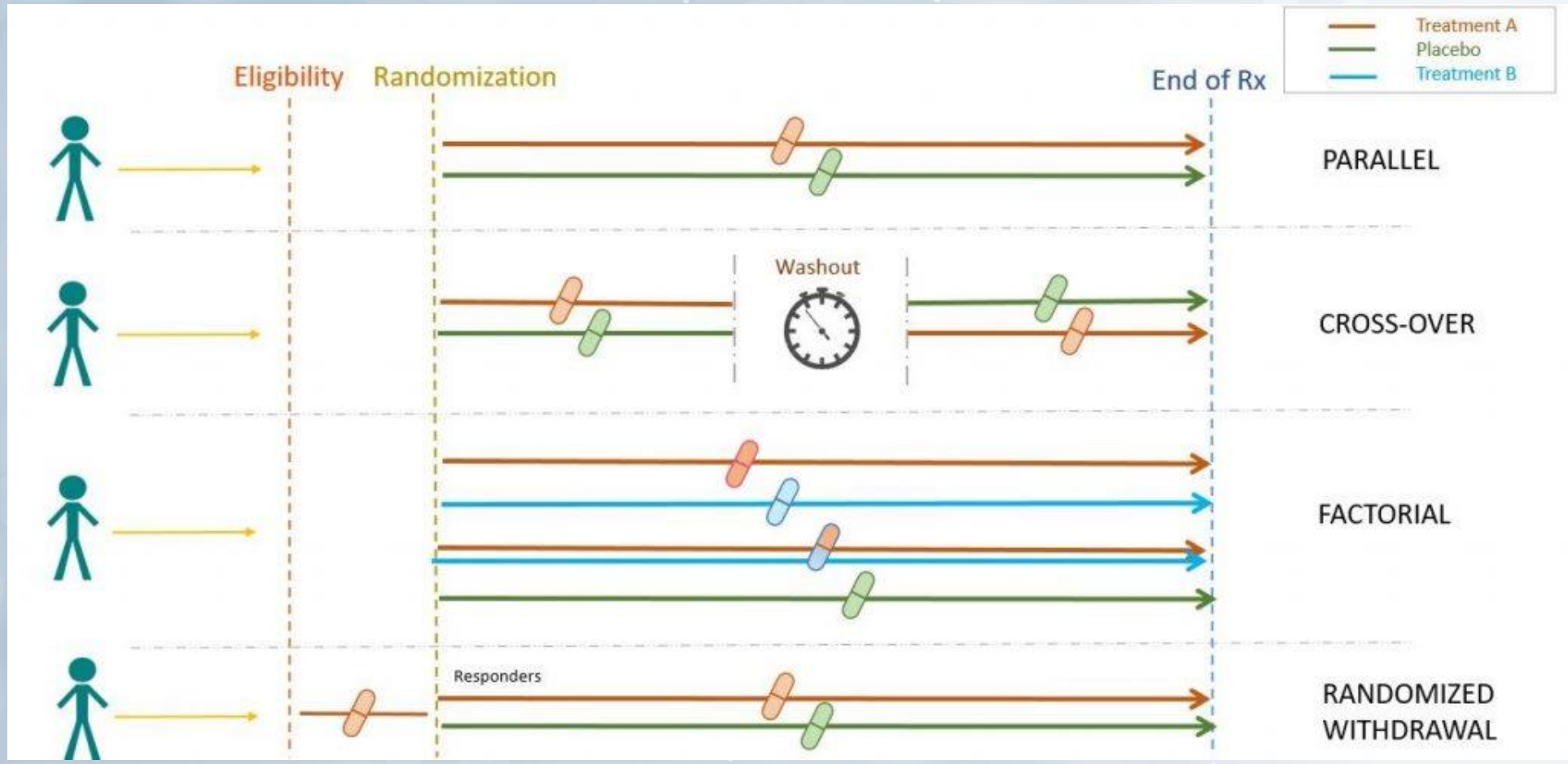
Traditional clinical trial phases

- Created for drug development purposes
- Phases are sequential and require specific approvals (**many years**)
- Not adapted to Investigator-initiated clinical trials



Traditional clinical trial designs

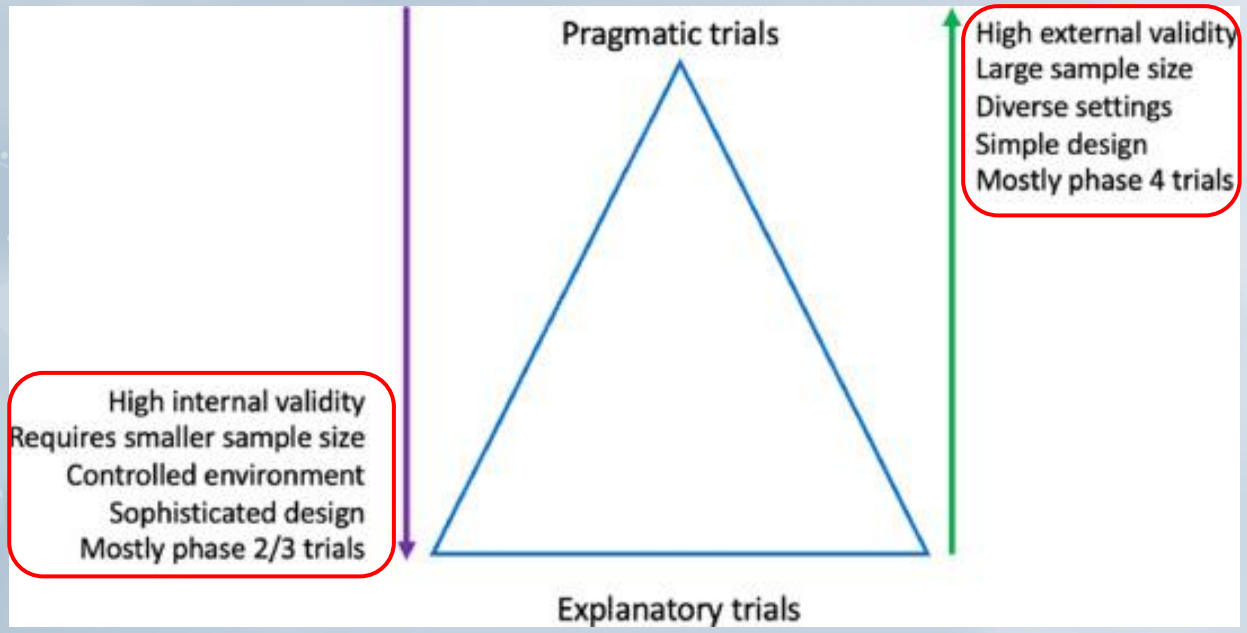


Traditional clinical trial designs- Limitations

- Typically, only one intervention and one disease subtype per trial (except factorial)
- Fixed design (several substantial amendments during the trial)
- Long development phases
- Not effectively address molecular heterogeneity
- Recruitment challenges (strict inclusion and exclusion criteria)
- Low patient engagement (number of visits to clinical sites, rescue therapies, etc)
- Not appropriate for addressing complex research questions (eg. disease evolution and need of other interventions, etc)
- Large number of participants being exposed to ineffective therapies and wasted resources

Investigator initiated clinical trials

Industry driven clinical trials



Pragmatic clinical trials

Example

Pragmatic point-of-care randomised trials using routinely collected electronic records

Health Technol Assess. 2014 Jul;18(43):1-146. doi: 10.3310/hta18430

Patients with a medical history of COPD who, in the opinion of their GP, had an acute exacerbation of COPD, who did not require immediate referral to specialist care for treatment of COPD exacerbation and consented to participation.

randomized

immediate (prophylactic)
The choice of antibiotic was left to the GP

deferred or non-use of antibiotics

End points:
Hospital admission for COPD exacerbation
Prescribing of oral corticosteroids (as recorded in the EHRs)

Traditional methodologies issues

Fixed designs
Large number of participants being exposed to ineffective therapies

Only one intervention and one disease per trial
Not effectively address molecular heterogeneity

Recruitment challenges strict inclusion and exclusion criteria

Low patient engagement

New trial methodologies

Adaptive

COMPLEX Designs

Master protocols

Trials within cohorts (TWiCs)

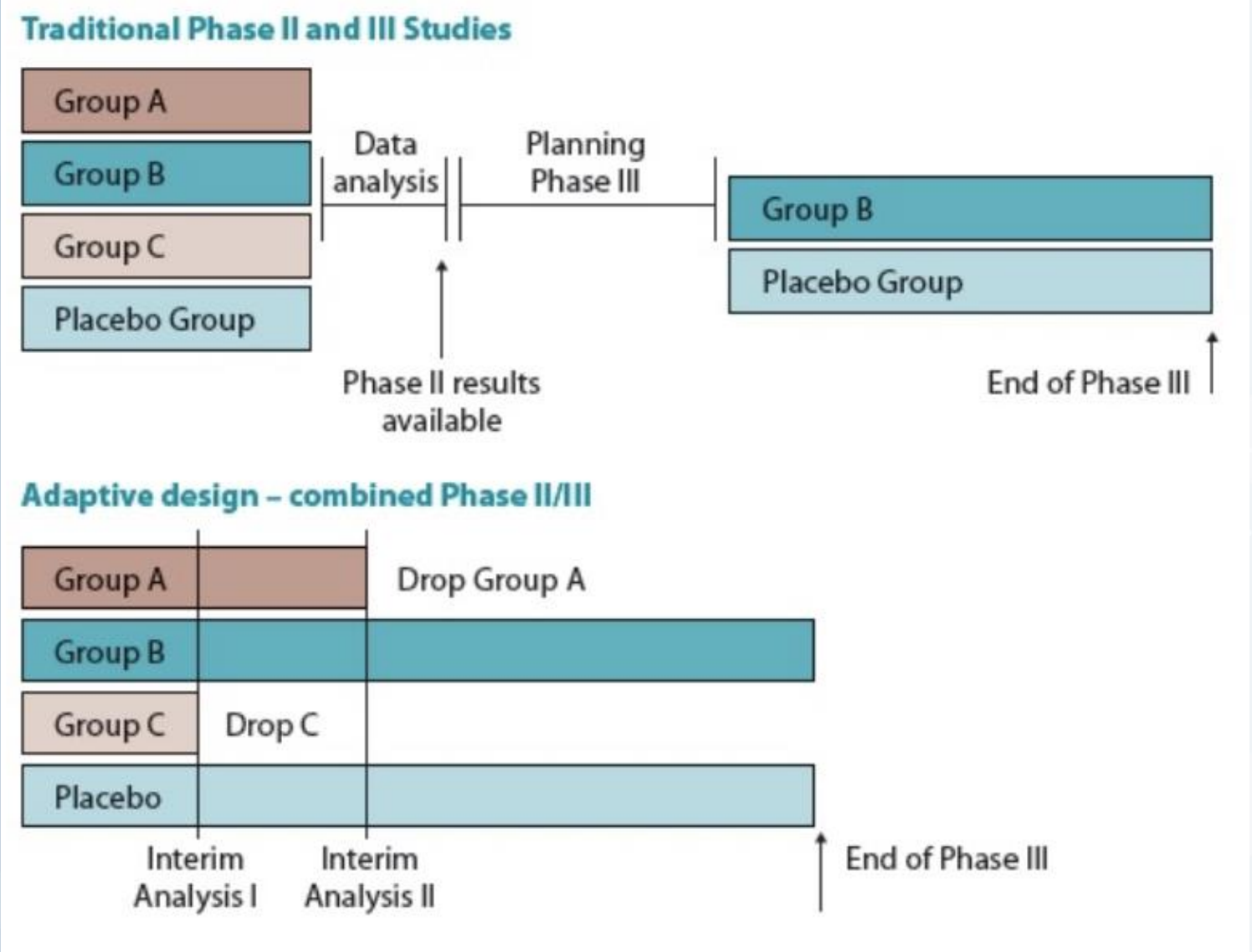
Pragmatic

Decentralized

Adaptive Classical

Adaptive design allows prespecified modification to different aspects of the trial.

Adaptation can be applied to sample size refinement or to recruitment strategies on the basis of new prognostic data



Adaptive

- Accelerate drug development and innovation
- Maximized patient welfare by reducing exposure to ineffective or less safety treatments at the earliest possible point.
- Minimized waste of resources if intervention are ineffective
- Fewer patients needed
- Designs more attractive to participants
- Flexible designs (improve the chances of success)
- Foster collaboration
- Reduce the costs

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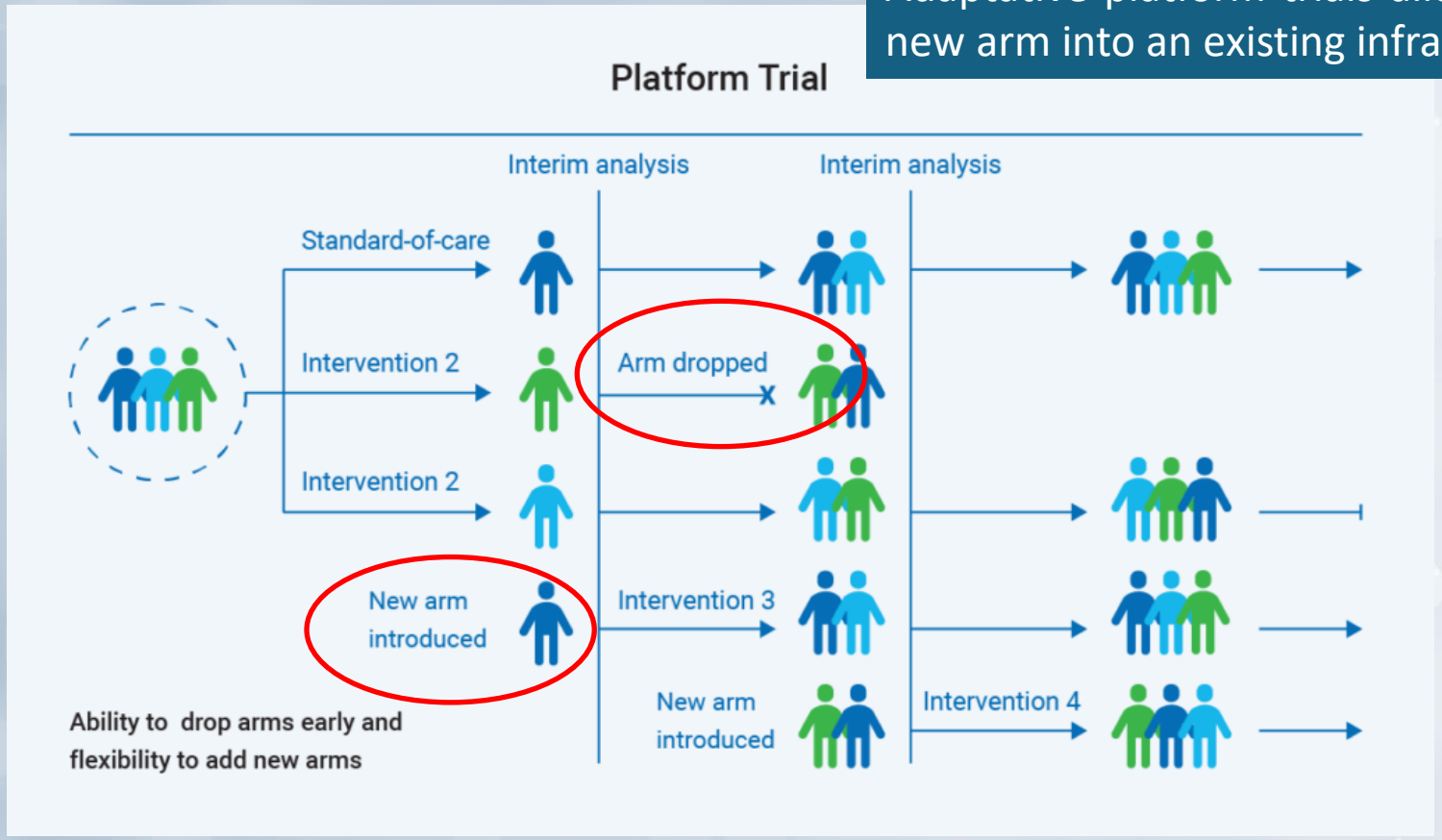
Adaptive Platform trials

Adaptative platform trials allows the efficient incorporation of new arm into an existing infrastructure.



Adaptive with new arms*

Multiple targeted therapies*
- new
- repurposing

Different funders*
- public
- industry

One control arm

Perpetual*

*Comparison between adaptive and adaptive in platform

Master Protocols (platform, basket and umbrella)

A protocol describing the key features of a complex clinical trial that encompasses common elements to all its **sub-protocols**, that can allow for the investigation of **multiple Investigation medicinal products or diseases/conditions,** and that specifies the shared framework across sub-protocols.

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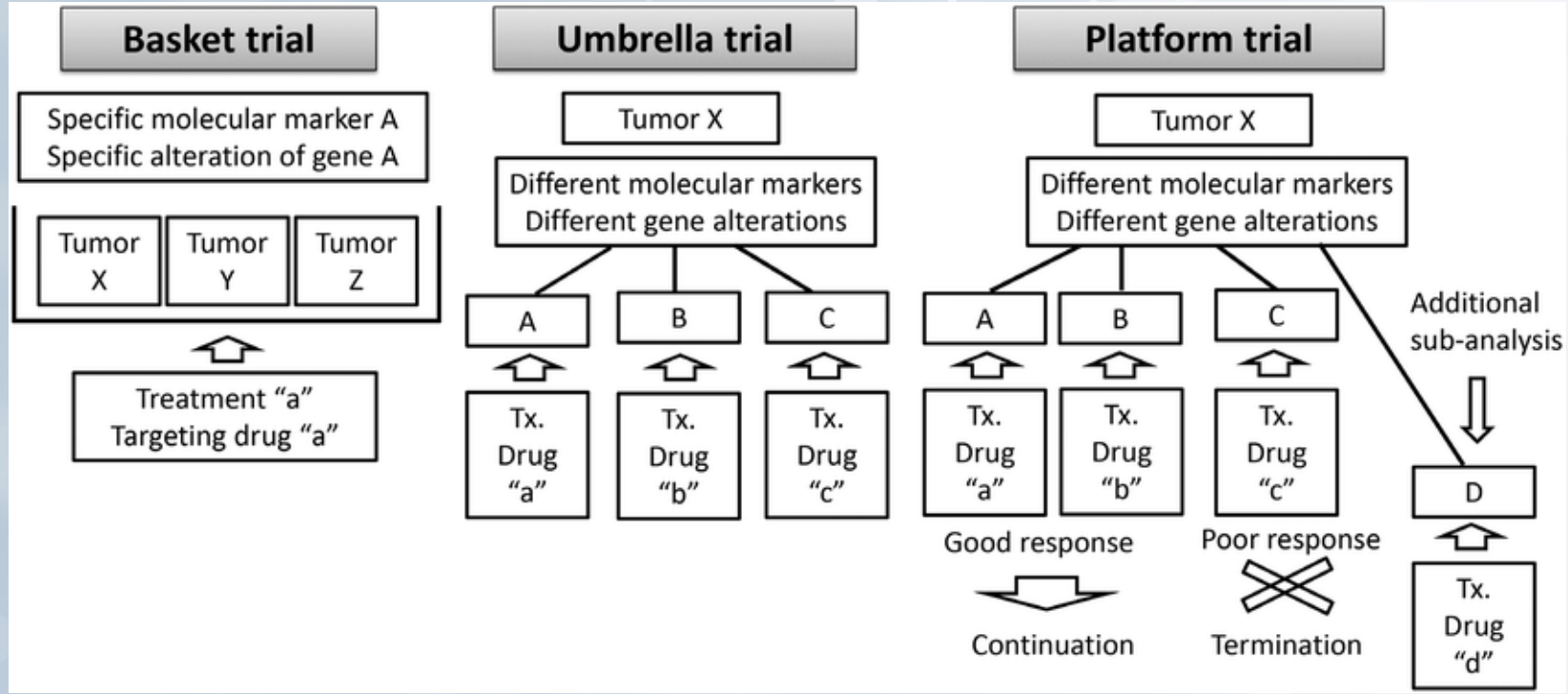
Master Protocols

One drug/target for multiple diseases
or
One disease with multiple geno/phenotypes



And
new arms

Neurologia Medico-chirurgica 2020, 60(11):531-542. DOI:10.2176/nmc.ra.2020-0175

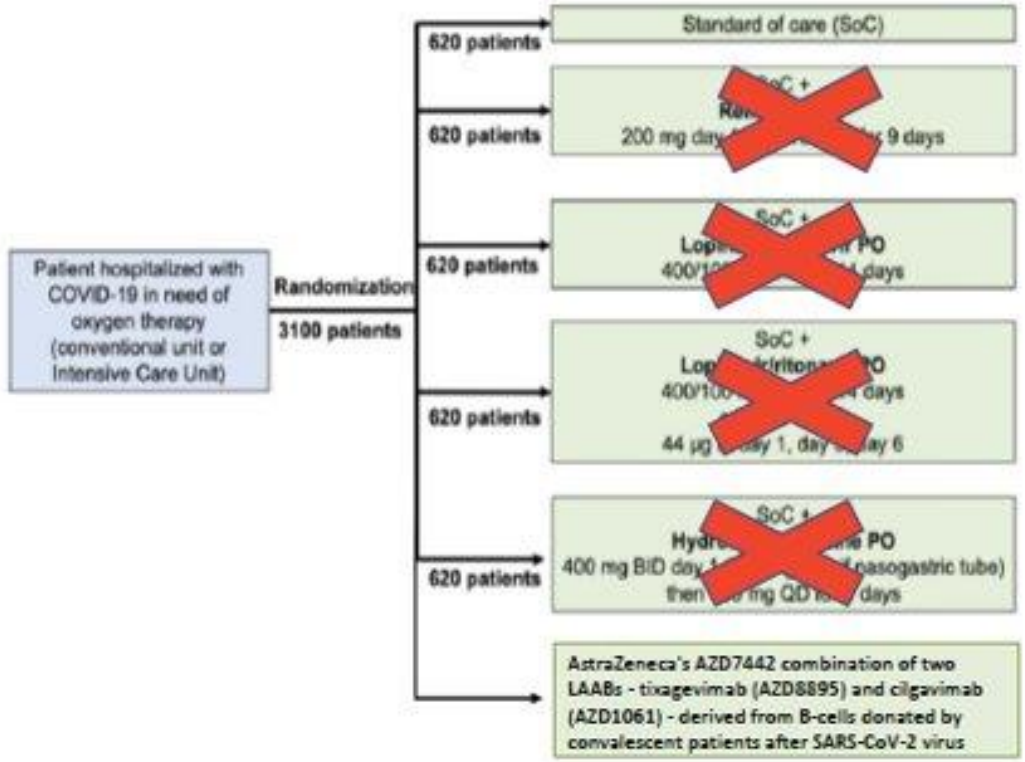
The pandemia fostered the implementation of complex trial designs

EU RESPONSE

Example

DISCOVERY

Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy)



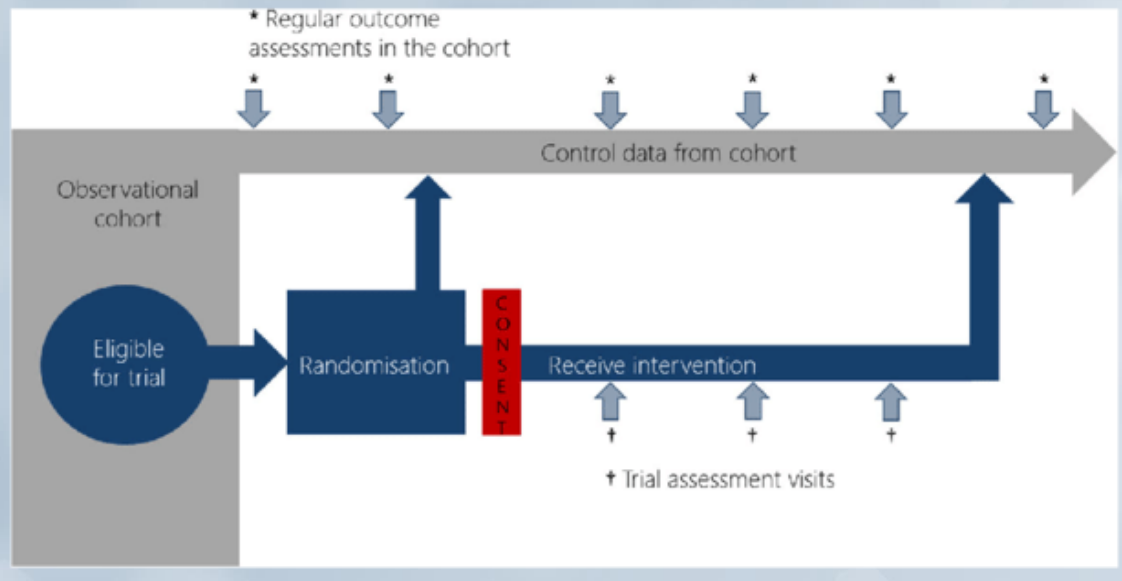
Phase III, adaptive, platform, controlled,open-label, multicentre clinical trial in hospitalised patients with COVID-19 in need of oxygen therapy

Funded by EU's Horizon 2020 and several EU national public funders

Master protocols general characteristics and challengers

- Confusion regarding the appropriate classification of master protocol designs, mislabelling and inconsistency
- High complexity prior to trial initiation, involves collaboration between multiple entities. Who pays the preparation?
- Who pays the platform? The importance of robust public infrastructure and appropriate resource allocation. Non-profit organizations naturally emerge as ideal candidates to sponsor master protocol trials.
- A trial design intended for perpetual enrolment does not conform to the present public and private funding mechanisms
- Management challenges: operational activities occur concurrently rather than sequentially,
- Numerous statistical challenges are associated with conducting master protocol designs: subgroup analysis; interim analyses, the choice between Bayesian/frequentist decision rules, trade-off between power and sample size, appropriate sample size calculation, whether to borrow information, and how to control of type I error rate present further challenges
- False-negative and false-positive patients due inherent diagnostic inaccuracies of all biomarker-guided assays.
- ....

Trial within cohorts (TWiCs)



- A randomized controlled trial that is nested within a cohort study.
- The cohort study provides the data collection infrastructure for the trial while the trial tests a specific intervention.
- Participants are followed longitudinally over time, and the trial intervention is randomly assigned to a subset of the cohort.

- Capture all relevant outcomes, especially if these outcomes are rare or take a long time to develop
- Allows multiple interventions for the same condition
- Patients in the control arm without specific ICF

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Key characteristics of TwiCs design include:

- Efficient Recruitment but a risk of insufficient cohort data for proper elegibility
- No placebo-controlled trials (TwiCs rely on the use of standard care as the comparator arm)
- Real World Scenarios: a more realistic assessment of intervention impact in actual clinical settings.
- More relevant outcomes (patient-centric approach)
- Establishing cohorts optimize the use of resources (cost-effectiveness)
- Study the long-term impact of interventions (Longitudinal Understanding)
- Allows several trials within the same cohort (Addressing Multiple Research Questions)
- Who pays and maintains the cohort? The importance of public infrastructures and public owners
- Unsuitable for explanatory trials that require tightly controlled conditions to assess specific intervention impacts (poor control of the control arm)

Up to now the majority of TwiCs studies have focused on evaluating therapies such physiotherapy, exercise, and radiotherapy rather than investigational medicinal products (IMPs)

Decentralized Trials (DCTs)

reduce the patient burden of hospital centered activities and facilitate participation

also known as a site-less, direct-to-patient, hybrid, remote, or virtual clinical trials

- Enable participants to:
  - perform trials activities at home and/or at local health care facilities (data collection through wearables, telemedicine visits, electronic diaries, phone calls, online appointments)
  - real-time data collection
  - receive study medicine shipments at home
  - provide their consent electronically
- Data collected in DCTs are expected to be more representative of the real world
- May adopt a hybrid model (combining conventional and decentralized elements)
- Not suitable for all research questions
- Ethical considerations linked to the usage of digital health technologies (e.g., eConsent, telehealth, apps, wearable devices and Electronic Patient-Reported Outcomes) and the misuse of the personal data by the services providers interacting with participants in their homes or other locations beyond trial site
- Internal validity issues related to the collection of data (participants, primary care, etc)
- etc

New designs and methodologies
Are we ready? A promise or a reality?

Registries***	Trial Design				
	Adaptive platform Trials**	Umbrella Trials	Basket Trials	Decentralized Trials	TWiCs
Records screened	454	93	169	42	24
PUBLICATIONS*	**121**	**54**	**55**	**48**	**33**

7644 publications relevant articles (2015-2023) → 316 full reading
5 systematic analysis

*Protocols, primary results, critical appraisals
** Most adaptive but not in platform
*** WHO International Clinical Trials Registry Platform (WHO-ICTRP); EU Clinical Trials Register (EU-CTR); ClinicalTrial.gov

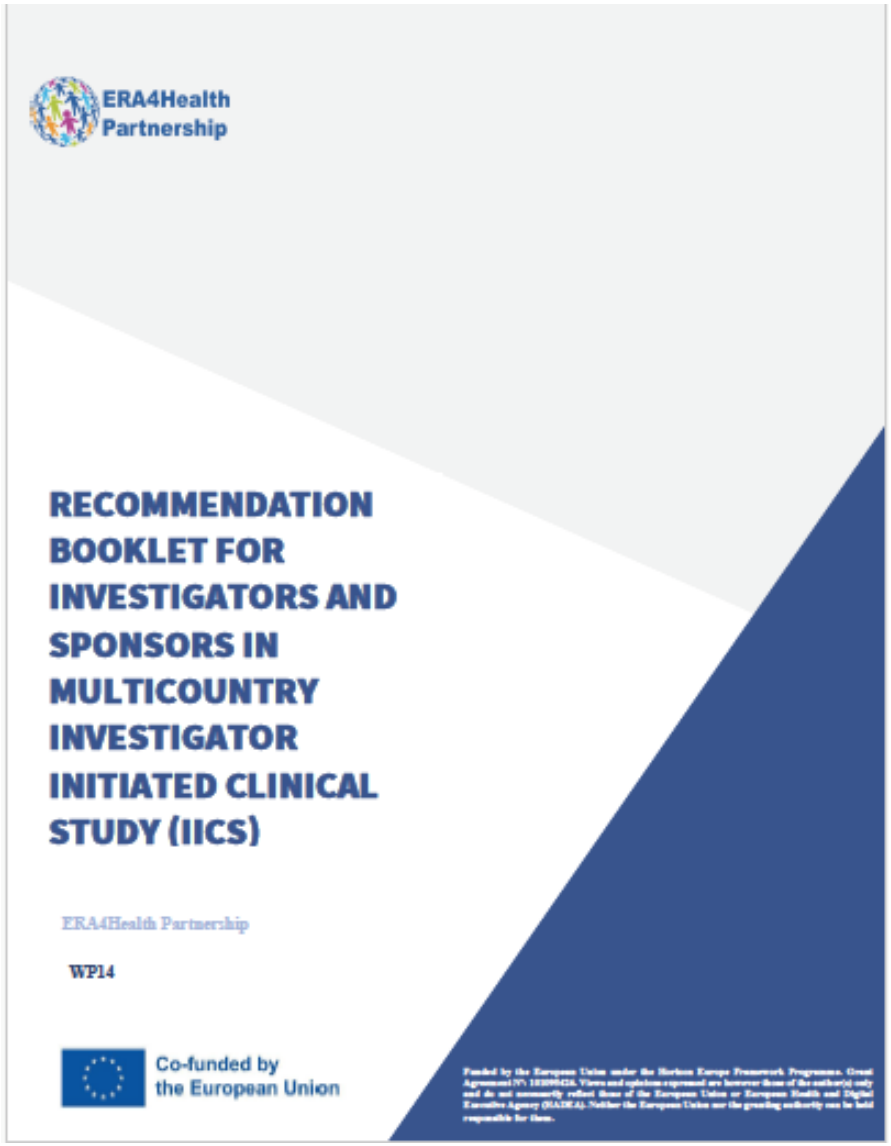
A considerable level of experience and maturity in the field.

Several stakeholders have already developed guidelines, initiatives, and tools, underscoring the significance of these methodologies in shaping the future of clinical research

Most of the trials coordinated by the USA and UK

New funding models should prioritize long-term investments in creating and maintaining cohorts, sustainable common infrastructure, screening platforms, and disease networks

Figure 9: Importance of collaborative efforts to overcome challenges and advance innovative trial methodologies in clinical research (orange). Recommendation for funders (green), regulators (blue), and sponsors/investigators (pink)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RECOMMENDATION BOOKLET FOR INVESTIGATORS AND SPONSORS IN MULTICOUNTRY INVESTIGATOR INITIATED CLINICAL STUDY (IICS)
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Thank you for your time.