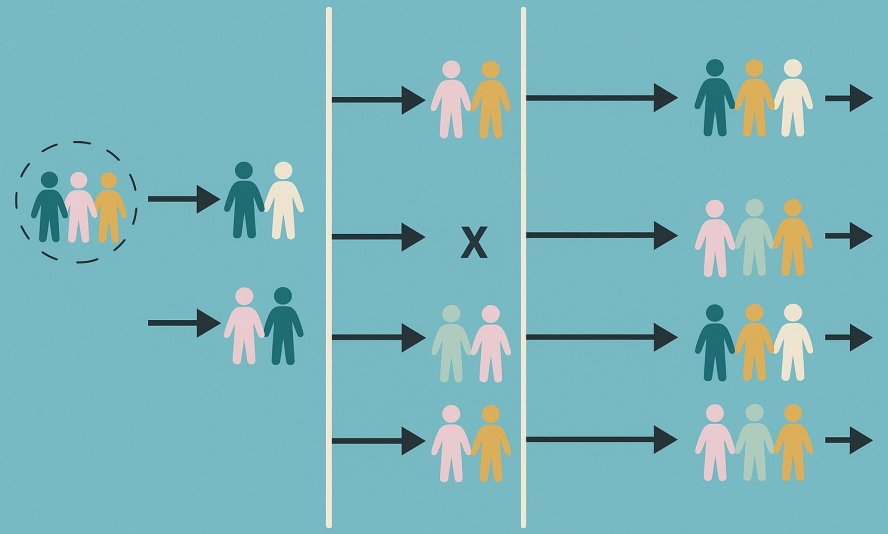
PLATFORM TRIALS

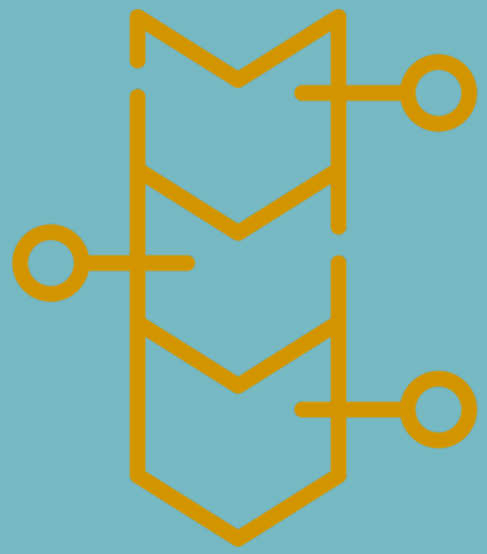
Clinical Opportunities and Methodological Challenges

Dr Edouard Lhomme

Webinar QuanTIM | 17th October 2025



OUTLINE



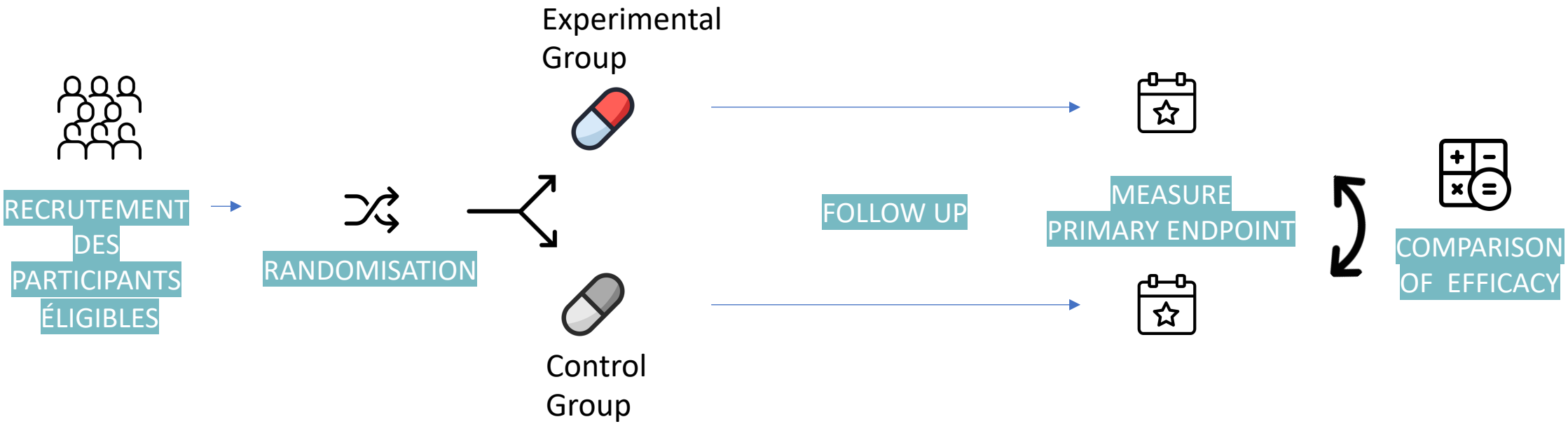
- **Introduction** : Key definition, design, the promise
- **Methodological challenges**
- **COVID-19**: Exemple of **COVERAGE France**
- **Operational and logistical aspects**
- **Conclusion**

1. INTRODUCTION

Definitions and promises of Platform trials

Traditional randomized clinical trials

- **OBJECTIVE**: Evaluate the safety and efficacy of a treatment / intervention for some illness or condition



Typically: - **ONE very specific question** about **ONE single intervention**
- **Infrastructure** (lab, staff, trial documentation, …) closed or dismantled at the end of the study

What is a platform trial ?

- A platform trial is a **type of randomized controlled trial** (RCT)
  - Done to **compare multiple treatments / interventions** by comparing them against a shared control
  - **Open ended**: **new interventions can be added, assessed, and removed** as time goes on
  - **Flexible/ adaptative**: interim analysis, update control arm, …
- Also known as **"multi-arm, multi-stage" (MAMS) trial**
- Way to do research **more efficiently** with fewer participants, to **compare many study treatments in a single disease**

what is the best drug for this disease?

« Master Protocol »

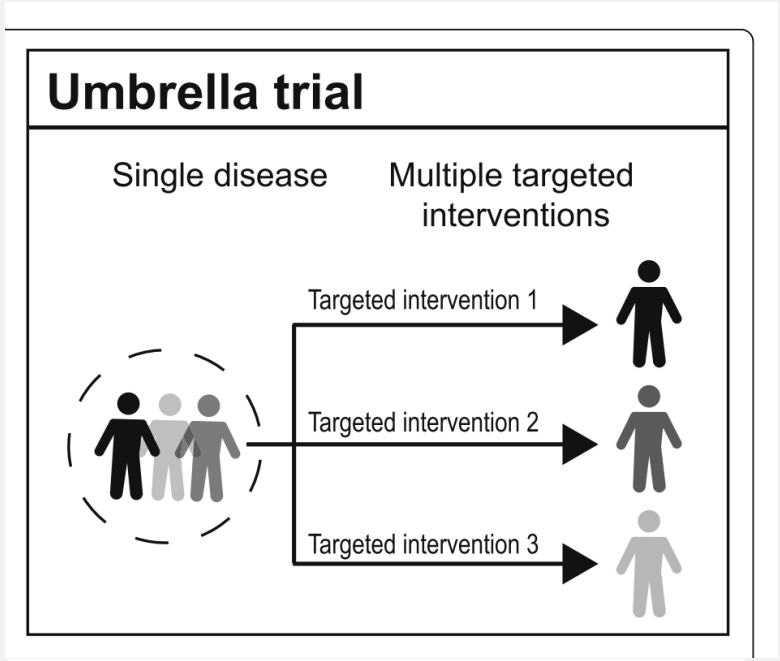
- Platform trial uses **Master Protocol** to evaluate the different study treatments in the same way, using the same design

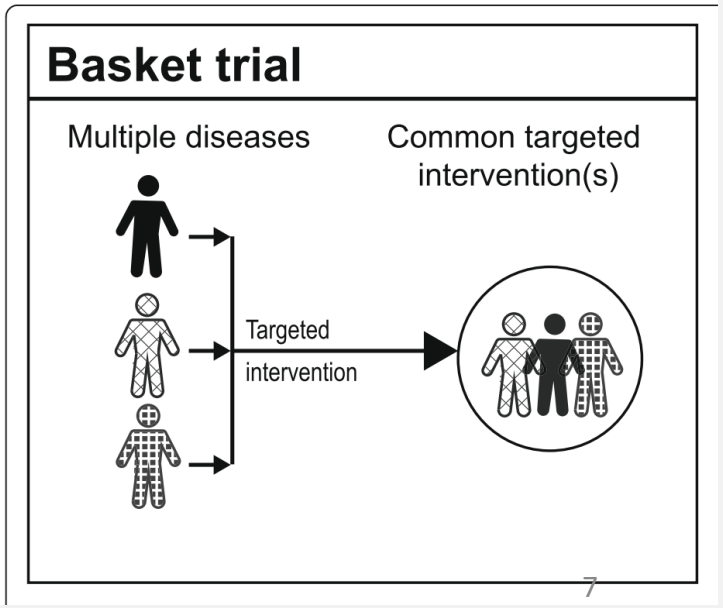
- The term “*master protocol*” refers to a single overarching design developed to evaluate multiple hypotheses

« Master protocols »

Table 1. Types of Master Protocols.

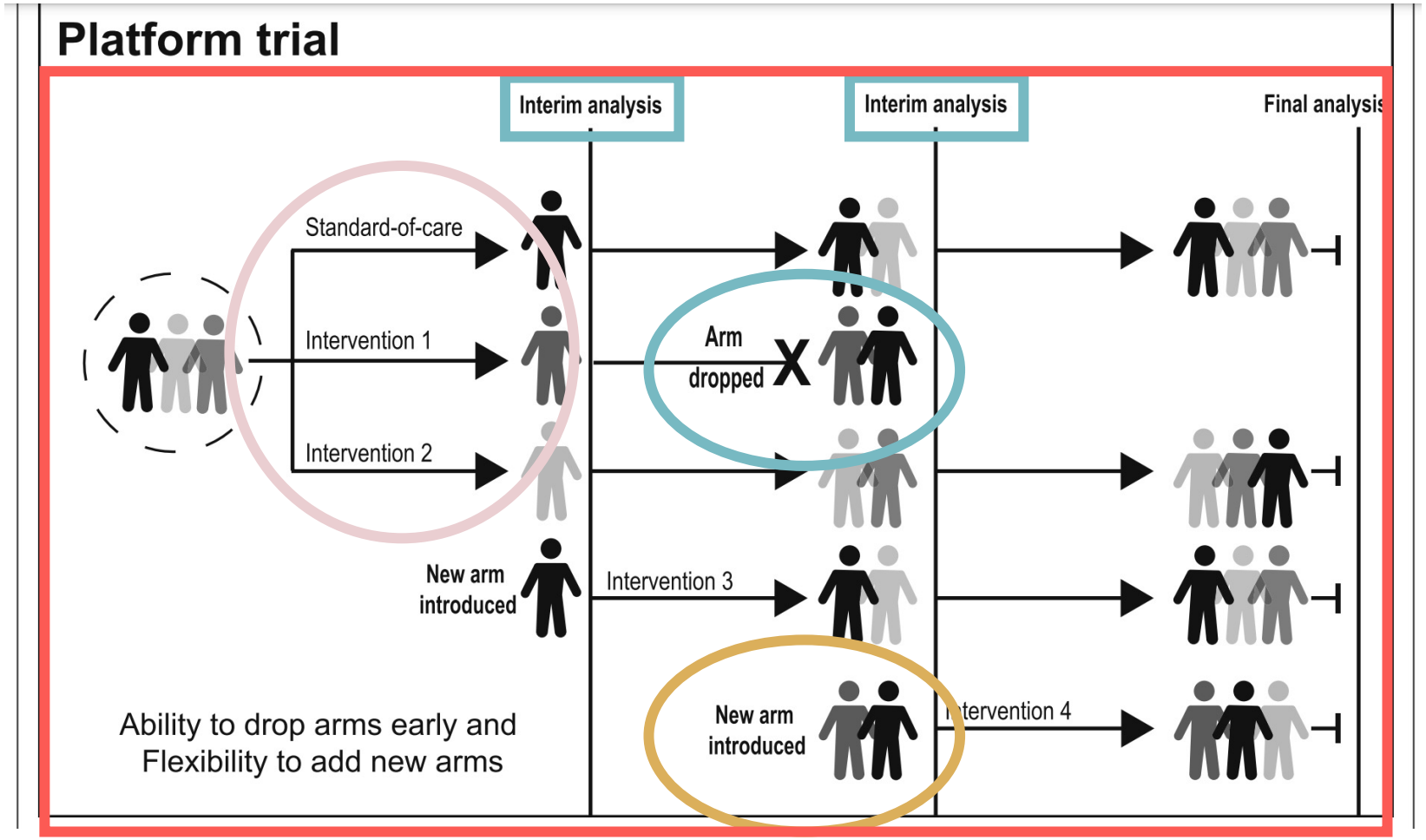
Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm





Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med. 2017

Platform trial design



Evaluate multiple interventions against a **common control group (SoC)**

Pre-specified adaptive rules (interim analysis) to allow for the discontinuation of one or more effective/ ineffective interventions

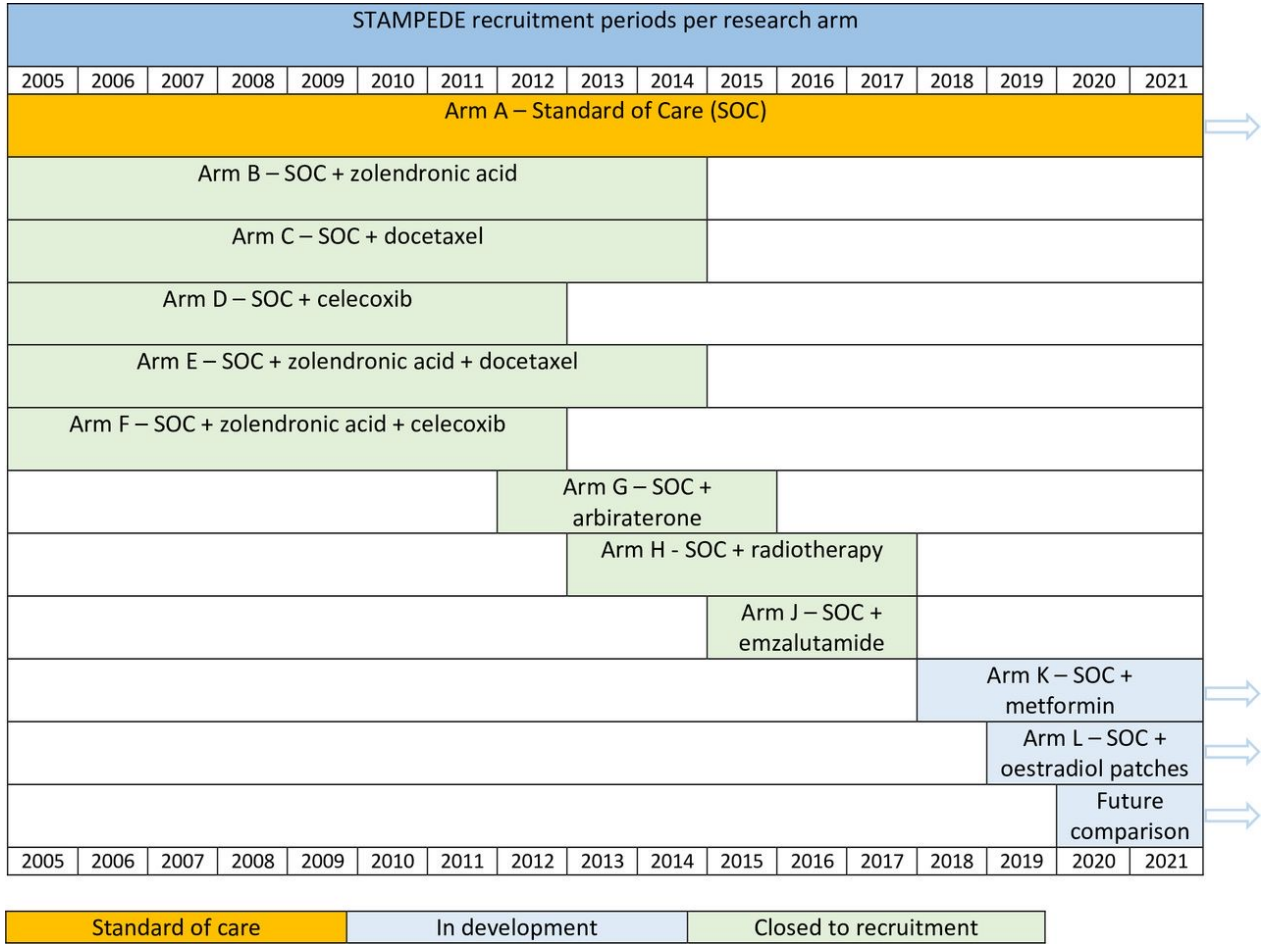
Add one or more intervention during the trial

Shared infrastructure

Park JJH, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials. 2019

2004: the first Platform trial

STAMPEDE trial (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy)



- **Treatment of men with advanced or metastatic prostate cancer**
- **Opened in 2005 with 6 arms** (5 experimental arms + SoC) with 2 planned interim analyses
- Since opening, the initial five experimental arms have been closed and new arms have been added subsequently

Platform trial: Strong increase since 2020

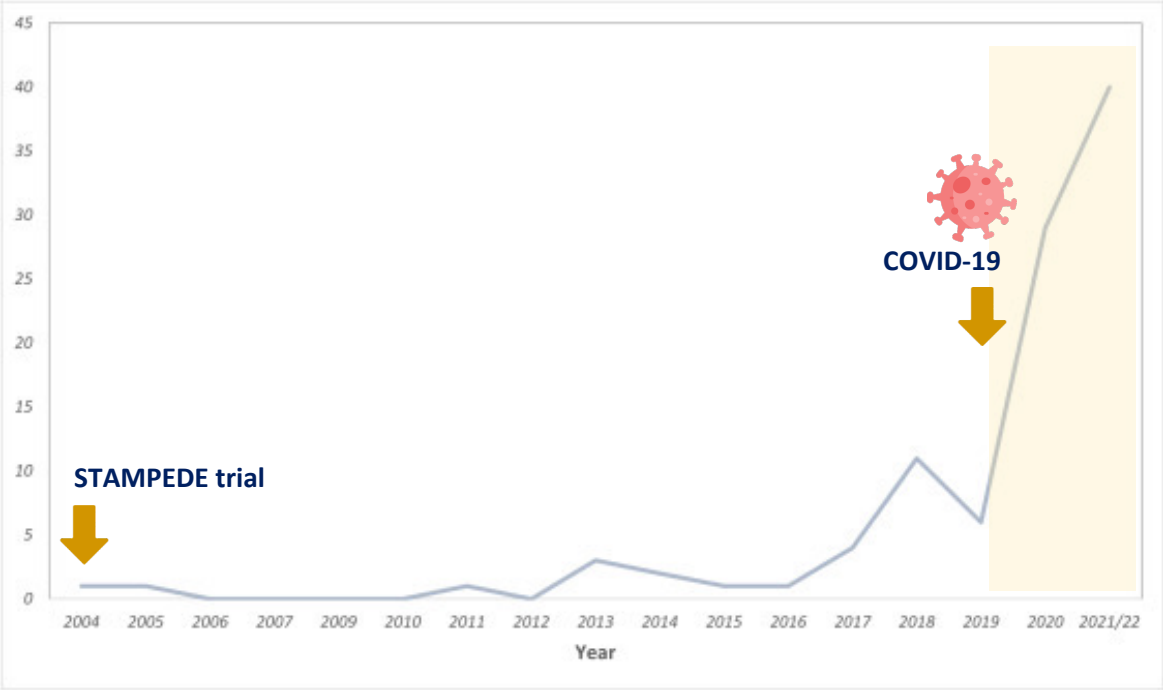


Fig. 2 Incidence in platform trial registrations from 2004 to 2022.

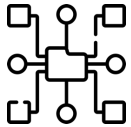
- A total of **98 randomized platform trials**
- **68.3% were registered between 2020 and 2022** (COVID-19 pandemic)
- **Towards diversification of pathologies** (e.g., neurodegenerative disorders, multiple sclerosis)

Why plateform trial ?

Faster + More efficient evidence generation (time, cost)

Flexibility + Adaptability (novel therapies, new questions..)

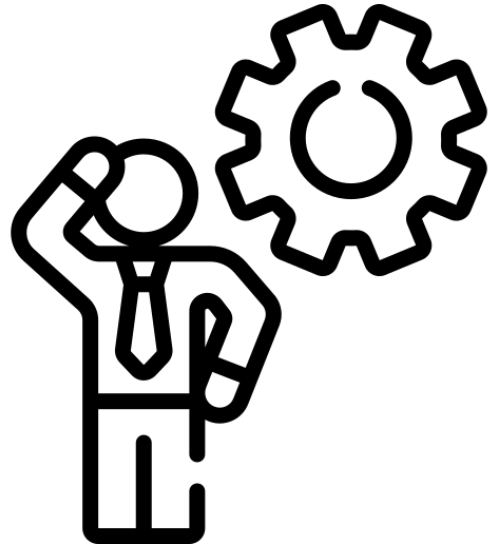
Clinical & public health impact (access to effective treatment)



Collaborative and sustainable Framework

2. METHODOLOGICAL CHALLENGES

- Control arm and comparisons
- Control of the type one error
- Interim analysis

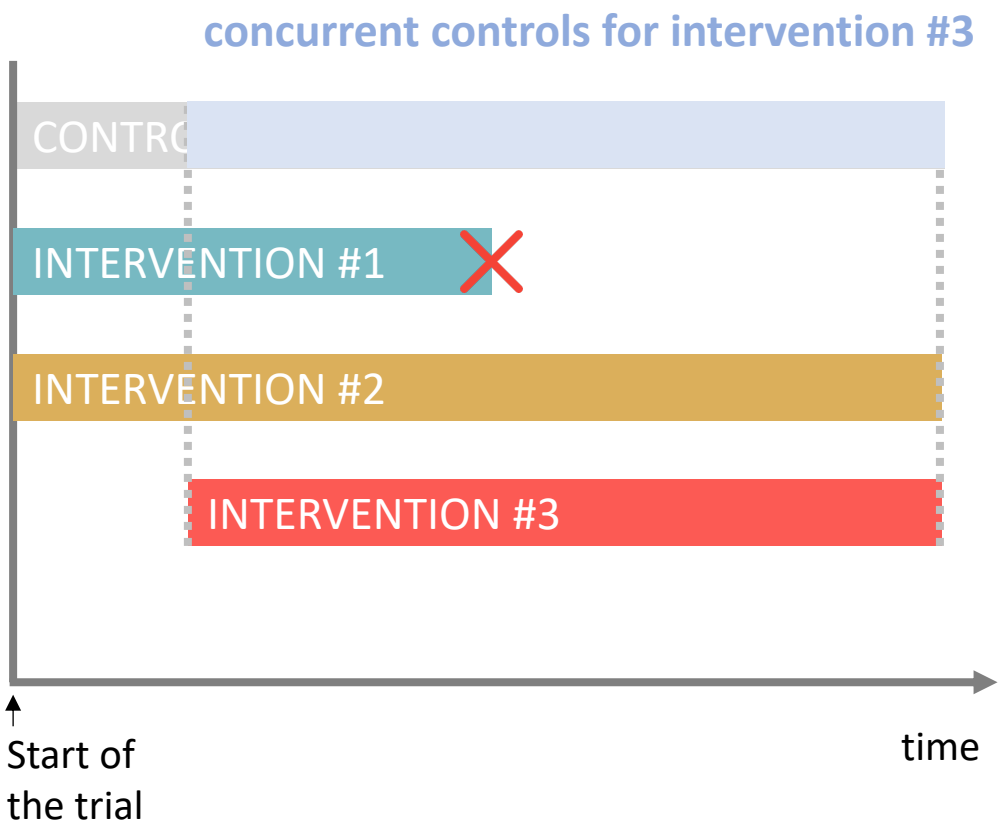


Definition of the control arm

- **Control arm= current Standard of Care (SoC)**

- **The control group/ SoC may be updated during platform trials**
  - As interventions prove effective or ineffective over time
  - Due to the approval of a new drug or new scientific evidence
  - Thus, it is no longer ethical to randomize human subjects into the previous SOC
  - Continuation of the trial with SoC updates for further improvement of the new standard of care

Comparison with control arm



- **Comparative analyses should only be performed between an expermental group and the common control group**, not between experimental treatment arms

- **Comparison with concurrent controls** to limit confounding biases / maintain comparability between groups

Recommendations FDA U.S. Food and Drug Administration. (2024). *Master Protocols for Drug and Biological Product Development: Guidance for Industry*. U.S. Department of Health and Human Services.

Control of the type one error

3 INDEPENDANT TRIALS

TRIAL #1

CONTROL ARM

INTERVENTION #1

TRIAL #2

CONTROL ARM

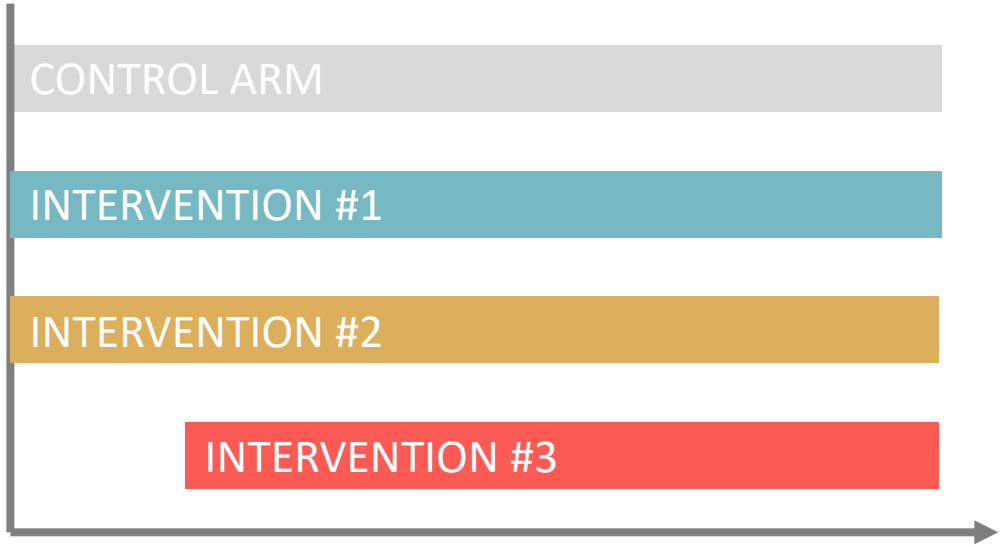
INTERVENTION #2

TRIAL #3

CONTROL ARM

INTERVENTION #3

1 MAMS TRIAL

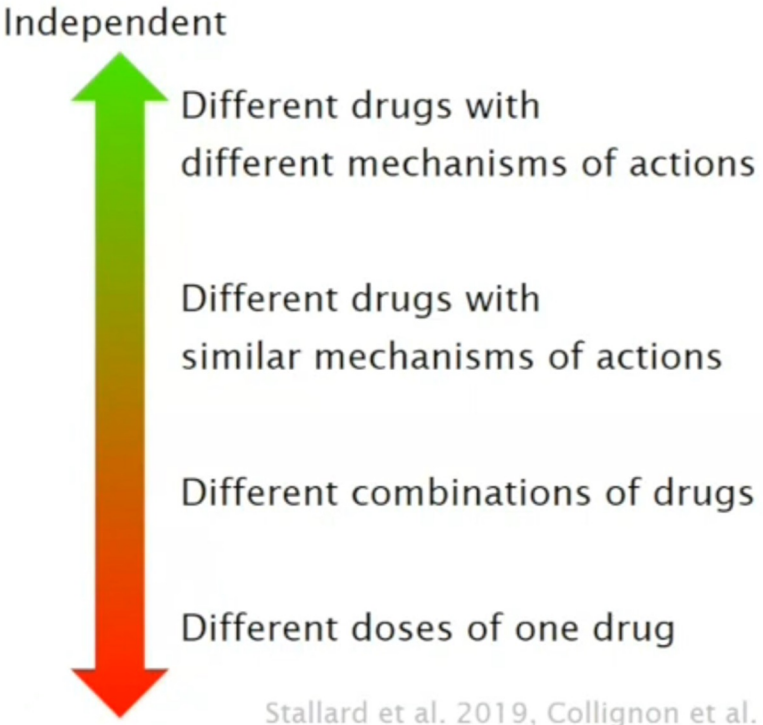


Adjust for the multiplicity of tests related to the different comparisons of interventions 1 to 3?

Control of the type one error

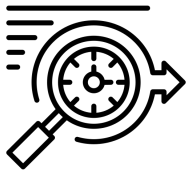
NO need to adjust WHEN hypotheses are **inferentially** independent

- Hypotheses are inferentially independent, if **the truth or falsehood of one hypothesis is unrelated to the truth and falsehood of the other hypotheses**.
- no extrapolation from one hypotheses to the the other is possible.
- If we did separate trials, we would also not adjust for multiplicity (and the shared control group leads to a lower FWER anyway)



Stallard et al. 2019, Collignon et al. 2020a, 2020b Park & Weir (2020), Bretz & König (2020), Nguyen al (2022)
EU-PEARL session on multiplicity first stakeholder workshop

Planification of interim analyzes



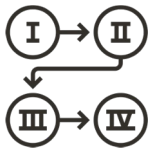
- **Interim statistical analyses with pre-specified decision rules**
  - **Early termination for futility:** when the intervention has little or no chance of producing the desired clinical benefits, even if more participants are randomized to that intervention group
  - **Early termination for efficacy:** an intervention may be declared effective before the maximum recruitment target for that intervention is reached

- **Requirements**
  - Pre-specification of interim analysis plans and consideration of type 1 error
  - Conservative choice of efficacy and statistical superiority thresholds for early termination
  - Important role of the DSMB (unblinded data review/recommendations)

Others aspects

- **Open-label or blinded** trial ?

72% open-labelled



- **Early phase or pivotal phase trial** ?
  (phase 3 / marketing authorization)

- **Type of analysis :**

Frequentist or Bayesian approaches ?

66% frequentist

3. COVID-19
Exemple of COVERAGE France

Essai COVERAGE

PLATEFORME COVERAGE FRANCE :

A MULTICENTER RANDOMIZED CLINICAL TRIAL USING A MULTI-ARM MULTI-STAGE ADAPTIVE DESIGN (MAMS) TO EVALUATE SEVERAL EXPERIMENTAL TREATMENTS FOR COVID-19 IN OUTPATIENTS

Investigator-Coordinator : Pr D Malvy & X Anglaret **| Sponsor :** CHU de Bordeaux **| Priorité Nationale Recherche COVID-19**

Clinicaltrials.gov: NCT04510194

COVERAGE France

- **Objective**: Evaluate the efficacy and tolerance of different treatments to improve the outcome in non-hospitalized COVID19+ patients with risk factors of severity

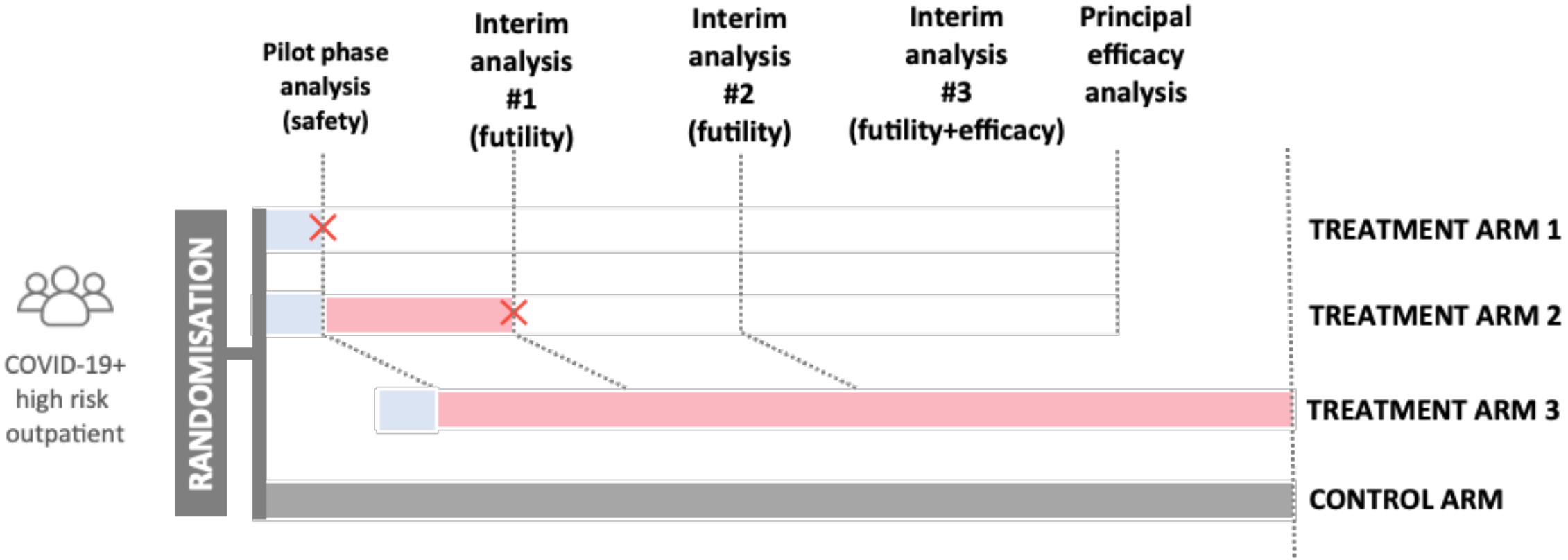
- **Design:** French multicenter, phase 3, superiority, randomized controlled, open-labelled, multi-arm multi-stage trial

- **Participants were randomized** between several experimental strategies or one control strategy

- **3 interim analyses** futility +/- early efficacy after inclusion of 119, 235 and 403 participants - & a final primary analysis (n= 666)

Trial design

Example with 3 active treatment arms



- Some candidate treatments were studied at certain investigator sites

COVERAGE : Sample size

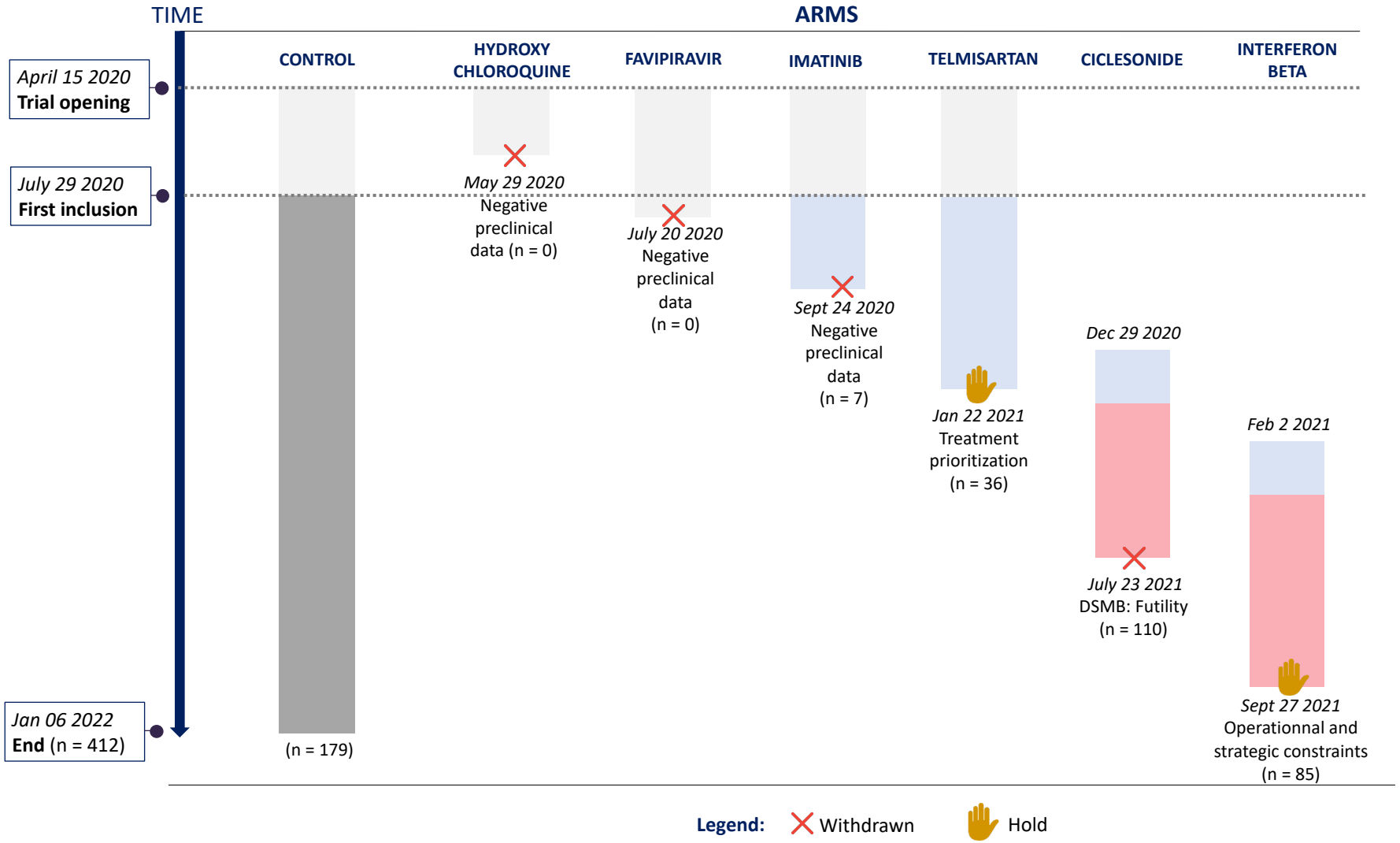
- **Hypothesis:** An experimental arm will reduce the incidence of the primary endpoint by at least 50%, with an expected incidence of 7.5% in the control arm.
- These hypotheses were adjusted secondarily by the DSMB during the study.

ANALYSES	TRIGGER: Number of participants who reached D14	OBJECTIVE(S)	ONE-SIDED ALPHA RISK FOR SUPERIORTY	POWER
Interim n°1	119	Futility	0.65	0.95
Interim n°2	235	Futility	0.45	0.95
Interim n°3	403	Futility	0.25	0.95
		Preliminary efficacy	Calculated by O'Brien-Fleming	
Principal analysis	666	Efficacy	0.025	0.80
Sensitivity analysis	End of the study	Efficacy at D28	0.025	

Package NStageBin of STATA

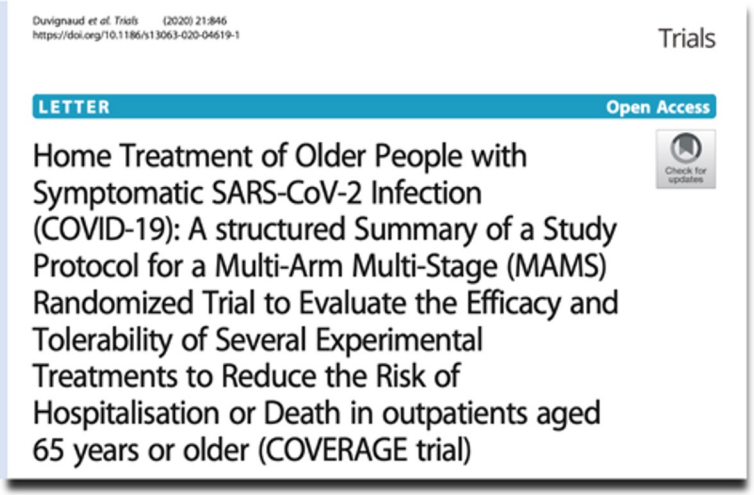
OVERVIEW OF THE COVERAGE TRIAL CONDUCT

Since its implementation in March 2020, 412 participants were included. The flexible design allowed multiple adaptations such as removal or adding of arms, and adaptations of eligibility and stratification criteria.



Scientific publications

TRIAL PROTOCOL



Duvignaud *et al. Trials* (2020) 21:846
https://doi.org/10.1186/s13063-020-04619-1

Trials

LETTER — Open Access

Home Treatment of Older People with Symptomatic SARS-CoV-2 Infection (COVID-19): A structured Summary of a Study Protocol for a Multi-Arm Multi-Stage (MAMS) Randomized Trial to Evaluate the Efficacy and Tolerability of Several Experimental Treatments to Reduce the Risk of Hospitalisation or Death in outpatients aged 65 years or older (COVERAGE trial)

SOCIAL SCIENCES SUBSTUDY

Grenier *et al. Archives of Public Health* (2022) 80:245
https://doi.org/10.1186/s13690-022-00999-9

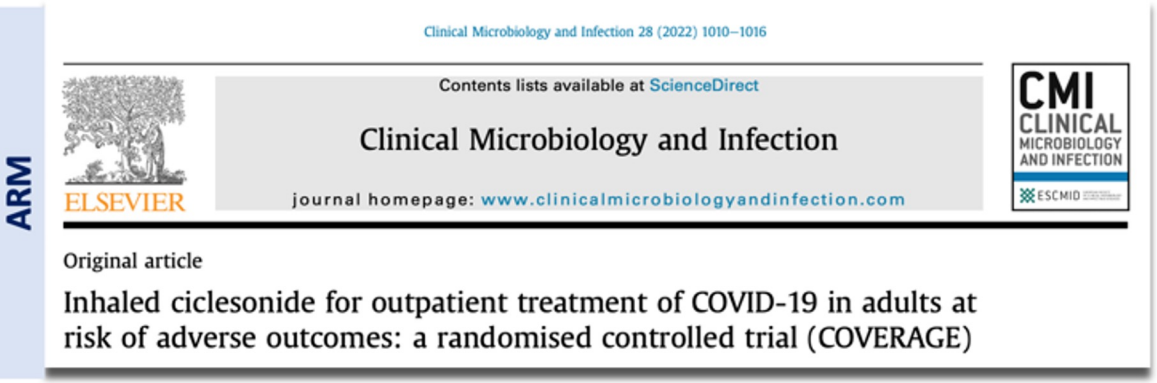
Archives of Public Health

RESEARCH — Open Access

Implementing an outpatient clinical trial on COVID-19 treatment in an emergency epidemic context: a mixed methods study among operational and research stakeholders within the Coverage trial, Bordeaux (France)

Carine Grenier[1,2,3†], Macha Loniewski[1,2,3†], Mélanie Plazy[1,2,3], Racha Onaisi[4], Marie-Hélène Doucet[1,2,3], Jean-Philippe Joseph[4], Alexandre Duvignaud[1,2,3,5], Denis Malvy[1,2,3,5], Xavier Anglaret[1,2,3], Joanna Orne-Gliemann[1,2,3*] and the Coverage study group

CICLESONIDE ARM



Clinical Microbiology and Infection 28 (2022) 1010–1016

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Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

ELSEVIER

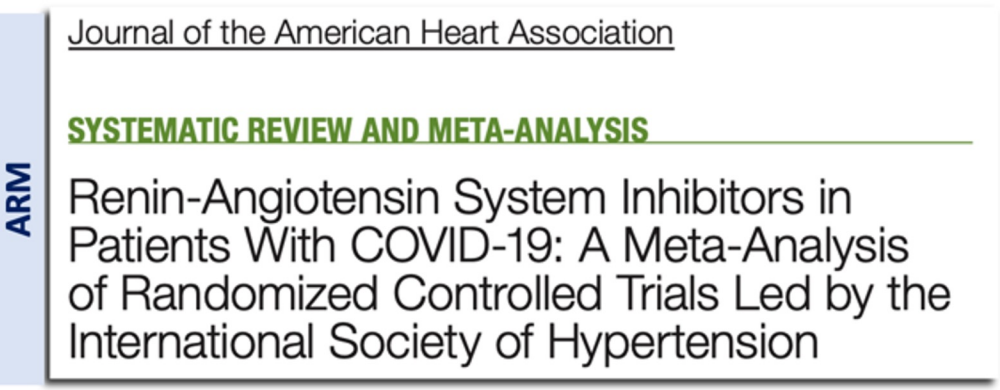
CMI CLINICAL MICROBIOLOGY AND INFECTION

ESCMID

Original article

Inhaled ciclesonide for outpatient treatment of COVID-19 in adults at risk of adverse outcomes: a randomised controlled trial (COVERAGE)

TELMISARTAN ARM



Journal of the American Heart Association

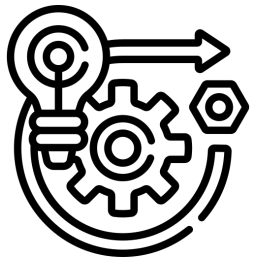
SYSTEMATIC REVIEW AND META-ANALYSIS

Renin-Angiotensin System Inhibitors in Patients With COVID-19: A Meta-Analysis of Randomized Controlled Trials Led by the International Society of Hypertension

ONGOING

- Interferon arm
- Immunological substudy
- Lessons learned

4. OPERATIONAL AND LOGISTICAL ASPECTS



METHODOLOGY Open Access

Practical guidance for running late-phase platform protocols for clinical trials: lessons from experienced UK clinical trials units

Sharon B. Love[1*], Fay Cafferty[2], Claire Snowdon[2], Karen Carty[3], Joshua Savage[4], Philip Pallmann[5], Lucy McParland[6], Louise Brown[1], Lindsey Masters[1], Francesca Schiavone[1], Dominic Hague[1], Stephen Townsend[1], Claire Amos[1], Annabelle South[1], Kate Sturgeon[1], Ruth Langley[1], Timothy Maughan[7], Nicholas James[2], Emma Hall[2], Sarah Kernaghan[2], Judith Bliss[2], Nick Turner[2], Andrew Tutt[8], Christina Yap[2,9], Charlotte Firth[9], Anthony Kong[10], Hisham Mehanna[11], Colin Watts[12], Robert Hills[13], Ian Thomas[14], Mhairi Copland[15], Sue Bell[16], David Sebag-Montefiore[17], Robert Jones[18], Mahesh K. B. Parmar[1†] and Matthew R. Sydes[1†]

Love et al. Trials (2022) 23:757

PROTOCOL

- Importance of structuring **the protocol as a master protocol**, incorporating candidate treatments in an appendix, so that the protocol can be easily updated in the event of amendments to add or remove arms.

CENTRE HOSPITALIER UNIVERSITAIRE DE BORDEAUX

Essai randomisé pour évaluer la sécurité et l'efficacité de traitements pour diminuer le risque d'aggravation chez des personnes ambulatoires atteintes de COVID-19 ayant des facteurs de risque

Essai COVERAGE France

Code promoteur : CHUBX 2020/12

PROTOCOLE DE RECHERCHE INTERVENTIONNELLE IMPLIQUANT LA PERSONNE HUMAINE

(recherche de catégorie 1)

Version n°9.0 du X février 2021

Numéro EudraCT : 2020-001435-27

NCT04356495

Promoteur :
Centre Hospitalier Universitaire de Bordeaux, 12 rue Dubernat, 33400 Talence, France

SUPERVISION

- Importance of a **qualified and available scientific advisory board** and **Data safety monitoring board** to make decisions about the conduct of the trial

STATISTICAL ASPECTS

- Randomization: Importance of **well-defined randomization stratification factors** for both methodological and operational considerations. Needs a **smart randomization tool** for quick activation / deactivation of treatment arm per site
- eCRF: Needs **simple eCRF** to encourage consistency and completeness of data

- Requires a **significant amount of statistician time** compared to traditional trials; Need for a **senior statistician** with experience and training in adaptive trial

Table 3 Indicative snapshot in 2019 of the fulltime-equivalent (FTE/yr) staffing levels in two similarly sized platform protocols and a hypothetical traditional trial

Role	Traditional trial (200 randomised)	PlasmaMATCH (1200 screened, 200 randomised)	FOCUS4 (1400 screened, 400 randomised)[a]
Senior role	0.35	1	1
Statistician	0.35	1	1
Trial manager	1	1.5	2
Data manager	1	1.5	2
Data scientist/programmer	0.35	1	2
Trial assistant	1	1	1

[a] Approximate numbers given

The advantages of using a master protocol have their price!

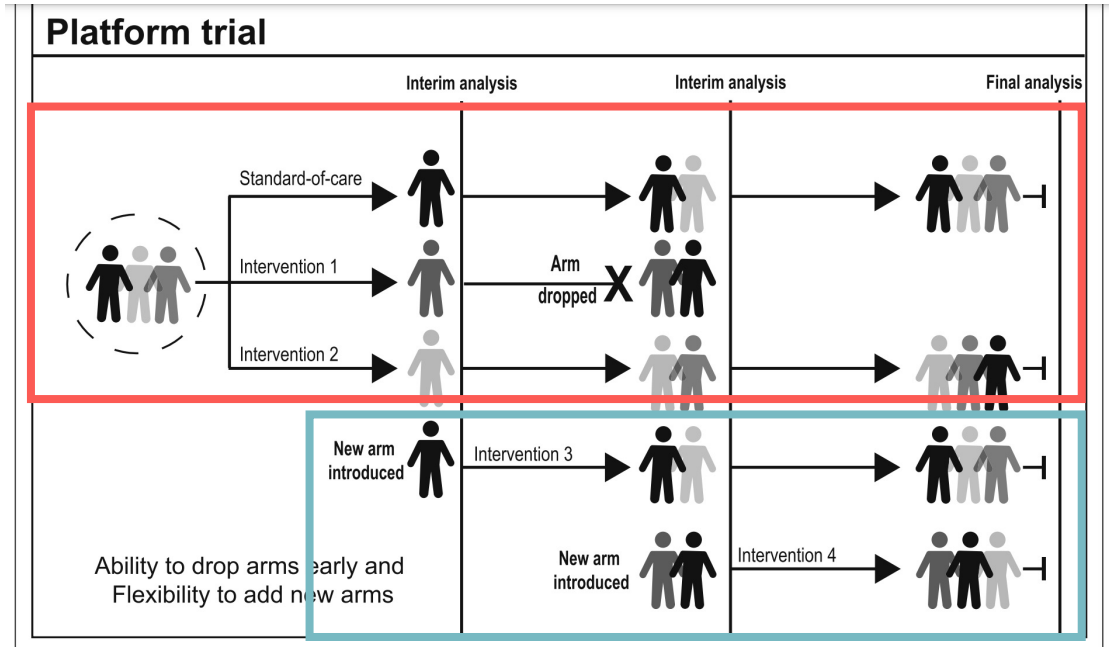
- **Increased planning and coordination**
  - Cost in terms of time and resources to set up the infrastructure needed for the trial, as well as increased initial planning and coordination to bring in more stakeholders

- **A large amount of work is required to set up a trial**
  - Multiple reasons: stakeholder coordination, infrastructure requirements, contracts
  - Development of statistical models and algorithms for adaptive design + randomization
  - Discussions with regulators and ethics committees

The challenge of funding

NEED LARGER FUNDING THAN TRADITIONNAL RCT

- **Traditional calls for proposals**
  - **National calls** (eg. PHRC-N / K)
  - **MESSIDOR** (methodology/infrastructure)
  - **Call for European funding proposals** (Horizon Europe, EDCTP3,…)
- **Issue: funding long-term sustainability?**
  - Subsequent submission, co-funding ++ (industrial or academic)



Conclusion

- **A type of randomized clinical trial** that allows **several intervention groups to be compared** simultaneously with a single control group, with **interim analyses and flexibility to discontinue or add new interventions**

- **One protocol and common infrastructure** enabling a broader set of objectives to be achieved more effectively than would be possible through independent trial

- Increasingly used in **various fields of medicine**, whereas they were previously dominated by **oncology and infectious diseases**

- Platform **trials increase the complexity of planning, conducting, and generating results from a clinical trial**

- Special thanks to Derek Dinard and Remi Sitta
- COVERAGE trial team and participants

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