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Pandemic preparedness

Potential clinical study designs for clinical trials intended to be conducted in case of an outbreak

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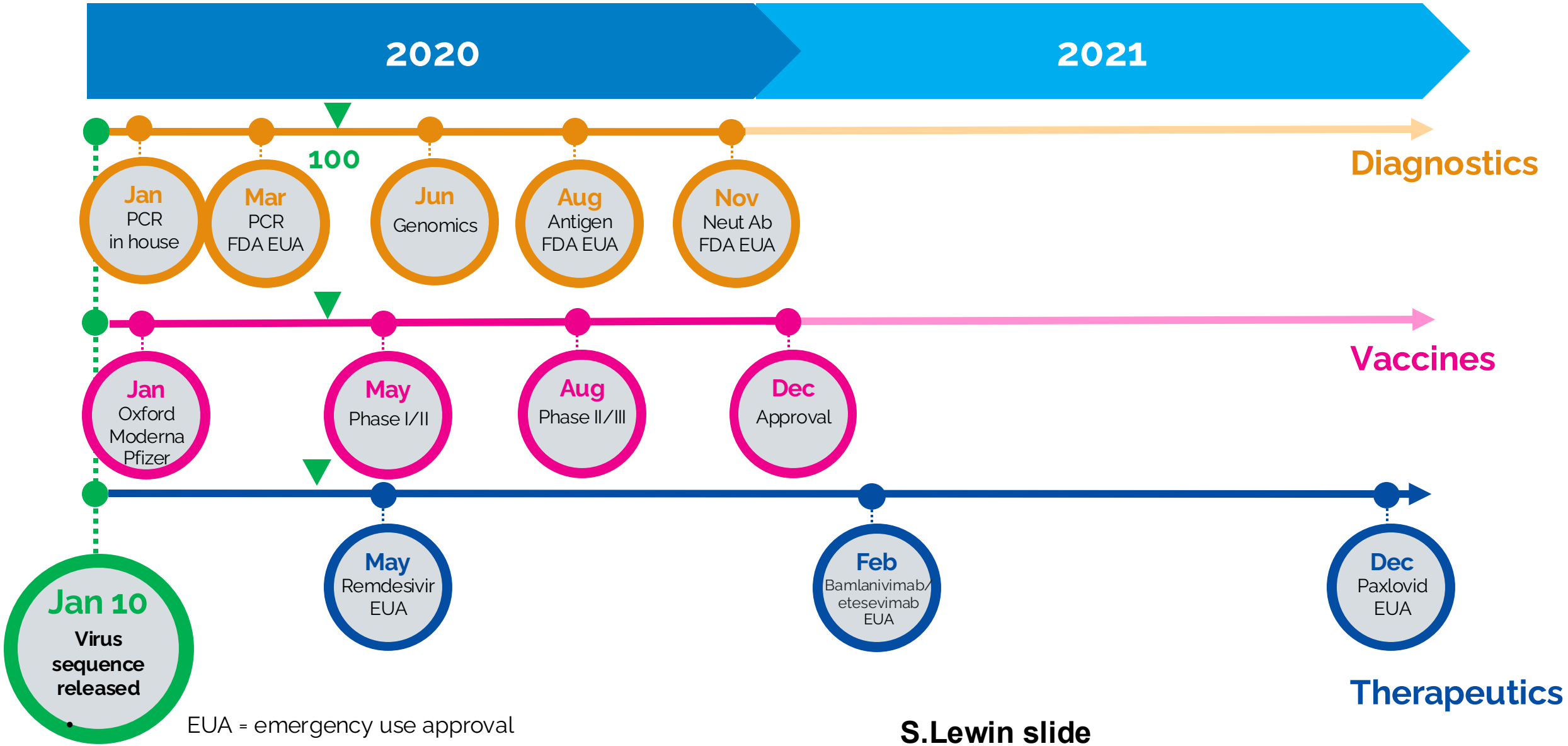
The 100 days mission for vaccines, diagnostics and therapeutics

The G7 initiative aspires for the world to be able to respond to the next Disease X with a new vaccine, treatment & diagnosis tests in just 100 days

S.Lewin slide

The 100 day mission: is it remotely feasible?



EUA = emergency use approval

S.Lewin slide

What are clinical questions?

- A question consisting of four main parts
- 1) Population: Who are we studying?
- 2) Intervention: What are we studying?
- 3) Control: What are we comparing with?
- 4) Outcome: What is the outcome?

PICO

Clinical trials intended to be conducted in case of an outbreak?

A clinical trial designed to answer several clinical questions : a clinical platform trial

Which clinical questions?

- 1) Population: Single or multiple
- 2) Intervention: Single or multiple
- 3) Control: Single or multiple (Standard of Care, placebo, active comparator)
- 4) Outcome: May depend on the population

- Example: What is the effect of different anti-viral or anti-inflammatory treatments compared to standard of care on 60-day mortality in hospitalised patients with with a respiratory viral infection ?

Platform trials designs elements

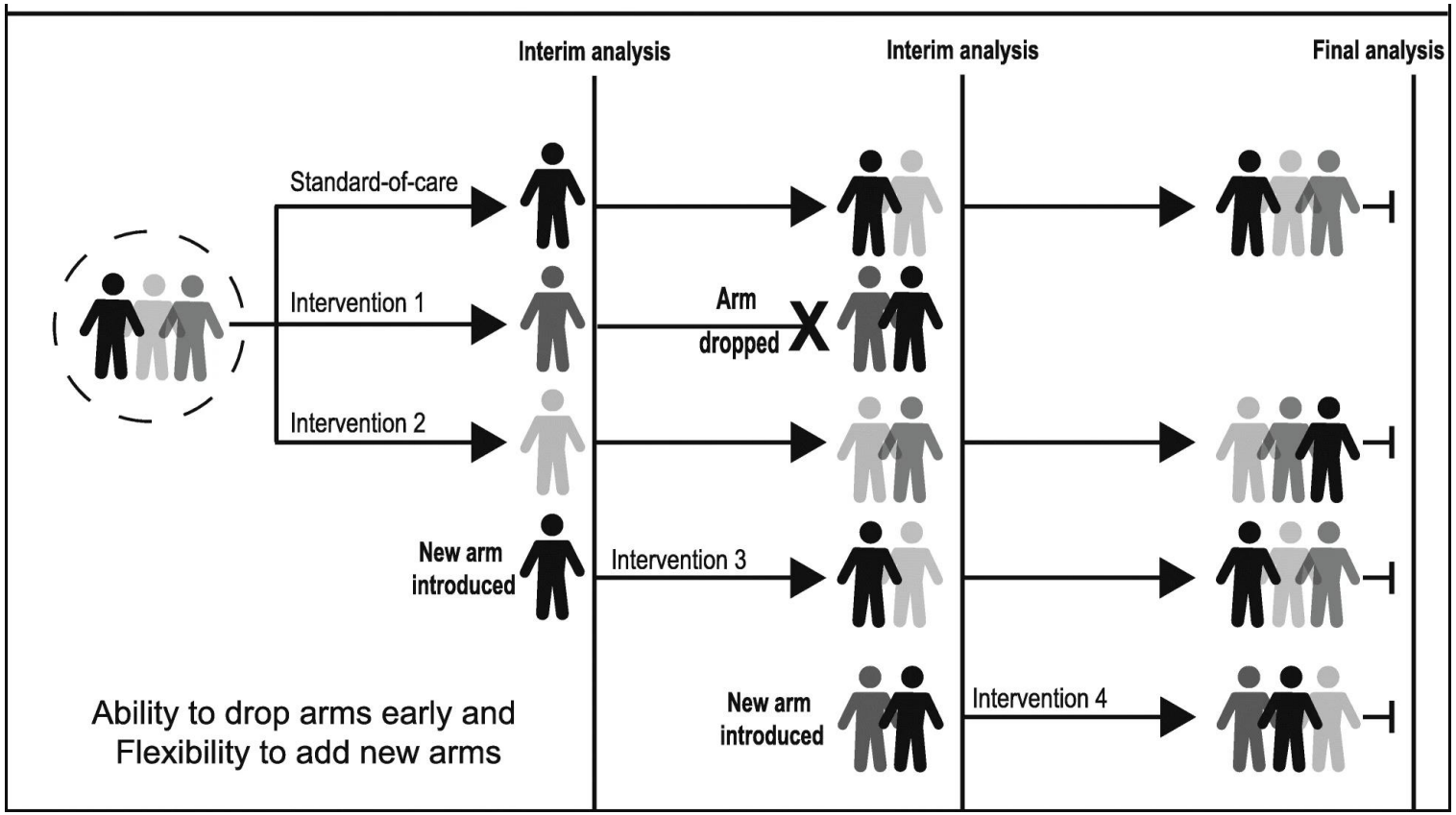
- Master protocols
- Trial platforms
- Multiple Arms, Multiple stages (MAMS)
- Seamless Phase II/III trials
- Adaptive randomisation
- Personalised medicine trials

Remember, goal of platform trials is effectiveness

Trial platforms

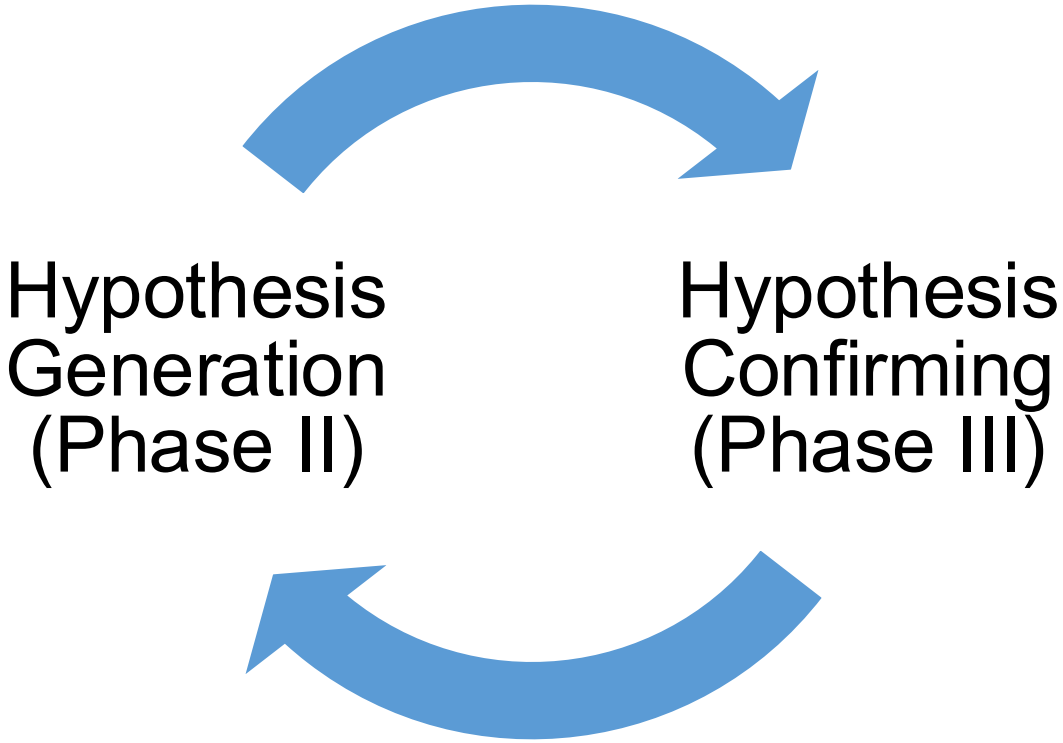
- Collection of clinical trials assessing different clinical questions
- Some set of common features
  - Common sponsor/investigator
  - Common protocol template
  - Common data capture system / eCRF /Data management
  - Common operational team
  - Common clinical site network
- Could build on a master protocol, but each trial only answers one question

Multi-arm, multi-stage (MAMS)



Park, J.J.H., Siden, E., Zoratti, M.J. *et al.* Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials*

Evidence development



Pros and cons

- Pros:
  - Efficiency
  - Time saving
  - Answer more clinical question

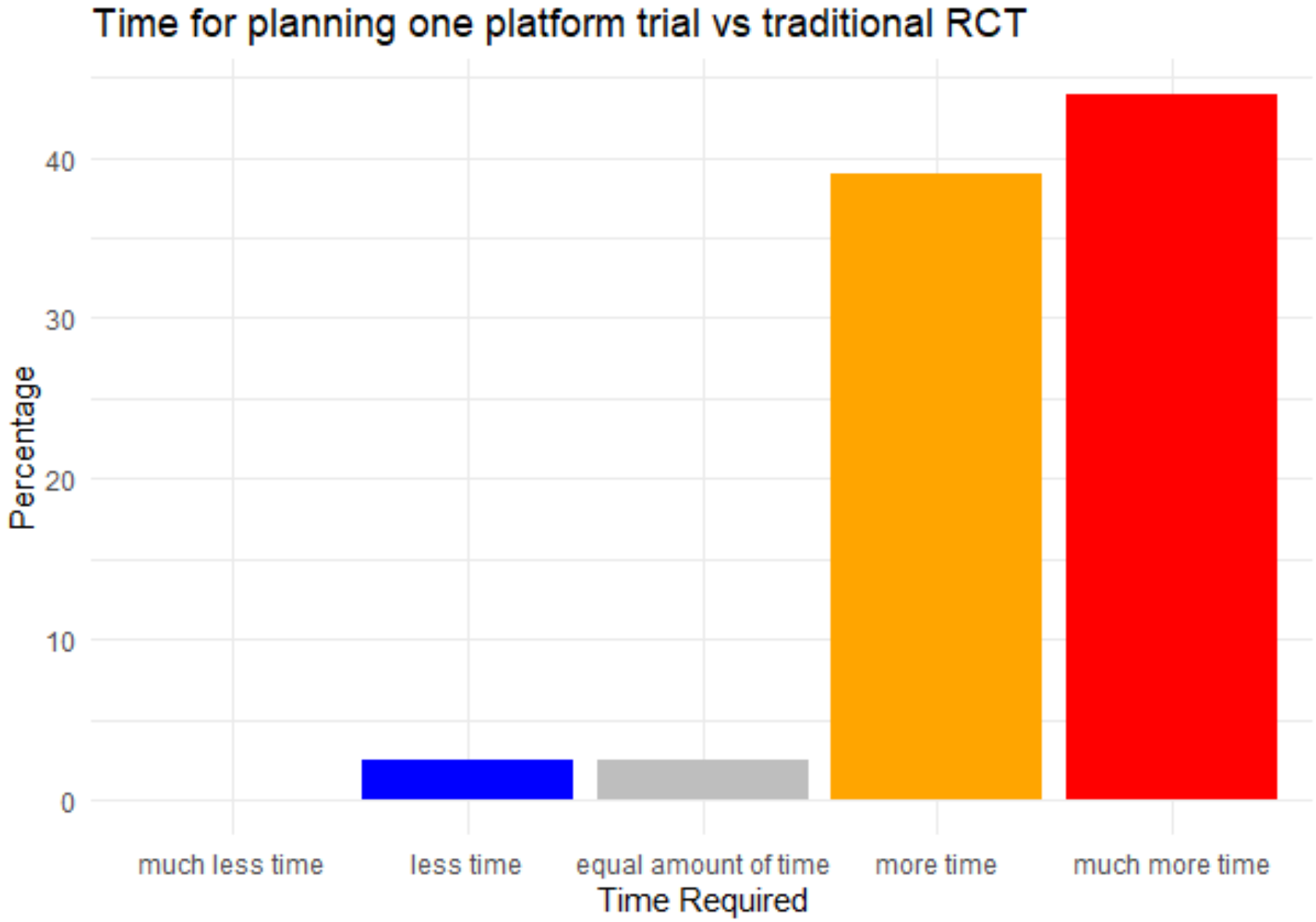
- Cons:
  - Complexity
  - Longer to set up and start
  - More challenging for regulators

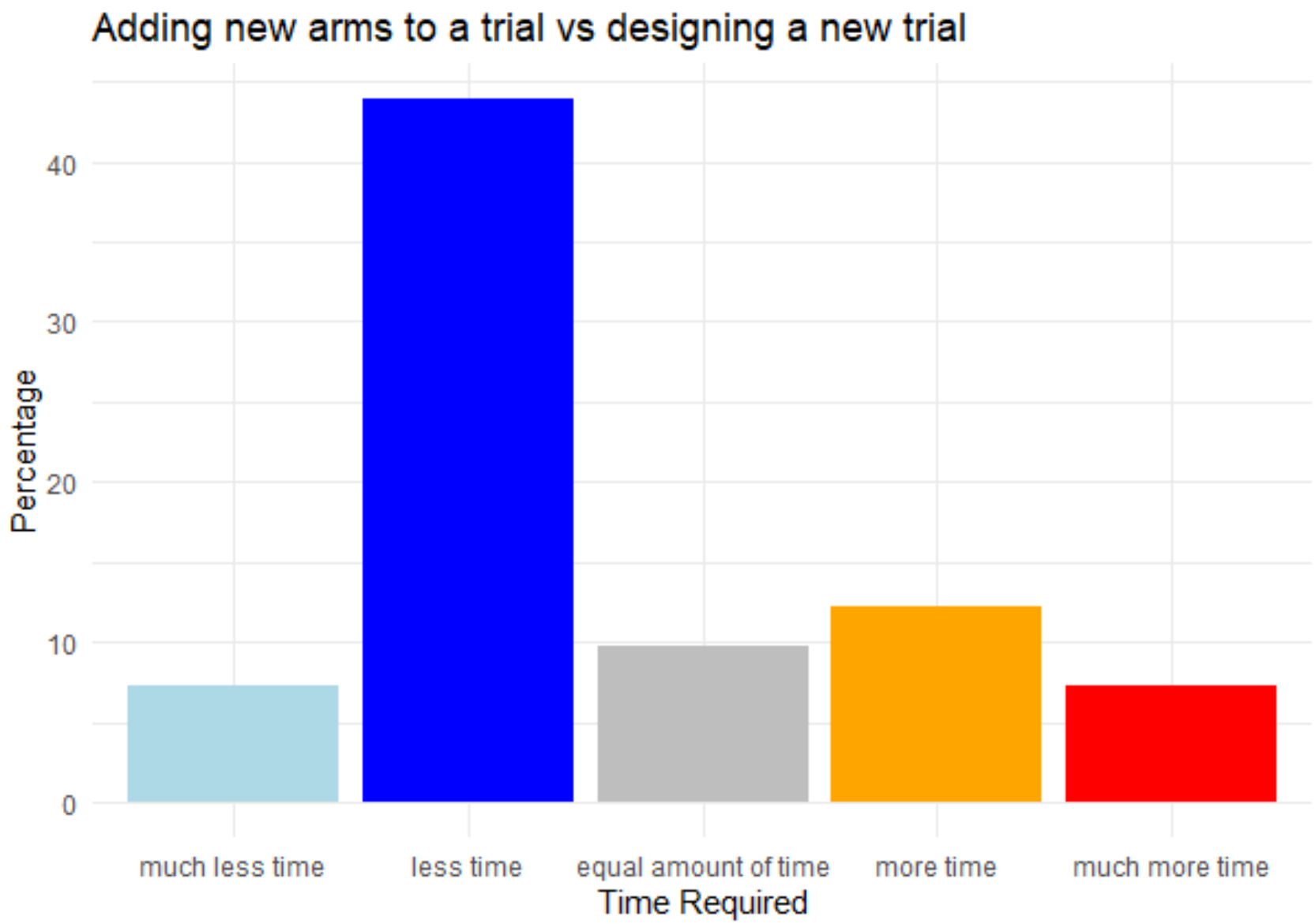
Survey

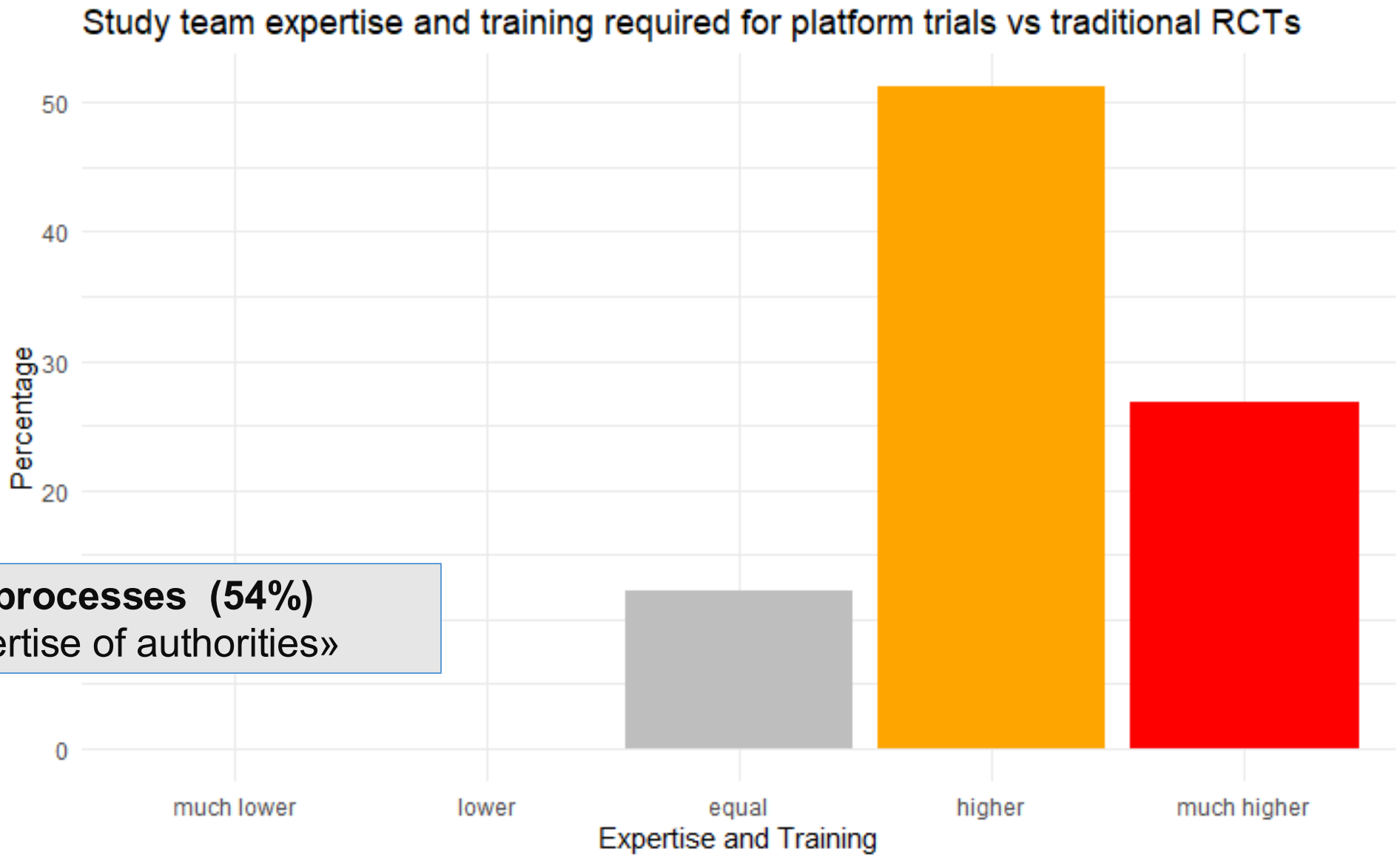
- Based on scoping review of 127 platform RCTs -> PIs & other stakeholders
- Beginning 2024
- **Response from 37 Platform trials (30%)**

- 48 respondents: - 36 PIs & staff members
  - 6 CTU members
  - 6 Ethics committee members

- Courtesy of Alexandra Griessbach & Matthias Briel for the EU-RESPONSE project







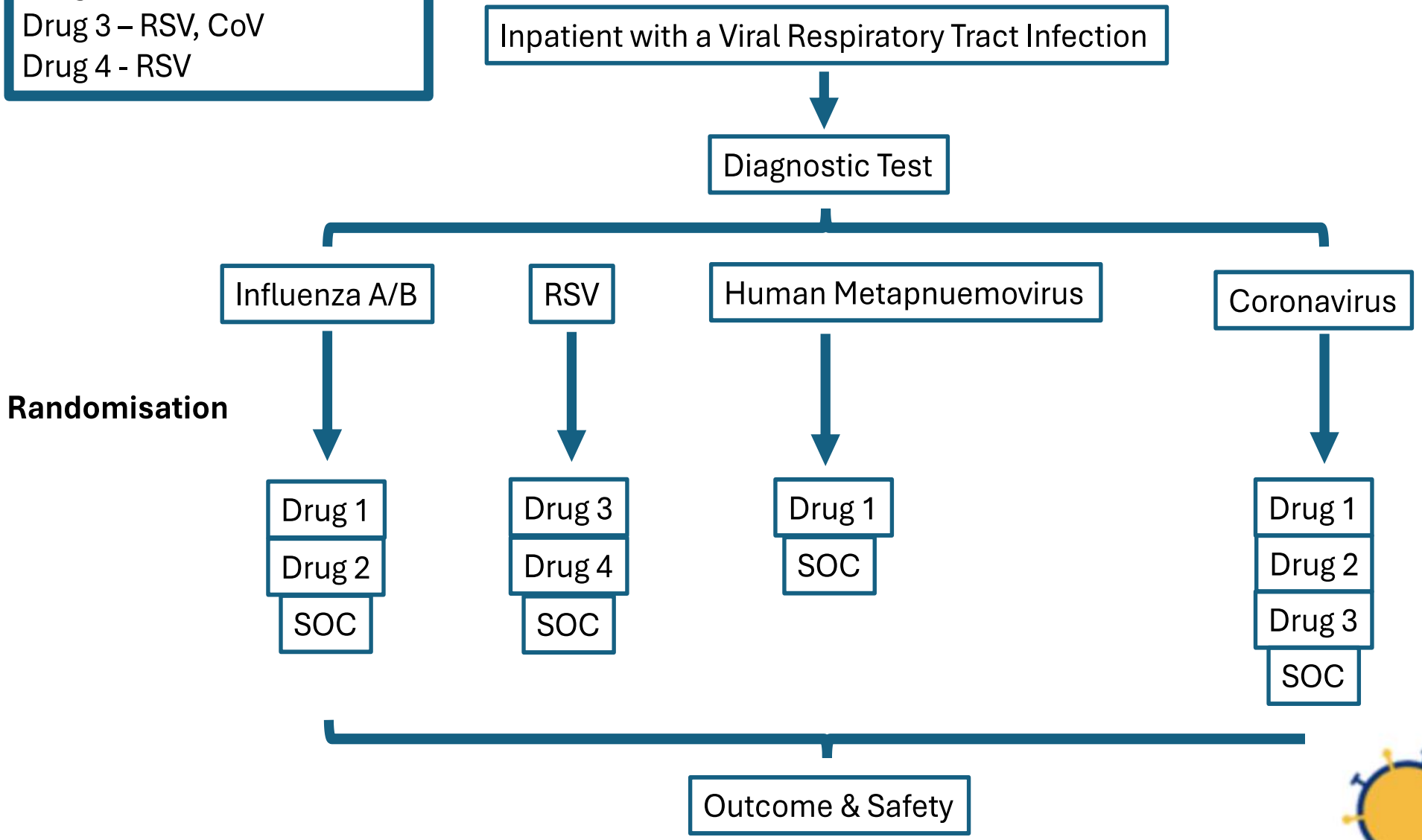
- **Regulatory processes (54%)**
  - «lack of expertise of authorities»

European **Pro**active **A**daptive **C**linical **T**rials Network within **EU Response**: **PROACT EU-Response**

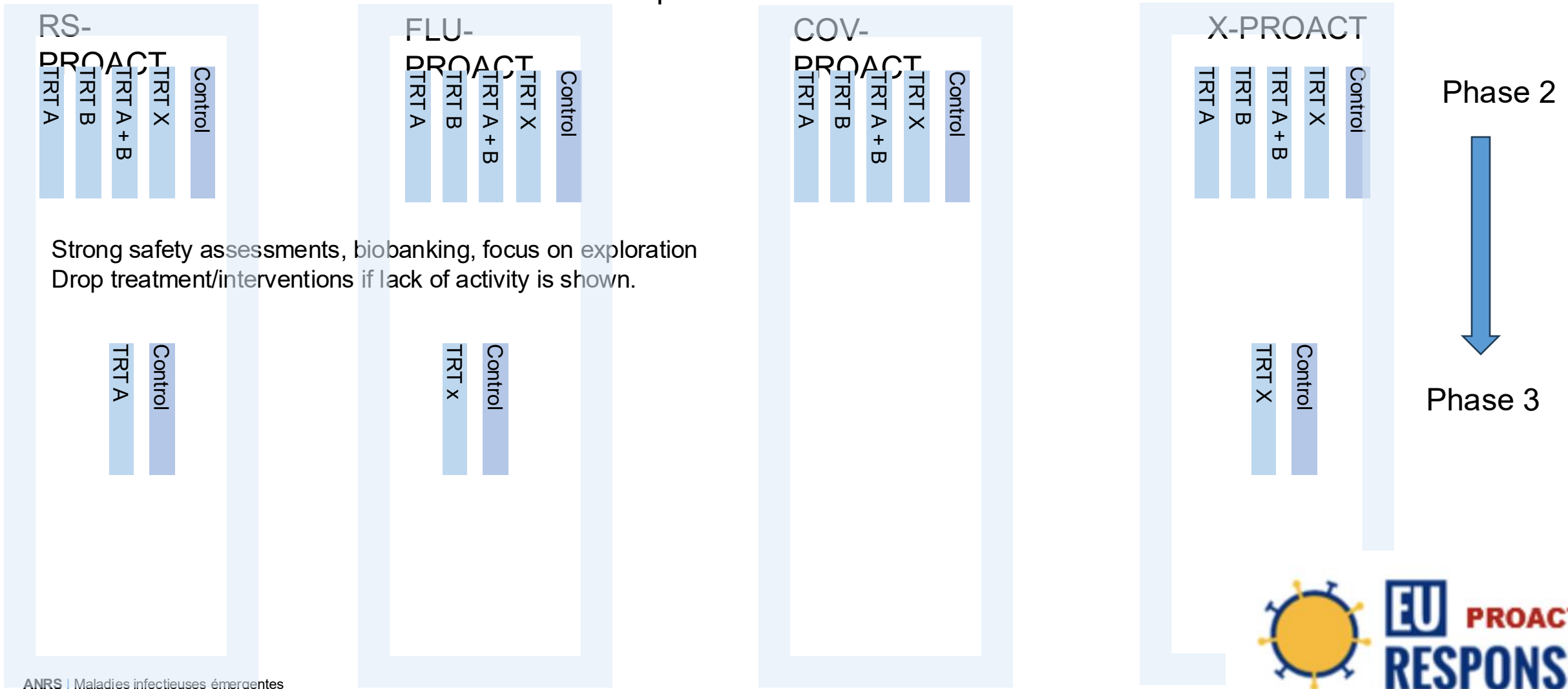
Primary objective: to explore the **safety** and **virological** efficacy of different investigational therapeutics relative to the control arms in patients hospitalized with a respiratory viral infection due to

- SARS-CoV2,
- Influenza A/B,
- RSV, or
- Human meta-pneumovirus (hMPV)

Drug 1 – Flu A/B, HMNV, CoV
Drug 2 – Flu A/B, CoV
Drug 3 – RSV, CoV
Drug 4 - RSV



EU-PROACT
Master protocol
Population: Hospitalised subjects with Viral Respiratory Tract Infection
- Overall design, used in Clinical trials agreements, used as text repository for the disease specific protocols

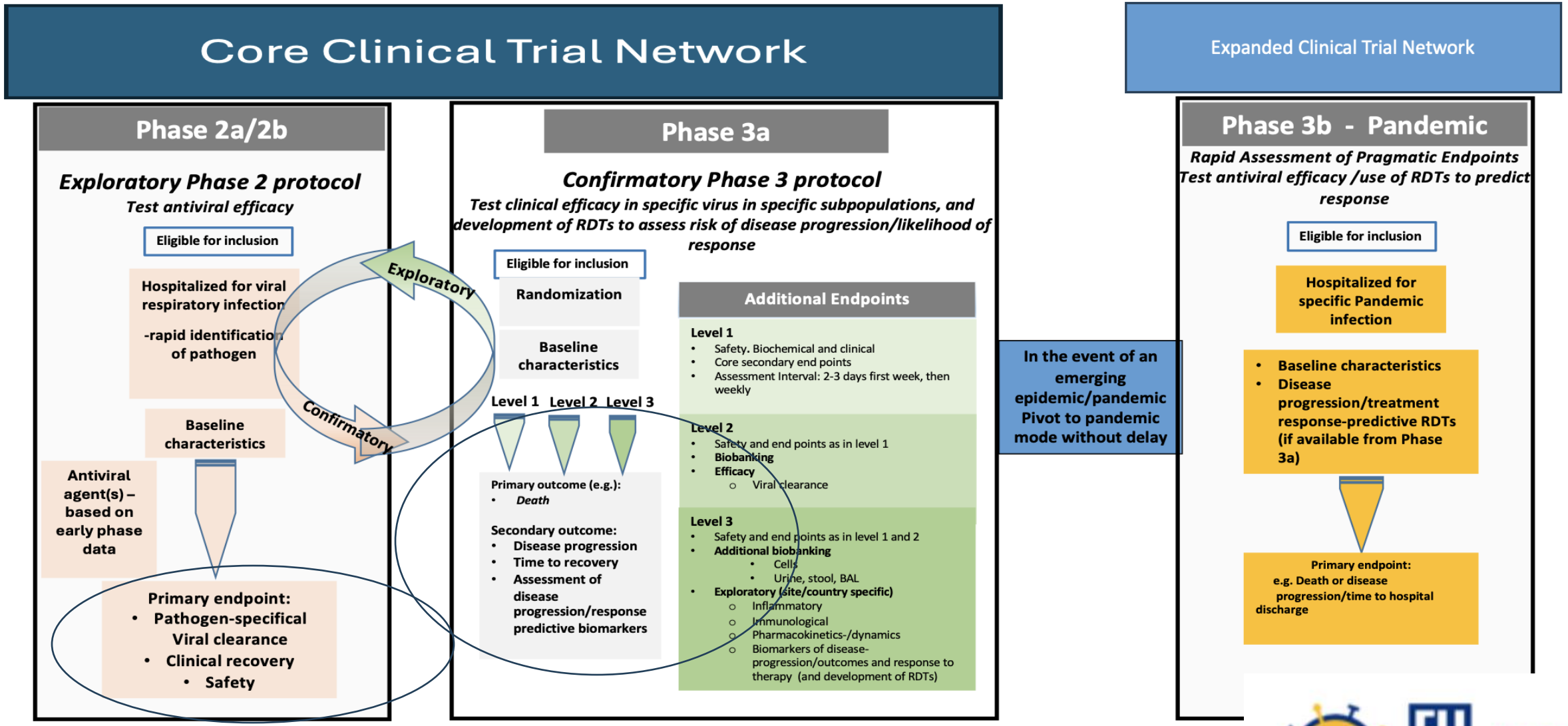


Control treatment

- SoC at the local hospital defined as the **best available treatment** according to **local hospital guidelines**

- **Placebo plus SoC** might be considered as control treatment if available, otherwise open- label SoC will be given against open-label intervention

Endpoints



Clinical efficacy?

Evaluate clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by:

a. Time to discharge from admission.

b. Changes in the WHO ordinal scale from study inclusion to days 7, 14, and 28 of follow-up. The score given to a patient is based on the first clinical assessment of a given day. The WHO ordinal scale is as follows:

1. Not hospitalized, no limitations on activities;
2. Not hospitalized, limitations on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, on non-invasive ventilation or high-flow oxygen devices;
6. Hospitalized, on invasive mechanical ventilation or extra-corporeal membrane oxygenation (ECMO),
7. Death

Other scores:
- National Early Warning Score (NEWS2)?
- Other?

Clinical efficacy?

c. Oxygenation:

- Oxygenation free days during the first 28 days
- Incidence and duration of new oxygen use, non-invasive ventilation or high-flow oxygen devices during the study

d. Mechanical Ventilation

- Ventilator free days during the first 28 days
- Incidence and duration of new mechanical ventilation use during the study

e. Hospitalization

- Duration of hospitalization (days)

f. Mortality

MPOX

An endemic virus in Africa (clusters)

May 2022 First cases of MPOX (UK MSM)

June-July 2022 ANRS | MIE, INRB, NIAID/NIH, WHO consultation: *for a global response to MPOX- how to best evaluate treatment efficacy*?

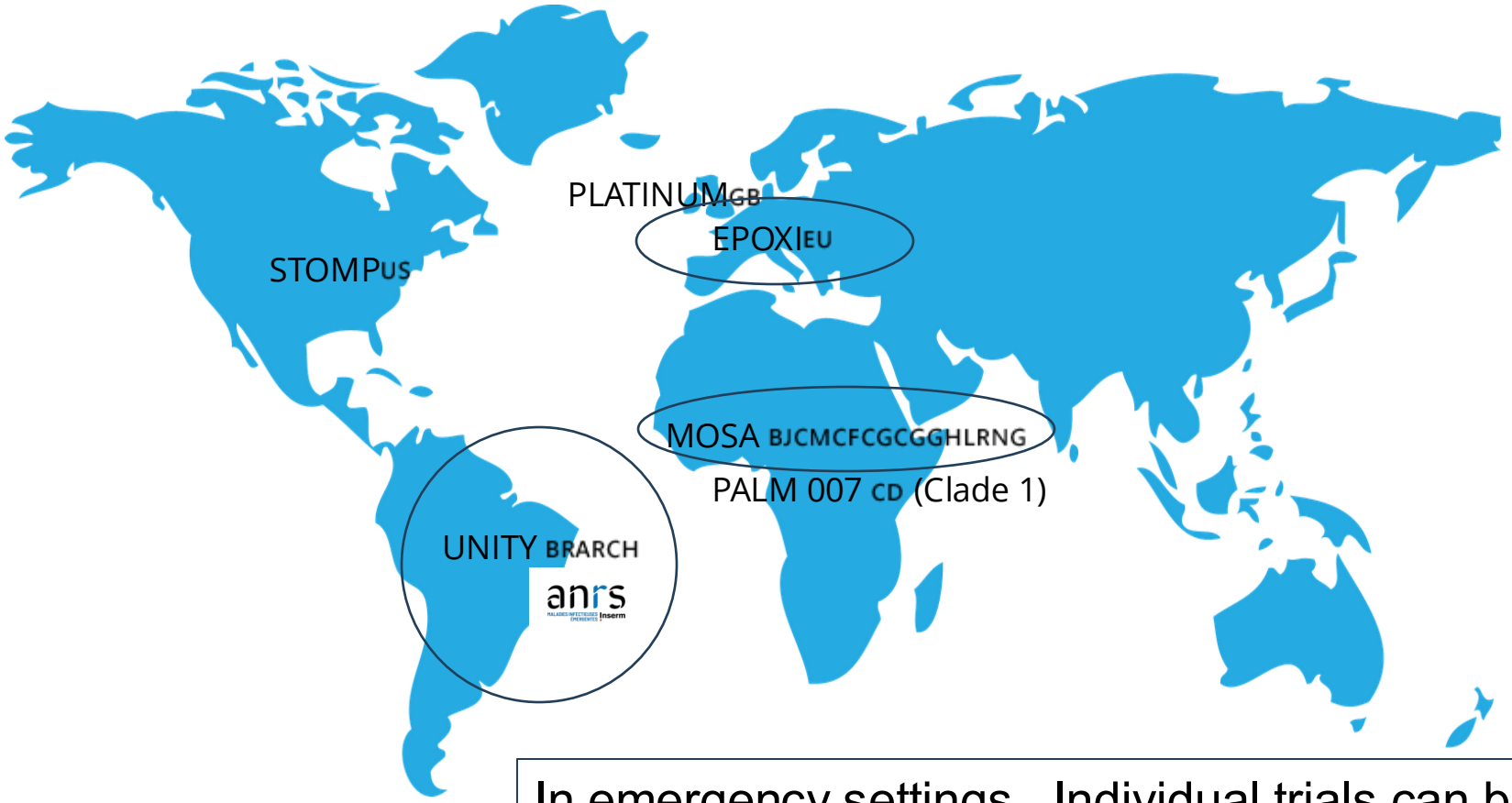
23 July 2022 **OMS Urgence de santé publique de portée internationale**

24 July 2022 CORE protocol publication on WHO website ***Multi-country clinical trial to evaluate safety and efficacy of treatments against MPOX*** *to facilitate integration of clinical research and promote reporting and global coordination (evidence generation)*

Multiple trials launced

MPX RESPONSE

UNITY
EPOXI



In emergency settings, Individual trials can be started in a timely manner, but final joint decision-making is performed by a prespecified conjoined analysis using data from the individual trials: harmonization of individual trial protocols and data models

Comparative study of three RCTs testing tecovirimat/placebo (Mpox)

	The UNITY study ANRS NCT05597735	STOMP Study of Tecovirimat for Mpox NIAID NCT05534984	PALM NIAID NCT05559099
	Symptomatic mpox any duration	Symptomatic mpox <u>< 14 d</u>	Lab confirmed mpox any duration (> or < 7d);
	> 14 yo **n=480**	Any age **n=336 – stopped by the DSMB**	> <u>3 kg</u> (64%<18y) **n=597**
	Time to complete lesion resolution	**Time to active lesion resolution**	**Time to lesion resolution**
	IAS 2025	CROI 2025	New Eng J Medicine April 2025

The federated trials approach; an opportunity for global collaboration in health emergencies

Authors: Inge Christoffer Olsen[1], Summer Zheng[2], Skerdi Haviari[3], Alain Amstuz[1,4], Yazdan Yazdanpanah[3,5], Franz König[6], Thomas R. Fleming[7], Matthias Briel[4] on behalf of the UNITY and STOMP study groups

A supplementary tool for emergencies and not a standard

- Separate sponsors
- Separate but consistent protocols
- Shared data repository
  - Complete sharing of blinded data
- Shared DSMB
  - With access to shared unblinded data to inform and make recommendations to the trials
- Planned combined analyses according to each protocol

MPX-RESPONSE has received funding from the European Union's Horizon Europe Research and Innovation programme under grant agreement 101115188

BE READY
Implementation of the ever-warm network

- **12.1 -** Establish the Ever-Warm EU-wide Network of networks (EWNN) for pandemic preparedness (*ANRS*)
- **12.2 -** Further identify the gaps and needs of current existing networks in Europe (*ECRIN*)
- **12.3 -** Setting up and establishing the governance structure, the trial management capacity, organisational structures and processes for the EWNN (*ANRS, NIPH*)
- **12.4 -** Coordinate the EWNN within and outside the EU (*ANRS, NIPH*)
- **12.5 -** Run clinical studies through the EWNN (*UNIVR, Penta*)
- **12.6 -** Identify opportunities for cross-network methodology development within observational studies and trials (*Epiconcept, UCL*)

Thank you for your attention and my sincere thanks to a dedicated team, extraordinarily committed in every corner of the world.