DES Infectiologie 2023

Recherche en Infectiologie – Ethique

Recherche en contexte d'urgence pandémique

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16/06/2020 = M+4
6425 patients

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on dexamethasone, 16 June 2020

Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19

Professor Peter Horby and Professor Martin Landray, chief investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial, said:

In March of this year, RECOVERY was established as a randomised clinical trial to test a range of potential treatments for COVID-19, including low-dose dexamethasone (a steroid treatment). Over 11,500 patients have been enrolled from over 175 NHS hospitals in the UK.

On 8 June, recruitment to the dexamethasone arm was halted since, in the view of the trial Steering Committee, sufficient patients had been enrolled to establish whether or not the drug had a meaningful benefit.

A total of 2104 patients were randomised to receive dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days and were compared with 4321 patients randomised to usual care alone. Among the patients who received usual care alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%).

Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75; p=0.14).

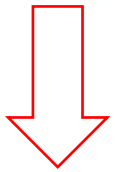
Nouvelle maladie
LA COMPRENDRE

Maintenir standard qualitatif de recherche
ACCELERATION

Coordination nationale
Connexions internationales
SYNERGIE

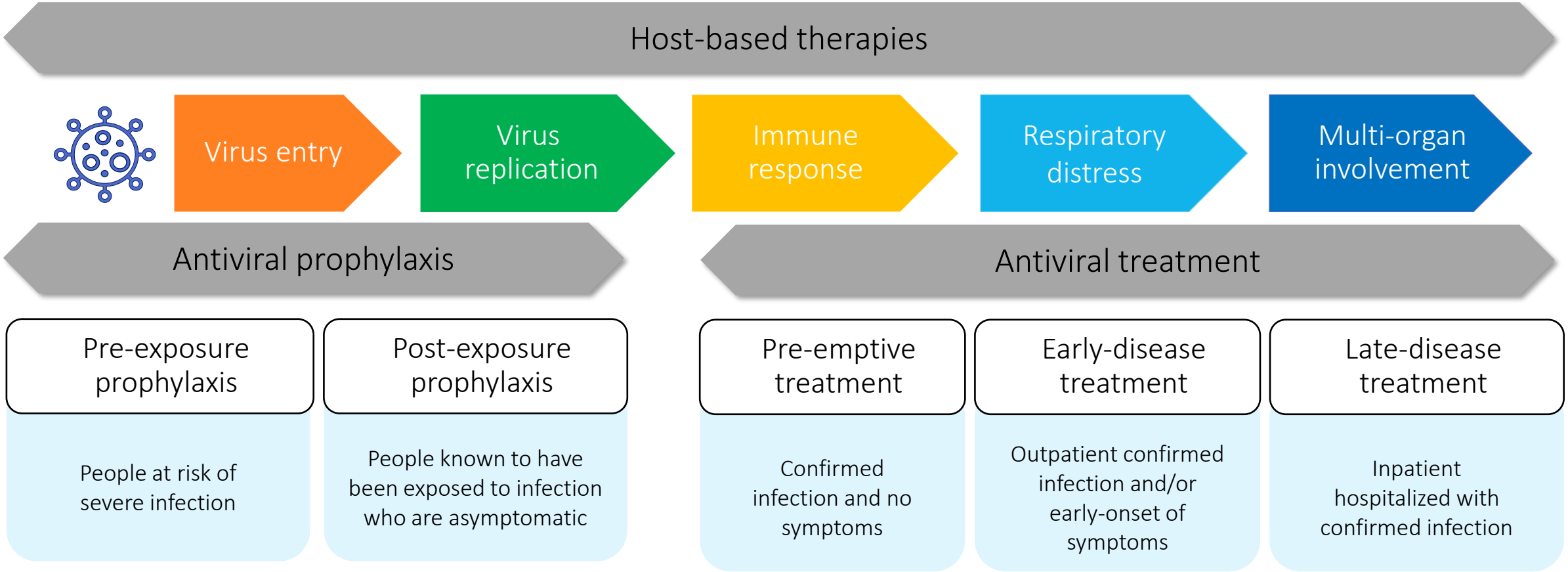
Recherche en phases

Activation d’un plan blanc de recherche



Recherche en reseau
R&D industriel/académique

Recherche en phases



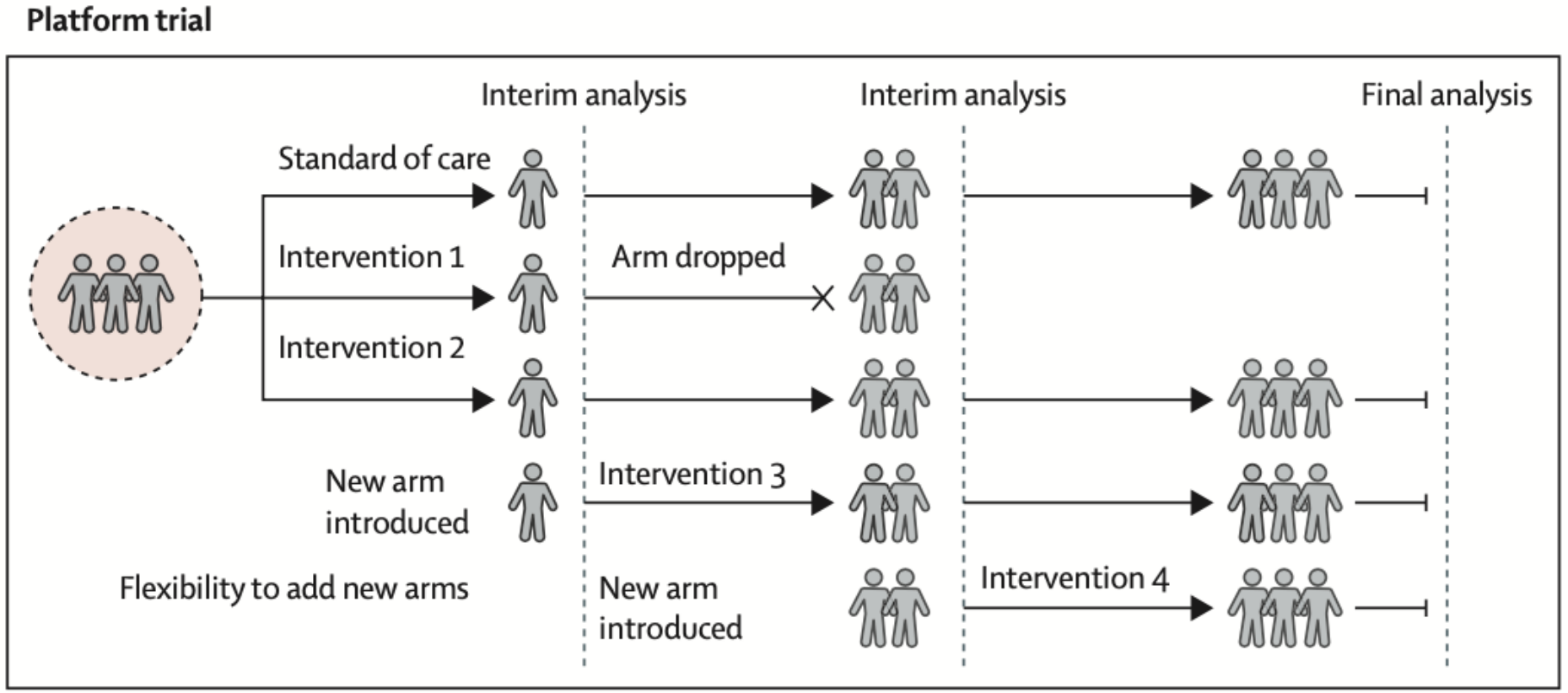
Au final, parcours du combattant si le réseau n'est pas déjà en place car :

Conduire un nouvel essai plateforme randomisé contrôlé interventionnel requière:

(i) un master protocol pré-travaillé et un plan d'analyse associé = blue-print
(ii) Les approbations des autorités institutionelles réglementaires, idéalement en fast-track
(iii) un/des financements(s) et leur gestion,
(iv) identifier les sites d'inclusion,
(v) la contractualisation avec et la formation de ces sites,
(vi) des RH en nb suffisant,
(vii) travailler le circuit du médicament,
(viii) établir le plan d'exploitation des données (analyses intérimaires),
(ix) s'appuyer sur un réseau de laboratoire de référence accrédités (microbiologie, immunomonitoring) et des centres de ressources biologiques (biocollections),
(x) dans une contexte de nouvelle maladie et d'essais en cours, le standard de soins évolue impliquant une/des adaptation(s) de l'intervention ---- > amendement(s) au protocole

Ce montage excède généralement 1 an.

Master protocol ---- > exemple d'essais plateformes adaptatifs



Platform trials have the flexibility of dropping ineffective interventions and adding new interventions during the trial, while evaluating several interventions against a common control.

Park JH Lancet Glob Health 2021; 9: e691–700

Randomized Clinical Trials (RCTs) during pandemics

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

	Traditional trial	Platform trial
Scope	Efficacy of a **single agent** in a homogeneous population.	Evaluating **multiple drugs** in a **heterogeneous** population, explicitly assuming bias.
Duration	**Finite**, based on the time required to answer the single primary question.	Potentially **long-term,** as required for evaluating sequential suitable treatments (rapidity).
N^0 treatment groups	Prespecified and generally limited.	Multiple treatment groups; number and treatment groups may change over time.
Allocation strategy	**Fixed randomization.**	**Adaptive** = individual treatment groups may be removed from the trial based on demonstrated **efficacy**, or **futility** or **harm**; but the trial continues with new experimental treatment(s).
Sponsor support	**Single** federal or industrial sponsor.	Multi-sponsoring, multi-national, academic and/or industry (flexibility).

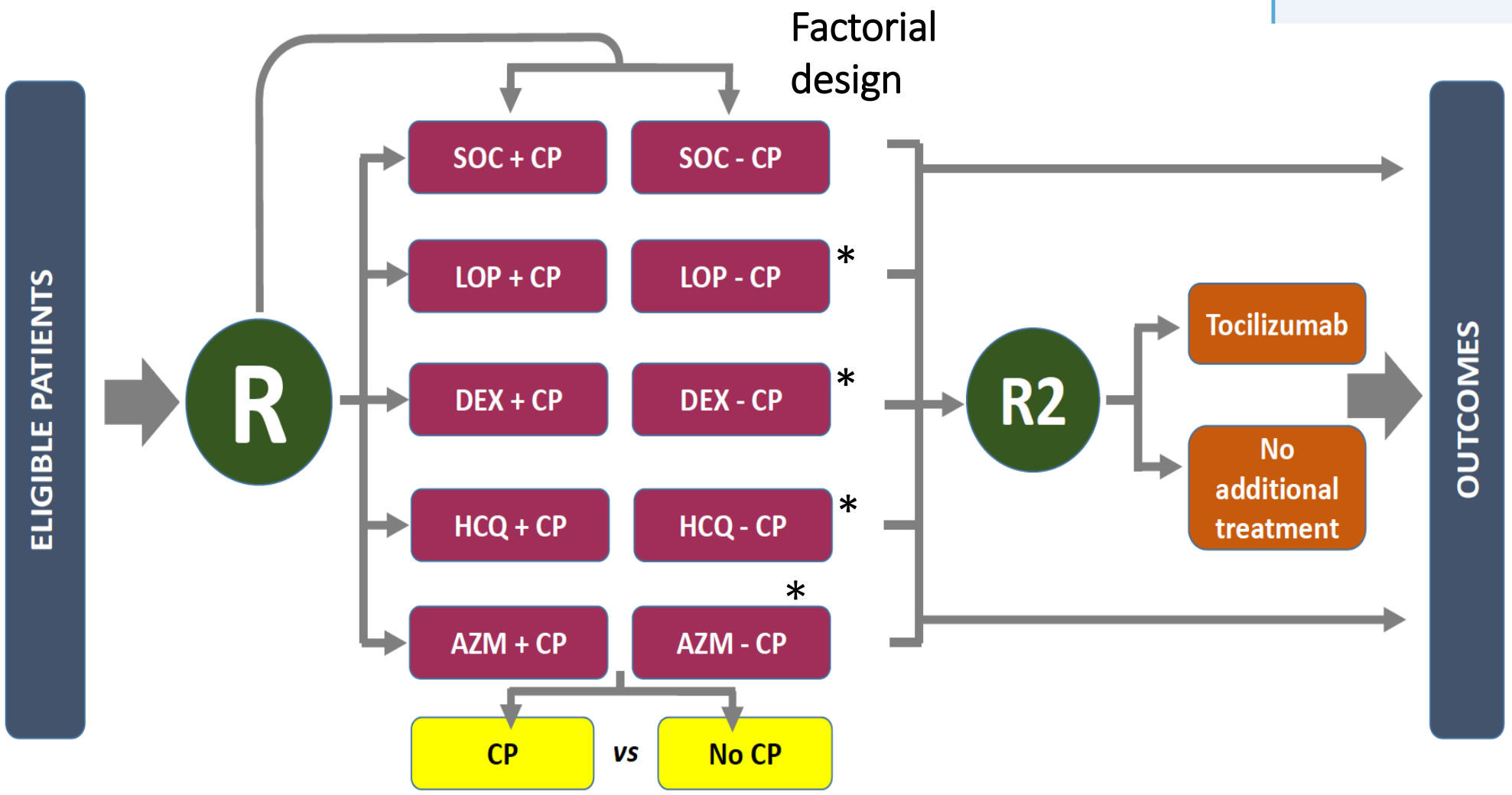
Berry SM, Connnor JT, Lewis RJ. JAMA 2015

RECOVERY
Randomised Evaluation of COVID-19 Therapy

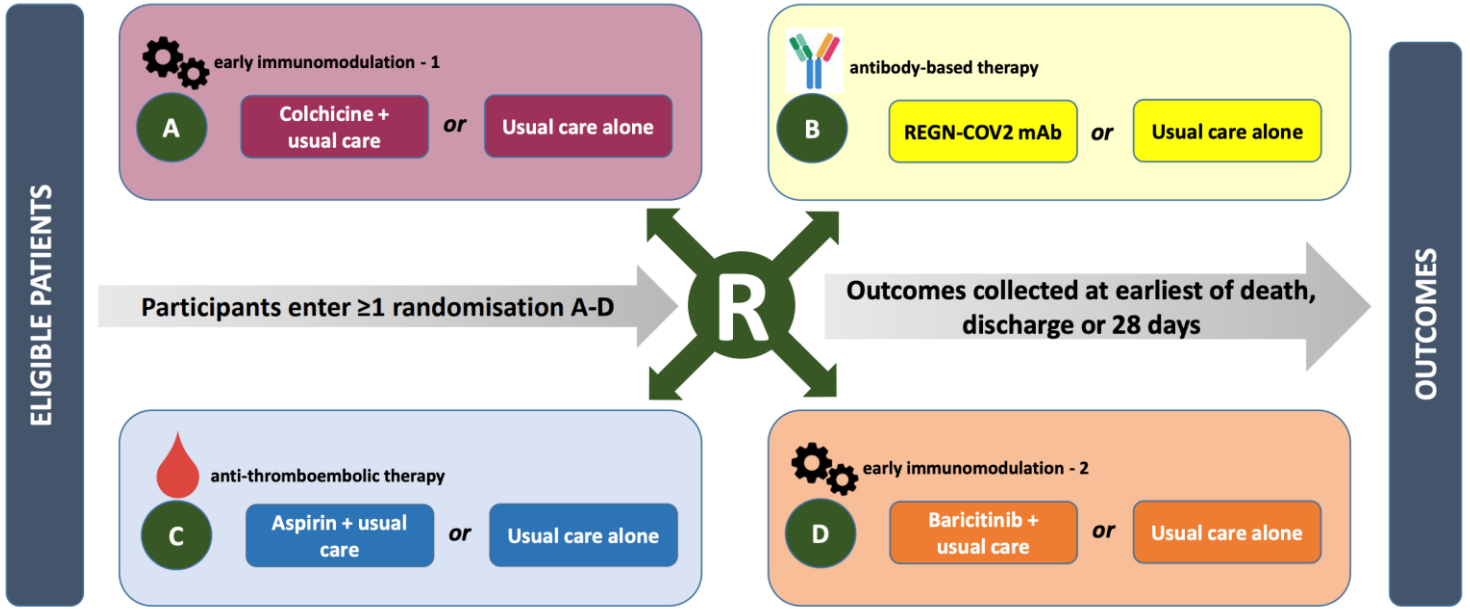
GLOBAL CUMULATIVE TOTALS

48590 Participants

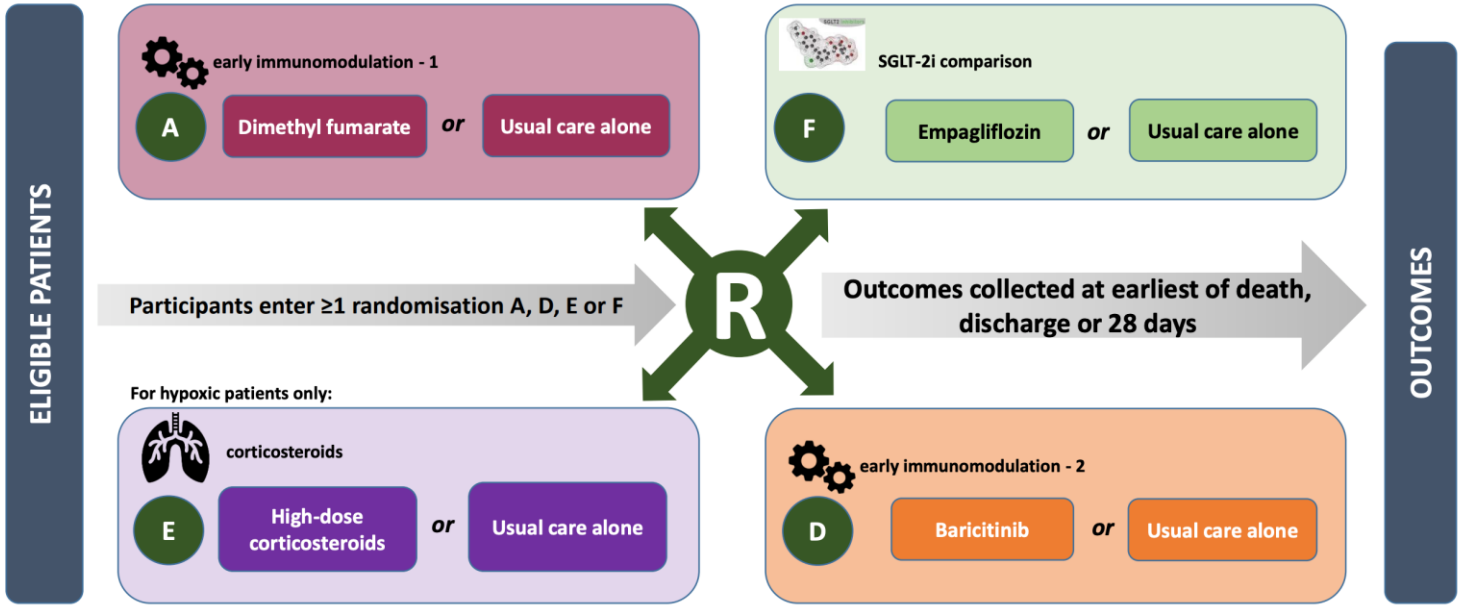
190 Active sites



Février 2021

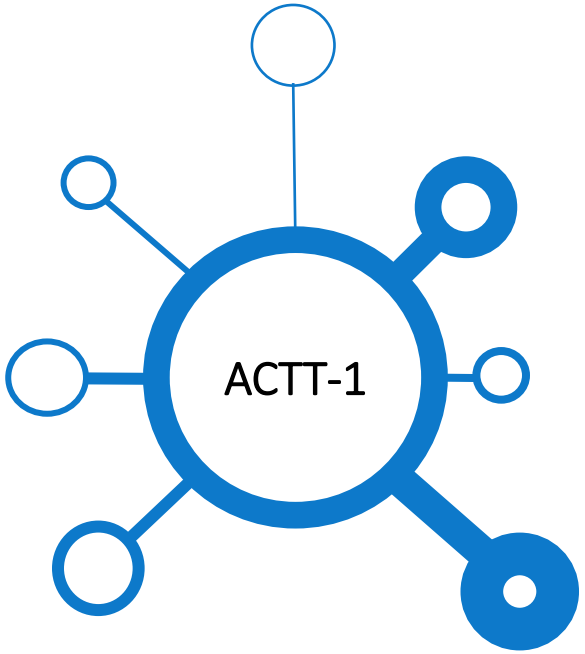


Juillet 2021

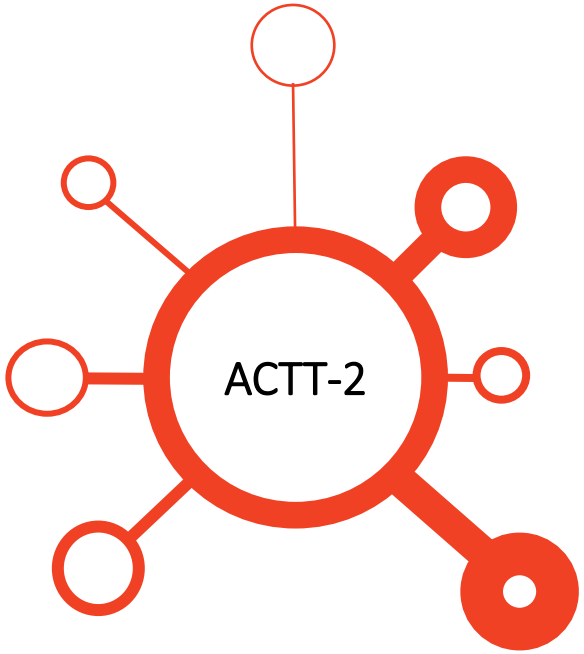


Adaptive Covid-19 Treatment Trial (ACTT)

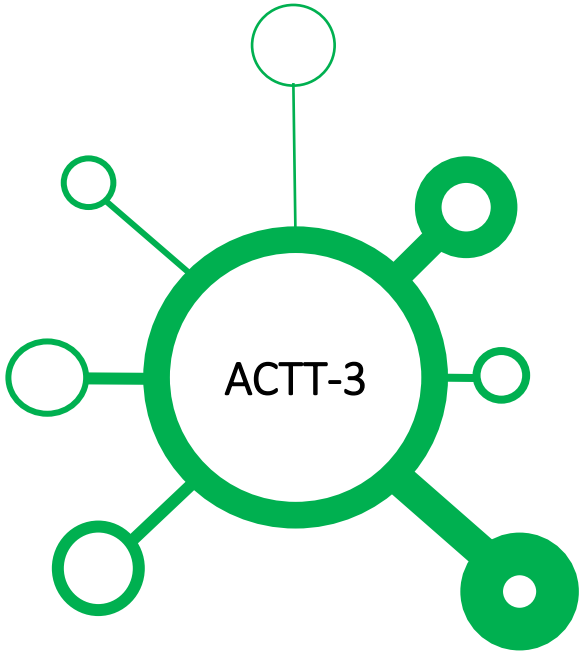
Adaptive platform to rapidly conduct **a series of phase III, randomized, double-blind, placebo-controlled trials**



Remdesivir *vs*. placebo
Start Feb. 21st, 2020
PUBLISHED[1]



Remdesivir + placebo
vs. Remdesivir + baricitinib
Start May 8th, 2020

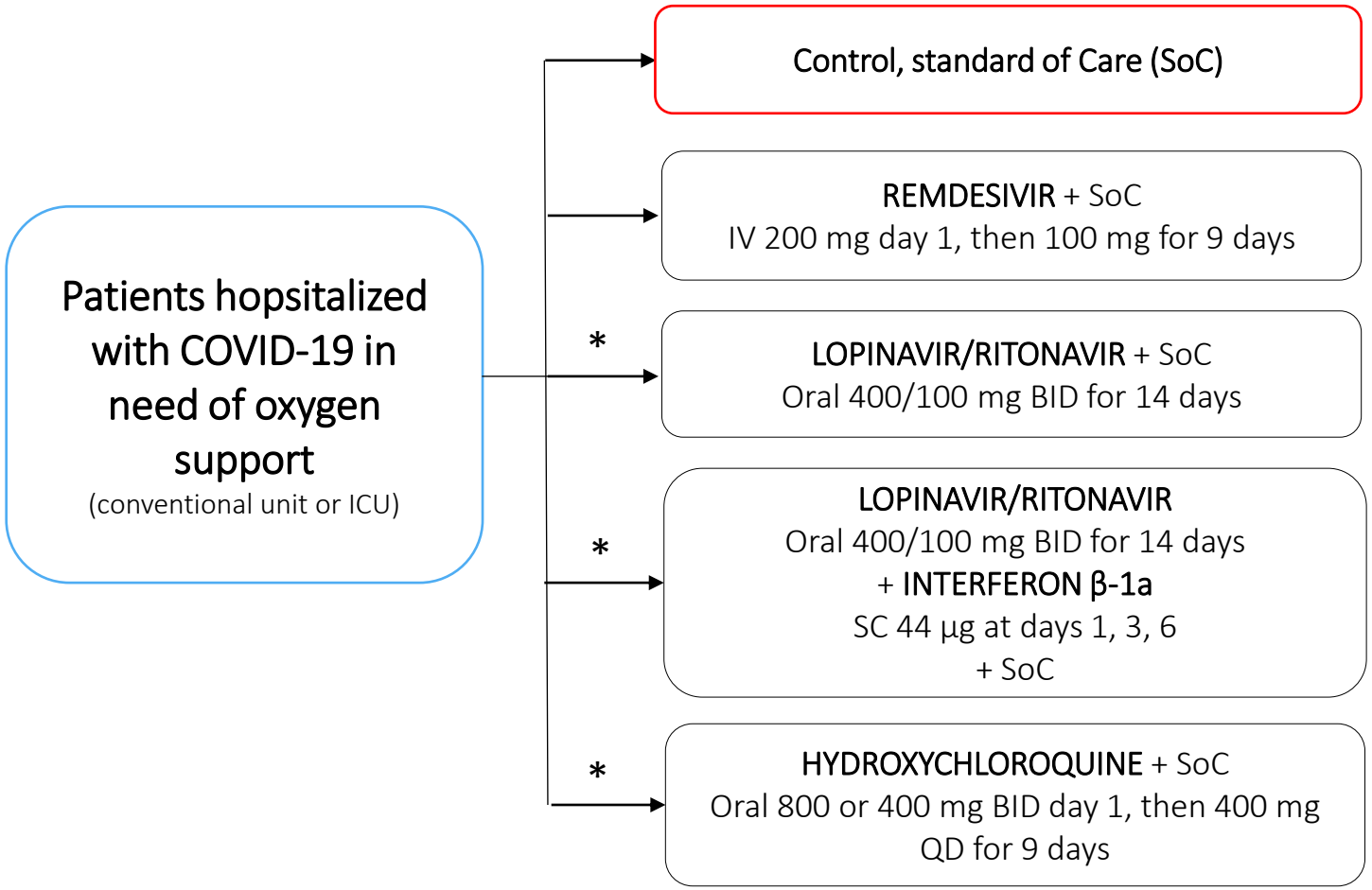


Remdesivir + placebo
vs. Remdesivir + IFN β-1a
Start August 4th, 2020
Publication pending

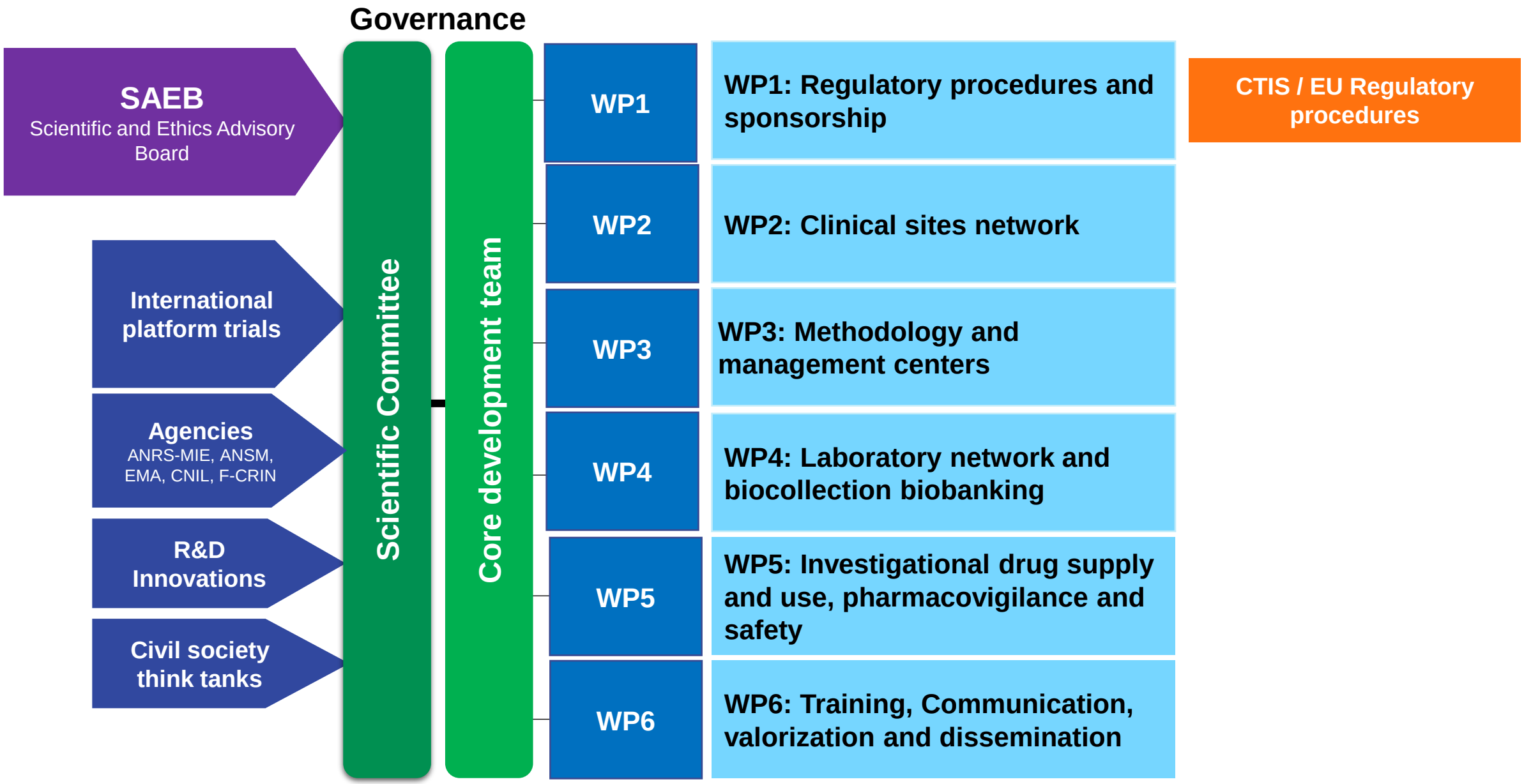
[1]*Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med. DOI: NEJMoa2007764*

World Health Organization

Adaptive platform to rapidly conduct a **phase III, randomized, open-labelled trials**



Organisation interne d’un essai plateforme



Messages clefs

Garder les mêmes standards qualitatifs de recherche mais en accéléré = anticipation/préparation

Fonctionner pendant et s'adapter aux perturbations/interruptions sociétales

Coordination nationale et connexion simultanée avec les plateformes internationales = réseaux

Pipeline R&D académique et industriel

Essais plateforme --- > trouver une balance entre le receuil de variables critiques "basiques" et des varibales plus "granulaires" permettant une stratification des patients

Tenir dans la durée = acculturation à la recherche en MIE à potential pandémique

Stratégies de communication et d'interface (médias, réseaux sociaux, population générale)