World Health Organization

Solidarity Trial Therapeutics

Special isirv-AVG Virtual Conference on 'Therapeutics for COVID-19'

Marie-Pierre Preziosi
On behalf of the Solidarity Trial team
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R&DBlueprint
Powering research
to prevent epidemics

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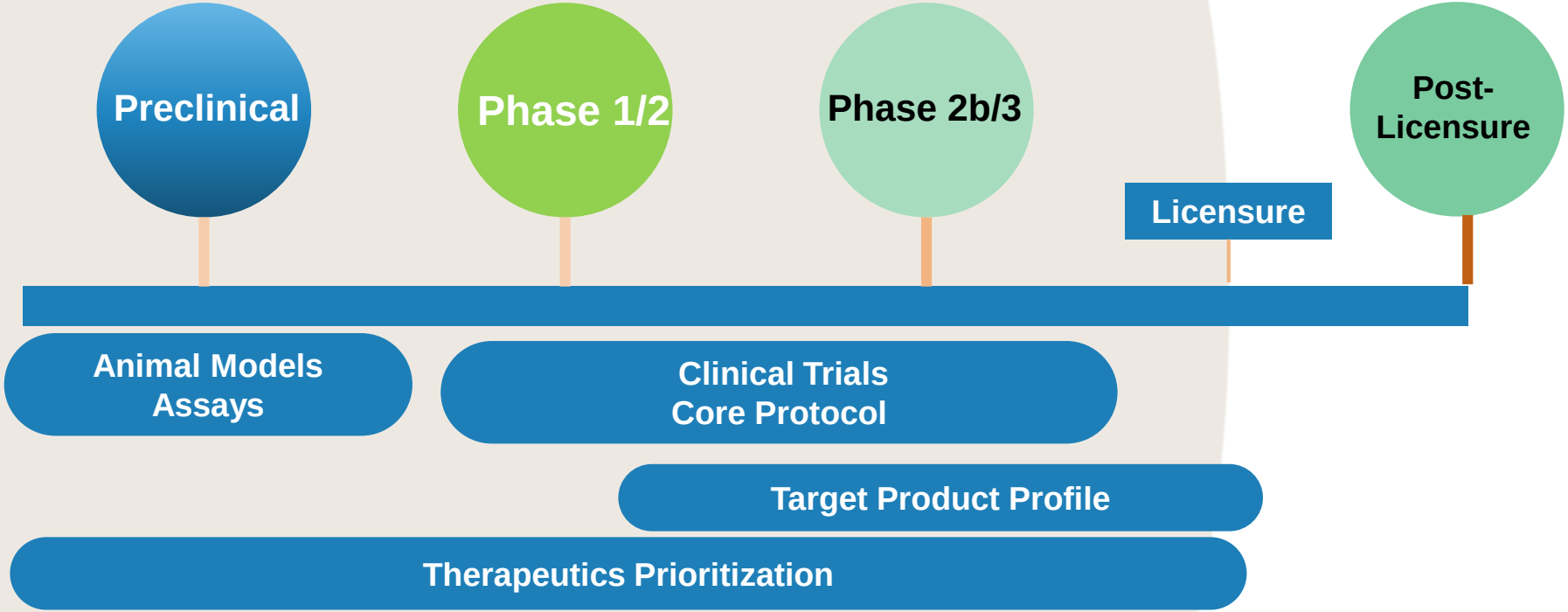
At the request of its 194 Member States in May 2015, the World Health Organization has convened a broad network of experts to develop an R&D Blueprint for Action to Prevent Epidemics

In the event of an outbreak, Blueprint activities will shift from R&D preparedness to an emergency R&D response plan

WHO's work to accelerate COVID-19 therapeutics evaluation



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https://www.who.int/teams/blueprint/covid-19

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1855 studies of COVID treatments in clinical trials registries

1052 of these trials are recruiting patients.

https://www.covid-nma.com/dataviz/

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Solidarity Trial - Therapeutics

Objectives

The aim of this core protocol is to compare the effects on major outcomes in hospital of the local standard of care alone *versus* the local standard of care plus one of four alternative anti-viral agents

- The primary outcome is **all-cause mortality**, subdivided by severity of disease at the time of randomisation. The major secondary outcomes are duration of hospital stay and time to first receiving ventilation (or intensive care)
- The secondary objectives are to assess any effects of these study drugs on **hospital duration** and **receipt of ventilation or intensive care**, and to identify any serious unexpected adverse reactions

Simplicity of procedures

To facilitate collaboration, even in hospitals that have become overloaded, patient enrolment and randomisation (via the internet) and all other trial procedures have been greatly streamlined, and no paperwork at all is required

Once a hospital has obtained approval to participate, informed consent is simple and electronic entry then takes only a few minutes

At the end of this, the randomly allocated treatment is displayed on the screen and is simultaneously confirmed by electronic messaging

Study population: inclusion, exclusion, and recruitment

Eligibility

- Eligible patients are **adults** (age ≥18 years)
- recently admitted as **inpatients**, or already in hospital,
- with definite COVID-19 for whom the responsible doctor would be willing to initiate any of the study treatment arms that might be allocated

Patient details

- Country, hospital (automatically generated)
- Confirmation that informed consent has been obtained
- Patient identifiers (automatically generated), including admission date, age and sex
- Patient characteristics (each yes/no): Smoking? Diabetes? Heart disease? Chronic liver disease? Chronic lung disease? Asthma? HIV infection? Active TB?
- COVID-19 severity (each yes/no): Shortness of breath? On oxygen? Already ventilated?
- IF lungs imaged, major bilateral abnormality? (infiltrations/patchy shadowing)

Randomisation

Patients are randomised through the study website equally between all the locally available treatment regimens

Local standard of care alone,

OR

local standard of care plus one of the study drugs

- Remdesivir (daily infusion for 10 days)
- Hydroxychloroquine (two oral loading doses, then orally twice daily for 10 days)
- Lopinavir with Ritonavir (orally twice daily for 14 days)
- Lopinavir with Ritonavir (ditto) plus Interferon (3 injections SC or a daily injection IV, over 6 days)

Follow-up

At discharge or death

- The patient's study ID
- Which study drugs were given (and for how many days)
- Whether ventilation or intensive care was received (and, if so, when)
- Date of discharge, or date and cause of death

Sample size

No specific sample size is specified is this public health emergency core protocol.

It was anticipated that at least several thousand patients will be recruited into the trial

The larger the numbers entered the more accurate the results will be, but the numbers that can be entered will depend critically on how large the epidemic becomes

Realistic, appropriate sample sizes could not be estimated at the start of the trial

Add-on studies

Particular countries, or particular groups of hospitals, collaborating are adding further measurements or observations, such as serial virology, serial blood gases or chemistry, serial lung imaging, or serial documentation of other aspects of disease status (e.g. through linkage to electronic healthcare records and routine medical databases)

While well-organised additional research studies of the natural history of the disease or of the effects of the trial treatments could well be valuable, they are not core requirements

Adaptive design

Extra arms (additional treatments) will be added while the trial is in progress

Interim analyses will be monitored by a Global Data and Safety Monitoring Committee

In the light of these, and any other evidence they seek, the committee will advise if in their view, be discontinued

Statistical considerations

The primary analyses compare the effects of treatment allocation on **all-cause in-hospital mortality**

The secondary analyses include evaluation of the effects of treatment allocation on the **duration of hospitalization and, use of ventilation or intensive care**

Key Roles and Study Governance

Interim trial analyses are monitored by a **Global Data and Safety Monitoring Committee**

Otherwise, the WHO, collaborators, and administrative staff (except those who produce the confidential analyses) will remain ignorant of the interim results

The evidence on mortality must be strong enough and the range of uncertainty around the results must be narrow enough to affect national and global treatment strategies

The Global Data Monitoring and Safety Committee independently evaluates these analyses and will inform the Executive Group of the Steering Committee if at any stage the results are sufficiently robust for general release and for affecting global recommendations

Monitoring

1. Global data monitoring by independent Academic collaborators
2. Local monitors
3. Data cleaning and verification by other Academic collaborators

Solidarity Trial - Therapeutics

1. Albania
2. Argentina
3. Austria
4. Bangladesh
5. Belgium
6. Brazil
7. Canada
8. Colombia
9. Dominican Rep.
10. Egypt
11. Ethiopia
12. Finland
13. France
14. Georgia
15. Honduras
16. India
17. Indonesia
18. Iran
19. Ireland
20. Italy
21. Kenya
22. Kuwait
23. Latvia
24. Lebanon
25. Lithuania
26. Luxembourg
27. Malaysia
28. Mali
29. Nigeria
30. North Macedonia
31. Norway
32. Oman
33. Pakistan
34. Panama
35. Paraguay
36. Peru
37. Philipppines
38. Portugal
39. Romania
40. Saudi Arabia
41. Sierra Leone
42. Slovakia
43. South Africa
44. Spain
45. Switzerland
46. United Arab Emirates

Nearly 500 hospitals

30 countries enrolling patients

16 other countries ready to start

All 6 Regions of WHO

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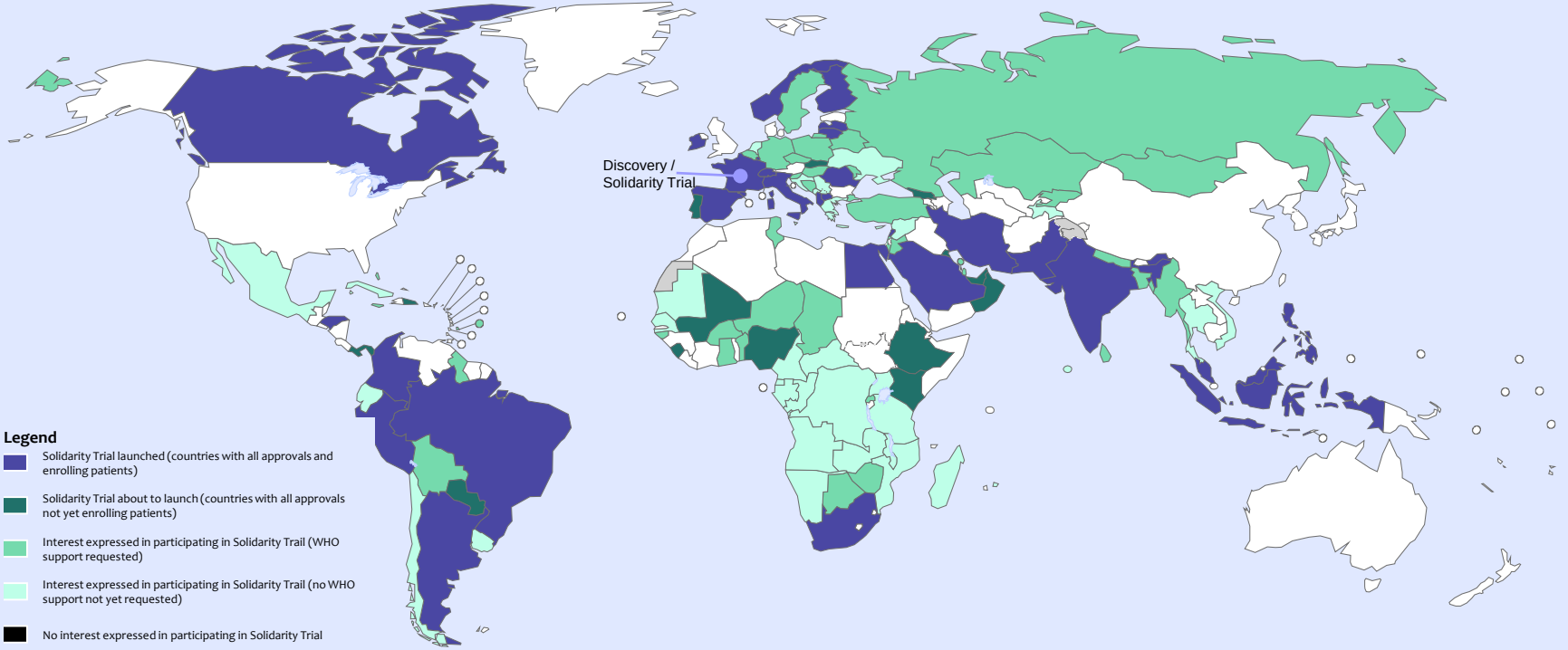
Solidarity Trial

Participating and enrolling countries (as of October 2, 2020)

Total number of patients recruited = nearly 12,000

Total number of participating hospitals = nearly 500



Nb.	Legend
29	Solidarity Trial launched (countries with all approvals and enrolling patients)
14	Solidarity Trial about to launch (countries with all approvals not yet enrolling patients)
38	Interest expressed in participating in Solidarity Trail (WHO support requested)
35	Interest expressed in participating in Solidarity Trail (no WHO support not yet requested)
78	No interest expressed in participating in Solidarity Trial

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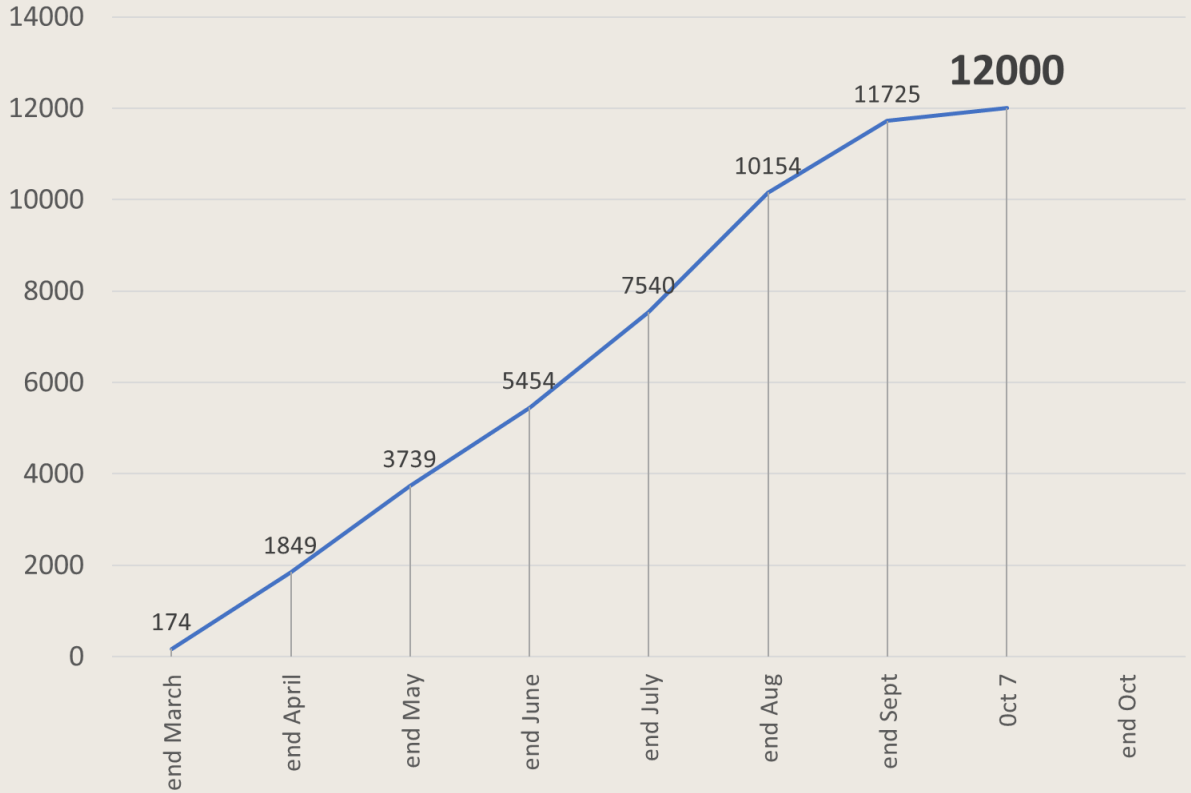
Number of hospitalised COVID-19 patients enrolled



What is next ?

Finalize interim analysis and publication:

- This international collaboration is co-ordinated through the WHO.
- Any wholly reliable interim findings on mortality will be disseminated rapidly by the WHO and will be published in the names of all collaborators

Include additional study drugs

- Antivirals
- Immunomodulators
  - including Monoclonal antibodies

The progress with the Solidarity Trial therapeutics has underlined the value and potential for global platform trials

*"**RECOVERY** and **SOLIDARITY** trials have set new standards and have shown that a combination of **old-fashioned randomization**, established **clinical-trials networks** and imaginative use of **modern information technology** can provide many rapid and reliable therapeutic answers, following the recently published rationale for pursuing **the magic of randomization** rather than the myth of real-world evidence"*

Kari A. O. Tikkinen et al, Nature Medicine Sept 2020