Solidarity Trial Therapeutics

*Special isirv-AVG Virtual Conference on ‘Therapeutics for COVID-19’*

Marie-Pierre Preziosi
On behalf of the Solidarity Trial team
8 October 2020
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

Preclinical

Animal Models Assays

Phase 1/2

Clinical Trials Core Protocol

Phase 2b/3

Target Product Profile

Post-Licensure

Licensure

Therapeutics Prioritization

https://www.who.int/teams/blueprint/covid-19
1855 studies of COVID treatments in clinical trials registries

1052 of these trials are recruiting patients.

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

Nearly 500 hospitals
30 countries enrolling patients
16 other countries ready to start
All 6 Regions of WHO
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

Legend
- Solidarity Trial launched (countries with all approvals and enrolling patients)
- Solidarity Trial about to launch (countries with all approvals not yet enrolling patients)
- Interest expressed in participating in Solidarity Trial (WHO support requested)
- Interest expressed in participating in Solidarity Trial (no WHO support not yet requested)
- No interest expressed in participating in Solidarity Trial

- Nb. 29
- Nb. 14
- Nb. 38
- Nb. 35
- Nb. 78
Number of hospitalised COVID-19 patients enrolled

- End March: 174
- End April: 1849
- End May: 3739
- End June: 5454
- End July: 7540
- End August: 10154
- End September: 11725
- Oct 7: 12000
- End Oct: (data not visible on graph)
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”