COVID-19: Why SOLIDARITY and DisCoVeRy trials may fail to bring informative and timely results?

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BACKGROUND

- On March 12th, 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic due to its fast-worldwide spread.
- No vaccine is available and no drug with proven efficacy has been approved. Robust clinical evidence on efficacy and safety is needed for the benefit-risk assessment in the approval of potential treatments for COVID-19.
- On March 18th, 2020, the WHO Director-General announced the launch of a multinational Phase III-IV clinical trial called SOLIDARITY to facilitate the rapid worldwide comparison of unproven treatments.
- As a part of SOLIDARITY trial program, France launched a satellite European trial called DisCoVeRy, which intends to analyze the efficacy and safety of treatment options for patients within a limited time frame.

OBJECTIVES

This study aimed to review the trial designs of SOLIDARITY and DisCoVeRy, analyze their strengths and weaknesses, and the feasibility of the two trials.

METHODS

- A systematic search of the European Clinical trial registry, the U.S. National Library of Medicine ClinicalTrials.gov, and the WHO's International Clinical Trials Registry Platform (ICTRP) was conducted on May 10th, 2020 to identify the study designs of the SOLIDARITY and DisCoVeRy trials.
- With regard to the SOLIDARITY study, the trials reported at national level in clinical trial registries were also identified.
- A supplementary search of PubMed, WHO's website, French authorities' websites including MESRI, MSS and Inserm, and Google search engine using the keywords of "SOLIDARITY trial" and "DisCoVeRy trial" was conducted to identify additional information on the progress of the two trials.

Table 1 Comparison of study design between Solidarity and Discovery trial

	Solidarity trial	Discovery trial
Trial ID	PER-010-20	NCT04315948
Trial title	Solidarity: An International Randomized Controlled Trial to Evaluate Non-Licensed Covid-19 Treatments in Addition to Standard of Care among Hospitalized Patients	Multi-centre, Adaptive, Randomized Trial of the Safety and Efficacy of Treatments of COVID-19 in Hospitalized Adults (DisCoVeRy)
Planned date of enrolment	03/04/2020	22/03/2020
Recruitment status	Not Recruiting	Recruiting
Date of last update	20/04/2020	29/04/2020
Target size	50,000	3,100
Planned countries	India; Iran; Thailand; Spain; Norway; Switzerland; South Africa; Argentina; Peru; Bahrain; Norway; Finland; Canada	Belgium, France, Germany Luxembourg, the Netherlands, Spain, Sweden, and the United Kingdom
Study type	Adaptive RCT	Adaptive RCT
Masking	Open Label	Open Label
Intervention model	Parallel assignment in Norway and Canada; no parallel and no cross over group in Spain, Italy, Norway and Finland	Parallel assignment
Phase	Phase 3/4	Phase 3
Inclusion Criteria	1. Adult ≥18 years 2. Laboratory-confirmed SARS-CoV-2 3. Hospitalized	1. Adult ≥18 years 2. Laboratory-confirmed SARS-CoV-2 infection a 3. Hospitalized 4. Acute respiratory failure requiring mechanical ventilation and/or supplemental oxygen.
Exclusion Criteria	1. Severe co-morbidity 2. Intolerance to the available study drugs 3. Pregnancy or breast feeding	1.Refusal to participate 2. ALT/AST levels > 5 times the upper limit of normal. 3. Stage 4 severe chronic kidney disease or requiring dialysis 4. Pregnancy or breast-feeding. 5. Patients previously treated with the available study drugs 6. Contraindication to the available study drugs including allergy 7. Severe depression or suicidal ideation
Intervention	1. Remdesivir 2. Lopinavir/ritonavir 3. Lopinavir/ritonavir and Interferon Beta-1A 4. Hydroxychloroquine	1. Remdesivir 2. Lopinavir/ritonavir 3. Lopinavir/ritonavir and Interferon Beta-1A 4. Hydroxychloroquine
Control	Standard of Care	Standard of Care

Table 2 Solidarity trial conducted in different countries

Trial ID	EUCTR2020-001366-11-ES	EUCTR2020-001366-11-IT	EUCTR2020-000982-18-NO	EUCTR2020-001784-88-FI	NCT04321616
Trial title	An international randomised trial of additional treatments for COVID-19 in hospitalised patients who are all receiving the local standard of care - Solidarity	An international randomised trial of additional treatments for COVID-19 in hospitalised patients who are all receiving the local standard of care - Solidarity	The NOR Solidarity multicenter trial on the efficacy of different anti-viral drugs in SARS-CoV-2 infected patients (COVID-19). - N-ReCOVID 19	WHO SOLIDARITY Finland: The multicenter trial on the efficacy of different anti-viral drugs in SARS-CoV-2 infected patients (COVID-19)	The (Norwegian) NOR Solidarity Multicenter Trial on the Efficacy of Different Anti-viral Drugs in SARS-CoV-2 Infected Patients
Planned date of enrolment	27/03/2020	09/04/2020	26/03/2020	N/A	28/03/2020
Recruitment status	Authorised	Authorised	Authorised	Authorised	Recruiting
Date of last update	14/04/2020	29/04/2020	04/052020	29/04/2020	27/04/2020
Target size	2500	600	1218	300	700
Countries	Spain	Italy	Norway	Finland	Norway
Study type	RCT	RCT	RCT	RCT	RCT
Masking	Open Label	Open Label	Open Label	Open Label	Open Label
Intervention model	No Parallel assignment	No Parallel assignment	No Parallel assignment	No Parallel assignment	Parallel Assignment
Phase	Phase 4	Phase 3	Phase 3	Phase 3	Phase 2/Phase 3
Inclusion Criteria	1. Adult ≥18 years 2.Confirmed SARS-2-CoV-2 infection 3. Hospitalized	1. Adult ≥18 years 2.Confirmed SARS-2-CoV-2 infection 3. Hospitalized	1. Adult ≥18 years 2.Confirmed SARS-2-CoV-2 infection 3. Hospitalized	1. Adult ≥18 years 2. Confirmed SARS-2-CoV-2 infection 3. Hospitalized	1. Adult ≥18 years 2. Confirmed SARS-2-CoV-2 infection 3. Hospitalized
Exclusion Criteria	1. Known allergy or contra-indications to investigational products 2.Refusal to participate 3.Already receiving any of the study drugs	1. Known allergy or contra-indications to investigational products 2. Refusal to participate 3.Already receiving any of the study drugs	1.Severe co-morbidity 2. ALT/AST > 5 times the upper limit of normal 3.Known intolerance to the available study drugs 4.Pregnancy or breast feeding 5.Already receiving any of the study drugs	1. Severe co-morbidity 2. ALT/AST > 5 times the upper limit of normal 3. Known intolerance to the available study drugs 4. Pregnancy or breast feeding 5. Already receiving any of the study drugs	1. Severe co-morbidity 2. ALT/AST > 5 times the upper limit of normal 3. Known intolerance to the available study drugs 4. Pregnancy or breast feeding 5. Already receiving any of the study drugs
Intervention	1. Remdesivir 2. Chloroquine 3.Lopinavir/Ritonavir 4. Interferon beta-1a	1. Remdesivir 2. Chloroquine 3.Lopinavir/Ritonavir 4. Interferon beta-1a	1. Hydroxychloroquine 2. Remdesivir	1. Hydroxychloroquine 2. Remdesivir	1. Hydroxychloroquine 2.Remdesivir
Control	Standard of Care	Standard of Care	Standard of Care	Standard of Care	Standard of Care

RESULTS

- The SOLIDARITY trial and the DisCoVeRy trial mostly shared the same characteristics, such as study objective (to assess the efficacy and safety of potential interventions against the standard of care in hospitalized COVID-19 patients), interventions (remdesivir, lopinavir-ritonavir, lopinavir-ritonavir-interferon beta, and hydroxychloroquine), and population selection (hospitalized adult patients with laboratory-confirmed COVID-19, and with or without respiratory failure) (Table 1).
- Initially launched on April 3rd and March 22nd, 2020, the SOLIDARITY trial and the DisCoVeRy trial targeted 50,000 patients and 3,100 patients, respectively (Table 1).
- The primary endpoint is all-cause mortality in the SOLIDARITY trial and severity rating on a 7-point ordinal scale at day 15 in the DisCoVeRy trial with an extensive data collection for secondary end points representing more than 100 variables (Table 1 and Table 2).
- This design made the data collection inapplicable in a pandemic. However, the SOLIDARITY trial allowed customization for country-specific studies, sample size, endpoints contributing to significant deviation from the original protocol.

CONCLUSIONS

- From the logistic perspective, both trials lacked the resources to secure aligned and high-quality implementation.
- This review called for a pandemic task force with operational experts from the front-line of COVID-19 treatment to inform policymakers to make pragmatic and effective decisions when launching joined effort for trials.

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