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Protocol for the DisCoVeRy trial: multicentre, adaptive, randomised trial of the safety and efficacy of treatments for COVID-19 in hospitalised adults

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ABSTRACT

Introduction To find effective and safe treatments for COVID-19, the WHO recommended to systemically evaluate experimental therapeutics in collaborative randomised clinical trials. As COVID-19 was spreading in Europe, the French national institute for Health and Medical Research (Inserm) established a transdisciplinary team to develop a multi-arm randomised controlled trial named DisCoVeRy. The objective of the trial is to evaluate the clinical efficacy and safety of different investigational re-purposed therapeutics relative to Standard of Care (SoC) in patients hospitalised with COVID-19.

Methods and analysis DisCoVeRy is a phase III, open-label, adaptive, controlled, multicentre clinical trial in which hospitalised patients with COVID-19 in need of oxygen therapy are randomised between five arms: (1) a control group managed with SoC and four therapeutic arms with re-purposed antiviral agents: (2) remdesivir + SoC, (3) lopinavir/ritonavir + SoC, (4) lopinavir/ritonavir associated with interferon (IFN)-β–1a + SoC and (5) hydroxychloroquine + SoC. The primary endpoint is the clinical status at Day 15 on the 7-point ordinal scale of the WHO Master Protocol (V.3.0, 3 March 2020). This trial involves patients hospitalised in conventional departments or intensive care units both from academic or non-academic hospitals throughout Europe. A sample size of 3100 patients (620 patients per arm) is targeted. This trial has begun on 22 March 2020. Since 5 April 2020, DisCoVeRy has been an add-on trial of the Solidarity consortium of trials conducted by the WHO in Europe and worldwide. On 8 June 2020, 754 patients have been included.

Ethics and dissemination Inserm is the sponsor of DisCoVeRy. Ethical approval has been obtained from the institutional review board on 13 March 2020 (20.03.06.51744) and from the French National Agency for Medicines and Health Products (ANSM) on 9 March 2020. Results will be submitted for publication in peer-reviewed journals.

Trial registration number NCT04315948 Eudra-CT 2020-000936-23.

Strengths and limitations of this study

- The DisCoVeRy clinical trial is an adaptive, randomised, open-label clinical trial that aims to evaluate the safety and efficacy of four antiviral therapeutic strategies as compared with standard of care in hospitalised adult patients diagnosed with COVID-19.
- Therapeutic strategies can be modified according to new evidence: an arm can become the standard of care if proved superior to others, arms can be discontinued if proved inferior to others and arms can be added if new candidate therapeutic strategies emerge.
- DisCoVeRy is an add-on trial of the Solidarity consortium of trials, conducted under the aegis of the WHO and data on common endpoints are shared with the Solidarity consortium.
- DisCoVeRy is not a placebo-controlled trial and is not double-blind because of the complexity of blinding treatments with different mode of administration (intravenous, subcutaneous or oral) and the need to initiate the trial very rapidly.
- DisCoVeRy includes patients who are hospitalised in need of oxygen therapy, it does not target patients at the early phase of the disease nor include anti-inflammatory agents that can be used as part of the standard of care in any arm.

INTRODUCTION

Background and scope

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third coronavirus that has crossed the species barrier to cause deadly pneumonia in humans since the beginning of the 21st century, after SARS-CoV[1 2] and Middle-East respiratory syndrome coronavirus[3] (MERS-CoV) in 2002 and 2012, respectively. The first case of infection with the SARS-CoV-2 was reported in the city of Wuhan, China, on 31 December 2019. The associated disease was named 'coronavirus disease 2019' (abbreviated 'COVID-19'). The emergence and the spread of SARS-CoV-2 is an unprecedented challenge, vividly illustrating the pace at which a viral outbreak can progress among a highly interlinked and susceptible global population. At the beginning of March 2020, when this clinical trial was designed, COVID-19 had spread to more than 100 countries and affected more than 100 000 individuals. Consistently, the WHO declared COVID-19 pandemic on 11 March 2020.[4]

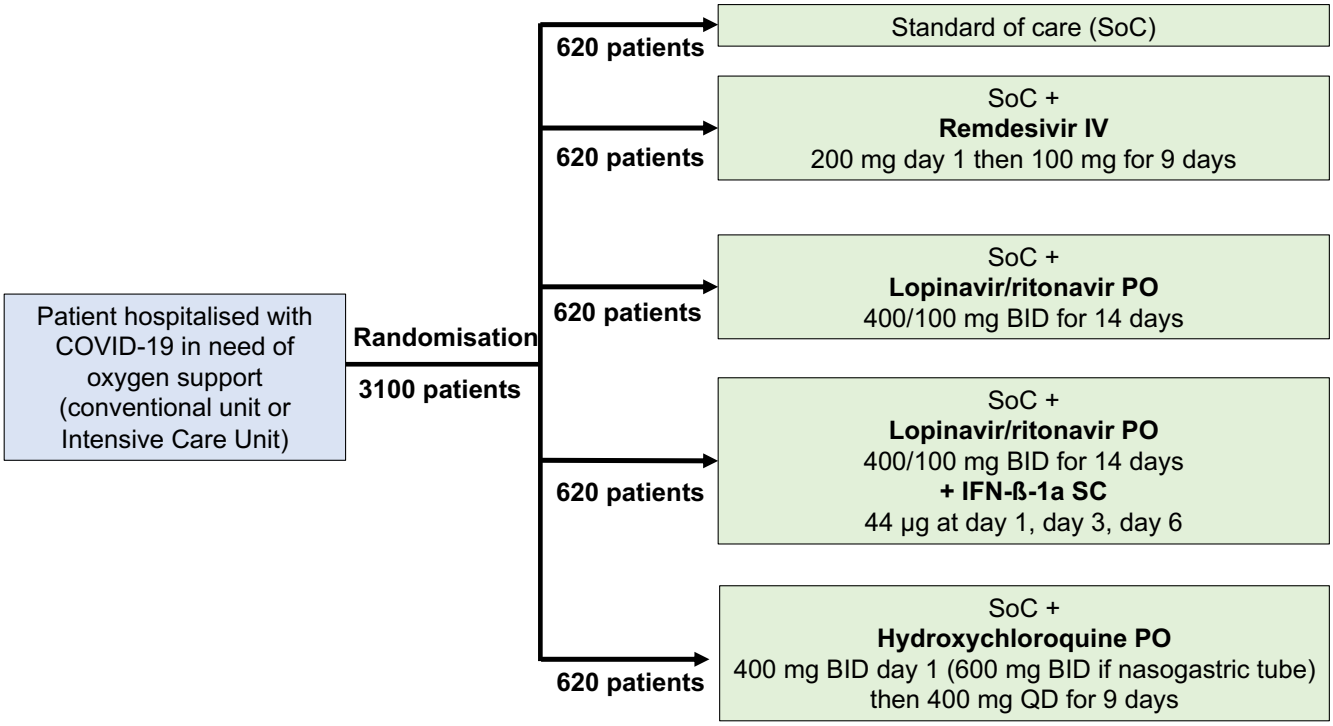

Figure 1 DisCoVeRy trial arms, drugs and dosing schedule. BID, two times per day; IFN, interferon; IV, intravenous; PO, by mouth; QD, every day.

Although many drugs have in vitro activity against various coronaviruses, no clinical evidence at that time supported the efficacy and safety of any drug against any coronavirus in humans, including SARS-CoV-2. The rapid and simultaneous combination of supportive care and randomised controlled trials (RCT) is the only way to find effective and safe treatments for COVID-19 that could improve patients' management. WHO thus recommended researchers around the world to systemically evaluate experimental therapeutics in RCT and to gather initiatives in large trials that could provide strong evidence about which treatment are safe and effective.

As COVID-19 was spreading in Europe, the French national institute for Health and Medical Research (Inserm) established a transdisciplinary team to develop a multi-arm randomised controlled trial to rapidly provide reliable evidence about the efficacy and safety of therapeutics in comparison to a standard of care control arm. The WHO Master Protocol for therapeutics against COVID-19 V.3.0 (3 March 2020) published by the WHO R&D Blueprint Working Group[5] was used as a template for this clinical trial. Subsequently, the DisCoVeRy trial was launched in France on 22 March 2020. International cooperation being essential in outbreak science and public health, and in actions to prevent transfrontier disease progression, the DisCoVeRy trial intends to bring together several European countries.

Objective

The objective of the DisCoVeRy trial is to evaluate the clinical efficacy and safety of different investigational therapeutics relative to Standard of Care (SoC) in patients hospitalised with COVID-19.

METHODS AND ANALYSIS

Design and general information

DisCoVeRy is a phase III, open-label, adaptive, randomised, controlled, multicentre clinical trial designed to evaluate the safety and efficacy of re-purposed therapeutic interventions in hospitalised adult patients diagnosed with COVID-19. This trial involves patients both from academic or non-academic hospitals throughout Europe, with Inserm as the sponsor. Study sites can be obtained from the sponsor's representative (contact: helene.esperou@inserm.fr). The protocol described in this article is the V.7.0 of the DisCoVeRy protocol approved on 5th April.

The DisCoVeRy RCT has five arms: (1) a control group managed SoC and four therapeutic arms with re-purposed antiviral agents: (2) remdesivir + SoC, (3) lopinavir/ritonavir + SoC, (4) lopinavir/ritonavir associated with interferon (IFN)-β−1a + SoC and (5) hydroxychloroquine + SoC (figure 1). The arms have not been modified between the V.1 and V.7 of the protocol. Included participants cannot be treated with antivirals other than the study medications allocated by randomisation, but non-antiviral drugs such as steroids, immunomodulatory agents (eg, anti-interleukin 6 drugs), or antibiotics can be used as part of the standard of care. This is an open-label trial but all investigators are unaware of aggregate outcomes during the study. The design is adaptive on decision of

the Data and Safety Monitoring Board (DSMB): arms can be discontinued if proved inferior to others, an existing arm can become the standard of care if proved superior and arms can be added if new candidate therapeutic strategies emerge. The trial has been registered at the ClinicalTrials.org registry as NCT04315948 and on the European Clinical Trials Database as 2020-000936-23.

Participants

For the duration of the study, the sponsor has subscribed an insurance policy covering the sponsor's own third-party liability as well as the third-party liability of all the investigators involved in the study (€600 000 per participant for bodily injury and property damage combined and €5 000 000 per trial in total. The maximum amount of compensation could vary depending on the country).

Inclusion criteria

Patients must fulfil the following criteria prior to trial enrolment:

1. Adult ≥18 years of age at time of enrolment;
2. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen <72 hours prior to randomisation;
3. Hospitalised patients with illness of any duration, and at least one of the following:
   - Clinical assessment of pulmonary infection (evidence of rales/crackles on exam) AND saturation in oxygen (SpO_2)≤94% on room air, or
   - Acute respiratory failure requiring supplemental oxygen, high flow oxygen devices, non-invasive ventilation and/or mechanical ventilation;
4. Women of childbearing potential must agree to use contraception for the duration of the study.

Non-inclusion criteria

Patients with any of the following criteria are not eligible for trial enrolment:

1. Refusal to participate expressed by patient or legally authorised representative if they are present;
2. Spontaneous blood alanineaminotransferase/aspartateaminotransferase (ALT/AST) levels >5 times the upper limit of normal;
3. Stage 4 severe chronic kidney disease or requiring dialysis (ie, eGFR (estimated glomerular filtration rate) <30 mL/min);
4. Pregnancy or breast feeding;
5. Anticipated transfer to another hospital, which is not a study site within 72 hours;
6. Patients previously treated with one of the antivirals evaluated in the trial (ie, remdesivir, interferon ß–1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days;
7. Contraindication to any study medication including allergy;
8. Use of medications that are contraindicated with lopinavir/ritonavir, that is, drugs whose metabolism is highly dependent on the isoform CYP3A with narrow therapeutic range (eg, amiodarone, colchicine, simvastatin);
9. Use of medications that are contraindicated with hydroxychloroquine: citalopram, escitalopram, hydroxyzine, domperidone, piperaquine;
10. HIV infection under combination antiretroviral therapy;
11. History of severe depression or attempted suicide or current suicidal ideation;
12. Corrected QT interval superior to 500 milliseconds (as calculated with the Fridericia formula).

Randomisation

Patients are randomly assigned in a 1:1:1:1:1 ratio into one of the five groups. The randomisation list is computer-generated, with blocks of various sizes and stratified by region (according to the administrative definition in each country) and severity of illness at enrolment (severe disease: patients requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); moderate disease: patients not requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical ventilation nor ECMO). The randomisation list is implemented in the electronic case report form to ensure appropriate allocation concealment.

Experimental design

Study treatments

The participants are allocated in one of five arms (figure 1).

Patients included in the remdesivir group receive 200 mg intravenous loading dose on Day 1, followed by a 100 mg one time per day intravenous maintenance dose for the duration of the hospitalisation and up to a 10 days' total course. Remdesivir is administered through a 30 to 60 min intravenous infusion.

Patients included in the lopinavir/ritonavir group receive 400 mg lopinavir and 100 mg ritonavir administered every 12 hours for 14 days in tablet form. For patients who are unable to take medications by mouth, the lopinavir/ritonavir (400 mg lopinavir/100 mg ritonavir) is administered as a 5 mL suspension every 12 hours for 14 days via a nasogastric tube.

Patients included in the lopinavir/ritonavir + interferon ß–1a group receive, in addition to lopinavir/ritonavir as described above, interferon ß–1a administered subcutaneously at the dose of 44 µg on Day 1, Day 3 and Day 6 (total of three doses). No dosage adjustment is provided for renal or hepatic impairment for IFN-ß–1a.

Patients included in the hydroxychloroquine group receive a loading dose of 400 mg twice daily for 1 day followed by 400 mg once daily for 9 days. The rationale for this loading dose has been published.[6]

Patients included in the control group receive the standard of care of their recruitment centre. Investigational drugs were kindly provided by pharmaceutical firms.

Rationale for study treatments

Remdesivir (GS-5734) is a broad-spectrum nucleotide prodrug inhibiting RNA-dependent polymerase activity among a diverse group of RNA viruses including filoviruses (eg, Ebola, Sudan, Marburg), paramyxoviruses (eg, RSV, Nipah, Hendra) and pathogenic coronaviruses.[7–9] Studies in human airway epithelial cell assays demonstrated that remdesivir inhibits replication of coronaviruses, including MERS-CoV.[10] Remdesivir has shown an in vitro activity on SARS-CoV-2[11] and a clinical benefit in rhesus macaques infected with SARS-CoV-2.[12] A large RCT has shown that remdesivir shortened the time to recovery in adults hospitalised with COVID-19 as compared with placebo but the results were not significant for mortality.[13]

Lopinavir/ritonavir is a fixed-dose combination used in HIV infection that has shown an in vitro activity against SARS-CoV in several studies.[14] A structure-based study suggested that the spatial structure of the lopinavir/ritonavir binding site was conserved between SARS-CoV and SARS-CoV-2.[15] The results of an open RCT evaluating lopinavir/ritonavir for COVID-19 were published on 18 March 2020.[16] In this trial, adults with confirmed COVID-19 and hypoxaemia (SpO_2 <94 %) were randomised to lopinavir/ritonavir (n=99) or standard of care (n=100). No significant difference between the two groups was observed on the time to clinical improvement on a 7-item ordinal scale. (HR of improvement 1.31; 95% CI 0.95 to 1.80) but a trend to lower mortality rate was observed (19.0% vs 27.1%) in the 90 patients (45.2% of the total) receiving lopinavir/ritonavir less than 12 days after the beginning of the symptoms.

Interferon (IFN)-ß−1 is a broad-spectrum antiviral drug belonging to the type interferons. Type 1 IFN treatment has shown an activity against MERS-CoV and SARS-CoV in numerous experiments, both in vitro and in vivo.[17–19] Type 1 interferon is currently being tested for MERS-CoV in the MIRACLE clinical trial.[20] SARS-CoV-2 displays in vitro a substantial susceptibility to IFN-α[21] and data regarding the potential activity of type 1 interferons on SARS-CoV-2 has been reviewed recently.[22] A RCT found that COVID-19 patients treated with a triple combination interferon beta-1b, lopinavir-ritonavir and ribavirin had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days (IQR 5 to 11)) than the control group up (12 days[8–15]; HR 4.37 (95% CI 1.86 to 10.24), p=0.0010).[23]

The in vitro antiviral activity of hydroxychloroquine has been known for a long time[24] and was described on a number of viruses including SARS-CoV.[25 26] Regarding COVID-19, recent publications reported an in vitro activity of hydroxychloroquine on SARS-CoV-2[11 27] and non-randomised observational studies provided conflicting clinical results.[28 29] A RCT on post-exposure prophylaxis for COVID-19 found that hydroxychloroquine did not prevent illness compatible with COVID-19 or confirmed infection.[30]

Participant timeline

Clinical evaluations for efficacy and safety are performed at baseline, daily while the patient is hospitalised and at 15 days (±2 days) and 29 days (±3 days) (table 1, figure 2).

Upper (nasopharyngeal swab) and/or lower (endotracheal aspiration) respiratory tract and blood samples for centralised analysis of the SARS-CoV-2 kinetics are collected at baseline and at days 3 (±1 day), 5 (±1 day), 8 (±1 day), 11 (±1 day), 15 (±2 days) and 29 (±3 days). Real-time (RT)-PCR methods for SARS-COV-2 detection in participating centres are different but their performances were all validated by French National Reference Center for Viral Respiratory Infections and viral loads are determined using the specific French National Reference Center RT-PCR IP4.[31] For each sample, the viral load is measured by a specific SARS-COV-2 RT-PCR and normalised according to the number of cells in each sample. This method is validated to monitor viral load kinetics over time and expressed in standardised unit log of number of viral copies/10 000 cells.

Blood samples for pharmacokinetic analysis are collected:

- For remdesivir, to measure plasma and intracellular concentrations at days 1, 2, 5, 8 and 11;
- For lopinavir, to measure plasma concentrations at days 1, 3 (±1 day), 6 (±1 day), 8 (±1 day) and 11 (±1 day);
- For IFN ß−1-a, to measure plasma concentrations at days 3 and 6;
- For hydroxychloroquine, to measure plasma concentrations at days 1, 3 (±1 day), 5 (±1 day), 8 (±1 day) and 11 (±1 day).

Thoracic imaging by X-ray or CT scan are performed at baseline, and at days 8 (±1 day), 15 (±2 days) and 29 (±3 days).

Biological evaluations for safety are performed at baseline and at days 3 (±1 day), 5 (±1 day), 8 (±1 day), 11 (±1 day), 15 (±2 days) and 29 (±3 days).

A sample collection is constituted for each patient (biobank) including whole blood and plasma at baseline and plasma at days 3 (±1 day), 5 (±1 day), 8 (±1 day), 11 (±1 day), 15 (±2 days) and 29 (±3 days). The biobank will be used to conduct ancillary analyses that remain to be determined.

Primary endpoint

The primary endpoint is the clinical status at Day 15 on the 7-point ordinal scale of the WHO Master Protocol (V.3.0, 3 March 2020):

1. Not hospitalised, no limitation on activities;
2. Not hospitalised, limitation on activities;
3. Hospitalised, not requiring supplemental oxygen;
4. Hospitalised, requiring supplemental oxygen;
5. Hospitalised, on non-invasive ventilation or high flow oxygen devices;
6. Hospitalised, on invasive mechanical ventilation or ECMO;
7. Death.

Table 1 Schedule of enrolment, interventions and assessment in the DisCoVeRy trial

Day±window	Screening	Baseline*	D1	D2-D14†	D15† ±2	D29† ±3	D90
Eligibility							
Informed consent	X						
Demographics and medical history	X						
EKG	X						
Review SARS-CoV-2 PCR results	X						
Study intervention							
Randomisation		X					
Standard of Care (SoC)							
Or SoC plus administration of lopinavir/ritonavir			Lopinavir/ritonavir for 14 days				
Or SoC plus administration of lopinavir/ritonavir in association with interferon ß1a			Lopinavir/ritonavir for 14 days Interferon ß–1a day 1, day 3, day 6 or until discharge (after at least two doses)				
Or SoC plus administration of remdesivir			Daily administration until discharge (after at least 5 days) or day 10				
Or SoC plus administration of hydroxychloroquine			Daily administration until day 10				
Study procedures							
Vital signs including SpO_2		X	X	Daily until discharge	X	X	
Clinical data collection		X	X	Daily until discharge	X	X	X
Electrocardiogram (EKG)‡	X			Days 3, 5 and 8			
Medication review	X		X	Daily until discharge	X	X	
Adverse event evaluation			X	Daily until discharge	X	X	X
Safety laboratory							
Safety haematology, chemistry and liver tests	X§		X¶	Days 3, 5, 8 and 11 (all ±1 day)	X	X	
Pregnancy test for females of childbearing potential	X§				X	X	
Plasma concentration of lopinavir			X	Days 3, 6, 8 and 11 (all ±1 day)			
Plasma concentration of hydroxychloroquine			X	Days 3, 5, 8 and 11 (all ±1 day)			
Plasma and intracellular concentration of remdesivir			X	Days 2, 5 and 8 if hospitalised			
Plasma concentration of interferon ß–1a				Days 3 to 6 if hospitalised			
Research laboratory							
Biobank (whole blood and plasma)**		X**		Days 3, 5, 8 and 11 (all ±1 day)	X	X	
Plasma for PCR SARS-CoV-2††		X		Day 3, 5, 8 and 11 (all ±1 day)			
Nasopharyngeal swab or lower respiratory tract samples††		X		Day 3, 5, 8 and 11 (all ±1 day)	X	X	
Thoracic CT scan or chest X-ray		X		Day 8 (±1 day)	X	X	
Whole blood for genetic analysis		X					

*Baseline assessments should be performed prior to study drug administration.
†If discharged from the hospital, visits and safety assessments are conducted in the outpatient setting.
‡An electrocardiogram (EKG) with calculation of the corrected QT (Fridericia formula) is reviewed at screening and monitored at Day 3, 5 and 8 in patients treated with hydroxychloroquine.
§Laboratory tests performed in the 48 hours prior to enrolment are accepted for determination of eligibility.
¶Any laboratory tests performed in the 24 hours before randomisation can be used for baseline and Day 1.
**For the biobank, whole blood is only collected at baseline.
††For each sample, the viral load is measured by a specific SARS-COV-2 real-time (RT)-PCR and normalised according the number of cells in each sample. This method is validated to monitor viral load kinetics over time and expressed in standardised unit log of number of viral copies/10 000 cells.
D, day.

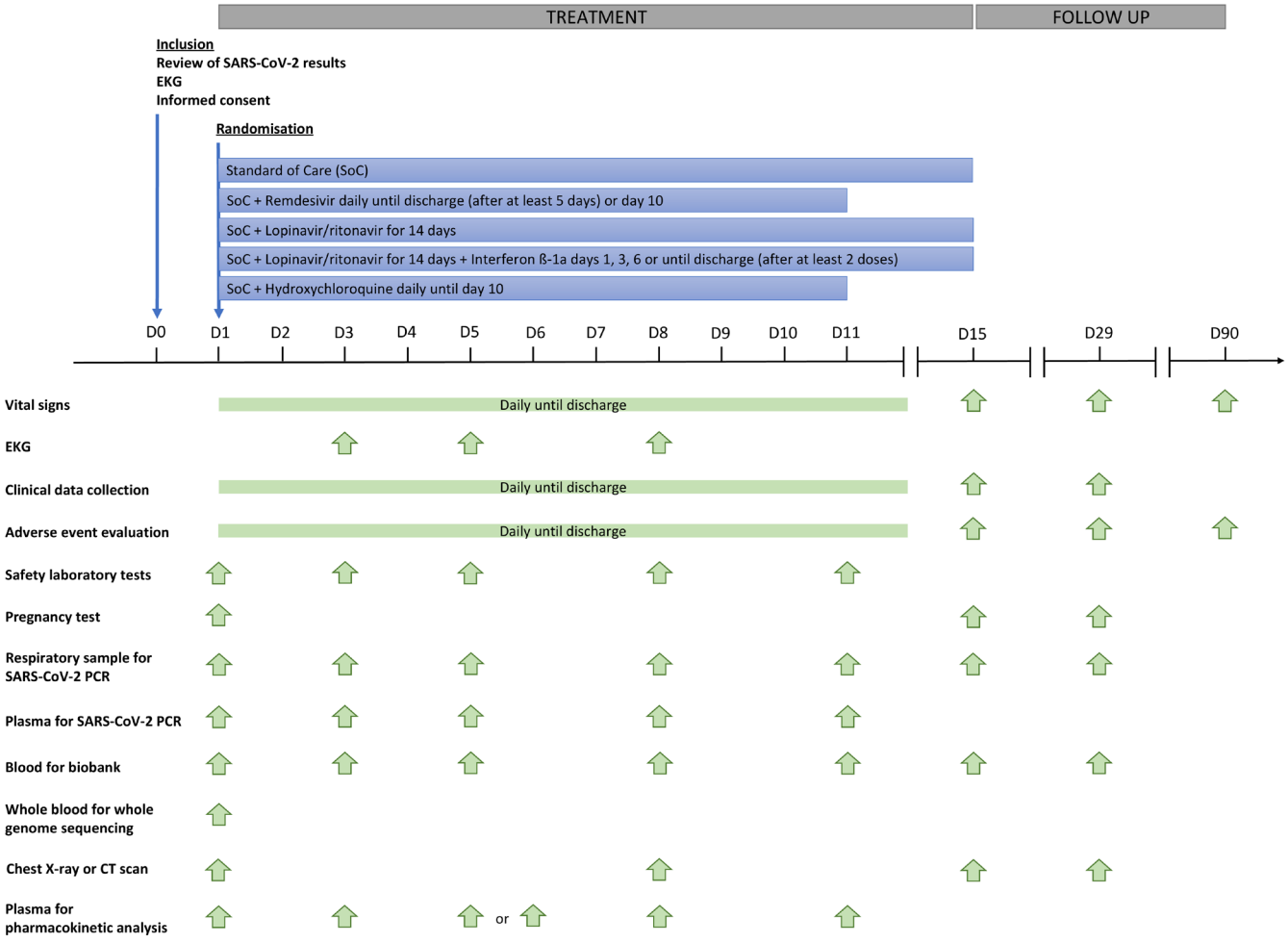

Figure 2 Schematic representation of the experimental design of the DisCoVeRy clinical trial. D, day.

For the scores 1 and 2, limitation of the activities refers to the pre-COVID-19 clinical status, in order to take into account potential pre-existing limitations.

Secondary endpoints

Secondary endpoints are classified as efficacy or safety endpoints.

Efficacy secondary endpoints

1. 7-point ordinal scale
   - Time to an improvement of one category from admission on the ordinal scale.
   - Subject clinical status on the ordinal scale on Days 3, 5, 8, 11 and 29.
   - Mean change in the ranking on the ordinal scale from baseline to Days 3, 5, 8, 11, 15 and 29 from baseline.
2. National Early Warning Score (NEWS)
   - The time to discharge or to a NEWS of ≤2 and maintained for 24 hours, whichever occurs first.
   - Change from baseline to Days 3, 5, 8, 11, 15 and 29 in NEWS.
3. Oxygenation
   - Oxygenation free days in the first 28 days (to Day 29).
   - Incidence and duration of new oxygen use, non-invasive ventilation or high flow oxygen devices during the study.
4. Mechanical ventilation
   - Ventilator free days in the first 28 days (to Day 29).
   - Incidence and duration of new mechanical ventilation use during the study.
5. Hospitalisation
   - Duration of hospitalisation (days).
6. Mortality
   - In-hospital mortality.
   - 28-day mortality.
   - 90-day mortality.

Safety secondary endpoints

1. Cumulative incidence of any grade 3 and 4 adverse events;
2. Cumulative incidence of any serious adverse event;
3. Proportion of patients with a premature discontinuation or temporary suspension of the study drug, for any reason;
4. Grade changes in biological parameters, as measured using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (white

cell count, haemoglobin, platelets, creatinine, blood electrolytes (including kaliemia), prothrombin time and international normalised ratio, glucose, total bilirubin, ALT, and AST) over time.

Exploratory endpoints

1. Qualitative and quantitative PCR for SARS-CoV-2 normalised according to the number of sample cells in nasopharyngeal or lower respiratory tract samples on days 1, 3, 5, 8, 11, 15 and 29;
2. Qualitative and quantitative PCR for SARS-CoV-2 in blood on days 1, 3, 5, 8 and 11;
3. Development of resistance of SARS-CoV-2 in nasopharyngeal or lower respiratory tract samples at days 3, 5, 8, 11, 15 and 29;
4. Whole genome sequencing of participants to identify genetic variants associated with (1) the development of severe clinical disease and (2) the response in terms of safety and efficacy to investigational antiviral drugs;
5. Imagery assessment through chest X-ray or thoracic CT scan on days 1, 8, 15 and 29, depending on availability in centre;
6. Study drugs concentrations, sampled while the participant is hospitalised:
   - For remdesivir, as assessed by plasma concentration after the end of infusion on day 1, trough plasma and intracellular concentrations before the second dose administration on day 2, and trough plasma concentration on days 5 and 8;
   - For lopinavir, peak plasma concentration measured 4 hours after the first administration and trough plasma concentrations measured just before the second administration and on days 3, 6, 8 and 11;
   - For IFN ß–1-a, trough plasma concentration on days 3 and 6;
   - For hydroxychloroquine, peak plasma concentration measured 4 hours after the first administration and trough plasma concentrations measured just before the second administration and on days 3, 5, 8 and 11.

Data collection

The trial is conducted in accordance with relevant regulations and standard operating procedures, including data protection. The data are collected on an electronic case report form. Clinical site monitoring is conducted to ensure that the rights are protected and confirm the integrity of collected data. The persons responsible for the quality control of the data take all necessary precautions to ensure the confidentiality of information regarding investigational medicinal products, the trial, trial participants and in particular the identity of the participants and the results obtained.

Safety and adverse events monitoring

All adverse events are collected regardless of their grade of severity. The choice of continuing therapy is at the discretion of the investigator. All adverse events are classified in grades from mild (grade 1) to life threatening (grade 4) following the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (V.2.1 of July 2017) of the National Institute of Health and National Institute of Allergy and Infectious Diseases of the US Department of Health and Human Services.

Statistical considerations

General considerations

Continuous variables will be summarised by the mean, SD, median, IQR, minimum and maximum. The change from baseline will be compared using Student's t-test or a Wilcoxon-Mann-Whitney test if the normality assumption does not hold.

Categorical data will be summarised with the number and proportion of patients. Data will be compared using ORs and a Fisher's exact test.

All statistical tests will be two-sided with type I error of 0.05. As there are four comparisons, each treatment group will be compared with the control group with a two-sided type I error of 0.0125. Subgroup analyses for the primary and secondary endpoints will evaluate the treatment effect across the following subgroups: disease severity at inclusion, geographical region, duration of symptoms prior to enrolment, age and sex. A forest plot will display CIs across subgroups. Interaction tests will be conducted to determine whether the effect of treatment varies by subgroup.

Sample size computation

A sample size of 3100 patients (620 patients per arm) is targeted. The sample size was determined assuming the following scenario under standard of care for each item of the ordinal scale: 1: 42%, 2: 38%, 3: 8%, 4: 7%, 5: 2%, 6: 1% and 7: 2%.

There is significant uncertainty with these assumptions given the limited data available. Since a large proportion of patients are moderately ill patients, we power the study for an OR of 1.5 (an OR higher than 1 indicates superiority of the experimental treatment over the control for each ordinal scale category), with 90% power and using an overall one-sided type I error rate of 0.05.[32] Adjusting for multiplicity of four pairwise comparisons with the control arm in a 5-arm setting, the (one-sided) false positive error rate would be 0.00625, (which requires achieving two-sided p=0.0125). The samples size might evolve whenever any treatment arm is withdrawn or added to the trial.

Definition of analysis sets

The intention-to-treat population is defined as all randomised patients, where patients are analysed in their randomisation group whether they have or not followed the allocated treatment. The modified intention-to-treat population is defined as all randomised patients who did receive at least one dose of the allocated treatment.

The primary and efficacy secondary analysis will be conducted on the intention-to-treat population. Safety

analyses will be based on the modified intention-to-treat population.

Adaptive design

This study is intended to allow for adaptations with the ability to add a new experimental arm if one becomes available. The current plan is to evaluate the primary endpoint on day 15. If additional data become available to add an experimental therapy, analyses of experimental arms will be performed comparing concurrently enrolled control subjects. If one treatment crosses an efficacy stopping boundary, this treatment may become the new control arm for comparisons. This approach was used in the recent PALM Ebola therapy randomised clinical trial.[33]

Interim analyses

Interim analyses will be by the independent statistician of the DSMB. There are no formal stopping rules for efficacy or safety. The DSMB will make recommendations taking into consideration the totality of the evidence from the efficacy and safety outcomes as they accumulate, as well as external evidence.

For efficacy, the statistical analysis will be done on the primary endpoint, the 7-point ordinal scale at 15 days, and be based on the Haybittle-Peto rule.[34 35] That is, if any active treatment is superior to control at $p<0.001$ then consideration will be given to stopping early for efficacy. This would have major implications; hence the stopping boundary is stringent in the spirit of requiring proof beyond reasonable doubt.

For futility, that is, stopping because an active treatment appears ineffective, the statistical analysis will be done with the primary endpoint. Comparing an active treatment with control, if the upper 95% confidence limit for the common OR is less than 1.25 then consideration be given to stopping that treatment for futility. All the above is intended for all randomised patients. Analyses will be stratified by baseline severity of disease. For safety, no pre-specify stopping guideline will be defined because there are various aspects of potential harm that could be studied. However, to allow for some caution, any safety signal on serious adverse event, that is, active treatment worse than control, requires $p<0.01$ to merit consideration of stopping that treatment arm.

Final analysis of the primary endpoint

The primary outcome uses a 7-point ordinal scale analysed using a proportional odds model. This model assumes that the treatment to control OR of being classified in a given severity category 'i' or better is the same for each category. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the control and experimental treatment arms (ie, whether the common OR differs is 1). ORs are then interpreted as the odds of being 'lower' or 'higher' on the ordinal scale across the entire range of the scale. The hypothesis test is, for large sample sizes, nearly the same as the Wilcoxon rank-sum test. Therefore, the procedure produces a valid p value regardless of whether the proportional odds model is correct. Nonetheless, estimation and CIs do require the model to be correct. Accordingly, we will evaluate model fit using a goodness-of-fit likelihood ratio test. The validity of the proportionality assumption will be evaluated and tested. To deal with potential missing data, the last observation will be carried forward until the next available value.

Analysis of secondary endpoints

Differences in time-to-event endpoints by treatment will be summarised with Kaplan-Meier curves and 95% CI; and cumulative incidence plots, for time-to-event endpoints with competing risk (eg, death). Duration of event will be summarised according to median days with quartiles. Incidence data will be summarised as percent with 95% CI. Time-to-event endpoints will be compared using the log-rank test. For time-to-event endpoints with a competing risk Fine and Gray models will be used. All tests will be stratified by the baseline severity.

Committees for the research

The DisCoVeRy French Trial Management Team has developed and implemented the protocol in France (online supplemental file). A DisCoVeRy European Steering Committee has been constituted to serve as the governance organ for the trial. It provides the overall supervision of the trial, including for the relations with European stakeholders, the Steering Committee and the Executive Committee of the Solidarity trial (see below). It ensures that the trial is conducted in accordance with ethical principles and respects participants' safety, take any decision on any changes made to the design of the DisCoVeRy trial, and on the reporting of the trial results, including regarding the publication policy.

An international independent DSMB has been constituted to preserve the interests of trial participants, to monitor the main outcome measures (including safety and efficacy) and to monitor the overall conduct of the trial. Based on interim analyses of the data, it will make recommendations about early study closure or changes to the trial, including adding or removing treatment arms. The DSMB will meet after 100 participants are included into the study, and then every 200 new patients are included, with a maximum of one DSMB meeting per week. Other ad hoc reviews will be undertaken if there are specific safety concerns. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews.

Intertwinement with WHO Solidarity programme

Since 5 April 2020, DisCoVeRy has been an add-on trial of the Solidarity programme conducted by the WHO in Europe and worldwide. The same treatments are evaluated in DisCoVeRy and in Solidarity. Solidarity has three endpoints which are also secondary endpoints of

DisCoVeRy: (1) mortality during hospitalisation (the primary endpoint of Solidarity), (2) length of hospital stay and (3) time to mechanical ventilation or transfer to intensive care. At each DisCoVeRy DSMB meeting, the recommendations will be transmitted to the Data and Safety Monitoring Committee of Solidarity. The Executive Committee of Solidarity will ultimately issue recommendations on the different treatments evaluated, allowing a unique communication on each of the treatments evaluated.

Patient and public involvement

No patients were involved in the design or implementation of this study.

ETHICS AND DISSEMINATION

Ethics approval

Inserm is the sponsor of DisCoVeRy in Europe. Ethical approval was first obtained in France from the institutional review board on 13 March 2020 (Comité de Protection des Personnes Ile de France 3, approval number 20.03.06.51744), and the trial received approval by the French National Agency for Medicines and Health Products (ANSM) on 9 March 2020. The protocol described in this article is the V.7.0 of the DisCoVeRy protocol approved on 5 April 2020. Any substantial amendment made to the protocol by the coordinating investigator is sent to local ethics committee and health authorities in each country for approval, prior to implementation. The sponsor shall have the right to audit any centre participating in the study and may appoint an auditor to carry out such an audit. Such right to audit shall include access to all relevant documents and other information relating to the clinical trial. If the sponsor decides to audit the trial, only one audit will be performed

Informed consent

Prior to any act carried out as part of the research, subjects receive a concise and focussed presentation of key information about the clinical trial, verbally and with a written consent form. An emergency consent procedure with the legal guardian or relatives of the patient has been put in place for patients who are unable to consent. The informed consent form of the study contains information's about possible data sharing and biological specimens sharing for ancillary studies. Participants are also provided with a link to a website where they can find all information about data sharing. The forms have been reviewed by the ethics committee that authorised the trial.

Dissemination

Results will be communicated at scientific meetings and submitted for publication in peer-reviewed journals. According to the information sheet, participants will be informed of the overall results at the end of the trial. In addition, participants are informed of the discontinuation of a treatment arm in the trial after validation by the ethics committee.

DISCUSSION

Strengths and limitations of the DisCoVeRy trial design

The DisCoVeRy clinical trial is a randomised, open clinical trial that aims to evaluate the safety and efficacy of possible therapeutic agents in hospitalised adult patients diagnosed with COVID-19. The design of DisCoVeRy is adaptive meaning that it can adapt to the ongoing production of evidence and to interim analyses by discontinuing arms that are proved inferior to others, selecting an existing arm as the standard of care if proved superior to others and adding arms if new candidate therapeutic strategies emerge.

As detailed above, DisCoVeRy is an add-on trial of the Solidarity trial, conducted under the aegis of the WHO in Europe and worldwide. Sharing the data from DisCoVeRy relevant to the Solidarity trial (inclusion data and data related to the Solidarity endpoints) increases the number of participants for whom this data is available and thus leads to a faster conclusion on the effectiveness, deleterious effect or ineffectiveness of the treatments evaluated. Inclusion in a same strategy of hospitalised patients with severe (patients requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical ventilation or ECMO) or moderate disease will allow to evaluate the different drug candidates in different clinical situations. Moreover, by including patients at different times in their clinical history of COVID-19, we will be able to study when is the best time to start an antiviral agent in relation to the delay of symptoms. The collection of samples for pharmacological monitoring, viral kinetics and medical imaging will provide crucial data to analyse the pharmacokinetics/pharmacodynamics (PK/PD) of evaluated drugs and the effect of treatment on the virological and radiological evolution. A biobank has also been planned to conduct further analyses that still remain to be determined. However, DisCoVeRy will not provide data on treatments for COVID-19 at an early phase, before there is a need for hospitalisation. As only antiviral agents are evaluated in DisCoVeRy, we will not be able to evaluate the efficacy of immunomodulatory agents, including corticosteroids.

Strengths and limitations of real-time interventional research in the setting of a pandemic

DisCoVeRy is not a placebo-controlled trial and is not double-blind because of the complexity of blinding treatments with different mode of administration (intravenous, subcutaneous or oral) and the need to initiate the trial very rapidly. Moreover, in a recent meta-epidemiological study, no evidence was found that lack of blinding of patients, healthcare providers or outcome assessors had an impact on effect estimates in randomised clinical trials.[36]

Integrating clinical trials of experimental therapeutics is an increasingly recognised part of the response during infectious disease outbreaks. Since the Ebola outbreak in West Africa and subsequent outbreaks in the Democratic Republic of Congo, clinical trials of investigative drugs have been fully integrated in the epidemic response.[37–39] Implementing large clinical trial is both direly needed and particularly challenging during a pandemic. Indeed, the pandemic context compels us to organise clinical trials urgently while keeping methodological requirements of the highest level which is the only way to provide reliable answers for clinicians. The selection of the best candidate drugs for a new outbreak is a major challenge and a strength of the DisCoVeRy trial is that its adaptive design allows to add new arms if good evidence emerges while the trial is continuing that some other treatment(s) should also be evaluated. There have been controversies regarding the candidate treatments that should be selected for COVID-19 clinical trials and notably regarding hydroxychloroquine. Hydroxychloroquine was identified at the beginning of the pandemic as a candidate treatment based on preliminary data and quickly became the most tested treatment in the world for COVID-19.[40 41] However, many of the articles supporting hydroxychloroquine suffered from methodological shortcomings and were in fact non-informative.[42] Hydroxychloroquine has been widely promoted as soon as February 2020 as an effective drug by some scientists and politics,[43] leading to difficulties in recruiting patients in randomised clinical trials such as DisCoVeRy.[44] This is why the ever-changing scientific background supporting the use of each candidate treatment should be clear, detailed and regularly updated and pragmatic, adaptive clinical trials should be encouraged. Transparency, consistency and quality of design are more crucial than ever during pandemics to provide relevant and reliable data.

TRIAL STATUS

This trial has begun on 22 March 2020. On 28 July 2020, 801 patients have been included.

DATA SHARING PLAN

Study protocol and statistical analysis plan will be openly available. Systematic individual patient data sharing is not intended, but all requests for the trial's data will be considered by the French DisCoVeRy Trial Management Team.

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REFERENCES

1 Drosten C, Günther S, Preiser W, *et al*. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003;348:1967–76.
2 Ksiazek TG, Erdman D, Goldsmith CS, *et al*. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003;348:1953–66.
3 Zaki AM, van Boheemen S, Bestebroer TM, *et al*. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012;367:1814–20.
4 World Health Organization. WHO characterizes COVID-19 as a pandemic, 2020. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen [Accessed 14 Mar 2020].
5 World Health Organization. WHO R&D blueprint novel coronavirus COVID-19 therapeutic trial synopsis, 2020. Available: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf [Accessed 10 Mar 2020].
6 Lê MP, Peiffer-Smadja N, Guedj J, *et al*. Rationale of a loading dose initiation for hydroxychloroquine treatment in COVID-19 infection in the discovery trial. *J Antimicrob Chemother*.
7 Lo MK, Jordan R, Arvey A, *et al*. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and paramyxoviruses. *Sci Rep* 2017;7:43395.
8 Lo MK, Feldmann F, Gary JM, *et al*. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. *Sci Transl Med* 2019;11. doi:10.1126/scitranslmed.aau9242. [Epub ahead of print: 29 May 2019].
9 Warren TK, Jordan R, Lo MK, *et al*. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* 2016;531:381–5.
10 Sheahan TP, Sims AC, Graham RL, *et al*. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* 2017;9:eaal3653.
11 Wang M, Cao R, Zhang L, *et al*. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–71.
12 Williamson BN, Feldmann F, Schwarz B, *et al*. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature* 2020;7.
13 Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the treatment of Covid-19 - preliminary report. *N Engl J Med* 2020;NEJMoa2007764.
14 Groneberg DA, Poutanen SM, Low DE, *et al*. Treatment and vaccines for severe acute respiratory syndrome. *Lancet Infect Dis* 2005;5:147–55.
15 Liu X, Wang X-J. Potential inhibitors for 2019-nCoV coronavirus M protease from clinically approved medicines. *bioRxiv* 2020.
16 Cao B, Wang Y, Wen D, *et al*. A trial of Lopinavir-Ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382:1787–99.
17 Stockman LJ, Bellamy R, Garner P. Sars: systematic review of treatment effects. *PLoS Med* 2006;3:e343.
18 Sheahan TP, Sims AC, Leist SR, *et al*. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020;11:222.
19 Chan JF-W, Yao Y, Yeung M-L, *et al*. Treatment with Lopinavir/Ritonavir or Interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis* 2015;212:1904–13.
20 Arabi YM, Alothman A, Balkhy HH, *et al*. Treatment of middle East respiratory syndrome with a combination of lopinavir-ritonavir and interferon-β1b (miracle trial): study protocol for a randomized controlled trial. *Trials* 2018;19:81.
21 Lokugamage KG, Hage A, Schindewolf C, *et al*. SARS-CoV-2 is sensitive to type I interferon pretreatment. *bioRxiv*2020.
22 Sallard E, Lescure F-X, Yazdanpanah Y, *et al*. Type 1 interferons as a potential treatment against COVID-19. *Antiviral Res* 2020;178:104791.
23 Hung IF-N, Lung K-C, Tso EY-K, *et al*. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020;395:1695–704.
24 Miller DK, Lenard J, Antihistaminics LJ. Antihistaminics, local anesthetics, and other amines as antiviral agents. *Proc Natl Acad Sci U S A* 1981;78:3605–9.
25 Keyaerts E, Vijgen L, Maes P, *et al*. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochem Biophys Res Commun* 2004;323:264–8.
26 Touret F, de Lamballerie X. Of chloroquine and COVID-19. *Antiviral Res* 2020;177:104762.
27 Liu J, Cao R, Xu M, *et al*. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020;6:16.
28 Taccone FS, Gorham J, Vincent J-L. Hydroxychloroquine in the management of critically ill patients with COVID-19: the need for an evidence base. *Lancet Respir Med* 2020;8:539–41.
29 Geleris J, Sun Y, Platt J, *et al*. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020;382:2411–8.
30 Boulware DR, Pullen MF, Bangdiwala AS, *et al*. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med* 2020;383:517–25.
31 Etievant S, Bal A, Escuret V, *et al*. Performance assessment of SARS-CoV-2 PCR assays developed by who referral laboratories. *J Clin Med* 2020;9:1871.
32 Whitehead J. Sample size calculations for ordered categorical data. *Stat Med* 1993;12:2257–71.
33 Mulangu S, Dodd LE, Davey RT, *et al*. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019;381:2293–303.
34 Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971;44:793–7.
35 Peto R, Pike MC, Armitage P, *et al*. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976;34:585–612.
36 Moustgaard H, Clayton GL, Jones HE, *et al*. Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study. *BMJ* 2020;51:l6802.
37 Nakkazi E. Randomised controlled trial begins for Ebola therapeutics. *Lancet* 2018;392:2338.
38 Sissoko D, Laouenan C, Folkesson E, *et al*. Experimental treatment with Favipiravir for Ebola virus disease (the JIKI trial): a historically controlled, single-arm proof-of-concept trial in guinea. *PLoS Med* 2016;13:e1001967.
39 Fallah MP, Skrip LA. Ebola therapies: an unconventionally calculated risk. *Lancet* 2019;393:850–2.
40 Fragkou PC, Belhadi D, Peiffer-Smadja N, *et al*. Review of trials currently testing treatment and prevention of COVID-19. *Clin Microbiol Infect* 2020;26:988–98.
41 Peiffer-Smadja N, Lescure F-X, Sallard E, *et al*. Anticovid, a comprehensive open-access real-time platform of registered clinical studies for COVID-19. *J Antimicrob Chemother*.
42 Peiffer-Smadja N, Costagliola D. RE: early outpatient treatment of symptomatic, high-risk COVID-19 patients that should be RAMPED-UP immediately as key to the pandemic crisis. *Am J Epidemiol* 2020. doi:10.1093/aje/kwaa151. [Epub ahead of print: 20 Jul 2020].
43 Sattui SE, Liew JW, Graef ER, *et al*. Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19. *Expert Rev Clin Immunol* 2020:1–8.
44 Laurent L. We've lost time in the race for a Covid-19 cure. Washington Post, 2020. Available: https://www.washingtonpost.com/business/weve-losttime-in-the-race-for-a-covid-19-cure/2020/04/29/78dff872-89df-11ea-80df-d24b35a568ae_story.html [Accessed 24 Jul 2020].