What makes the UK Recovery trial more pragmatic than the European Discovery trial?

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Abstract

Objective: The objective of this study was to review the study design and preliminary results of the Recovery trial and analyze the implementability of the Recovery trial by comparing it with the European Discovery trial.

Method: The study design of the Recovery trial in the latest version of protocol was described and deeply analyzed to address the issue of implementation of the trial. A comparative analysis of study design and implementation between the UK Recovery trial and the European Discovery trial was conducted following the description.

Results: The Recovery trial is a pragmatic, randomized, controlled, adaptive, open-label clinical trial. The study design of the Recovery trial was reported in the ISRCTN registry, the EU Clinical Trials Register and the U.S. National Library of Medicine ClinicalTrials.gov registry. Initially published on the 13th March 2020, the study protocol of the Recovery trial has been updated five times at the time of this writing. More than 11,000 patients have been enrolled and 80% have completed the follow-up. Thousands of health care professionals at 175 Trusts in the UK have been involved.

Conclusion: The Recovery trial applies a study design to address the issue of implementation in the context of the COVID-19 pandemic and emergency. It was conceptually pragmatic with a clear vision to address the top priority: the control of mortality and rational use of scarce resources. By contrast, the Discovery trial was designed as an intellectual exercise and consequently failed to address the issue of implementation in emergency.

Keywords:

Introduction

First reported in late December 2019 in China, a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had caused a pandemic coronavirus disease 2019 (COVID-19) within three months [1]. Thus far, there are numbers of possible therapeutic agents available for COVID-19, but no treatment with proved efficacy exits.

As of 4 June 2020, there have been more than 3,000 trials registered in the Chinese Clinical Trial Registry (CHICTR), the European Clinical trial registry, the U.S. National Library of Medicine ClinicalTrials.gov, and the World Health Organization (WHO)'s International Clinical Trials Registry Platform (ICTRP), as well as others, to test potential therapies which may improve outcomes in COVID-19 patients [2]. A multinational adaptive clinical trial called the Solidarity trial was launched by WHO on 18th March 2020, to compare the efficacy and safety of remdesivir, lopinavir/ritonavir, lopinavir/ritonavir with interferon β-1α and hydroxychloroquine (HCQ) with standard of care (SoC) in COVID-19 patients [3]. France started a European adaptive clinical trial, named the Discovery trial, to assess the four identical experiment treatments against COVID-19, which will be complemented as part of the Solidarity trial [4]. Inspired by the Solidarity trial, the UK also set up another adaptive trial called Recovery to evaluate several possible treatments, including lopinavir/ritonavir, low-dose dexamethasone, HCQ, azithromycin, tocilizumab and convalescent plasma in the latest version of clinical trial protocol [5]. The objective of this study was to review the study design and preliminary results of the Recovery trial and analyze the implementability of the Recovery trial by comparing it with the European Discovery trial.

Methods

The study design of the Recovery trial in the latest version of protocol was described and deeply analyzed to address the issue of implementation of the trial, including study objective, timeline, population, sample size, interventions, randomization, endpoints, status and preliminary results. A comparative analysis of study design and implementation between the UK Recovery trial and the European Discovery trial [6] was conducted following the description.

Result

The Recovery trial is a pragmatic, randomized, controlled, adaptive, open-label clinical trial.

The study design of the Recovery trial was reported in the ISRCTN registry [7], the EU Clinical Trials Register [8] and the U.S. National Library of Medicine ClinicalTrials.gov registry [9]. The study design of the UK Recovery trial in the protocol of the latest version [10] is presented in Table 1 and compared with that of the European Discovery trial [6].

Study objective

The Recovery trial aims to provide information to support fast decision making in the context of an emergency where no evidence is robust enough to guide the national and global therapeutic strategy of COVID-19.

Timelines

The trial was reported to launch on 19th March 2020, and the primary completion date of the trial was estimated to be December 2020.

Population and sample size

The following group of patients were included: hospitalized at any time with proven or clinically suspected COVID-19, which could be confirmed after inclusion, and patients who would not be put at risk during the study.

Intervention and randomization

The initial interventions include lopinavir-ritonavir in combination, HCQ, low-dose corticosteroids, and azithromycin, which are given in addition to SoC. Optional treatment of tocilizumab for patients with progressive COVID-19 was introduced in the 4th amendment of the trial protocol [10] and convalescent plasma was introduced as an additional treatment arm in the 6th amendment of the trial protocol [10].

All interventions to be tested were advised by the UK New and Emergent Respiratory Virus Threat Advisory Group (NERVTAG).

A complex randomization is implemented with a first randomization in two parts based on a factorial design and an optional second randomization for patients with progressive COVID-19. The first randomization of part A is performed between, no additional treatment, lopinavir/ritonavir, HCQ, low-dose corticosteroids, and azithromycin. The first randomization of part B is simultaneously performed between convalescent plasma versus and no additional treatment. The second randomization is then performed optionally between tocilizumab and no additional treatment for patients with markers of systemic inflammation.

Endpoints

Endpoints in the Recovery trial are driven by an emergent request of reducing mortality, hospitalization, and recourse to ventilation.

All endpoints are reported at day 28 and eventually up to 6 months after randomization in the primary analysis. A longer-term follow-up will be sought potentially up to 10 years through linkage to electronic healthcare records.

All-cause mortality at day 28 is the primary endpoint.

Three secondary endpoints are collected, including duration of hospital stays, proportion of patient ventilated and duration of ventilation, and a composite endpoint of ventilation and death deducted from the secondary endpoints.

Two other endpoints are collected, including the proportion of patient requiring renal replacement and development of new cardiac arrhythmia.

Status and preliminary results

Initially published on the 13th March 2020, the study protocol of the Recovery trial has been updated five times at the time of this writing [10]. The major changes in the five updated versions compared to the initial version were presented in Table 1. After just nine days from the initial agreement set up on the 13th March of 2020, the first patient was recruited. The HCQ arm was added in the 2nd amendment on 21th March, the azithromycin arm was added and primary outcome was changed from in-hospital death to death within 28 days after randomization in the 3rd amendment on 7th April, a second randomization to tocilizumab versus SoC among patients with progressive COVID-19 was added in the 4th amendment on 14 April, children were added to the study population in the 5th amendment on 24th April, and the

convalescent plasma arm was added in the 6th amendment on 14th May. Moreover, the HCQ arm was stopped for enrolling participants based on the preliminary results on 5 June. On the 5th June 2020, the preliminary results of the Recovery trial were published in a press release [11]. More than 11,000 patients have been enrolled and 80% have completed the follow-up. Thousands of health care professionals at 175 Trusts in the UK have been involved.

The independent Data Monitoring Committee reviewed the results in the HCQ arm of 1,542 patients versus the SoC arm of 3,112 patients. The borderline significance of HCQ in the primary endpoint of 28-day mortality was reported with a rate ratio of 1.11 (95% Confidence interval 0.98-1.26). As around 20% of patients are still on treatment (300 patients for the HCQ arm and 600 patients for the SoC arm), the results may become statistically significant with the sample still on treatment. No additional benefit of HCQ in the secondary endpoints was shown.

Discussion

Study design and implementation of the Recovery trial

Unlike the Discovery trial, the Recovery trial is not connected to the Solidarity trial advised by the WHO expert group, even though they are similar types of study and future combination of data of two trials have been suggested to deal with the potential heterogeneity between populations in the Recovery trial protocol.

Adopting a pragmatic attitude, the UK simplifies the study procedures in an informed consent, patient enrolment, randomization, data entry and collection of follow-up information to ensure overloaded hospitals can contribute to the study and achieve critical outcomes, including mortality, at the earliest.

As an adaptive, randomized, open-label clinical trial, the Recovery trial is in line with all the trials derived from Solidarity, allowing to adjust the number of treatment arms based on the new information or the preliminary results. However, the Recovery trial is more pragmatic compared with several other Solidarity national or regional customized trials.

Adaptive design

The Recovery trial is flexible and pragmatic because of patient enrolment via the internet with limited inclusion/exclusion criteria, the possibility to adjust the investigational drugs based on the local context, and the simplified way to collect outcomes at a single timepoint by contacting participants in person, by phone or by review of medical records. Ancillary studies piggybacked onto the main trial make it possible that any additional valuable data will be collected. Initially launched on the 13th March 2020, the Recovery trial has published five substantial amendments, showing the high flexibility and the implementability of the conduct of the trial.

Population and sample size

The range of the included population is broad. Together with the pragmatic design, it obviously favors external validity over internal validity. In a situation of the pandemic, the external validity supports the generalizability of the results, which is critical for decision making in an emergency.

The sample size was considered to be around 12,000 patients, but the protocol clearly states that there are too many uncertainties to set a sample size at the start of the trial and adjustments may be done based on the results of milestone analysis, evolution of the pandemic or other factors.

Interventions and randomization

The randomization is complex in terms of the factorial design, but in practice the procedure is very simple and centralized for the investigators.

The later introduction of new interventions, including convalescent plasma and discontinuation of HCQ, proves that the management of patients in the UK is well organized and the emerging therapies with an unproven benefit is well monitored and rapidly introduced in the trial to generate knowledge on efficacy. This avoids wide uncontrolled use of unproven benefit therapies.

Remdesivir, as well as interferon, was not considered in the Recovery trial. Remdesivir is a branded product with a lot of ongoing trials conducted by the manufacturer. Therefore, it may be less meaningful that a publicly funded study engages in the assessment of remdesivir in parallel. Results will be made available by the manufacturer. Products with potential efficacy and low costs appear to be the decision driver from the perspective of a public healthcare organization. However, patients who are already receiving remdesivir can still be recruited into the Recovery trial since remdesivir has no known drug-drug interactions with one of the Recovery treatments [12]. The decision not to introduce interferon is wise since it had been already reported by several Chinese studies that the cytokine storm was a major issue in the progression of COVID-19 [13, 14] and interferon had not been proven to address the issue of inflammation in such case. Tocilizumab was already approved for controlling cytokine storm in patients receiving CAR-T cells [15, 16] and improved the clinical outcome in severe and critical COVID-19 patients, as reported by a Chinese retrospective study of a small sample size [17]. Except for tocilizumab, all relevant products have lost patent protection and data protection in the UK, making them easy to produce, access and cheap treatment options in case they prove to be effective.

The Recovery trial has proven to be a true adaptive study in practice with several adaptive changes in accordance with their protocol.

Endpoints

Endpoints are simple, easy to capture, straight and match a policy decision maker's expectation.

The collection of simple and straight endpoints and a long-term follow-up via electronic records in the Recovery trial make it possible to perform ancillary studies piggybacked onto the main trial by using any relevant information collected at different centers. This again offers flexibility to investigators willing to investigate more topics.

Status and preliminary results

The preliminary results of the Recovery trial released on the 5 June 2020 proved no significant efficacy of HCQ for the treatment of COVID-19.

Although more information is still needed to deeply scrutinize the results, it is the first time that a well conducted clinical trial brings likely robust evidence to support a clear decision-making that HCQ should not be used for hospitalized COVID-19 patients. The patients' profile and the statistical analysis in the trial will be critical to inform the decision-making.

Comparison between the Discovery trial and the Recovery trial

As part of the Solidarity trial program, the Discovery trial is a satellite European trial launched by France. While initially committed to participating in the European Discovery trial, the UK launched the Recovery

trial by themselves to address simple and straight questions: the impact of treatments on mortality, the length of hospitalization and the use of ventilators.

Study design

The primary endpoint in the Discovery trial is the severity rating on a 7-point ordinal scale at day 15, which is complex. The primary endpoint in the Recovery trial, however, is the simple and straight binary rate of mortality. The Discovery trial collected 23 secondary endpoints and five other endpoints at different timepoints repeatedly, eventually leaving more than 100 endpoints to be collected by overloaded healthcare professionals with little or no support. By contrast, three secondary endpoints including a composite one and two other endpoints were collected in the Recovery trial at day 28 and at month 6. The duration of follow-up is 90 days in the Discovery trial and 28 days in the Recovery trial with a longer-term follow-up via an electronic database.

The interventions tested in the Discovery trial replicate the ones proposed by WHO and ignore azithromycin, which may be effective, and tocilizumab, which are effective in controlling cytokine storm. However, testing remdesivir at the time when there was no scientific evidence to believe it may work and that it was still in patent protection, raises the concern of a lack of consideration from the perspective of a public healthcare organization. Also, as the manufacturer of remdesivir was launching trials to test the value of remdesivir, it would be reasonable to wait for the results of the several manufacturers' trials. But from the perspective of academic research, the situation may be different.

HCQ has received lots of attention and has been through an initial exclusion, addition of inclusion and eventual suspension in both the Discovery trial and the Recovery trial. The principal investigators in the Discovery trial were apparently influenced by the French Divided Scientific Community and took against HCQ. Following the high-level mediation, HCQ was later included in the Discovery trial [18-20]. While the French scientific community was divided in the discussions based on the intimate conviction and limited data, the British medical community united behind a joint statement of the Chief Medical Officers of England, Wales, Scotland and Northern Ireland and the NHS Medical Director, launched successfully the Recovery trial.

The adaptive design was fully applied in the Recovery trial, leading to the addition of new interventions, including the convalescent plasma arm and the discontinuation of HCQ arm, which has been less addressed in the Discovery trial.

The results of the Discovery trial are expected to be available in March 2023 [6], while the results of the Recovery trial are expected by December 2020 [9].

Issue of implementation

In the obvious absence of resources to secure high-quality implementation in the context of the COVID-19 pandemic, the Discovery trial was more an intellectual exercise focusing on the academic high standard methodology and state-of-the-art evidence, rather than a practically implementable study addressing the willingness to generate the best evidence in the context of emergency. However, the Recovery trial aims to address the need of decision-makers to control the mortality and minimize the burden of hospital resource use.

Although targeted 3,100 patients over eight countries, the Discovery trial only enrolled less than 1,000 patients in France and failed to involve additional countries except one patient in Luxembourg.

The Recovery trial attracted international funding from the Bill and Melinda Gates foundation and quoted the following UK institutions as collaborators in their clinical trial registry filling: UK Research and Innovation, National Institute for Health Research (NIHR), Welcomed foundation, Department for International Development, Health Data Research, Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding.

The Discovery trial, however, failed to aggregate any sponsor or collaborator in their clinical trial registry filling, except for the French National Institute of Health and Medical Research. Several bodies did support the Discovery trial, but they may not be considered as important visible partners for the public as in the case of the Recovery trial. The final decision of the UK not to join the European Discovery trial may end up being a wise decision.

Conclusion

The Recovery trial applies a study design to address the issue of implementation in the context of the COVID-19 pandemic and emergency. It was conceptually pragmatic with a clear vision to address the top priority: the control of mortality and rational use of scarce resources.

The study design of the Recovery trial is not only pragmatic by design, but also adaptive. These two features are not just theoretical but also practical. The high flexibility in the conduct of the trail because of the limited number of outcomes and the minimalized inclusion/exclusion criteria contributes to the success of the Recovery trial. The adaptive design feature was fully addressed by the adjustment of the intervention arms based on the new information and the preliminary result.

The interventions were driven by a strong public health consideration to include potentially effective, off-patent, and low-cost products easy to speedily produce on a large scale, the efficacy evidence of tocilizumab on controlling cytokine storm, and the need to inform urgent decision-making in the context of COVID-19 pandemic.

By contrast, the Discovery trial was designed as an intellectual exercise and consequently failed to address the issue of implementation in emergency.

These two studies illustrate important cultural differences. On one side, France is driven by Jacobinism [21] in constant opposition to regionalism. On the other side, different countries, which despite a strong feeling of individuality, united in one kingdom.

So far, the UK was the only country capable to conduct a robust nationwide study independently and to produce the first results to inform policy decision-makers.

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Tables and figures

Table 1 Substantial amendments and statements in the Recovery trial

Version number	Date	Brief Description of Changes
1.0	13-Mar-2020	Initial version.
2.0	21-Mar-2020	Addition of hydroxychloroquine. Administrative changes and other clarifications.
3.0	07-Apr-2020	Extension of eligibility to those with suspected COVID-19. Addition of azithromycin arm. Addition of inclusion of adults who permanently lack capacity. Change to primary outcome from in-hospital death to death within 28 days of randomization.
4.0	14-Apr-2020	Addition of second randomization to tocilizumab vs. standard of care among patients with progressive COVID-19.
5.0	24-Apr-2020	Addition of children to study population.
	14-May-2020	Addition of convalescent plasma.
6.0	27-May-2020	Patients who are already receiving remdesivir can still be recruited into RECOVERY and receive any of the available study treatments. RECOVERY participants can receive remdesivir and continue their assigned treatment(s) in RECOVERY. Information will be collected in RECOVERY on use of remdesivir at the baseline and during the hospital stay.
	05-June-2020	There is no beneficial effect of hydroxychloroquine in patients

hospitalized with COVID-19. The RECOVERY trial has decided to stop enrolling participants to the hydroxychloroquine arm with immediate effect.

Table 2 Comparison of study design between the Recovery trial and the Discovery trial

	Recovery trial	Discovery trial
Trial title	Randomized Evaluation of COVID-19 Therapy (RECOVERY)	Multi-center, Adaptive, Randomized Trial of the Safety and Efficacy of Treatments of COVID-19 in Hospitalized Adults (DisCoVeRy)
Planned date of enrolment	19/03/2020	22/03/2020
Recruitment status	Recruiting	Recruiting
Date of last update	05/06/2020	05/06/2020
Estimated Primary Completion Date	2020 December	2023 March
Target size	12,000	3,100
Planned countries	The United Kingdom (open to add-on studies)	Belgium, France, Germany, Luxembourg, the Netherlands, Spain, Sweden, and the United Kingdom
Study type	Adaptive, open-label RCT	Adaptive, open-label RCT
Phase	Phase 2/3	Phase 3
Inclusion Criteria	1.Hospitalized 2.SARS-CoV-2 infection (clinically suspected or laboratory-confirmed) 3.No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial 4. Patients receiving other treatments can still enter the trial as long as no known drug-drug interactions.	1. Adult ≥18 years of age at the time of enrolment. 2. Has laboratory-confirmed SARS-CoV-2 infection 3. Hospitalized patients with illness of any duration, and with clinical evidence of rales/crackles on an exam or SpO2 ≤ 94% on room air, or acute respiratory failure requiring mechanical ventilation
Exclusion Criteria	1. Patients with specific contraindication to one of the active drug treatment arms.2. Patients who lack capacity and would not wish to participate in the trial.	1.Refusal to participate expressed by the patient or legally authorized representative if they are present 2. Spontaneous blood 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. 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 (i.e. remdesivir, interferon ß-1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days 7. Contraindication to any study medication 8. Use of medications that are contraindicated with study medication

9. Human immunodeficiency virus infection

10. History of severe depression or attempted suicide or current suicidal ideation

Intervention (dosing, if available)	Main randomization part A: 1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge 2. Corticosteroid in the form of dexamethasone: administered as an oral (liquid or tablets) or intravenous preparation 6 mg once daily for 10 days. In pregnancy or breastfeeding women, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead of dexamethasone. 3. Hydroxychloroquine: by mouth for a total of 10 days (day1 0h 800mg, 6h 800mg,12h 400mg,24h4 00mg, then 400mg q12h for 9 days) (suspended) 4. Azithromycin 500mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days Main randomization part B: Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomization) and 2 (with a minimum of 12-hour interval between 1st and 2nd units).(added in the amendment) Second randomization for patients with progressive COVID-19: Tocilizumab by intravenous infusion with the dose determined by body weight. (added in the amendment)	1.Remdesivir (200 mg on Day 1, followed by a 100 mg once daily for the duration of the hospitalization up to 10 days total course) 2.Lopinavir/ritonavir (400 lopinavir mg/100 mg ritonavir every 12 h for 14 days in tablet or administered as a 5-ml suspension every 12 h for 14 days via a pre-existing or newly placed nasogastric tube) 3.Lopinavir/ritonavir (400 lopinavir mg/100 mg ritonavir every 12 h for 14 days in tablet or administered as a 5-ml suspension every 12 h for 14 days via a pre-existing or newly placed nasogastric tube) and Interferon Beta-1A (44 μg for a total of 3 doses in 6 days) 4.Hydroxychloroquine (400 mg twice daily for one day followed by 400 mg once daily for 9 days) (suspended)
Control (dosing, if available)	Standard of care	Standard of care
Number of amendments of intervention	4 (addition of hydroxychloroquine, azithromycin and convalescent plasma, and suspension of hydroxychloroquine)	2 (addition and suspension) of hydroxychloroquine
Primary outcome	All-cause mortality at 28 days after randomization.	Percentage of subjects reporting each severity rating on a 7-point ordinal scale at day 15

Secondary outcomes	1. Duration of hospital stays at day 28 and at month 6 2. Proportion of patient ventilated and duration of ventilation at day 28 and at month 6 3, Composite end point of ventilation and death at day 28 and at month 6	1. Percentage of subjects reporting each severity rating on a 7-point on an ordinal scale at days 3, 5, 8, 11, 15 and 29 2. The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first at days 3, 5, 8, 11, 15 and 29 3. Number of oxygenation free days in the first 28 days 4. Incidence of new oxygen use, non-invasive ventilation or high flow oxygen devices during the trial of 29 days 5. Duration of new oxygen use, non-invasive ventilation or high flow oxygen devices during the trial of 29 days 6. Ventilator free days in the first 28 days 7. Incidence of new mechanical ventilation use in 29 days 8. Duration of hospitalization 9. Rate of mortality at day 28 and 90 10. Cumulative incidence of serious adverse events in 29 days 11. Cumulative incidence of Grade 3 and 4 adverse events in 29 days 12. Number of participants with a discontinuation or temporary suspension of study drugs in 29 days 13. Changes from baseline in blood white cell count in 29 days 14. Changes from baseline in haemoglobin in 29 days 15. Changes from baseline in platelets in 29 days 16. Changes from baseline in creatinine in 29 days 17. Changes from baseline in blood electrolytes (including kalemia) in 29 days 18. Changes from baseline in prothrombin time in 29 days 19. Changes from baseline in international normalized ratio in 29 days 20. Changes from baseline in glucose in 29 days 21. Changes from baseline in total bilirubin in 29 days 22. Changes from baseline in alanine aminotransferase in 29 days 23. Changes from baseline in aspartate aminotransferase in 29 days
Other outcomes	1. Proportion of patient requiring renal replacement at day 28 and at month 6 2. Development of new cardiac arrhythmia at day 28 and at month 6	1. Percent of subjects with SARS-CoV-2 detectable in nasopharyngeal sample at days 3, 5, 8, 11, 15, and 29 2. Quantitative SARS-CoV-2 virus in nasopharyngeal sample at days 3, 5, 8, 11, 15, and 29 3. Quantitative SARS-CoV-2 virus in blood at days 3, 5, 8, 11, 15, and 29 4. Plasma concentration of lopinavir at days 1, 3, 5, 8 and 11 5. Plasma concentration of hydroxychloroquine at days 1, 3, 5, 8 and 11

RCT: randomized controlled trial