14.1 In Practice: RECOVERY Trial

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Learning Objectives

This chapter will help readers understand and describe:

- The principles guiding the design of the Randomised Evaluation of COVID-19 Therapy Trial (RECOVERY)
- Elements essential to the implementation of the trial
- The potential benefits of streamlined point-of-care clinical trials in low- and middle-income settings

1 Introduction

Clinical trials of therapeutics are challenging even at the best of times, and, until recently, the barriers to high-quality clinical trials during health emergencies have seemed almost insurmountable. The routine burden of trial design, financing, ethical and regulatory approvals, contracting, drug supply, information and technology (IT) systems, training, etc., are compounded by extreme time pressures, political and operational constraints, and unpredictability.

At least 3000 coronavirus disease 2019 (COVID-19) treatment trials, evaluating hundreds of different therapies, have been planned since the start of the pandemic, and over 500 have reported results, but nearly all have been too small to provide answers clear enough to guide clinical practice or direct future research. As a result, we have been dependent on relatively few large trials to produce most of the reliable data on COVID-19 treatment. The RECOVERY Trial (Randomised Evaluation of COVID-19 Therapy) is the largest. At the time of writing, it had enrolled over 48,500 patients and produced clear answers on 11 therapies (RECOVERY trial 2023).

2 Early Foundations for COVID-19 Trials

2.1 Randomized Controlled Trials

The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) is a global, grass-roots federation of clinical research networks established in 2009 to improve clinical research for epidemic and pandemic infectious diseases (ISARIC 2020). Through ISARIC, trusted peer-to-peer relationships have been established that allowed a rapid, collaborative response to the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In the early days of 2020, clinical researchers within ISARIC worked together, utilizing experience with Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia, to support the rapid launch of therapeutic trials in COVID-19 in China. These included the very first randomized controlled trial in COVID-19 (Cao et al. 2020) and the very first placebo-controlled randomized trial (Wang et al. 2020). The rapid containment of COVID-19 in China meant that these trials did not achieve sufficient enrollment to provide definitive answers. Still, they did establish expectations for the rigorous study of therapeutics in COVID-19. As COVID-19 spread globally, the experience and achievements of these early trials in China informed the decision to fund and support the RECOVERY trial (Fig. 1).

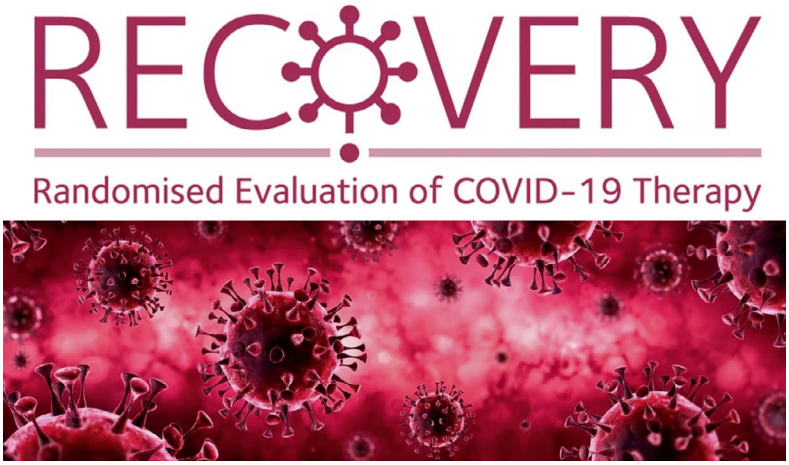


Fig. 1 Recovery logo and representation of SARS-CoV-2. (Nuffield Dept of Medicine, Oxford)

3 Principles

The design of RECOVERY was predicated on the recognition that most treatment effects are modest (perhaps reducing risk only by about one quarter), but such effect sizes on important outcomes would be very worthwhile, for example, a reduction of "only" 15–20% in the risk of death in patients hospitalized with COVID-19. A few principles were followed to reliably identify or rule out such treatment effects in the context of the pandemic.

- It needed to be ***randomized*** to ensure systematic errors (biases), such as those introduced when patient characteristics influence the treatment they receive, were substantially smaller than the treatment effect to be measured. RECOVERY initially compared multiple treatment arms with a shared control group and latterly used factorial randomization, in which patients are randomized to active treatment or usual care independently for each of the suitable study treatments. These features have meant that each patient contributed to an average of two treatment comparisons, doubling the effective size of the trial.
- It needed to be ***large*** to ensure systematic errors were substantially smaller than the treatment effect to be measured. Many trials, especially for diseases that are hard to study, apply various techniques to reduce the required sample size. These techniques include unrealistic effect sizes (such as a 50% reduction in mortality) or surrogate measures for meaningful clinical endpoints. COVID-19 was a pandemic of an acute viral illness with mortality concentrated in older patients with comorbidities: case numbers were unlikely to be limiting factors and "miracle" drugs resulting in large reductions in mortality were also unlikely. In the context of a pandemic likely to infect a large proportion of the world's population, modest effect sizes, such as a 20% reduction in mortality, could have a huge overall benefit. As such, a large trial was both desirable and feasible.
- It needed to be ***quick***. Therapeutics for epidemic infections can only be fully evaluated during an epidemic. The pandemic was moving very quickly, and previous experiences with the initial outbreak in Wuhan and other epidemic infections have shown that speed is of the essence if the infection wave is to be caught and sufficient patients enrolled to provide reliable answers.
- It needed to be ***simple***. Given the need for speed and scale, coupled with enormous impending stresses on the healthcare system and healthcare workers, simplicity was a necessity. The trial was designed to have minimal impact on frontline healthcare staff. Simplicity was achieved by simultaneously going back to first principles and fully utilizing new opportunities, such as data linkage. Due to the impracticality of

implementing a placebo-controlled design for multiple agents across hundreds of sites quickly, the objective and easily measurable clinical endpoint of survival was chosen.

Eligibility criteria were simple and trial processes (including paperwork) were minimized. The protocol was deliberately flexible so that it was suitable for a wide range of settings, allowing:

- A broad range of patients to be enrolled in large numbers, including children and pregnant women
- Randomization between only those treatment arms that are *both* available at the study-site hospital *and* not believed by the enrolling doctor to be contraindicated (e.g., by co-morbid conditions or concomitant medications)
- Treatment arms to be added or removed according to the emerging evidence
- Additional sub-studies could be added to provide more detailed information on side effects or sub-categorization of patient types, but these were not the primary objective and were not required for participation

4 Implementation

RECOVERY was established at unprecedented speed. The first draft of the protocol was available on March 10, 2020, it was submitted for regulatory and ethics review on March 13, received both approvals on March 17, and enrolled the first patient on March 19. Consequently, RECOVERY fully captured the first wave of COVID-19 in the UK, with the first 1000 patients recruited within 2 weeks and over 10,000 within 2 months. We have estimated that a delay of 2 weeks (starting recruitment on 8 April) would have missed the first 2500 recruitments and delayed the final dexamethasone results by 4 months (from mid-June to mid-October) (Fig. 2).

4.1 Infrastructure and Implementation

The RECOVERY trial captured the entire first wave of infections in the UK and enrolled more than 500 patients per day across about 175 clinical sites at its peak. This achievement owed much to the simplicity of design but also to the unique UK health research infra-

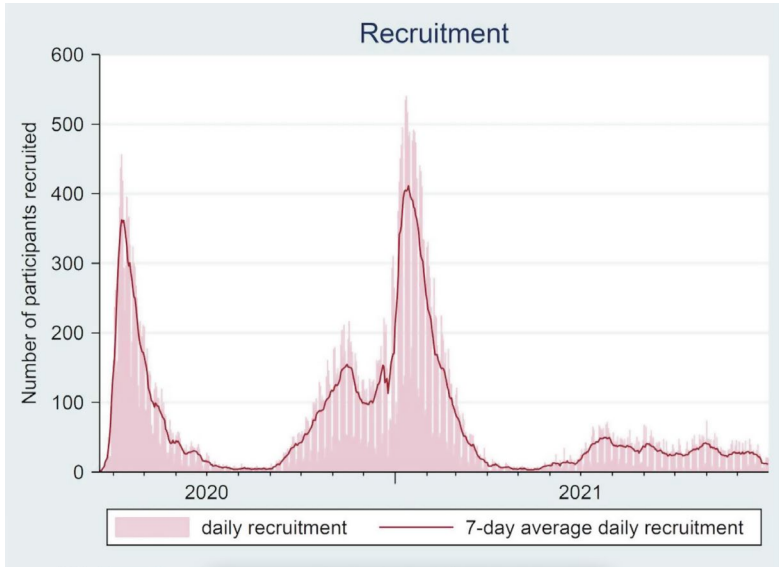


Fig. 2 RECOVERY trial recruitment over time. (Authors)

structure and environment. Four critical elements were:

1. *A national, publicly funded healthcare system*, the National Health Service (NHS). This national, standardized infrastructure enabled some key efficiencies. A single ethical committee could provide approval that was accepted by all NHS hospitals, without needing individual, site-level ethical approval. Due to similarities in contractual and legal structures, a single standard clinical trial agreement was acceptable to all sites.
2. *A national, publicly funded health research infrastructure*, the National Institutes of Health Research (NIHR): The NIHR was established in 2006 to create a health research infrastructure within the NHS. It is funded by the UK Government. The NIHR supports clinical research nurses and other vital resources for research delivery within the NHS. In 2012, in response to the poor research response to the 2009 influenza pandemic, the NIHR created a portfolio of hibernating studies that were given the status of "Urgent Public Health" (UPH) studies. This status was reenacted in 2020 and a process was initiated to designate *Urgent Public Health Research Studies for COVID*-19 (Ustianowski and Harman 2022). The designation was via an application to the NIHR Urgent Public Health Group. UPH-designated studies were prioritized for support by the NIHR infrastructure and staff. These fast-tracked, prioritized COVID-19 studies placed the UK at the forefront of global efforts to establish effective treatments against the disease.
3. *Centralized leadership through Chief Medical Officers* (CMOs): The UK has four CMOs, one for each constituent nation (England, Wales, Scotland, and Northern Ireland). These four CMOs communicated with one another at least weekly during the pandemic and supported a coordinated response, including health research. RECOVERY was designated as a national priority clinical trial. On April 1, 2020 the four CMOs, along with the NHS National Medical Director, sent a joint letter to all NHS hospitals asking that "*every effort is made to enroll COVID-19 patients in the national priority clinical trials*." The letter further stated, "*While it is for every individual clinician to make prescribing decisions, we strongly discourage the use of off-licence treatments outside of a trial, where participation in a trial is possible. The use of treatments outside of a trial, where participation was possible, is a wasted opportunity to create information that will benefit others. The evidence will be used to inform treatment decisions and benefit patients in the immediate future*."[1]
4. *A national, standardized digital health records system—NHS Digital*: Using linkage to national healthcare and viral statistics records for the measurement of trial outcomes reduces the need for data collection by local teams and improves the completeness of follow-up, improving the reliability of study outcomes. This also allows low-cost, long-term follow-up.

5 Impact and International Expansion

Within just over 100 days of opening, RECOVERY provided clear results that enabled three changes in global clinical practice: hydroxychloroquine, dexamethasone, and lopinavir-ritonavir. The results of RECOVERY had a major impact on global COVID-19 treatment guidelines and have been accepted by multiple regulatory authorities, including the U.S. Food and Drug Administration.

The early success of RECOVERY led to requests to open the trial outside the UK. While the healthcare systems in most other countries do not have the advantages of the UK, the international expansion of RECOVERY, particularly to low- and middle-income settings, is a test case for the

1 ► https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103012.

wider use of streamlined clinical trial designs to fast-track improvement in healthcare globally. Successful expansion outside of the UK was demonstrated by the evaluation of higher dose dexamethasone in COVID-19, where more than half of the participants were recruited from low- and middle-income settings (RECOVERY Collaborative Group 2023).

Streamlined point-of-care clinical trials offer many benefits, but ensuring the acceptability of the results to regulatory authorities is critical (Califf et al. 2022). Proportionate risk adaptations were necessary in order to implement RECOVERY quickly and widely, and they have proven largely acceptable to regulators who have provided market authorization for new treatments for COVID-19 based on the results of RECOVERY.

Discussion Questions

1. What are the guiding principles in the design of the RECOVERY trial?
2. Provide examples illustrative of the inherent flexibility of RECOVERY.
3. Describe the critical elements that facilitated the implementation of the RECOVERY trial.
4. How would one conduct similar studies outside the United Kingdom?

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