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The RECOVERY trial platform: a milestone in the development and execution of treatment evaluation during an epidemic

PP Glasziou[3] and KAO Tikkinen[1,2]

[1]Department of Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[2]Department of Surgery, South Karelian Central Hospital, Lappeenranta, Finland
[3]Institute for Evidence Based Healthcare, Bond University, Gold Coast, Australia
Corresponding author: PP Glasziou. Email: pglaszio@bond.ac.uk

> Any treatment given for coronavirus other than general supportive care, treatment for underlying conditions, and antibiotics for secondary bacterial complications, should currently be as part of a trial, where that is possible.
> Letter from Chief Medical Officers of Wales, Scotland, Northern Ireland, England to NHS Staff

Creation of the RECOVERY trial platform during the COVID-19 pandemic has been a milestone in clinical trial processes. The RECOVERY trial platform has been built on Richard Peto's promotion since the 1970s of large, simple trials using factorial designs to make more than two treatment comparisons.[1–4] The RECOVERY trial platform (hereafter 'RECOVERY') has extended that model with some novel design features, particularly a very rapid set-up and recruitment process. RECOVERY has set new benchmarks for trial efficiency. Importantly, results obtained through RECOVERY have had a strong impact on clinical practice and clinical guidelines *during* the COVID-19 pandemic – a feat not achieved during any previous pandemic.

In parallel to RECOVERY, WHO has also created and coordinated a large multi-country trial platform with a similar protocol to RECOVERY. By the end of January 2021, WHO's SOLIDARITY platform had enrolled over 14,000 patients in more than 400 hospitals in over 30 countries, and it has provided by far the most statistically precise estimate of the effects of remdesivir in COVID-19. Interim remdesivir results were published in December 2020[5] and the final analyses are expected to be published in autumn 2021. At the end of January 2021, trial recruitment using the SOLIDARITY platform was paused to deal with several logistic difficulties, but recruitment resumed in early August 2021.

Although the important lessons resulting from the RECOVERY and SOLIDARITY trial platform experiences are similar,[6] in this commentary we focus on RECOVERY. In brief, the '*R*andomised *E*valuation of *COV*ID-19 therapy (RECOVERY)' trial is a randomised, controlled, open-label, adaptive, trial platform enabling comparisons of a range of possible treatments with usual care in patients hospitalised with COVID-19. The initial four experimental arms were: (i) lopinavir-ritonavir (commonly used to treat HIV), (ii) low-dose dexamethasone, (iii) azithromycin (a commonly used antibiotic) and (iv) hydroxychloroquine. Using its adaptive design and successful recruitment, RECOVERY has also already assessed the effects of (v) aspirin, (vi) colchicine, (vii) convalescent plasma, (viii) Regeneron's monoclonal antibody cocktail and (ix) tocilizumab. As of 15 August 2021, RECOVERY is being used to test (x) baricitinib (an immunomodulatory drug used in rheumatoid arthritis), (xi) dimethyl fumarate (an immunomodulatory drug used in psoriasis and multiple sclerosis) and (xii) high-dose vs. standard dose of corticosteroids.

The RECOVERY protocol is available for use by investigators everywhere to design their own randomised trials to help identify treatments for COVID-19 with important beneficial effects. https://www.isrctn.com/ISRCTN50189673

Some special features of RECOVERY include:

1. Simplicity (use of Second International Study of Infarct Survival (ISIS-2)[7] protocol)

This James Lind Library article will be updated at intervals to add information about the development of the RECOVERY trial platform and the treatment evidence obtained.

2. Trial platform design, with four arms and a control group (2× size of the treatment arms)
3. Rapid set-up and recruitment – protocol in two days, first patient recruited nine days later.

Simplicity

The protocol, written over two days (Table 1) was adapted from the large, simple, pragmatic trials exemplified by the ISIS trials (e.g. ISIS-2[7]) and the GISSI trials (e.g. GISSI,[8] Maggioni et al.,[9] Tognoni et al.[10]) using broad, simple, inclusion criteria and minimising data collection to enable participation by COVID-19-stretched hospitals. The design of RECOVERY was based on ISIS-2 protocol – a large, simple, pragmatic trial[7] important features of which included:

- broad, simple inclusion criteria;
- central randomisation;
- no requirement for additional biological samples or extraneous data collection and
- use of the simple, unambiguous primary outcome of all-cause mortality.

Platform design

The trial platform design[11] has meant that treatment arms could be dropped or added during the process of running RECOVERY trials. For example, on

Table 1. TIMELINE of the RECOVERY trial – see https://www.recoverytrial.net/news

March 2020	9–10: Discussions and first protocol written 13: Submitted for ethics review 19: First patient enrolled in Oxford
April 2020	3: RECOVERY platform trial rolled out across the UK, with almost 1000 patients recruited in 15 days through 132 participating hospitals By day 21, over 400 patients were being recruited every day
May 2020	23: Convalescent plasma arm added (in factorial design)
June 2020	3: First patient (a child) receives convalescent plasma through RECOVERY 5: Announcement that no important benefit of hydroxychloroquine in hospitalised patients with COVID-19 had been detected (MedRxiv pre-print in June; full report published in October 2020) 16: Low-cost dexamethasone shown to reduce death by up to one-third in hospitalised patients with severe respiratory complications of COVID-19 (MedaRxiv preprint in June; full report published in July 2020) 29: No important benefit detected from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY (full report published in October 2020)
Sept 2020	14: Regeneron's REGN-VOV2 investigational antibody cocktail arm added
Nov 2020	6: Aspirin arm added 27: Colchicine arm added
Dec 2020	14: No benefit from azithromycin detected in patients hospitalised with COVID-19 (full report published in February 2021)
Jan 2021	15: No benefit from convalescent plasma found in patients hospitalised with COVID-19 (full report published in May 2021)
Feb 2021	2: Baricitinib arm added 5: No benefit from colchicine found in patients hospitalised with COVID-19 (pre-print published in May 2021) 11: Tocilizumab shown to reduce deaths (full report published in April 2021). 18: Indonesia and Nepal among the first non-UK countries to join the international version of RECOVERY
June 2021	8: No benefit from aspirin found for patients hospitalised with COVID-19 (pre-print published in June 2021) 11: 40,000 patients randomised 16: Regeneron's monoclonal antibody combination found to reduce deaths in hospitalised COVID-19 patients who have not mounted their own immune response (pre-print published in June 2021)

23 May 2020, a convalescent plasma arm was added (using a factorial design) – a treatment first used more than 100 years ago.[12]

Because there were four arms in the initial RECOVERY trials, the control arm was made twice as large as the individual treatment arms. Since a 2:1 ratio has nearly the same power as a 1:1 ratio for the same total numbers, the 2:1 ratio of controls:treatment for each arm improved the power of each comparison.[13]

Rapid set-up, recruitment and reporting

RECOVERY has been remarkable, going from first meeting to first patient recruited in a record-setting nine days, recruiting 13% of all COVID-19 hospitalised patients in the UK during the first COVID-19 wave; and a few months later giving clear answers on the effectiveness of dexamethasone. Importantly, to minimise delay, results were reported in MedRxiv in June,[14] and a preliminary report was published in the New England Journal of Medicine the following month; but the full publication was not published until February 2021.[15] At the same time, RECOVERY reported that no beneficial effect of hydroxychloroquine and lopinavir had been detected.[16,17] A year later, RECOVERY reported beneficial effects of tocilizumab and Regeneron's monoclonal antibody cocktail[18,19] and that no benefit had been detected from aspirin, colchicine or convalescent plasma in hospitalised COVID-19 patients.[20–22]

Some keys to the successful recruitment by RECOVERY trials were:

- simple, pragmatic designs;
- the pre-existing National Health Service clinical trials network and
- strong national support from the Chief Medical Officers in England, Scotland, Wales and Northern Ireland.

The pre-existing National Institute for Health Research Network in the UK meant that there was a decision-communication structure to prioritise the RECOVERY trial platform and research nurses in place at recruiting centres. Because of its simple features, many of the less research-experienced hospitals became among the best recruiters to RECOVERY trials.

The success of the RECOVERY platform trials has been facilitated by the willingness of UK National Health Service doctors to randomise unproven treatments (rather than, as in many other countries, obstructing randomisation by incorporating unproven drugs into local practice guidelines).

A strong letter of support from UK Chief Medical Officers emphasised that support for RECOVERY was a part of clinical care: 'Use of treatments outside of a trial, where participation was possible, is a wasted opportunity to create information that will benefit others' (https://www.recoverytrial.net/files/professional-downloads/the-importance-of-covid-19-clinical-trials.pdf)

Conclusions

The features above are not unique to RECOVERY but the combination of all of them appears to have been ground-breaking. While there have been several previous platform trials,[23] most have been in oncology. One previous pandemic attempt occurred in the 2014 Ebola outbreak in West Africa, but it was not possible to launch it before the outbreak had subsided.[23]

Although the evidence generated using the RECOVERY trials platform is clinically important, the lessons for the medical and research community about processes are perhaps of even greater importance and worthy of detailed study. Simple, large-scale trials are key to obtaining clear clinical answers to vital questions. The RECOVERY trial platform has demonstrated that it is possible to answer multiple treatment questions reliably during a pandemic. This is an important lesson for future pandemics, but it is also relevant to non-pandemic treatment questions.[24] Funders and trialists would do well to study carefully what made the success of RECOVERY possible, and what other lessons there are for adapting the clinical trials ecosystem during pandemics.[25]

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