Australia needs a prioritised national research strategy for clinical trials in a pandemic: lessons learned from COVID-19

Developing a pathway to prioritise clinical research and prepare for future pandemics remains an urgent need

The emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), sparking a global pandemic,[1] has driven an imperative to quickly design and conduct treatment studies. We strongly propose a national, coordinated approach for randomised controlled trials (RCTs) for coronavirus disease 2019 (COVID-19), future pandemics and inter-pandemic periods in Australia. Our reflections represent those of the Australasian COVID-19 Trial (ASCOT)[2] steering committee, as we have considered the challenges of conducting a clinical trial during the COVID-19 pandemic in Australia.

To find effective therapeutic options for COVID-19, various approaches to coordination and prioritisation of clinical research have been taken globally. There are more than 3000 relevant RCTs now registered.[3] Among these, the key practice-changing trials have been well coordinated, pragmatic, publicly supported by government, and funded by national research agencies.[4] The standout examples are the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial in the United Kingdom;[5] the "Solidarity" clinical trial for COVID-19 treatments, run by the World Health Organization (WHO);[6] the Adaptive COVID-19 Treatment Trial (ACTT) in the United States;[7] and the Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), which involves participating sites in 21 countries.[8] In addition, the prior development of national clinical research networks and infrastructure for improved patient care has strengthened pandemic responsiveness. For example, the UK National Institute for Health Research, with a hospital-based trial infrastructure of clinical research units, was recruiting > 2000 patients per day to RCTs before COVID-19.[9] When COVID-19 trials were prioritised in the UK, the existing infrastructure was ready to support pragmatic studies such as RECOVERY and REMAP-CAP. Almost 40 000 participants have been randomised in RECOVERY,[5] and the UK has been the best recruiting nation globally for REMAP-CAP (with > 4400 of > 6000 participants recruited).[8]

Through an open letter from the UK's Chief Medical Officers, RECOVERY was prioritised by the UK National Health Service as the preferred clinical trial at all its hospitals.[10] Similarly, the Solidarity trial has been recommended by the WHO and implemented in > 30 countries. REMAP-CAP had a global intensive care unit network predating the pandemic, with National Health and Medical Research Council (NHMRC) of Australia and philanthropic funding, and was rapidly adapted to incorporate therapeutic options for COVID-19. The ACTT and the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)[11] partnership have been sponsored and funded by the US National Institutes of Health, with coordination for study sites within and outside the US, leveraging a well established network for human immunodeficiency virus (HIV) trials known as the International Network for Strategic Initiatives in Global HIV Trials.[12]

Minimisation of regulatory requirements, facilitating rapid ethics and governance approvals and swift commencement of clinical trials, meant that these nationally or internationally coordinated trials have quickly evaluated repurposed therapeutic agents for COVID-19 for both efficacy and futility. Dexamethasone reduced 28-day mortality in RECOVERY[13] and hydrocortisone was beneficial in critically ill patients in REMAP-CAP;[14] remdesivir reduced the time to clinical recovery in patients receiving oxygen with pneumonitis in ACTT-1;[15] and interferon, hydroxychloroquine and lopinavir–ritonavir were not beneficial in RECOVERY and the Solidarity trial.[16-18] More recently, RECOVERY[19] and REMAP-CAP[20] have conclusively determined the benefit of tociluzimab, after six smaller trials found it to have no benefit.

Unlike the UK and parts of the US response, there has been little central coordination in Australia for the prioritisation and funding of trials. Nor was there a nationally resourced and coordinated trials infrastructure in existence before the COVID-19 pandemic. The NHMRC did invest in a pandemic preparedness Centre of Research Excellence, which was awarded to the Australian Partnership for Preparedness Research on Infectious Disease Emergencies (APPRISE) in 2016.[21] APPRISE has supported REMAP-CAP and provided seed funding to ASCOT. The Medical Research Future Fund (MRFF) has had two calls for clinical trials, in the first round awarding $6.8 million to seven clinical trials,[22] which we estimate to have enrolled < 10 patients with COVID-19, and subsequently $7.3 million to nine research teams to develop promising antiviral therapies with a pathway to clinical trials. The first MRFF round opened for applications on 23 March 2020, with results publicly announced on 2 June 2020, by which time the first wave of COVID-19 in Australia had receded. Over $48 million of MRFF funding has now been awarded to 43 projects, of which at least eight are phase 3 clinical trials for COVID-19

Asha C Bowen[1,2]
Steven YC Tong[3,4]
Joshua S Davis[5,6]

1 Perth Children's Hospital, Perth, WA.
2 Wesfarmers Centre for Vaccines and Infectious Diseases, Telethon Kids Institute, Perth, WA.
3 Victorian Infectious Diseases Service, Royal Melbourne Hospital, Doherty Institute, Melbourne, VIC.
4 University of Melbourne, Melbourne, VIC.
5 Menzies School of Health Research, Darwin, NT.
6 John Hunter Hospital, Newcastle, NSW.

asha.bowen@health.wa.gov.au

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therapeutics.[23] There have been an additional 30 phase 3 clinical trials registered in Australia.

There are benefits in the distributed approach to clinical trials. Competition for funding promotes high quality science. Several studies that provide similar results may improve confidence in the findings. Smaller studies may be more nimble and lower incidence settings better suited to phase 1 or 2 trials that provide important information to determine whether candidate drugs should progress to larger trials. However, there are also downsides to having multiple competing studies. Many research groups duplicate efforts in independently establishing trial infrastructure, including protocols, electronic databases, trial staff and trial committees. There can also be a burden on patients who may be approached about multiple studies. Ultimately, there is a substantial risk that each trial will end up underpowered to answer clinically relevant questions.

The success of RECOVERY and REMAP-CAP to conduct and complete practice changing trials is instructive. These platform trials have been able to rapidly adapt, incorporate new therapeutic modalities, and answer questions of critical importance. Phase 1 or 2 trials are important for progressing the pipeline of potentially effective therapeutics, but in an emerging pandemic, the importance of coordinated investment in definitive phase 3 trials cannot be underestimated. There are some risks in centralising resources into a small number of platforms. Poor design or trial conduct in one of these platform trials could be more detrimental compared with spreading this research across a broader number of trials. There may be fewer opportunities for involvement of researchers outside of these platforms. These risks may be mitigated by encouraging coordinated involvement of multiple groups with trials and content expertise, and ensuring there is a mix of early, mid and senior researchers.

Two critical factors have made it extremely challenging to run therapeutic COVID-19 trials in Australia. First, the unpredictability of the pandemic, and the small number of patients in Australia compared with other countries, has made patient recruitment difficult. Second, the swift accrual of patients and communication of results in overseas studies has resulted in the need to rapidly change protocols and drop interventions for which equipoise no longer existed. While these factors were beyond the control of clinical trialists, broader concerns in the Australian trial landscape are amenable to change.

Funding, ethical and governance approval processes for clinical trials in a pandemic need to be in place in advance. By the time funding for COVID-19 trials was available through national schemes, the first and second waves had passed. Because of the lag time between trial conceptualisation and approval, pre-existing infrastructure is required to enable trials to be operational early in a pandemic. For example, REMAP-CAP had been funded by the NHMRC for > 2 years and operational for severe community-acquired pneumonia in intensive care units. In the absence of nationally coordinated funding, philanthropy has played an important role in quickly supporting trials such as ASCOT, the BCG Vaccination to Reduce the Impact of COVID-19 in Healthcare Workers (BRACE) trial,[24] and REMAP-CAP. While we have a National Mutual Acceptance scheme for ethical approval of multicentre clinical trials in Australia, the requirement for governance approvals at each individual site creates substantial delays and critical roadblocks.

Moving forward, robust reflection on what has been learned thus far in the COVID-19 pandemic is needed. We recommend:

- A small number of national platforms in Australia, similar to RECOVERY in the UK, as the principal vehicle for publicly funded trials. Each of these platforms should focus on different disease phases (eg, outpatients, hospitalised/non-critical, intensive care) and include specific patient subgroups (eg, pregnant women, children, immunocompromised hosts). These platforms should be pandemic prepared, and between pandemics focus on relevant research incorporating researchers at all career phases to strengthen and grow the network. For example, REMAP-CAP was developed to answer community-acquired pneumonia questions and rapidly pivoted to incorporate COVID-19 as the pandemic emerged. The establishment of national platforms does not preclude the capacity for smaller phase 1 and 2 studies to be set up when a pandemic occurs. Indeed, there should be coordination of early phase studies as a streamlined pipeline to incorporation of promising agents into larger adaptive platform trials.
- Coordination of these platforms through defined coalitions of research groups to facilitate sharing of expertise and infrastructure, thus reducing the duplication of efforts and model collaboration across clinical trials.
- Rapid mobilisation of government funds, either through funding networked coalitions of research groups or competitive calls for consolidated large scale funding to self-identified coalitions (with rapid awarding of funding).
- Encouragement from federal and state chief health officers and health ministers for local site involvement in these platforms and creation of structures for mutually accepted governance approvals (similar to the National Mutual Acceptance scheme for ethics approval).

While this would have been most helpful early on, developing a pathway to prioritise clinical research and prepare for future pandemics remains an urgent need. There should be a scientific discussion at a national level to prioritise, support and coordinate a limited number of clinical trials, reducing the burden on patients, health systems and funders.

Furthermore, we recommend that a national pandemic clinical trials prioritisation panel be formed to advise the NHMRC, MRFF, chief health officers and

National Cabinet. Its key role would be to establish a streamlined approach to funding prioritised trial platforms, consider how to integrate applications for new trials with established trial platforms, and establish pathways for rapid ethical and governance approval of protocols in the context of a pandemic and advise on any gaps in research.

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