The landscape of COVID-19 trials in Australia

The research response in Australia has been rapid, but better coordination is imperative

The coronavirus disease 2019 (COVID-19) pandemic has seen clinical trials launched at exceptional speed in unprecedented numbers.[1] While this is a positive development, the rapidity of trial launches and the unpredictable nature of the pandemic bring challenges for the conduct of trials and evidence synthesis. Duplication of effort is a risk, and many trials alone are underpowered to find statistically significant effects for clinically important outcomes, including mortality.[1] In addition, the hard-to-predict waves of the pandemic may hinder recruitment due to declining cases or pose challenges to starting trials quickly in emerging hotspots.[2] Recruitment has been a particular issue in Australia due to low case numbers compared with other countries. Furthermore, funds in Australia were rapidly made available to support research addressing the pandemic, but little is known about how effectively these funds have been used to drive the global agenda of preventing, diagnosing and treating COVID-19. We aimed to derive an understanding of the current landscape of clinical trials addressing the COVID-19 pandemic in Australia and to what extent Australian researchers have responded to the global need for coordination and collaboration. Therefore, we searched the Australian New Zealand Clinical Trials Registry (ANZCTR) and ClinicalTrials.gov from 1 January to 16 November 2020, as these sources capture approximately 95% of registered trials recruiting in Australia.[3]

Research scale-up

The research scale-up in Australia during the COVID-19 pandemic has been impressive. Of 1637 studies registered, 1174 were interventional studies with a recruitment site in Australia. Of these, 56 were COVID-19 trials, targeting 33 757 participants (Supporting Information, figure 1). The trials characteristics are summarised in Box 1 (detailed information is included in the Supporting Information, tables 1–3). Four trials (7%) were completed and the remainder were recruiting (n = 26, 46%), not yet recruiting (n = 24, 43%), or withdrawn (n = 2, 4%; Supporting Information, tables 1–3). Most trials (n = 46, 82%) recruited only in Australia, while ten trials (16%) recruited in Australia and internationally. Forty trials (71%) had no commercial sponsor, and were funded by government or not-for-profit sources. Only seven trials (12%) included populations at high risk of poor outcomes from COVID-19 such as people with comorbidities (eg, cancer, cardiovascular disease, chronic kidney disease).

Nineteen (35%) were prevention trials. We identified ten (18%) vaccine trials, of which two repurposed existing vaccines for COVID-19 prevention and eight investigated efficacy using a COVID-19-specific antigen. Thirty-four (62%) were treatment trials, of which 22 (39%) were drug trials. A broad array of drug categories was investigated, including but not limited to immunosuppressants, immunostimulants, stem cell therapies, antivirals and anti-inflammatories. The merits, risks and proposed solutions of included trials are summarised in Box 2.

We identified an additional 12 COVID-19-related trials assessing indirect effects of the pandemic (Box 1 and Supporting Information, table 4). The majority (n = 11, 92%) investigated mental health issues related to uncertainty and isolation during the pandemic.

The impact of fast track procedures on scientific rigour and research prioritisation

The other side of the rapid emergence of trials is the haste with which funding, development and implementation happened, leading to concerns about research waste and prioritisation, and ethical and scientific rigour.[4] Adding concern is the fact that no full, publicly available protocols were identified for any of the included trials. Most organisations did not have fast track procedures in place at the start of the pandemic.[4] The development of publicly available, transparent procedures and standards for all stages of clinical trials (eg, development, funding, ethics, conduct, dissemination) should be an important lesson from the COVID-19 pandemic. Such standards must balance the urgency of advancing knowledge with the retention of ethical and scientific rigour.

Most of the included trials (89%) tested pharmaceutical drugs or devices, except for six trials: three telehealth applications for COVID-19-monitoring and rehabilitation, one lifestyle intervention, and one intervention on patient positioning during oxygenation. There were no trials on public health communication, community transmission prevention or long COVID-19 symptoms, pointing to omissions in research prioritisation. Furthermore, extensive media coverage and public opinion may have influenced prioritisation of interventions that were not particularly promising.[1,5] For instance, many simultaneous trials on hydroxychloroquine (six in Australia alone) may have put many patients unnecessarily at risk.

Untapped potential of innovative study designs

Australian COVID-19 trials tested a range of innovative interventions, such as vaccine techniques (nanoparticles and the delivery of genetic material in two vaccine trials) and digital health solutions for home-monitoring of mild COVID-19. Triallists demonstrated adaptability to transmission risks for in-person contact through innovation in trial conduct, with digital recruitment and delivery modes such as video calls or smartphone applications. Yet, innovation

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1 Characteristics of coronavirus disease 2019 (COVID-19) trials and COVID-19-related trials

Characteristics	COVID-19 trials	COVID-19-related trials	Overall
Total number of trials	56	12	68
Total participants across trials	33 757	2586	36 343
Participants per trial			
Median (IQR)	150 (33–395)	147 (94–280)	150 (37–395)
Mean (SD)	625 (1507)	215 (184)	551 (1374)
Trial status			
Not yet recruiting	24 (43%)	9 (75%)	33 (49%)
Recruiting	26 (46%)	3 (25%)	29 (43%)
Completed	4 (7%)	0	4 (5.9%)
Withdrawn	2 (4%)	0	2 (2.9%)
Trial phase*			
Phase 0	1/55 (2%)	0	1 (1%)
Phase 1	19/55 (35%)	1 (8%)	20 (30%)
Phase 2	5/55 (9%)	0 (0%)	5 (7%)
Phase 3	14/55 (25%)	0 (0%)	14 (21%)
Phase 4	2/55 (4%)	0 (0%)	2 (3%)
Not applicable (eg, not a drug trial)	14/55 (25%)	11 (92%)	25 (37%)
Recruitment country			
Australia only	46 (82%)	11 (92%)	57 (84%)
International (Australia and other country/countries)	10 (18%)	1 (8%)	11 (16%)
Purpose*			
Treatment, drug	24/55 (44%)	0	24 (36%)
Treatment, other	10/55 (18%)	9 (75%)	19 (28%)
Prevention, vaccine†	8/55 (14%)	0	8 (12%)
Prevention, other	11/55 (20%)	2 (17%)	13 (19%)
Other (eg, diagnosis, education)	2/55 (4%)	1 (8%)	3 (5%)
Included population			
Confirmed COVID-19	34 (61%)	1 (8%)	35 (51%)
Healthy volunteers	14 (25%)	3 (25%)	17 (25%)
Health care professional	6 (11%)	2 (17%)	8 (12%)
Individuals at high risk of poor outcomes	2 (4%)	6 (50%)	8 (12%)
Population age			
Adult (18–65 years)	9 (16%)	1 (8%)	10 (15%)
Older adult (age > 65 years)	2 (4%)	1 (8%)	3 (4%)
All ages	45 (80%)	10 (83%)	55 (81%)
Any blinding (personnel or participant)*			
Yes	19/49 (37%)	3/8 (38%)	22 (37%)
No	30/49 (63%)	5/8 (62%)	38 (63%)
Randomisation*			
Randomised controlled trial	44/54 (81%)	7 (58%)	51 (77%)
Non-randomised trial	10/54 (19%)	5 (42%)	15 (23%)
Trials using digital health solutions			
Yes	5 (9%)	12 (100%)	17 (25%)
No	51 (91%)	0	51 (75%)
Commercial involvement (sponsorship, collaboration or funding)			
No commercial involvement	40 (71%)	9 (75%)	49 (72%)
Commercial involvement	16 (29%)	3 (25%)	19 (28%)
Population with comorbidity			
Yes	7 (12%)	2 (17%)	9 (13%)
No	49 (88%)	10 (83%)	58 (87%)

IQR = interquartile range; SD = standard deviation.* No information available for one trial for trial phase and purpose, for seven trials for blinding (optional registration field), and for two trials for study design for COVID-19 trials. For COVID-19-related trials, no information was available for four trials for blinding (optional registration field). These trials were excluded from the analysis for these characteristics. One trial with a sample size of 30 000 was excluded from the sample size analyses. † Two vaccine clinical trials registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) were recorded as "treatment" for the "purpose of the study" field. ◆

2 Merits, risks and proposed solutions for coronavirus disease 2019 (COVID-19) trials in Australia

	Merits	Risks and research gaps	Proposed solutions
Speed of response	Rapid response to emerging pandemic	Haste in funding, development and implementation may have jeopardised scientific and ethical rigour	Develop protocols for fast track procedures in emergency scenarios balancing rigour and urgency
Number of trials and sample size	Impressive research scale-up, many trials being launched	Most trials relatively small, limited statistical power to detect effects on clinically important outcomes (eg, mortality)	Consider evidence synthesis opportunities throughout trial conduct, facilitate collaboration and coordination to enable pooling of data and results
Core outcomes and evidence synthesis	Core outcomes have been developed early in the pandemic to enable successful evidence synthesis	Data sharing/collaboration intentions are low	Encourage and create infrastructure for collaboration (eg, in prospective meta-analyses) through funding bodies and trial registries
		Low proportion of trials collecting core outcomes (eg, only 53% assess mortality)	Establish a recognition system for collaboration and data sharing following FAIR principles
Innovation	Range of innovative interventions (eg, vaccine solutions and digital health solutions) balanced with repurposing of existing treatments	Lack of innovation in trial design (eg, only two trials using adaptive designs)	Increase use of adaptive designs to respond to the rapidly changing evidence landscape
	Innovation in trial conduct (digital recruitment and delivery modes)		
Types of interventions and populations studied	Broad array of drug categories investigated	Extensive media coverage and public opinion may have misled research prioritisation (eg, too many hydroxychloroquine trials)	Improve research coordination and prioritisation through infrastructure (eg, funders, trial registries) to ensure a variety of priorities are met and to avoid duplication of effort
		Few non-pharmaceutical trials and no trials on public health communication or community transmission prevention	
		Few trials included populations at high risk of poor outcomes from COVID-19 such as those with comorbidities	

FAIR = findable, accessible, interoperable, reusable. ◆

in trial design was lacking. We identified only two trials using adaptive methods (Bayesian designs), which can respond to the rapidly changing landscape of treatment options and thus deliver results more efficiently.

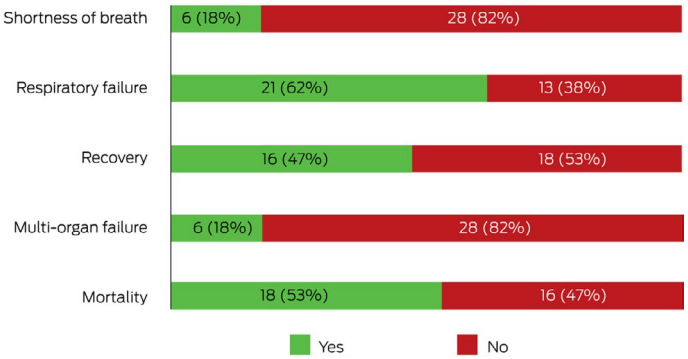
Trials often underpowered for clinical outcomes

The median target sample size was small (150; interquartile range, 33–395), meaning that, individually, trials were likely underpowered to detect differences in clinically important outcomes.[6] For example, to detect a 30% relative reduction in mortality (similar to that observed for corticosteroids[7]) with 80% power, a sample size of 4424 in a hospitalised population (with a baseline mortality rate around 7%[8]) would be needed (Supporting Information, figure 2). None of the identified treatment trials are sufficiently powered to detect such a difference in mortality; and with low case numbers in Australia, it seems unlikely that a single trial could obtain such large sample sizes.

Limited collection of core outcomes precludes evidence synthesis

Evidence synthesis in the form of a meta-analysis across trials is critical to obtain sufficient power to detect differences in core outcomes or subgroups of participants, particularly when individual trials are underpowered. Core outcome sets were agreed early in the pandemic and are evolving.[6] We assessed availability of the identified core outcomes mortality, respiratory failure, multi-organ failure, shortness of breath, and recovery (Supporting Information, table 5).[4] Of the 34 COVID-19 treatment trials in Australia, the proportion assessing each core outcome was low (Box 3). For

3 Core outcomes collection among 34 coronavirus disease 2019 (COVID-19) treatment trials



Only COVID-19 treatment trials (n = 34) are included in this analysis, as prevention or education trials or trials on indirect effects of COVID-19 (eg, mental health) may not collect these core outcomes. ◆

instance, only 53% (18 trials) assessed mortality, and 18% (six trials) assessed shortness of breath, whereas 63% (21 trials) assessed respiratory failure. Only one trial included all core outcomes, and ten trials (29%) included none. Thus, it will be impossible to synthesise results or make important comparisons for many of the trials.

Data sharing intentions low

The International Committee of Medical Journal Editors (ICMJE) declared data sharing an ethical obligation[9] to honour the risk trial participants take by increasing the likelihood that their participation results in useful findings.[2,9] Since the COVID-19 pandemic began, there have been several high profile calls for collaboration and data sharing across studies to enable more complex analyses and reliable effect estimates than would be obtained by simple combination of aggregate data.[2,10] These calls seem to pass largely unheard among triallists in Australia, with 80% (41 trials) indicating they are not planning to share data (Supporting Information, table 6). While these declarations at trial outset may be conservative and investigators may decide to share data later, they are still concerning. Frequently mentioned barriers to data sharing include a lack of understanding of the relevance, lack of resources to prepare data, insufficient academic recognition, and concerns about participant privacy, ethics approval and data misuse.[11] Structural support by funding bodies, research institutions, ethics committees and journal editors is needed to address barriers and facilitate data sharing.[11] This could include a recognition system for collaboration and data sharing and standardised moderated processes for data sharing following FAIR (findable, accessible, interoperable, reusable) principles.[12] No recognised FAIR data repository is yet available in Australia.[12]

Opportunities for strategic coordination and collaboration

As the COVID-19 pandemic evolves, the clinical and societal need for research evidence will continue. There may be shifts in research focus as our understanding of COVID-19 grows, perhaps to "long COVID-19" or other sequelae. Coordinating research efforts is a cost-effective, more reliable and timely way of achieving larger sample sizes and, thus, more impactful research evidence. Prospective meta-analyses and other next generation systematic review approaches provide suitable frameworks to coordinate such collaborative research efforts and to align key elements of study design, such as core outcomes.[13,14] Internationally, researchers have begun applying these frameworks to the pandemic,[2,10] including an influential prospective meta-analysis evaluating corticosteroid treatment for COVID-19.[7]

In Australia, the COVID-19 pandemic has led to rapid changes in some processes including fast-tracked funding, ethics approvals, trial registration, and publication.[15] Yet, too little has happened in creating infrastructure and funding for rapid collaboration, advanced adaptive methodologies and data sharing. In future, with adequate funding for technological innovation, clinical trial registries may play a key role in automatically connecting similar trials and facilitating collaboration. The COVID-19 pandemic presents a unique opportunity to improve collaborative infrastructure and methodologies, and advance future research across all health areas.

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Supporting Information

Additional Supporting Information is included with the online version of this article.

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