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Clinical Trials in Global Health 4

How COVID-19 has fundamentally changed clinical research in global health

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COVID-19 has had negative repercussions on the entire global population. Despite there being a common goal that should have unified resources and efforts, there have been an overwhelmingly large number of clinical trials that have been registered that are of questionable methodological quality. As the final paper of this Series, we discuss how the medical research community has responded to COVID-19. We recognise the incredible pressure that this pandemic has put on researchers, regulators, and policy makers, all of whom were doing their best to move quickly but safely in a time of tremendous uncertainty. However, the research community's response to the COVID-19 pandemic has prominently highlighted many fundamental issues that exist in clinical trial research under the current system and its incentive structures. The COVID-19 pandemic has not only re-emphasised the importance of well designed randomised clinical trials but also highlighted the need for large-scale clinical trials structured according to a master protocol in a coordinated and collaborative manner. There is also a need for structures and incentives to enable faster data sharing of anonymised datasets, and a need to provide similar opportunities to those in high-income countries for clinical trial research in low-resource regions where clinical trial research receives considerably less research funding.

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This is the fourth in a **Series** of four papers about clinical trials in global health

All papers in the **Series** are available at www.thelancet.com/series/clinical-trials-global-health

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Introduction

Since the beginning of this Series on clinical trials in global health, the global pandemic of COVID-19 has occurred. This major global health threat has highlighted the importance of global health by reminding us how diseases arising from a single country can affect all other countries, and how health risks and inequities transcend national borders. The pandemic has had negative ramifications on the entire global population. We recognise the incredible pressure this pandemic has put on researchers, regulators, and policy makers, all of whom are doing their best to move quickly but safely in a time of tremendous uncertainty, but the readiness of the research community to bring about rapidly informed decisions on the basis of research evidence has been inadequate. The challenges faced in the global response to initiate and coordinate COVID-19 clinical trials are not new, but the problems and limitations that have existed for clinical trial research have arguably become much more visible.

Despite there being a common goal that should unify resources and efforts, clinical research efforts around the world might easily be described as chaotic and exclusive of many low-income and middle-income countries (LMICs). The global collective clinical trial response to COVID-19 has occurred with inadequate collaboration between researchers. Inconclusive research findings from many clinical trials have re-emphasised the importance of high-quality clinical trial research.

As the final paper of this Series on global health trial research, we discuss the need to embrace coordination and collaboration instead of competition in medical and public health research. We specifically draw on the COVID-19 pandemic to describe how the research community has responded to the outbreak.

How the medical research community has responded to COVID-19

The new norm of publishing: quantity over quality

The COVID-19 pandemic's threat to global security and the economy has captured the entire world's attention. The number of COVID-19 cases continues to rise globally with little sign of slowing down.[1] The COVID-19 pandemic has mobilised researchers worldwide on a scale and timeframe that have never been seen before for one specific disease. In hopes of rapid discovery of therapeutics, vaccines, and diagnostics for COVID-19, a substantial amount of money is being invested towards clinical research. Despite the sheer volume of research

Key messages

- The incredible pressure that the COVID-19 pandemic has put on researchers, regulators, and policy makers, all of whom were doing their best to move quickly but safely in a time of tremendous uncertainty, should be recognised. However, the medical research community's response to COVID-19 has arguably been inefficient and wasteful, with an overwhelmingly large number of clinical trials having been registered and done with questionable methodological quality. The COVID-19 pandemic has highlighted the need for more coordination and collaboration in clinical trial research.
- Most clinical trials that have been done for COVID-19 have been too small in scale to provide conclusive evidence. Investing in large-scale clinical trials that can facilitate international collaboration will be important to generate high-quality data efficiently that can inform policy and change clinical and public health practices.
- Instead of independent clinical trials, coordination and collaboration could be more effectively facilitated by consolidating funds towards master protocols.
- Although sharing of individual participant-level data has historically proven to be challenging from both private and public researchers, as shown by the COVID-19 pandemic, there is a need to mandate data sharing, expedite systems to apportion credit for data sharing, and preserve commercial interests.

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and discussion on the research related to COVID-19, we will illustrate in this Series paper that we are not fighting this common fight very efficiently.

In response to COVID-19, the research community has rapidly adopted a new way of research dissemination but, unfortunately, how that research is being done has not changed. There has been a surge of COVID-19-related preprints and peer-reviewed publications on a scale that has never been seen in other areas of health-care research.[2–4] As of Sept 30, 2020, there were 9214 COVID-19-related preprints on major preprint servers such as *medRxiv* and *bioRxiv*.[5] The number of COVID-19 manuscripts being submitted for peer review has also greatly increased. For instance, *The Journal of the American Medical Association* has indicated that more than 11 000 manuscripts were submitted between Jan 1 and June 1, 2020, whereas around 4000 manuscripts were submitted during the same period in 2019.[4] Scientific journals have accelerated their peer review process to expedite the publications of studies for COVID-19.[2,4,6] One analysis shows that the time between submission and publication of articles on COVID-19 has decreased on average by around 50%, from 117 days down to 60.[6] This analysis also showed that the time to publication for research not related to COVID-19 has remained unaffected,[6] but it is probable that the number of research articles unrelated to COVID-19 has dropped considerably, with COVID-19 predominating in receipt of funding and attention from the research community.

There are clear merits of preprint servers and having a faster peer review process, as results can be disseminated quicker and potentially be used to inform policies and speed up the research and development (R&D) process for COVID-19 therapeutics and vaccines. Unfortunately, COVID-19 research has largely not been of high quality so far and many preprints, which are not peer-reviewed, were rushed to dissemination without sufficient oversight. The differentiation between preprints and peer-reviewed publications with appropriate oversight became blurred. The floods of preprints and publications from COVID-19 research have created confusion, not only among the scientific community, but also among the public, who are eagerly waiting for the scientific community to make the next breakthrough for COVID-19. The aim is to strike a balance between quickly disseminating data via preprint servers while ensuring that the work is scientifically credible.

The clinical trial landscape for COVID-19

During the COVID-19 pandemic, the importance of well designed randomised clinical trials has been re-emphasised,[7,8] owing to studies being published with questionable findings[9–12] and due to an overwhelming number of COVID-19 clinical trials that are being done without methodological rigour and adequate planning.[13] Close to 2516 clinical trials were registered globally as of Nov 27, 2020 with 1278 actively recruiting participants.[13] These trials are looking at patients in contexts ranging from pre-exposure prophylaxis through to severely ill hospitalised patients. The experimental interventions that are being evaluated vary greatly, ranging from herbal preparations through to invasive medical procedures, vaccines, and experimental stem-cell therapy. The majority of trials have involved patients who have been admitted to hospital, and few clinical trials have investigated earlier stages of the disease process such as pre-exposure, or post-exposure and outpatient treatment.[14] With regard to treatments, although there are more than 100 unique therapeutic agents being investigated, there is also substantial overlap and duplicated trial efforts as the majority of these trials are evaluating drugs that are already approved for other indications, such as hydroxychloroquine and lopinavir–ritonavir, but that are being repurposed for COVID-19.[13] These trials have, on average, planned sample sizes of fewer than 100 participants, and are typically evaluating only one experimental intervention.[13]

It is also striking that study dose regimen comparisons have largely been absent in the current trial landscape of COVID-19.[15] It is generally well accepted that confirming dose–response in a clinical environment is the foundation to defining an optimal dose regimen, the core clinical pharmacology principle that researchers are overlooking due to the urgency to find COVID-19 treatments. Failing to explore an adequate dose range or not including dosing that accounts for pharmacokinetic and pharmacodynamic variability in different patient populations can lead to an effective treatment being determined as falsely ineffective.[16] In addition to the requirements of determining a safe and effective dose, the shortage of clinical pharmacology in these clinical trials will potentially be problematic for manufacturing and scale-up efforts.[17] As a result, clinical pharmacology professional societies have issued global calls to action to accelerate the development of COVID-19 therapeutics, as the ignorance relating to the science of dosing has added to the inefficiencies of the global clinical trial landscape.[15]

The current trial landscape of COVID-19 highlights important issues that illustrate the inefficiencies of clinical trial research. Most COVID-19 trials are small, so they will not provide sufficient statistical power to detect a meaningful treatment effect. Most will never achieve their target recruitment numbers. Many are investigating identical or similar treatments with dose regimen selection being made without adequate clinical pharmacology. The preponderance of two-arm trials also leads to other important issues. Instead of doing multi-arm or platform trials with a common control group, the prevalence of two-arm trials has resulted in multiple redundant control groups, which is an another example of inefficient clinical trial practices. Different trials being run in the same region or institution

will ultimately compete for participants and delay recruitment into well designed trials that can provide reliable scientific evidence.[8] Given that many COVID-19 trials have been done across different geographical settings without standardised operating procedures and have been powered according to different endpoints, it has been difficult to make sense of the data from these trials.

Problems with published peer-reviewed trials

68 published peer-reviewed articles of randomised clinical trials on COVID-19 were available as of Dec 4, 2020 (appendix pp 2–4). Given the location of where the COVID-19 pandemic originated, a large proportion of this trial evidence (21 [31%] of the 68 clinical trials) comes from China. Most of these clinical trials have been done in the hospital setting (61 [90%] of 68). Hydroxychloroquine was the most commonly investigated intervention (14 [21%])[18–32] followed by lopinavir–ritonavir as either monotherapy[33,34] or combination therapy[35–37] (five [7%]), and remdesivir[38–41] (four [6%]).

14 (21%) trials did not report any information on sample size or power calculation.[19,42–54] The other trials that reported the sample size calculation had a median recruitment target of 186 (IQR 81·5–393) participants, highlighting that most of the trials were not large enough to provide convincing answers unless the treatment effect was overwhelmingly large. It is important to note that most of these COVID-19 trials were published without meeting their recruitment target due to the waning of the virus epidemiology in the studied regions. The median number of participants recruited into these published COVID-19 trials (87 [IQR 52–199]) was smaller than the median planned recruitment target. Of the 54 trials that reported information on planned sample size, 25 (46%) did not meet their recruitment target; in fact, on average they only recruited about half of their planned sample (median 52·3% [IQR 31·7–80·6%]).

Despite registered trials from 40 different countries worldwide, the epidemiology will vary across regions due to differences in physical distancing and other public health measures. We predict that a large number of COVID-19 trials will stop early, not for statistical reasons but because of insufficient recruiment.[13] For instance, despite the public health measures in China that reduced the number of active COVID-19 cases considerably, the number of clinical trials being registered in China, like many other countries around the world, has continued to rise.[13] Given that the recruitment target greatly exceeds the number of daily active cases in China, the fierce competition for patients has led to early termination of many of these trials in China. While the number of COVID-19 cases continues to rise globally, there is likely to be similar competition for patients between different trials being done in other regions of the world.

Trials stopped early for feasibility are always going to be underpowered and thereby prone to produce inconclusive findings. Most of the COVID-19 trials will be underpowered, either by design or because they are terminated before reaching their recruitment target. During non-pandemic settings, the standard solution to the challenge of underpowered studies is to pool the reported aggregated results using pairwise or network meta-analyses.[55,56] For COVID-19, there will be many challenges of doing meta-analyses with aggregated reported data. First, even within trials studying the same intervention, there is substantial heterogeneity in dose, duration, endpoints, and data collected between different trials. Second, there is, in general, a shortage of data sharing and no coordinated global approach to aggregate data. Lastly, trials that fail to reach their recruitment target are less likely to be published and thus not available for typical meta-analyses.

See Online for appendix

Integration of different trial datasets for individual participant-level data (IPD) meta-analyses might be the only solution in determining what works and is safe for COVID-19.[57] However, the inadequate number of data sharing mechanisms that exists for COVID-19 is a major obstacle. For instance, except for the the USA and Canada randomised clinical trial on post-exposure hydroxychloroquine,[23] the authors of other publications have either declined to share IPD or have indicated that the corresponding author can be contacted for data access (appendix pp 5–6). The process of obtaining de-identified IPD from corresponding authors is very inefficient and time consuming, and often does not result in data sharing.[58] Researchers who have attempted to acquire IPD from other published trials know too well that a statement indicating that data can be accessed on request by contacting the corresponding authors is often just a requirement of the publishing process that is not subsequently honoured.

The need for coordination and collaboration

The research community's fulfilment to study participants

When individuals participate in clinical trials, they often hope to gain some benefits from new treatment interventions, but they can end up exposing themselves to risks.[59] Given the experimental nature of clinical research, risks to participants could be unavoidable. Although the value of clinical trials for society is different from the benefits that clinical trial interventions have on individual participants, study participants expect and want their data to be used responsibly to advance science.[60] The advancement of science and improved public health outcomes require collaboration, which includes publishing of all data, regardless of the results, and releasing them to the research community.

A single data repository

Sharing of IPD has historically proven to be challenging.[58] Rather than data sharing being optional, for investigators of COVID-19 there is a need to mandate data sharing,

expedite systems to apportion credit for data sharing, and preserve commercial interests. In the current COVID-19 pandemic, the need to share and collaborate openly supersedes personal careers or organisational goals. Funders could facilitate data sharing by having a mandate of sharing anonymised data as a requirement for funding. Funders should also ensure that any publications resulting from secondary data analysis credit the data generators.

As the processes for dealing with personal privacy, data security, and data standardisation have become sufficiently more sophisticated over the past 10 years, there is no real barrier to centralising and sharing IPD from different clinical trials under one repository.[61] Investigators that have started clinical trials can utilise existing global clinical research data-sharing platforms, such as Vivli[61] and Health Data Research UK, in which data can be collectively and securely curated and analysed. The data from different trials can be pooled to answer meaningful public health questions, rather than staying inconclusive in isolation.[57]

For more on **Health Data Research UK** see www.hdruk.ac.uk

The need for rapid and robust clinical research for discovery of effective and safe therapeutics and vaccines has never been higher. Strengthening the public health response to COVID-19 will require larger collated IPD sets to facilitate the scientific precision required for accurate assessment of COVID-19 medical interventions. As COVID-19 has forced reconsideration of policies, processes, and interests, now is the time to advance scientific cooperation and shift the clinical research enterprise toward a data-sharing norm that can maximise the response to the COVID-19 pandemic in the service of public health. Given their small-scale design and inability to reach their recruitment target, most clinical trials done so far will not provide conclusive answers that can be used to inform new practices for COVID-19. If investigators of clinical trials all over the world share their data in a single data repository that is accessible to the research community, these data can be used collectively to make sense of which therapies work and are safe for patients with COVID-19. Key principles of data sharing are provided in panel 1.

Panel 1: Principles of data sharing

Data sharing in the context of clinical research can often be challenging. Researchers work in a global context and with a variety of internal and external tools for tracking clinical trial data. In tandem, legislation surrounding the transmission of personal or even anonymised health data varies worldwide and is subject to substantial scrutiny. Several international partners have worked through these hurdles and have developed key principles of data sharing, often referred to as the findable, accessible, interoperable, and reusable (FAIR) data principles. Findable data refers to developing a common system to allow for machine and human readable data with explicit and rich data identifiers to facilitate cross-collaboration. In the context of COVID-19 trials, an example could be unique patient identification numbers to ensure no inappropriate double-counting of data. Accessible data refers to the methods utilised to access and authenticate data, using a common protocol and facilitating security requirements for human data. In the context of COVID-19 trials, this method could be a validation process for researchers to access the shared data asset while ensuring appropriate clinical governance. Interoperable refers to the use of common language (ontology) to facilitate similar data standards. In the context of COVID-19 trials, this approach might involve harmonisation of key clinical characteristics (eg, disease severity) to enable appropriate selection of relevant data. Reusable refers to the end result of the FAIR principles, by creating a dataset that can be mined globally to ensure that relevant research might perpetuate through novel research questions and analytical capabilities, while retaining strong scientific rigour.

Smarter investments for clinical trial research

The aim of clinical trial research is to generate high-quality evidence to inform new clinical practices and public health policies. Given the scarcity of funding, funding clinical trial research can mean that there is less funding available to implement public health initiatives (and vice versa). Recognising this trade-off between clinical trial research and clinical practice and public health,[62] investments should be made that enable coordination and collaboration in clinical trial research. Smarter investments for clinical trial research—whereby funds are allocated to clinical trials that are asking important research questions and that are well designed—should be made so that the funded trials have a high probability of generating conclusive evidence that can inform clinical practice and public health policies. As currently experienced in the era of COVID-19, uncoordinated funding schemes will probably continue funding multiple independent trials that are too small to provide conclusive evidence.[13]

The COVID-19 pandemic has catalysed the acceptance of master protocols by the research community as there is a clear need for more structured and sustainable approaches to clinical trial evaluation (a detailed discussion of master protocol framework can be found in the second paper of this Series[63]). For instance, on Feb 18, 2020, WHO's R&D Blueprint—a global strategy and preparedness plan to increase the R&D processes of diagnostics, therapeutics, and vaccines during epidemics—released a core master protocol for COVID-19.[64–66] This core protocol outlined plans for clinical trial evaluation in hospitalised patients, including an ordinal clinical progression scale that was formulated by a special WHO committee.[66,67] WHO's core master protocol has been widely shared as a template for potential COVID-19 treatments across multiple sponsors and investigational teams and has helped to standardise clinical outcomes across different trials.[68]

Recognising the critical importance of discovering effective and safe interventions for COVID-19, WHO has also leveraged its international influence and is doing an adaptive platform trial called the Solidarity trial (panel 2). WHO's Solidarity I trial (ISRCTN83971151) has now been expanded to more than 100 countries worldwide since being announced on March 18, 2020, and is recruiting patients hospitalised with COVID-19.[69] In parallel with this trial, WHO will begin Solidarity II, a global serological study to better understand immunology

Panel 2: WHO's Solidarity I trial

The Solidarity I trial (ISRCTN83971151) is a multinational randomised clinical trial, co-sponsored by WHO and participating countries.[69] The Solidarity I trial enrols hospitalised adults (aged ≥18 years) with confirmed COVID-19 to compare four treatment options against standard of care to assess their relative effectiveness against COVID-19. Study drugs include remdesivir, hydroxychloroquine, lopinavir (fixed-dose combination with ritonavir), and interferon-β1a (mainly subcutaneous; initially with lopinavir). Although hydroxychloroquine was originally one of these four treatment options, on June 17, 2020, WHO announced that the hydroxychloroquine arm would be dropped. The Executive Group of the Solidarity trial and principal investigators based this decision on evidence from the Solidarity I trial, the UK's RECOVERY trial, and a Cochrane review.[70–72] WHO states that the evidence showed that treatment with hydroxychloroquine does not reduce mortality in patients with COVID-19 who have been hospitalised compared with standard of care.[69] However, the decision applied only to the Solidarity trial and not to studies evaluating hydroxychloroquine as a pre-exposure or post-exposure prophylaxis. Under the adopted master protocol framework outlined in WHO's R&D Blueprint,[64,73] adults with COVID-19 being admitted to participating hospitals are being managed in a standardised way across multiple different institutions. The local medical team is responsible for identifying any unsuitable study treatments for the consenting patients. Following this initial assessment, identifying details and conditions are digitally recorded, and the patient is randomly allocated to one of the treatment options in a common electronic data capture system. Anonymised information is collected at randomisation and at discharge or death for each patient, including: study drugs and dose; use and duration of ventilation or intensive care; and date of discharge or date and cause of death in hospital. A global data and safety monitoring committee are monitoring the safety and interim efficacy of the individual interventions. More than 12 000 patients had been recruited in 43 countries as of Oct 2, 2020, and more than 116 countries have expressed interest or joined the trial. WHO actively supports these countries with regard to the "ethical and regulatory approvals of the WHO core protocol; identification of hospitals participating in the trial; training of hospital clinicians on the web-based randomization and data system; and shipping the trial drugs as requested by each participating country".[74] WHO states that the Solidarity trial will reduce the time taken to design and complete randomised clinical trials by 80%. By recognising the importance of master protocols, this enables global comparisons to generate evidence to determine the relative effectiveness of treatments.

and other biological profiles of COVID-19.[75] WHO is also planning a prophylaxis study (Solidarity III) to evaluate possible therapeutic options that can prevent health-care workers and other high-risk populations from contracting SARS-CoV-2.[76]

The international collaboration for the Solidarity trials is being coordinated by WHO. To facilitate collaboration across different hospitals and different countries, WHO has streamlined the patient enrolment and centralised web-based randomisation procedures that do not require paperwork. Participating countries or groups of hospitals are not required to participate in serial virology or other serial documentations of disease status to ensure that the burden of research duties in participating hospitals is minimised. In addition to a centralised randomisation and data capture system, harmonised statistical support is being provided with interim analyses being monitored by a global data and safety monitoring committee under a core master protocol. WHO has also set up a COVID-19 Solidarity Response Fund to allow donations that will help fund the Solidarity trials.

Although misunderstanding of platform trials and master protocols is common,[77–79] integrated research efforts for trials of COVID-19 interventions and ideally for other areas of research should be structured through master protocols and platform trials. Platform trials are multi-arm perpetual clinical trials that allow comparison between all active drugs and, on the basis of interim evaluations, allow arms to be dropped or added mid-trial to improve efficiency.[77,79–81] A master protocol generally refers to a single overarching protocol designed to answer multiple interventional questions that would otherwise require several separate clinical trials.[79,82] Under the master protocol framework, platform trials (and other innovative clinical trials) often establish a large trial network with a common infrastructure across and within multiple institutions that are able to join and leave over time.[79–81] Between these institutions, common screening mechanisms, data collection, and other standardised operating procedures are implemented, creating a research ecosystem that can generate high-quality data and answer multiple research questions.[79,80]

The research ecosystem for preparedness and sustainability

Important lessons from COVID-19 have illustrated the need for pre-existing resource-efficient trial sites and capacity. Efficient clinical trial research requires trained personnel and strong clinical and laboratory infrastructure, data management systems, safety monitoring, and institutional oversight. Establishing a master protocol for a platform trial can help establish an efficient research ecosystem that is prepared for a future pandemic. For instance, before the COVID-19 pandemic occurred, a platform trial had already been prepared for a respiratory disease pandemic. The Randomised,

For more on the **WHO COVID-19 Solidarity Response Fund** see https://covid19responsefund.org/en/

Panel 3: REMAP-CAP trial

The Randomised, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP; NCT02735707) is a platform trial evaluating the effects of a range of interventions to improve the outcomes of patients admitted to the intensive care unit (ICU) with community-acquired pneumonia.[83] The adaptive trial design was planned, before the COVID-19 pandemic, for the evaluation of multiple treatments in the event of a respiratory pandemic resulting in critical illness. REMAP-CAP has since changed its original focus of community-acquired pneumonia to COVID-19. The trial spans 233 active sites with a total of 1195 patients, including 657 patients with suspected or confirmed COVID-19 (as of June 25, 2020). The existing infrastructure and protocol enabled REMAP-CAP to efficiently and rapidly adapt in the event of the COVID-19 outbreak. The key changes included "modification of the primary end-point, so that information is available more quickly; description of the statistical model that will be used to analyze data for patients with proven or suspected pandemic infection; description of changes to statistical thresholds for declaring an intervention to be equivalent, superior, or inferior to another; and specification of pathways that permit the Data Safety Monitoring Board to liaise directly with public health authorities if REMAP-CAP produces results that are of relevance to public health".[74] The COVID-19 domains of REMAP-CAP include the evaluation of long-term macrolide therapy as a modulator of immune function, and the evaluation of alternative corticosteroid strategies. An additional five domains specific to COVID-19 were granted ethical approval. These domains are: (1) antiviral therapy (no antiviral therapy for COVID-19 [and no placebo], lopinavir–ritonavir, hydroxychloroquine, and the combination of hydroxychloroquine and lopinavir–ritonavir); (2) immune modulation therapy (no immune-modulating therapy for COVID-19 [and no placebo], interferon beta, IL-1 receptor antagonist [anakinra], tocilizumab, and sarilumab); (3) antibody therapy (convalescent plasma); (4) therapeutic anticoagulation (low molecular-weight heparin or unfractionated heparin compared with standard pharmacological thromboprophylaxis); and (5) vitamin C (high-dose vitamin C for patients with severe community-acquired pneumonia including pneumonia caused by COVID-19). Additional interventions continue to be considered for introduction to the trial. Given that REMAP-CAP had planned for a respiratory pandemic using an adaptive clinical trial design before the COVID-19 pandemic, the already existing protocol and the trial's infrastructure was able to start enrolling patients with COVID-19 being admitted to ICUs across several countries.

For more on the **REMAP-CAP trial** see https://www.remapcap.org/

Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP; NCT02735707) is a platform trial that commenced on April 11, 2016.[83] REMAP-CAP was already enrolling patients being admitted to the intensive care unit (ICU) for community-acquired pneumonia and had a pre-written appendix as part of their master protocol for inclusion of an influenza-like population should a pandemic occur[83] (panel 3). Other trial sites have joined the REMAP-CAP for the COVID-19 outbreak, expanding its already large research ecosystem network to 233 active sites, and have randomised more than 600 patients admitted to the ICU with suspected or proven COVID-19.

For more on the **RECOVERY trial** see https://www.recoverytrial.net/

This foresight could represent an approach that funders and future trialists should consider by having a worst-case scenario in their planned master protocols. Strengthening the research ecosystem so that it is more resilient and dynamic will not only be important for the COVID-19 pandemic, but also for future pandemics and other diseases with high unmet needs that are difficult to treat. Master protocols can be leveraged to encourage collaborations to generate scientific evidence in a timely manner while promoting rigorous standards between different regions of the world. As seen with REMAP-CAP, the existing infrastructure established through the master protocol can also be leveraged and extended to other research questions, including critical questions regarding unanticipated pandemics (panel 3). Undoubtedly, developing a master protocol for all diseases and establishing clinical research networks will have its challenges, and will require foresight and a considerable amount of up-front work. But this model of research—large scale, collaborative, across borders, and designed to efficiently answer questions with patient-centred endpoints—will be essential for any new or re-emerging infectious disease outbreak.

National-level collaboration

National-level collaboration and buy-in from major stakeholders are important components of clinical trial research, which has been exemplified by the Randomised Evaluation of COVID-19 Therapy (RECOVERY; ISRCTN50189673; NCT04381936) trial during the COVID-19 pandemic (panel 4). The RECOVERY trial is a large adaptive platform trial evaluating multiple different interventions for patients hospitalised with COVID-19 across 176 hospitals in the UK. The national-level buy-in is highlighted in the joint letter written by the UK's four medical officers and the medical director for National Health Service (NHS) England and NHS Improvement on May 6, 2020, that encouraged physicians and hospitals to enrol patients into the RECOVERY trial and three other platform trials (ie, ACCORD, PRINCIPLE, and REMAP-CAP).[86] With such national buy-in and cooperation, this trial was able to rapidly recruit 11 841 patients in a short span of around 4 months (from March 19 to June 25, 2020), and this trial, to date, has generated the most convincing

Panel 4: **RECOVERY trial**

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial (ISRCTN50189673; NCT04381936) is a large adaptive platform trial with a factorial design that is evaluating multiple different interventions for hospitalised patients with SARS-CoV-2 infection against usual hospital care in the UK. As of June 25, 2020, 11 841 patients have been enrolled in the RECOVERY trial across 176 hospitals. Rapid recruitment for the trial was made possible due to unprecedented leadership and national-level collaborations across the UK. The RECOVERY trial, to date, has generated the most convincing evidence on the clinical efficacy of two different therapies for patients hospitalised with COVID-19. On June 5, 2020, the RECOVERY trial researchers announced their decision to discontinue their evaluation of hydroxychloroquine due to complete absence of clinical efficacy.[84] When data from 1542 patients were randomly assigned to hydroxychloroquine and were compared with 3132 patients randomly assigned to the control group, hydroxychloroquine did not show any clinical benefits on 28-day mortality (23·5% in the control group *vs* 25·7% in the hydroxychloroquine group; hazard ratio 1·11 [95% CI 0·98–1·26]). On June 22, 2020, the RECOVERY trial published their preliminary findings on low-dose dexamethasone (6 mg once daily for 10 days) as a preprint.[85] This analysis included data from 2104 patients who were randomly assigned to the dexamethasone group and 4321 patients randomly assigned to the control group. For the overall population, dexamethasone had an age-adjusted relative risk (RR) of 0·83 (95% CI 0·74–0·92) for 28-day mortality when compared with the control group (mortality rate of 21·6% in the dexamethasone group *vs* 24·6% in the control group). The mortality reduction benefits varied among patients that received different levels of respiratory support at randomisation. For instance, dexamethasone did not significantly reduce mortality in patients who did not receive any ventilation support (RR 1·22, 95% CI 0·93–1·61), but there were important mortality reduction benefits from dexamethasone for patients who received non-invasive ventilation (RR 0·80, 0·70–0·92) and invasive mechanical ventilation (RR 0·65, 0·51–0·82). As of Nov 26, 2020, the RECOVERY trial is investigating dexamethasone in children only, and colchicine, tocilizumab, convalescent plasma therapy, REGN-COV2 (casirivimab plus imdevimab), and aspirin in the prevention of mortality among inpatients with COVID-19 within the UK National Health Service hospitals. There might be also be new interventions that could be added into this large trial network established across the UK.

evidence on the complete absence of clinical efficacy of hydroxychloroquine and the clinical efficacy of dexamethasone for patients hospitalised with COVID-19.[84,85]

Capacity and infrastructure building in LMICs

There has been inadequate geographical representation of LMICs in the COVID-19 clinical trials landscape.[13,87] The majority of ongoing COVID-19 clinical trials are being done in the EU, the UK, and North America, and there are very few trials being done in Africa, south and southeast Asia, central America, and South America.[13,87] There is an essential need to expand evaluation of affordable and scalable COVID-19 interventions in low-resource settings, as they are often hit harder by the adverse effect of disasters and pandemics of this magnitude due to extreme poverty of their population and a fragile health-care system.[88,89]

Since most monetary funding for research in LMICs comes from outside the regions, there has almost always been a power imbalance between the researchers from the sponsoring high-income countries (HICs) and the researchers within LMICs.[90,91] HIC researchers should not just involve LMIC researchers as a means of recruiting trial participants; it is important to have a true collaborative scientific partnership from the project conception. More equitable collaborations between HICs and LMICs can have a multitude of benefits for global health research. Effective engagement with representatives from the study location can be an effective tool to formulate important research questions by identifying contextually adapted needs and priorities set by the country or countries in which the study is based. Effective engagement through equitable collaboration can improve contextual understanding of the study region so that appropriate interventions and trial design strategies are developed, leading to meaningful and valid outputs that can be used to inform policies, change public health, and benefit clinical practice.

Funding decisions about clinical trial research should aim to create long-term support for LMICs. Long-term human resource utilisation should be viewed as a top priority, as it can be an effective measure to address common concerns regarding education or training and the capacity of the region to undertake high-quality clinical trial research.[92] Efforts to build capacity for clinical trials have been led by organisations such as the Cochrane Collaboration and universities in which clinical trial capacity building is frequently provided as short workshops by visiting investigators.[93,94] Unfortunately, in global health research, investigators usually only recruit staff for the duration of the trial, when resources permit, and staff are removed from their jobs after completion of the trial. The short-term nature of many clinical trials often results in a subsequent loss of intellectual and infrastructural capacity when the trial has ended; therefore the opportunity to improve local capacity and infrastructure is missed. The capacity of regulatory and ethical oversight review committees in LMICs should also continue to be developed. A major hurdle in rapid regulatory and ethical oversight review committees in

LMICs is that the expert reviewers typically have full-time employment commitments in academia and volunteer or contribute part-time to the review committee. Capacity development should therefore extend beyond frameworks and systems and include the development of funding models to recruit and maintain dedicated expert reviewers.

To reach the long-term goal of building sustainable capacity for clinical research in LMICs, then it is important to move away from funding short-term small-scale clinical trials. Instead of multiple clinical trials that compete against each other, platform trials can create a framework in which multiple questions can be addressed over time in one large trial that can provide convincing and conclusive evidence.[8,64] Platform trials can also be used to improve capacity and infrastructure in LMICs. For instance, funding large-scale long-term platform trials can help to ensure long-term involvement of local staff, providing opportunities for the staff to develop skills and gain experience, ultimately helping to build technical and other research skills in the region. The overall process of clinical trial research should leave behind a footprint of expertise and a sustainable infrastructure. Beyond providing access to the interventions if they are shown to be superior to the standard of care, clinical trial research in LMICs should plan post-trial actions that contribute to the country's economy, such as long-term plans for human resources and infrastructure.

There is an immense potential to build sustained infrastructure in low-resource environments, reduce human resource challenges and costs, and more efficiently partner with LMIC communities. Perpetual clinical trials provide an opportunity to answer multiple questions about several interventions in the most efficient way imagined, paving a pathway for continuous improvement. Building on successful examples of perpetual trials, such as the Solidarity trial, REMAP-CAP, and the RECOVERY trial, and expansion into low-resource settings will allow for opportunities to build capacity and infrastructure in these countries. We hope for an openness by funders to embrace these innovative approaches for LMICs, not only for COVID-19 research, but also to answer other important clinical research questions. This approach would require a considerable amount of collaboration between researchers, but it is clear that collaborative research practices are important to prevent a chaotic, competitive landscape when doing clinical trial research in the future.

Conclusions

There is a need to improve coordination and collaboration in clinical trial research for global health. Under the current incentive system, clinical research efforts around the world will probably continue independently with issues that have been highlighted in the previous papers of this Series[95,96] and in this fourth paper through the example of COVID-19. We hope that the COVID-19 pandemic will become a historical turning point that leads to better coordination and collaboration within the medical research community, but this outcome will first require buy-in from funders and global health researchers (particularly those in HICs) who currently control the design of trials.

Contributors

JJHP and EJM conceptualised the paper. JJHP, RM, GES, CRR, EHD, JBN, GR, and EJM acquired and analysed the data. All authors interpreted the data. JJHP and EJM drafted the paper. All authors critically revised the manuscript for important intellectual content. EJM obtained the funding, and JJHP and EJM provided administrative, technical, and material support, and supervised the study.

Declaration of interests

We declare no competing interests.

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