

# Ethical rationale for better coordination of clinical research on COVID-19

Research Ethics  
1–10© The Author(s) 2020  
Article reuse guidelines:[sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)

DOI: 10.1177/1747016120931998

[journals.sagepub.com/home/rea](https://journals.sagepub.com/home/rea)**Francois Bompert** 

Drugs for Neglected Diseases initiative, Switzerland

## Abstract

Hundreds of clinical trials of potential treatments and vaccines for the “coronavirus 19 disease” (COVID-19) have been set up in record time. This is a remarkable reaction to the global pandemic, but the absence of a global coordination of clinical research efforts raises serious ethical concerns. Some COVID-19 patients might carry the burden of clinical trial involvement even though their trial cannot be completed as researchers are competing for patients. A shortage of medicines can occur when existing drugs are diverted for clinical trials. Research ethics committees are overburdened with multiple applications. A multitude of trials can also overstretch medical staff and risk neglecting non-COVID-19 patients. And finally, conflicting conclusions from a multitude of heterogeneous trials might lead to delays in public health decisions about life-saving issues. These challenges are made worse by the unpredictable evolution of epidemics, the active involvement of political decision-makers in scientific issues and the pressure of social media globally. While freedom to conduct research must be safeguarded, global health emergency situations would greatly benefit from effective international coordination mechanisms for clinical research.

## Keywords

Research ethics, epidemics, pandemics, COVID-19, coordination, clinical trials

---

## Corresponding author:

Francois Bompert, Drugs for Neglected Diseases initiative, 15 Chemin Louis Dunant, Geneva 1202, Switzerland.

Email: [fbompert@dndi.org](mailto:fbompert@dndi.org)

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

The COVID-19 pandemic has led to an unprecedented mobilisation of research teams in multiple fields, all around the globe. From the very first days of the epidemic in China, the lack of effective treatments sparked a new research priority, and clinical researchers set out to test existing medicines (Cao et al., 2020; Dorward and Gbinigie 2020, Chen et al. 2020) as well as experimental ones (Wang et al., 2020). These efforts were quickly emulated all around the world. Meanwhile, multiple national and international funding initiatives have emerged to financially support these efforts.

This considerable mobilisation of talents, creativity and resources over just a few weeks, at a time of an unprecedented public health and economic crisis, is worthy of praise. Nevertheless, the sheer number of research studies planned, and the lack of global prioritisation mechanisms for these studies, raises multiple ethical issues.

Research on COVID-19 is undertaken in multiple pertinent areas, including virology, physiopathology, epidemiology, clinical research for preventive vaccines, clinical research for therapeutic interventions, social science research, and so on. To illustrate potential ethical concerns, the following text describes clinical studies involving patients who are exposed to, or infected by, the new coronavirus.

## **Clinical studies of COVID-19**

The US ClinicalTrials.gov (2020) database, used by clinical researchers worldwide to register studies, shows a large number of clinical studies related to COVID-19 and to the virus that causes it, called SARS-CoV-2. On 1 May 2020, only three months after the outbreak was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) (30 January 2020), a total of 1141 COVID-19 and SARS-CoV-2 studies were referenced in this database. These included 683 ‘interventional’ studies, which involve the testing of one or more preventive or therapeutic interventions such as vaccines, medicines and biologics. On the same day, 980 studies were listed on the WHO’s International Clinical Trials Registry Platform (WHO ICTRP) (World Health Organisation, 2020). The two databases overlap to a limited extent but, overall, approximately 2000 clinical studies on COVID-19, not all of them testing medicines or vaccines, were registered at this time.

The Infectious Diseases Data Observatory (IDDO) performed a systematic review of 728 active COVID-19 trial registrations in the first three months of the outbreak (Maguire and Guérin, 2020). It found that the majority of investigations were small studies likely to be unpowered to provide solid evidence. It observed the limitations of many trial designs, highlighted the duplication of efforts and concluded that the lack of coordination ‘will likely result in underpowered studies individually unable to generate meaningful evidence for policy makers’.

It is perfectly understandable that a large number and variety of clinical studies are registered for a disease as new as COVID-19. Many unanswered questions exist. Most pressingly, what are the benefits and drawbacks of experimental treatments at various clinical stages of the disease? For instance, the clinical effectiveness or benefit of a treatment might be quite different for people recently exposed to the virus from that for severely ill patients in intensive care units. However, from examination of the many similarities in the study objectives, and drugs to be tested (as evident from public databases), multiple instances of duplication of efforts are obvious. This situation raises serious ethical concerns.

## **Ethical concerns regarding COVID-19 clinical studies**

A key ethical issue arising from the conduct of multiple trials with similar objectives concerns the appropriate involvement of patients. Many teams, in a wide variety of locations around the world, are asking similar research questions and will use similar approaches to answer these questions. Each study must enrol sufficient numbers of patients to ensure statistically robust conclusions. Roughly similar studies will look to recruit the same COVID-19 patients. There is a risk that small or poorly designed studies will delay the enrolment of patients in the best designed studies which are often the largest and longest ones. In addition, relatively small differences between the studies, for instance in the way data are collected, may prevent combining their data to reach more powerful conclusions. All these factors can lead to a delay in the identification of effective and ineffective interventions.

Scientific studies impose a burden on research participants. This burden should not be wasted, for instance, on studies which cannot recruit sufficient numbers of patients to reach valid conclusions. As Article 6 of the Declaration of Helsinki (World Medical Association, 2013) notes:

The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments).

If trials cannot be completed due to insufficient numbers of participants, no understanding of the effect of the tested medicines will be achieved and hence risks will be taken by research participants in vain (and resources wasted). Furthermore, if participants are randomised to receive either experimental interventions or placebo, risks are taken by those in the placebo group without any potential for benefit.

Another issue concerns the availability of medicines for people who need them the most. The race to test the same medicines in multiple settings leads to surge in demand for particular drug supplies for clinical trials. This increases the risk of

shortages that is particularly problematic when studies aim to ‘repurpose’ existing drugs. One such example is hydroxychloroquine, which is used daily by patients with autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus or malaria. Another example is lopinavir/ritonavir for the treatment of HIV infection. Both are currently under investigation in a large number of COVID-19 trials. The burden of HIV affects resource-limited countries disproportionately and when HIV drugs are in sudden high demand for clinical trials in high-income countries, they may not be available, in sufficient quantities, to people in lower income settings.

All clinical studies must be subjected to ethical review. When a vast number of clinical studies are submitted to ethical review bodies within a matter of a few weeks, this places an enormous burden on these structures. This, in turn, increases the possibility of hasty decision-making, errors and lapses in the usual ethical standards. ‘Ethics dumping’ refers to practices that would be ethically unacceptable in high-income settings but that are used in low- and middle-income countries, and South African researchers have alerted to the risk of ethics dumping in the COVID-19 situation (Farber, 2020).

Consequences for healthcare systems also need to be considered. In epidemic situations, research must be carried out whilst patients are being taken care of as a matter of urgency. Most COVID-19 clinical trials are necessarily run in hospitals that treat large numbers of patients. They require the collection of biological samples, diagnostic procedures and the collection of multiple types of data that are not all required for medical care and which create additional work. As a result, such research can place additional burdens on overstretched infrastructures and people who are fighting to save lives. It may also be the case that resources needed for COVID-19 clinical research are used at the expense of other health issues which might only become apparent once the epidemic has subsided.

In summary, multiple, uncoordinated research efforts escalate the risks of wasting time and resources that are particularly precious in times of health emergencies as summarized in Table 1. However, these issues need to be weighed against the need for innovative research to provide solutions at a time when they are required urgently.

## **Freedom to conduct research versus coordination of research efforts**

Innovative research thrives on creativity and freedom but is often bound by external factors (Lempiälä and Vanharanta, 2017). Finding the right balance between freedom and control for researchers is crucial and the reckoning often involves acceptance of diffuse efforts and the risk of failure. By way of illustration, work on retroviruses, a relatively marginal research area at the time, led to the

**Table 1.** Summary of ethical issues that arise from multiple uncoordinated clinical studies

Who/what is affected	Ethical issue
<b>Research participants</b>	Carrying the burden of clinical trial participation in studies that may not be completed due to insufficient recruitment of research participants
<b>Patients requiring drugs for treatments</b>	Repurposing of existing drugs to test in COVID-19 trials can lead to a shortage of the drugs for patients who need them for their usual treatment purpose
<b>Ethical review boards (ERBs)</b>	Overburdening of ERBs with multiple applications in a short space of time increases the risk of ethical oversights
<b>Non-COVID-19 patients and health staff</b>	Hosting clinical trials in hospitals that are already stretched due to the pandemic risks neglect of non-COVID-19 patients and imposes large burdens on staff and other resources
<b>Research outcomes</b>	The conduct of multiple clinical trials on similar topics, that are of varying types and quality, raises the risk of conflicting conclusions on the outcomes of the research
<b>Public health decisions</b>	Conflicting research outcomes at a time of global health emergency risks delaying public health decisions on life-saving issues

identification of the HIV virus only two years after the disease was first described (Barré-Sinoussi et al., 1983). In this instance, basic creative research enabled early diagnosis of HIV and ultimately sped up the discovery of drugs needed urgently in applied research.

However, in the case of COVID-19 clinical research, the risk of disparate efforts should be proactively minimized for the aforementioned ethical reasons as well as the following two points.

First, resources need to be pooled for logistical and financial reasons. Clinical research for COVID-19 is likely to involve tens of thousands of people, some of them highly skilled. These include the many people, organisations and resources that need to be mobilized to perform clinical studies over many months and years, as well as the infected patients, their families and their caregivers. The human and financial costs of clinical research to society are considerable. As an example, within the European DisCoVeRy trial (NIH, 2020), that intends to recruit 3200 patients, the cost of studying 1 patient is estimated at €5000 (Morin, 2020). To involve tens of thousands of researchers in overly similar studies will put a high drain on resources in a time when a major economic recession is inevitable.

Second, focused efforts are critical in epidemic situations since it is largely impossible to predict the future evolution of the disease, in terms of both its geographical distribution and its impact on human beings. The future evolution of the

disease depends on multiple factors such as immunity development, impact of control measures, the effect of climate on virus circulation, human movements, the virus infectivity evolution, and so on. Hence, efforts need to be coordinated among multiple countries. As noted earlier, in epidemic situations, it is of vital importance to optimize the positioning of clinical research studies in regions and facilities that are most likely to recruit the required numbers of patients, who meet the inclusion characteristics as dictated by the study hypothesis, in the best possible time frame. Hundreds of studies competing for patients across multiple countries do not create the best environment for research, as each study needs to recruit to the optimal number before any conclusions can be drawn. There is a serious risk that decisive scientific questions will take a lot of time to be answered and this will delay public health interventions that are needed to control the pandemic. In other words, a smaller number of focused, large-scale trials, that recruit to target swiftly, have a much higher chance of affording the information that is needed to combat the pandemic than a larger number of disparate trials.

## A challenging environment

In medical research, major treatment innovations can emerge when a consensus is drawn from results of several clinical studies with similar conclusions. These results will have been published in scientific journals following review and criticism from peer scientists. The consensus process takes time and often requires years to complete. In the context of the COVID-19 pandemic, this process is challenged because it is perceived as being too slow. One example is the ‘spike paper’.<sup>1</sup>

Although the usual scientific publication process from submission to publication is measured in months, the spike paper blazed through it in 9 days . . . [The Executive Publisher of *Science*] remembers telling reviewers to drop everything in order to expedite the process. (Gelfand, 2020)

This pandemic is the first one to occur in a world that is hyperconnected and highly polarized. The press and social media are eager to announce and comment upon preliminary scientific data and this can create worldwide controversies; the early spotlight upon hydroxychloroquine as a potential therapeutic for COVID-19 offers a vivid illustration of such.

An article by Gautret et al. (2020) described preliminary data from patients treated with this drug. This publication ignited a global debate over its efficacy and safety and 175 clinical trials testing hydroxychloroquine were registered in the US ClinicalTrials.gov (2020) database. This debate, still ongoing, has been intense in the press and social media and, adding to the confusion, several countries’ political leaders have been outspoken with their opinions. As a result, we now see highly polarized opinions between supporters and opponents of hydroxychloroquine. In

such a controversy, scientific arguments are often voiced to support preconceived views and political positioning. As declared by Ledford (2020) recently, this global controversy is delaying the ability of the scientific community to establish the precise usefulness of this drug, delaying either its wide deployment if proven useful or its rapid withdrawal as a treatment option if proven unsuccessful.

There is a major tension between the time required to conduct quality scientific research and interpret scientific findings which are often nuanced and the need for political decision-makers to take fully scrutinized public health decisions. In this environment, fast, widespread local action might appear preferable to more time-consuming coordinated global efforts; this is based on short termism and can result in the ethical issues summarized in Table 1.

## Positive signs

The need for coordination of clinical research in emergency situations is widely understood as indicated by various national and international initiatives that have emerged since the very first days of the pandemic. For instance, France has activated its REsearch and ACTion targeting emerging infectious diseases (REACTing) collaborative network (INSERM, 2020) and the UK's National Health Service (NHS) has an approval process that categorizes key studies as 'Urgent Public Health Research Studies for COVID-19' (National Institute for Health Research, 2020). The WHO activated its R&D Blueprint, a global preparedness plan created after the West Africa Ebola epidemic, mobilized working groups and made multiple information resources available online (World Health Organisation, n.d.). The WHO also launched a clinical trial entitled 'Solidarity' to focus international clinical research efforts on four of the most promising potential treatments for COVID-19 (World Health Organisation, n.d. a). Meanwhile, the European Union has set up the ERAvsCORONA Action Plan to coordinate priority research and innovation actions, including new funding mechanisms and data sharing platforms (European Union, 2020). In low- and middle-income countries, a coalition was launched that provides a platform for dialogue on COVID-19 R&D efforts between research institutions (DNDi, 2020).

And the Infectious Diseases Data Observatory (IDDO) (Maguire and Guérin, 2020) initiative that summarizes the characteristics of COVID-19 clinical trial registrations on a weekly basis is one of the tools researchers will be able to use to avoid duplication of efforts and ensure optimal methodology.

## Conclusion – a need for better global coordination

In spite of the positive signs, reflecting on the number of clinical studies on COVID-19 registered to date, it is apparent that these coordinating efforts have not

focused scientists worldwide on a very limited, internationally agreed upon, number of top priorities.

Given that some clinical trials might never be completed due to lack of patients; that a shortage of existing medicines might occur; that ethical review boards are likely to be overburdened; that non-COVID-19 patients might be neglected by overstretched hospital staff; and that conflicting conclusions from a multitude of heterogeneous trials might lead to serious delays in public health decisions, something needs to be done.

Robust mechanisms are needed to steer efforts towards priority goals for the common good, while respecting the creativity that is necessary for innovative scientific investigation. Such mechanisms should combine scientific review and funding allocation processes and be managed by an independent and universally entrusted global body or network of regional bodies. This would require sound political consensus on a global scale, regarding the value of multilateral mechanisms and institutions for public health. Such consensus does not exist at this time but might yet emerge from the current crisis.

## Acknowledgements

The assistance of Prof Doris Schroeder and Dr Kate Chatfield for editorial and reviewer comments is gratefully acknowledged as well as that of Prof Philippe J Guérin who also provided early access to the IDDO publication (Maguire 2020).

## Funding

All articles in Research Ethics are published as open access. There are no submission charges and no Article Processing Charges as these are fully funded by institutions through Knowledge Unlatched, resulting in no direct charge to authors. For more information about Knowledge Unlatched please see here: <https://www.knowledgeunlatched.org>.

## ORCID iD

Francois Bompard  <https://orcid.org/0000-0002-5766-8066>

## Note

1. A hypothesis from US scientists about the molecular structure of the ‘spike protein’ which the SARS-CoV-2 virus uses to invade human cells (Wrapp et al., 2020).

## References

- Barré-Sinoussi F, Chermann J, Rey F, et al. (1983) Isolation of a T-lymphotropic retrovirus from a patient at risk for Acquired Immune Deficiency Syndrome (AIDS). *Science* 4599(220): 868–871. DOI: 10.1126/science.6189183.
- Cao B, Wang Y, Wen D, et al. (2020) A trial of Lopinavir–Ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine* 382: 1787–1799. DOI: 10.1056/NEJMoa2001282.

- Chen Z, Hu J, Zhang Z, et al. (2020) Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *Preprint Posted April, 10, 2020*. medRxiv; 2020;03.22.20040758; DOI: 10.1101/2020.03.22.20040758.
- ClinicalTrials.gov Available at: <https://clinicaltrials.gov/ct2/home> (accessed 2 May 2020).
- DNDi (2020) Coalition launched to accelerate research on the prevention and treatment of COVID-19 in low- and middle-income countries. Available at: <https://www.dndi.org/2020/media-centre/press-releases/coalition-launched-accelerate-research-covid19-low-middle-income-countries/> (accessed 1 May 2020).
- Dorward J and Gbinigie K (2020) Lopinavir/ritonavir: a rapid review of effectiveness in COVID-19, centre for evidence-based medicine. Available at: <https://www.cebm.net/covid-19/lopinavir-ritonavir-a-rapid-review-of-the-evidence-for-effectiveness-in-treating-covid/> (accessed 6 May 2020).
- European Union (EU) (2020) First “EVA vs CORONA” Action Plan. Available at: [https://ec.europa.eu/info/sites/info/files/research\\_and\\_innovation/research\\_by\\_area/documents/ec\\_rtd\\_era-vs-corona\\_0.pdf](https://ec.europa.eu/info/sites/info/files/research_and_innovation/research_by_area/documents/ec_rtd_era-vs-corona_0.pdf) (accessed 3 May 2020).
- Farber T (2020) Should we cut red tape in pandemic panic? *Times Select* 24 April. Available at: <https://select.timeslive.co.za/news/2020-04-24-in-rush-for-a-virus-cure-is-it-okay-to-dump-ethics-or-at-least-bend-them/> (accessed 7 May 2020).
- Gao J, Tian Z and Yang X (2020) Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of covid-19 associated pneumonia in clinical studies. *Biosci Trends*. Online First. DOI: 10.5582/bst.2020.01047.
- Gautret P, Lagier JC, Parola P, et al (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*. Online First. DOI: 10.1016/j.ijantimicag.2020.105949.
- Gelfand A (2020) In COVID-19 research, the need for speed. . . and accuracy. *Global Health Now*. Available at: <https://www.globalhealthnow.org/2020-04/covid-19-research-need-speed-and-accuracy> (accessed 6 May 2020).
- INSERM (2020) REACTing. Available at: <https://reacting.inserm.fr/> DOI: 10.1001/jama.2020.4742 (accessed 2 May 2020).
- Ledford H (2020) Chloroquine hype is derailing the search for coronavirus treatments. *Nature* 2020; 580: 573. DOI: 10.1038/d41586-020-01165-3.
- Lempiälä T and Vanharanta O (2017) Rethinking the control–freedom paradox in innovation: toward a multifaceted understanding of creative freedom. *The Journal of Applied Behavioral Science* 54(1): 62–87. DOI: 10.1177/0021886317727458
- Maguire BJ and Guérin PJ (2020) Baseline results of a living systematic review for COVID-19 clinical trial registrations. *Wellcome Open Research*. In print.
- Morin H (2020). Coronavirus : l’essai clinique Discovery englué faute de coopération européenne. *Le Monde* May 7. (accessed 7 May 2020).
- NIH ClinicalTrials.gov. Trial of treatments for COVID-19 in hospitalized adults (DisCoVeRy). Available at: <https://clinicaltrials.gov/ct2/show/NCT04315948> (accessed 7 May 2020).
- National Institute for Health Research (NIHR) (2020) Urgent public health COVID-19 studies. Available at: <https://www.nihr.ac.uk/covid-studies/> (accessed 2 May 2020).
- Wang M, Cao R, Zhang L, et al. (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research* 30(3): 269–271.

- World Health Organisation (WHO) (n.d.) Coronavirus disease (COVID-19) pandemic. Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019> (accessed 1 May 2020).
- World Health Organisation (WHO) (n.d. a) “Solidarity” clinical trial for COVID-19 treatments. Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments> (accessed 2 May 2020).
- World Health Organisation (WHO) (2020) COVID-19 Studies from the World Health Organization Database. Available at: [https://clinicaltrials.gov/ct2/who\\_table](https://clinicaltrials.gov/ct2/who_table) (accessed 1 May 2020).
- World Medical Association (WMA) (2013) Declaration of Helsinki. Ethical principles for medical research involving human subjects. Available at: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (accessed 3 May 2020).
- Wrapp D, Wang N, Corbett KS, et al. (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 367(6483): 1260–1263. DOI: 10.1126/science.abb2507