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COVID-19 and the generation of novel scientific knowledge: Research questions and study designs

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Abstract

Rationale, aims, and objectives: One of the sectors challenged by the COVID-19 pandemic is medical research. COVID-19 originates from a novel coronavirus (SARS-CoV-2) and the scientific community is faced with the daunting task of creating a novel model for this pandemic or, in other words, creating novel science. This paper is the first part of a series of two papers that explore the intricate relationship between the different challenges that have hindered biomedical research and the generation of scientific knowledge during the COVID-19 pandemic.

Methods: During the early stages of the pandemic, research conducted on hydroxychloroquine (HCQ) was chaotic and sparked several heated debates with respect to the scientific methods used and the quality of knowledge generated. Research on HCQ is used as a case study in both papers. The authors explored biomedical databases, peer-reviewed journals, pre-print servers, and media articles to identify relevant literature on HCQ and COVID-19, and examined philosophical perspectives on medical research in the context of this pandemic and previous global health challenges.

Results: This paper demonstrates that a lack of prioritization among research questions and therapeutics was responsible for the duplication of clinical trials and the dispersion of precious resources. Study designs, aimed at minimising biases and increasing objectivity, were, instead, the subject of fruitless oppositions. The duplication of research works, combined with poor-quality research, has greatly contributed to slowing down the creation of novel scientific knowledge.

Conclusions: The COVID-19 pandemic presented challenges in terms of (1) finding and prioritising relevant research questions and (2) choosing study designs that are appropriate for a time of emergency.

KEYWORDS
epistemology, evidence-based medicine, medical research, philosophy of medicine

1 | INTRODUCTION

On March 11, 2020, what was first described as cases of pneumonia of unknown cause originating from Wuhan was labelled as a pandemic by the WHO. As the COVID-19 pandemic progresses, nations and supranational organizations face a multitude of challenges that impact every facet of society. One of the sectors challenged by the COVID-19 pandemic—and the focus of this paper—is medical research. COVID-19 originates from a novel coronavirus (SARS-CoV-2) and the scientific community has been faced with the daunting task

of creating a novel model for the COVID-19 pandemic or, in other words, creating novel science (ie, knowledge that is unexpected in light of received scientific opinion).* Since January 2020, researchers have attempted to uncover the origin of the virus and its mechanism of replication and have rapidly developed diagnostic tools and a number of vaccine candidates that are still under review.

Building on the experiences of past epidemics—specifically, the 2014-2016 Ebola outbreak—the WHO identified research as an ethical imperative† and an essential part of the response to health emergencies.[5,6] Research is equally essential for generating a knowledge base about the present pandemic, as well as future global health challenges. This newfound consciousness for what is now characterized as "epidemic preparedness" can be traced back to the 2003 SARS outbreak. The last Ebola epidemic represented a turning point in epidemic preparedness efforts: following this outbreak, the pace at which policymakers and academics developed tools to address the next health emergency increased exponentially.[7] The creation of the term 'Disease X', representing the threat of a pandemic caused by a currently unknown pathogen, as well as the development of initiatives, such as the WHO R&D Blueprint[8] and the Coalition for Epidemic Preparedness Innovations (CEPI), are evidence that there has, indeed, been a shift in consciousness. While the COVID-19 pandemic response has evidently been informed and shaped by these inter-epidemic efforts, generating valuable scientific knowledge during an emergency remains a challenge. In this context, one candidate drug, hydroxychloroquine (HCQ), sparked particular interest among members of the scientific community and will serve as a case study for this paper. HCQ is an antimalarial drug, whose toxicity profile is well-known for approved conditions, such as rheumatoid arthritis and systemic lupus erythematosus. It was thought that HCQ could inhibit the pH-dependent steps of SARS-CoV-2 replication.[9] So far, and especially during the early stages of the pandemic, research conducted on this drug was chaotic and sparked several heated debates with respect to the scientific methods used and the quality of knowledge generated.

In the context of uncertainty and urgency associated with the COVID-19 pandemic, two strategies, which Angus[10] calls "exploitation" and "exploration", seem to be in tension with one another.‡ According to Angus, "exploitation refers to acting on current knowledge, habits, or beliefs despite uncertainty. This is the 'just do it' option: give various therapies (eg, chloroquine) to affected patients based on current knowledge or a hunch. Exploration refers to actions taken to generate new knowledge and reduce uncertainty, for example, testing therapies in an RCT. This is the 'must learn' option. Currently, these approaches are framed as a choice: do something (treat the patient) or learn something (test the drug)."[10(p.1895)] In other words, some prefer to take action quickly despite uncertainty, while others choose to wait for robust evidence before taking any action. The effort to find the right balance between the two underlies most of the challenges that have hindered medical research. Different authors have started to identify some of these challenges, such as patient inclusion in clinical trials,[11] data sharing,[12] publication ethics,[13] and research waste.[14] These articles, which tend to be short columns or editorials, typically focus on very specific issues. However, since these challenges tend to compound each other, it is also enlightening to look at them from a broader perspective and examine their intricate relationships.

In the context of COVID-19 and medical research, the question at hand is the generation of a valuable and actionable body of novel scientific knowledge in a relatively short timeframe. The literature suggests that a set of specific issues often complicate the generation of knowledge, regardless of whether research is conducted in a time of emergency or not. These issues are:

1. Inappropriate research questions and study designs. Chalmers and Glasziou[15] argue that "choosing the wrong questions for research"[15(p.86)] and "doing studies that are unnecessary, or poorly designed"[15(p.87)] result in research waste (ie, scientific knowledge that does not have practical value or is not translated into practice).
2. Data collection and sharing. Data collection and sharing presented a challenge during the H1N5 outbreak in Indonesia, the 2015 Zika outbreak and the 2014-2016 Ebola outbreak, among others.§

While undoubtedly there are several ways to examine this issue, this paper will take the position that at least four elements are needed to generate valuable scientific knowledge: (1) relevant research questions, (2) adequate and rigorous study designs, and appropriate ways to (3) evaluate, and (4) report newly acquired knowledge. This first part of a larger study will examine challenges presented by the COVID-19 pandemic in terms of the first two elements. A follow-up paper will turn to the third and fourth elements.

2 | PRIORITISING RELEVANT RESEARCH QUESTIONS

Ensuring that research questions are relevant to the COVID-19 response is the first step in the generation of valuable knowledge. Without relevant research questions (including the identification of appropriate populations, interventions and outcomes), actionable findings cannot be generated. The difficulty lies in that it is often difficult to identify a clear, testable and relevant hypothesis at the beginning of an outbreak, when information about the pathogen is scarce and fleeting.[17] Prioritising relevant research questions during a pandemic is crucial and can be justified on ethical and practical considerations.

2.1 | Ethical and practical justifications

Following the 2014-2016 Ebola outbreak, seven principles guiding research during health emergencies were identified. These principles are outlined in the National Academy of Medicine (NAM) report[16]: (1) scientific and social value, (2) respect for persons, (3) community engagement, (4) concern for participant welfare and interests, (5) favourable risk-benefit balance, (6) justice in the distribution of benefits and burdens, (7) post-trial access.¶ The first principle, which

is the one that is most pertinent to this paper, is formulated as follows: "A clinical study's value depends on the quality of the scientific information produced and the relevance of the information to addressing public health or clinical issues"**.[18(p.477)] However, the criteria to determine whether a study has more value than another remain unclear. According to the NAM report, the information produced by a trial must justify the risks and the allocation of resources and be of sufficient quality to inform decisions.††[16] A trial must also address "an important clinical question that cannot be rapidly answered by other means".[17(p.390)] However, relying on these criteria to prioritize research questions during a pandemic might be unsatisfactory since the way these criteria are to be operationalized was never explicitly outlined. A research question can be considered irrelevant if there is insufficient evidence warranting the investigation of the hypothesis or if it is already under investigation. In step with Chalmers and Glasziou,[15] this paper takes the position that patients and clinicians should be involved in the prioritization process so that their needs and the questions under investigation are better aligned. While this is crucial to facilitate research, how to accomplish this goal in a time of emergency has yet to be theorized, much less put into practice.

From a practical perspective, and even under normal circumstances, choosing an inappropriate research question results in a waste of financial and physical resources.[15] The 2014-2016 Ebola epidemic demonstrated that prioritising research questions is crucial to avoid overwhelming clinical networks.‡‡[16] The tension between research and care is often associated with a high cost,[20] and is especially salient during health emergencies.[10] Healthcare workers have continuously been under pressure because of the growing number of COVID-19 patients, the risks of infections, the lack of equipment, and the pre-existing frailties of health care systems. Until research and care become integrated, every trial runs the risk of being a burden for the healthcare system, even more so if the research question is not directly relevant to the pandemic response. Ideally, during a pandemic, funding should be available for external research teams so as to alleviate the clinical staff's workload.[17]

During the 2014-2016 Ebola outbreak, researchers investigated a large number of therapeutics for which the evidence available was very limited. The WHO staff, research funding agencies, and ethics boards were overwhelmed by a large number of proposals. As such, the authors of the NAM Report recommended that "in the event of a rapidly progressing outbreak it is critical to create a mechanism to prioritize investigational agents for study and limit the conduct of the clinical trials to a small number of products, focusing on those with the most promising preclinical or human clinical data, in order to maximize the likelihood that meaningful results will be generated."[16(p.46)] The lesson from these considerations, then, is that pursuit of irrelevant research questions can be explained by an absence of (1) research prioritization and (2) mechanisms to avoid the duplication of research works. In the next section, this paper will examine whether these two issues have been adequately addressed since the last Ebola outbreak.

2.2 | Absence of prioritization

Building on experiences from past outbreaks, the 2016 WHO R&D Blueprint[8] recommended developing a research roadmap for each new epidemic, as well as Target Product Profiles for the corresponding pathogens. On March 12, 2020, the WHO published a Research Roadmap for COVID-19,[1] which purports to identify knowledge gaps and prioritize urgent questions. The working group concluded that the following nine areas require particular attention§§:

1. Virus natural history, transmission and diagnostics,
2. Virus origin and management measures at the human-animal interface,
3. Epidemiological studies,
4. Clinical management,
5. Infection prevention and control,
6. Candidate therapeutics R&D,
7. Candidate vaccines R&D,
8. Ethics considerations for research,
9. Social sciences in the outbreak response.

This broad list covers most, if not all, research directions and does not provide any sort of ranking. Additionally, the WHO has no international jurisdiction and only provided this list as a recommendation. Regardless of whether this prioritization is considered authoritative, there seems to be no proportionality between the WHO's recommendations and research efforts since the onset of the pandemic. Indeed, the diversity of areas prioritized by the WHO has not been reflected in practice: what we have witnessed is a striking emphasis on the development of therapeutics and vaccines with surprisingly little attention given to non-drug interventions, which, interestingly, represent the primary response to COVID-19.[14] It is arguable that efforts should not be exclusively focused on pharmaceutical interventions, especially given the experiences of past epidemics (with the possible exception of smallpox) that have testified that vaccines and therapeutics represent the least promising (and the most time-consuming) options. Research on transmission and mitigation strategies, while not as lucrative, is equally crucial for protecting populations.¶¶ Until legal bases and incentives are created to encourage a plurality of research objectives, this issue will most likely remain.

To address the NAM's recommendation to limit the number of therapeutics investigated, WHO working groups started, as early as January 24, 2020, to work on therapeutics prioritization.[21] These working groups established a dozen criteria—preclinical efficacy in non-human primates, safety profiles from non-clinical studies, and quality of manufacturing as mandatory criteria[22]—and generated a shortlist of around 25 candidate drugs. A few months later, by April 2020, a new list included over 150 therapeutics (or combinations of therapeutics),[23] which appears counter-productive with respect to their first prioritization efforts. Moreover, there is a discrepancy between what has been prioritized—and the evidence behind it—and what is being studied. As of January 16, 2021, 272 of the 2409 trials tested HCQ, whereas only 40 tested Remdesivir.[24] However, the

WHO stated in January 2020 that "Remdesivir was considered the most promising candidate based on the broad antiviral spectrum, the in-vitro and in-vivo data available […] and the extensive clinical safety database."[21(p.9)] One of the reasons why such a high number of studies were performed on HCQ compared to Remdesivir is the relatively low cost of (and ease of access to) HCQ. On the other hand, carrying out a study on Remdesivir involved making arrangements with Gilead. The opportunity cost is another essential determinant in defining what research questions are pursued. At first sight, HCQ was a promising candidate therapeutic given its low cost and wide availability. For the same reason, it was an attractive investigational treatment for researchers.

2.3 | Duplication of research works

Redundancy in research works results in the dispersed allocation of scarce resources (studies are competing for hospital infrastructure, staff, funding, and patient base), which slows down the creation of novel scientific knowledge. This challenge is specific to the COVID-19 pandemic since relatively few trials were conducted during past epidemics (none during the 2003 SARS outbreak,[17] 18 during the 2014-2016 Ebola epidemic[16]). Patient enrolment is challenging during a health emergency and, by limiting the number of trials, as suggested in the NAM report, the chances of enroling enough patients and reaching definite conclusions are maximized.[16] By the time a trial starts, the number of patients admitted to the ICU has largely decreased (due to the implementation of non-pharmaceutical interventions), making it difficult to reach a pre-specified sample size.[11] Part of the difficulty is that obtaining ethics approval takes time. During the 2003 SARS outbreak in Toronto, the 18-day delay between the official beginning of the outbreak, and the ethics approval of the first clinical trial (which, ultimately, was not conducted), resulted in a loss of 60% of patients who could have been enroled.[17] To address this issue, international organizations,[5,25] as well as scholars,[26,27] developed a system of expedited ethics reviews.*** In the context of COVID-19, the issue is compounded by the difficulties of approving and implementing multi-site protocols, given the differences in national resources and healthcare systems. This has posed numerous challenges to the rapid launching of multi-site trials, such as SOLIDARITY and DISCOVERY (the French-led arm of SOLIDARITY).[28] By overwhelming ethics committees and regulatory bodies, the duplication of trials has exacerbated the difficulties associated with red tape that is often excessive.

Mechanisms to limit the number of trials allowed to proceed have not been established since the last Ebola outbreak. While it was reasonable, at the beginning of the pandemic, to expect that HCQ would be tested as a cure, prophylaxis and in combination with other therapeutics, such a high number of studies (272) was not justified. Ideally, trial registration should provide information on what trials are in progress and de-incentivize duplication. However, this rarely happens in practice, especially considering the strong academic and financial incentives that have been in place since the beginning of the outbreak. There is no legal basis for an international body to examine all trial proposals and determine which trials are allowed to proceed. The R&D Blueprint acknowledges this issue, stating that to avoid "unnecessary duplication […] appropriate incentives and other measures" can be implemented[8(p.11)]. However, there is no additional information on what those incentives might be. A few platforms, such as the Trial Innovation Network, SMART IRB or the COVID19 CP, aim to create incentives and facilitators for collaboration at the clinical level. SMART IRB describes itself as: "a platform designed to ease common challenges associated with initiating multi-site research."[29] The other two platforms expedite approval for proposals that create multi-site collaborations.[30,31] †††Unfortunately, their lack of exposure, partnering institutions, and resources explains the persistence of this issue.

While the objective should be to minimize duplication of research as much as possible, it is clear that duplication is sometimes desirable, especially when the scientific community wishes to have higher confidence in research findings (through replication of studies). In the context of this pandemic, the duplication of research on vaccines is, for example, both appropriate and desirable, given the need for equitable access to vaccines that are suitable for a range of populations, settings, and storage requirements.[32] However, having different research groups chasing the same irrelevant research question should be avoided.

While lessons learned from the last Ebola outbreak helped researchers prioritize research questions and identify candidate therapeutics, the duplication of research remains a problem. This issue is compounded by a large number of researchers who exclusively want to work on vaccine and drug development. To address these challenges, the priority is to clearly define what a "relevant" research question is and to strengthen coordination efforts. While these two steps are crucial in facilitating the generation of valuable scientific knowledge during health emergencies, it will not be sufficient unless behaviours and mindsets also change.‡‡‡

3 | IDENTIFYING APPROPRIATE DESIGNS

Since the beginning of the pandemic, researchers seem to have embarked on a quest to find a "miracle" study design—but disagree on what that design should be. As such, researchers advocate for what they consider to be the best methodological approach while condemning all others. Past health emergencies have also witnessed several disputes regarding how clinical trials ought to be designed, thereby, further delaying their launching.§§§[16] The 2009 H1N1 and the 2014-2016 Ebola outbreaks revealed the need for a portfolio of designs that are best suited to a health emergency. This rise in consciousness incentivized scholars to develop new designs meant to address the various challenges engendered by a pandemic. These initiatives resulted in the development of the SOLIDARITY and REMAP-CAP trials, launched on March 18 and April 9, 2020, respectively.[33,34]

With respect to research conducted on HCQ, the question of study designs sparked lengthy debates across the scientific community, politicians and the public alike. Most parties to this debate

acknowledge that the quality of findings generated has been poor.[35,36] Glasziou, Sanders and Hoffman bemoan "a deluge of poor quality research [that] is sabotaging an effective evidence based response."[14(p.1)] While it is outside the scope of this paper to conduct a systematic review of all the studies on HCQ and determine its efficacy, it might prove useful to outline some of the characteristics of these studies, such as the number of participants, the type of study design, the publication format and the study's conclusions and limitations. For the purpose of this paper, studies on the efficacy of HCQ as a treatment (not prophylaxis) published between January and July 17, 2020 were selected (35 studies). By July 17, the general consensus was that HCQ would not be an effective treatment for COVID-19[37] (most trials, including the WHO SOLIDARITY trial,[38] had removed their HCQ arm and emergency authorizations were revoked[39]). These characteristics are summarized in Appendix A and shed some light on the research conducted since the beginning of the COVID-19 pandemic:

1. Lack of methods transparency: the most striking example is Gao and colleagues' letter of declaration of results.[40]
2. Limitations and biases: all 35 studies have been widely criticized and considered methodologically very biased by several commentators.[41-46]
3. Inconsistent results: 13 studies show benefits of HCQ,[40,47-58] 18 report no significant benefit[59-75] and four report increased risks.[76-79]
4. Significant number of retracted studies: three studies on HCQ were retracted[50,78,80] and another was the subject of a statement of concern from Elsevier and is currently under investigation.[47]
5. Large amount of non-peer-reviewed articles: only 15 of these studies were peer-reviewed.
6. Lack of adverse event reporting: 17 studies did not formally report adverse events, which is, however, one of the major concerns clinicians have when prescribing HCQ. Indeed, HCQ is known to cause renal, hepatic and cardiovascular adverse effects.[9] COVID-19 patients in the ICU are more likely to have co-morbidities (including renal, hepatic and cardiovascular dysfunctions) and be given high doses of HCQ, thereby increasing the risks of adverse events. Starting in July 2020, studies tended to report adverse events more systematically.

This paper will now analyse the three major strategies that have been suggested since the beginning of the pandemic (traditional designs, Big Data and REMAP-CAP) to determine if a "miracle" design can, indeed, be found.

3.1 | Traditional designs

A vocal constituency of the scientific community advocates for maintaining the standards and methods generally used outside of health emergencies.[81] Simple designs that have been frequently used in the past are thought to help preserve scientific rigour without the prospect of overwhelming the clinical network.[82] While the first few completed clinical trials on HCQ were received from China, the anti-malarial drug was placed under the international spotlight due to two French studies that were published in March 2020.[47,49] Despite their methodological limitations (see Appendix A), the advertisement made by Raoult (one of the authors of these French studies) and politicians[83] sparked hope and controversy among the population, with the result that another team of researchers decided to replicate the study by performing a prospective case series of 11 patients. However, this study did not yield conclusive findings.[60] This is a typical example where researchers were obligated to replicate knowledge generated instead of building on it, thereby slowing down research efforts. At the time, Raoult claimed that a situation of emergency is a licence to abandon the scientific method and a call to action (ie, population-wide distribution of HCQ).[¶¶¶84] As such, he agitated against RCTs as being unduly time-consuming and contended that including placebos and control groups is unethical.[84] This debate can be traced back to the last Ebola outbreak[86] but seems to have been settled, for the most part, since then.[****] Regardless, clinicians might rightfully be torn between attempting to cure patients with what is available and continuing unabated with their research. However, while Raoult referenced the Hippocratic Oath to justify giving HCQ to every patient, regardless of the risks,[84] it seems reasonable to respond to Raoult that this very same Hippocratic Oath ("first do no harm") mandates against imprudent, population-wide prescriptions of investigational drugs. This brings us to reflect on the prescription of off-label drug use. This practice is widespread[††††87] but 73% of off-label drugs are supported by very poor or no scientific evidence.[88] Prescribing off-label drugs can also undermine research efforts since data cannot be collected on patients who are prescribed the investigational treatment.[36,90‡‡‡‡] The 2014-2016 Ebola outbreak incentivized the WHO to create MEURI (Monitored Emergency Use of Unregistered Interventions), which stipulates that the distribution of investigational treatments outside of clinical trials is only allowed if the following criteria are met[§§§§5]:

1. Lack of effective treatment,
2. Absence of clinical trials,
3. Availability of efficacy and safety data,
4. Ethical approval,
5. Implementation of risk mitigation strategies,
6. Acquisition of patients' informed consents,
7. Consistent monitoring of patients and sharing of results with the scientific community.[91]

Since criteria 2 and 7 are not met in the context of this pandemic, this paper takes the position, in agreement with Caplan and colleagues, that while "there may be a role for MEURI in COVID-19, [the] unconstrained, unevaluated use of therapeutics under the guise of compassionate use or panicked rhetoric about right-to-try must be aggressively discouraged in order for scientists to learn what regimens or vaccines actually work"[91(p.2753)].

Following these two politicized studies, which polarized public and scientific opinion, it became evident for many that only a RCT would provide definite conclusions regarding the efficacy of HCQ. However, the preliminary results of the UK RECOVERY trial (an adaptive factorial trial[92-94]), released on June 5, 2020, suggested that a RCT is far from bringing all the answers. The DMC stated that the interim results, based on 4674 patients, revealed "no beneficial effects of hydroxychloroquine" and that they had decided to "stop enrolling participants to the hydroxychloroquine arm [...] with immediate effect".[95] Nevertheless, researchers were quick to criticize these findings, even though they came from a RCT that, supposedly, ranks high in the evidence hierarchy.¶¶¶¶ The first concern regarding the trial was related to the unusually high dosage of HCQ. Indeed, patients received 2400 mg of HCQ in the first 24 hours, which is well above the dosage recommended by the FDA on the Emergency Use Authorization (800 mg).[96] While this dosage decision is explained in the protocol on the basis of available data of the IC_{50} for SARS-CoV-2 (how much substance in needed in plasma to inhibit the virus by 50%),*****[94] it remains unclear whether this dosage was warranted and did not pose an unreasonable risk to patients. The population of patients selected was also questioned. Some argued that patients who received HCQ in this trial (mainly severely ill patients) would not benefit from receiving the treatment. This is because COVID-19 is a three-stage disease with an initial viral replication phase, followed by a pulmonary phase and then a "cytokine storm" causing tissue damage (when patients are in the ICU).[97] Giving HCQ, an antiviral, would, thus, only be beneficial for patients who were still in the early stages of the disease. This example shows that results from a seemingly well designed, large RCT can be criticized because the trial's hypothesis is not relevant given the available evidence. This consideration reiterates the importance of a relevant question: regardless of the type of study design, if the research question (population and intervention, in the case of RECOVERY) is not appropriate, then research findings will not be generalizable to the intended target population.†††††

3.2 | Big data and electronic health records

Angus describes the advantages of using Big Data and Electronic Health Records (EHRs) in clinical research as follows: "The information is relatively inexpensive, generated as a by-product of patient care (overcoming the cost problem), and both specific to individuals (ie, adequately narrow) and, *en masse*, descriptive of the entire delivery system (ie, adequately broad). No individuals are randomized, so the ethical issues appear less complex. The richness and immediacy of these new data could allow tailored treatment decisions in real time, overcoming delays in knowledge translation."[98(p.767)] Such an approach was used in an observational study published by Mehra and colleagues on May 22, 2020. This study on 96 031 patients concluded that HCQ was associated with a higher risk of mortality and cardiac arrhythmia.[78] Immediately following this publication, guidelines on the use of HCQ changed dramatically: on May 25, 2020, the WHO suspended all HCQ arms and national trials followed in its path.[99] The French Minister of Health suspended the authorization he had exceptionally issued on the use of HCQ in the clinical setting.[100] The large sample size, which is often—incorrectly—associated with high-quality findings, was used as justification to make these decisions. However, concerns about the study data were quickly raised, first on Twitter,[101] and then in an open letter addressed to *The Lancet*, which outlined 10 concerns, including discrepancies with government data and inadequate statistical adjustments.[102] Three out of the four authors retracted the study on June 5, 2020,[103] which led the WHO and national policymakers to resume clinical trials.[99] In addition to the negative consequences that these contradicting decisions might have had on clinical trials, this study also contributed to making COVID-19 patients following a HCQ treatment even more concerned about their vital prognosis.

Thus, generating data quickly is not helpful if the data collection methods are inappropriate or if the data only supports limited conclusions, which clearly was the case of the data collected by the COVID-19 4CE Consortium.‡‡‡‡‡[104] Using patient-level data, if collected adequately and internationally, would yield more generalizable findings than those that are currently available. Nevertheless, advocating for this approach seems to overlook the numerous challenges that remain to be addressed. First, the question of patient privacy and re-identification is often seen as a significant barrier to the sharing of EHRs.[106] Besides, there are currently no incentives to share clinical data since there is no mechanism for academic recognition and data ownership.§§§§§[107-109] Researchers might prefer to wait until they have conclusions to publish rather than share their raw data.

3.3 | REMAP-CAP

The third approach, advocated by Angus[10] and others,[110,111] is to choose an adaptive design that is "pre-planned, pre-approved and practiced"[112(p.12)] during the inter-epidemic period. Such a design, REMAP-CAP, which stands for Randomized, Embedded (into clinical care), Multifactorial, Adaptive, Platform trial for Community-Acquired Pneumonia (CAP), was developed following the H1N1 outbreak.[113] Following the approval of the core protocol and the pandemic appendix, the trial was launched in 2016 and, as of January 16, 2021, includes 290 sites in 19 countries.[11] Enrolment of COVID-19 patients started soon after the beginning of the pandemic. This design combines elements from a platform trial, upon which multiple research questions can be investigated, and an adaptive trial, which allows for design modifications based on a Bayesian analysis of interim results.[114-118] We are told that this design addresses a "disease or condition, rather than a particular intervention"[118(p.797)], which can be helpful when investigating emerging pathogens, such as SARS-CoV-2. The different adaptations used in REMAP-CAP are¶¶¶¶¶[119]:

- Enrichment: population modifications are made if the treatment proves to be more efficient on a subset of the population.

According to Angus, this allows for a "precision medicine" approach and a better estimation of the intervention's effects on individual patients.[98]

- Treatment arms: addition or termination of arms based on interim results and simulations.
- Patient allocation: Response-Adaptive Randomization (RAR) allows participants to become more likely to be enroled in the more promising arm as evidence accumulate.

According to Angus, REMAP trials are most adequate to accommodate the complex web of constraints that a pandemic generates.[114] RAR tends to shorten the time required to generate conclusive findings and to decrease the number of participants needed,[118,120] which minimizes challenges around patient inclusion. By allowing more participants into the more promising arm, RAR might also be a partial response to clinicians' concerns about randomization.[121] The organization of the protocol (core protocol and appendices for each new arm) also facilitates ethics approval.[118]

However, these designs also have practical and statistical limitations.****** An adaptive trial requires a tremendous amount of pre-trial planning and simulations in order to pre-specify the statistical methods and algorithms used to evaluate interim results.[118] Given the uncertainty associated with any pandemic, one can question how much of the trial can actually be planned ahead of time. RAR, while admittedly more intuitive, can also result in a population drift.[121] Participants know that the later they enter the trial, the more chances they have of being allocated to the more promising arm. As such, patients who enrol later are more likely to be healthier since they can afford to wait.†††††† Finally, REMAP-CAP, as any multi-site trial, risks having different "standard of care" practices across sites, due to socio-economic differences. A lack of mechanisms for data harmonization makes it difficult to compare data and generalize results.[104] "Standard of care" guidelines for COVID-19 patients might also change over time, as new evidence arises.[123]

While a REMAP design should not be considered flawless, it seems to adequately address some of the challenges imposed by a pandemic, provided, of course, that it is conducted properly. Given the amount of pre-trial planning required before launching an adaptive trial, it must be designed before the onset of an outbreak, which is why REMAP-CAP has an advantage over other adaptive trials. If the results live up to expectations, REMAP-CAP will show that aiming for a personalized approach to medicine and a learning healthcare system is possible, even during a pandemic.[10,124] However, results and data from the HCQ arm of this trial have yet to be released,‡‡‡‡‡‡ making it impossible to assert with certainty that it is the most appropriate design for an emergency.

As demonstrated above, all three approaches have very distinct justifications. Advocates of traditional designs value studies conducted at the bedside that do not overwhelm the clinical staff. Relying on EHRs is often considered as less time and resource-consuming. Finally, advocates of the REMAP trial highlight the ethical and practical benefits of removing less promising treatment arms. RECOVERY and REMAP-CAP (two large, randomized trials) also endorse different values. The rationale behind RECOVERY is to conduct "the simplest [trial] as possible": healthcare systems should not be further overwhelmed by a complex protocol.§§§§§§125 REMAP-CAP, on the other hand, and while claiming that the trial is embedded into clinical care, offers a very complex protocol and has yet to show how this integration between research and care works.

During the inter-epidemic period, the question of which design is preferable has been addressed but discussions have resulted in very few definite answers. In the context of the COVID-19 pandemic, members of the scientific community have widely divergent views on what they consider to be the most appropriate design during health emergencies.[10] Given the above considerations, the inescapable conclusion is that the quest for a single, perfect design is futile. Instead, in order to ensure a better alignment between information clinicians and policymakers need and information that is generated by research, two objectives should be pursued: maintaining scientific rigour while embracing a methodological pluralism stipulating that the value of a plurality of designs is its prospect for the acceleration of the generation of scientific knowledge.

4 | DISCUSSION

This first paper has demonstrated that the COVID-19 pandemic has presented challenges to the generation of novel scientific knowledge in terms of (1) finding and prioritising relevant research questions and (2) choosing study designs that are appropriate for a time of emergency. First, a lack of prioritization among research questions and candidate therapeutics, in part at least, has been responsible for the duplication of research works and the dispersion of scarce resources. Because research questions have not always matched the needs of clinicians and policymakers, it is critical that the end-users of research become more actively engaged in the identification of relevant research questions.[15] The duplication of research works, combined with poor-quality research, has greatly contributed to slowing down the creation of novel scientific knowledge. Efforts remain to be made in at least two areas: (1) finding mechanisms to limit the number of candidate therapeutics being investigated and the number of trials allowed to proceed and (2) facilitating collaboration by creating platforms with more exposure and resources. With respect to study designs, this paper has demonstrated that the scientific community embarked on a quest to find the most appropriate design during a time of emergency fraught with danger to the public. Issues raised during previous health emergencies (around patient inclusion, randomization and trial adaptability in light of new findings) has led to the creation of interesting designs, such as the REMAP-CAP trial. However, in the context of the COVID-19 pandemic (and, specifically, research on HCQ), the choice of study designs has been the subject of fruitless oppositions. These oppositions, as well as the overall low methodological quality of studies on HCQ, suggest that methodological rigour and the notion of design complementarity have sometimes been abandoned.

5 | POSTSCRIPT

In a follow-up paper, we will continue to explore the relationship between the different challenges that have hindered biomedical research and the generation of novel scientific knowledge during the COVID-19 pandemic. In this second paper, we will turn to the challenges presented by the COVID-19 pandemic in terms of (3) evaluating evidence for the purpose of making evidence-based decisions and (4) sharing scientific findings with the rest of the scientific community and the general public. In a time where confusion, uncertainty and fear rule, and where mitigation strategies rely on people's adherence to science-based guidelines, this second paper will demonstrate the importance of communicating scientific findings, and their limitations, in a clear and transparent manner.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Lucie Perillat: Conceptualization, Investigation, Writing – original draft preparation, Writing – review and editing. **Brian Baigrie**: Conceptualization, Writing – review and editing.

ENDNOTES

* In *A Coordinated Global Research Roadmap: 2019 Novel Coronavirus* (2020),[1] the WHO repeatedly describes the role of the scientific community as identifying and addressing "knowledge gaps" (see p. 2, 4, 9). However, the issue extends far beyond filling knowledge gaps. The initial model of the COVID-19 pandemic was primarily based on lessons the scientific community learned from the 2003 SARS epidemic and SARS-CoV (the virus causing SARS). Given the approximate 80% similarity between the genomes of the two viruses[2,3] and the similarities in transmission routes, it was widely assumed that conclusions about SARS-CoV could be extrapolated to SARS-CoV-2. However, Wilder-Smith and colleagues[4] call attention to the fact that these viruses are very different, and assumptions about infectious periods, transmission and severity do not always hold. More than filling knowledge gaps, the scientific community needs to create a new scientific model for COVID-19.

† Section 8 (p. 30-34) of the *WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (2016)[5] outlines the appropriate role of research during health emergencies. The central argument of this section is that "there is a moral obligation to learn as much as possible as quickly as possible, in order to inform the ongoing public health response, and to allow for proper scientific evaluation of new interventions being tested."[5(p.30)] This WHO document provides guidance on fast-tracking ethics reviews, integrating research and public health responses and selecting appropriate research methods.

‡ Angus[10] locates the source of this tension in the institutional structure of medicine, which is organized in a way that ensures that clinical practice (doing) and clinical research (learning) are separate tasks. Angus contends that there are "huge costs to this division, including delays in knowledge acquisition and dissemination. In normal times, these costs are somewhat suppressed or ignored, but in a crisis such as the COVID-19 pandemic, they come into sharp focus"[10(p.1895)].

§ The specific examples of the H1N5 outbreak in Indonesia and the 2015 Zika outbreak are described in sect. 4, in the second paper of this series. As for Ebola, the author of the National Academy of Medicine (NAM) report[16] identified data sharing as a central issue during the outbreak. Recommendation 2b states that "Data collection should begin as soon as possible, and data should be shared and coordinated in a central database to advance an understanding of the natural history of the disease and of the best practices for standard of care. This information should also be used to inform protocols for clinical trials."[16(p.10)] In the report, the authors argue that the inappropriate prioritization of investigational treatments (ie, interventions and, to an extent, research questions) and the inappropriate choice of study designs also complicated the generation of a robust body of knowledge[16(sect.2)].

¶ These seven principles are outlined on p. 53 to 61 of the NAM report (2017).[16] They were selected by the report committee using the following documents as a framework: Nuremberg Code (1947), Belmont Report (1979), Convention on Human Rights and Biomedicine (1977), UNESCO Declaration (2005), HHS Common Rule (2009), WMA Declaration of Helsinki (2013), CIOMS Ethical Guidelines (2016).

** When summarising the findings of the NAM report,[16] Edwards and Kochhar[18] mention that "the knowledge gained must justify the risks to the subjects and the costs associated with the trials"[18(p.478)]. However, how this is to be determined and quantified remains unclear in the article. The importance of the distinction for a theory of evidence between the validity (reliability) of evidence and the relevance (weight) of evidence is argued by Baigrie and Mercuri.[19]

†† The "Scientific and Social Value" principle is detailed in sect. 2 (p. 54-55) of the NAM report (2017).[16]

‡‡ Sect. 2, *Planning Clinical Trials* (p. 45-46) of the NAM report (2017)[16] outlines the authors' recommendations for planning trials and prioritizing candidate therapeutics.

§§ These nine areas are outlined on p. 9 of the *WHO Research Roadmap for COVID-19* (Selected Knowledge Gaps section).[1] The goals of the Research Roadmap are outlined as follows: "To accelerate research that can contribute to containing the spread of this epidemic and facilitate that those affected receive optimal care; while integrating innovation fully within each thematic research area."[1(p.2)] However, there is no explicit justification behind the decision to select the nine areas listed above as research priorities.

¶¶ The WHO published this list on March 12, 2020, at a time when public health guidelines did not include infection control strategies, such as face coverings or international travel regulations. This can partly explain why research direction 5 did not receive much attention at the time. However, even after the WHO pivoted and recommended infection prevention and source control strategies, the emphasis of research efforts remained on vaccines and therapeutics.

*** In sect. 8 of the *WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (2016),[5] it is recommended that there should be greater collaboration between national research governance systems and local research ethics committees. The authors also suggest that the development of advance reviews of generic protocols can help expedite ethics reviews. Tansey and colleagues[26] developed a framework for expedited reviews that rely on proportionality and procedural flexibility.

††† COVID19 CP does not only act as a trial repository but encourages collaboration between trials. However, it primarily focuses on collaboration between RCTs, as opposed to observational and electronic medical records data.[31] As will be argued in sect. 3, in the second paper, there has been a tendency to disproportionately rely on RCTs since

the beginning of the COVID-19 pandemic. The COVID19 CP's decision to focus on RCTs is yet another example that is indicative of this tendency. During a health emergency, strengthening collaboration for any research enterprise (and not only randomized controlled trials) is crucial.

‡‡‡ The authors would like to emphasize that the question at hand here is the regulation and governance of medical research during an emergency. The question of knowing whether policymakers should prioritize mitigation strategies, therapeutics or vaccines (ie, divide resources equally or favour a single strategy) is an important but distinct issue that is best addressed once more hindsight is acquired. Past health emergencies have shown that vaccines are usually developed in a second phase, after research on repurposed drugs and mitigation strategies have been carried out. This is to be expected considering the time that it takes to develop, approve and manufacture a vaccine. Whether the COVID-19 pandemic will result in the modification of research responses to a health emergency remains to be seen.

§§§ Sect. 2 (p. 46-75) of the NAM report (2017)[16] examines the question of choosing appropriate trial designs during a health emergency. During the 2014-2016 Ebola outbreak, stakeholders agreed that "too much time was spent debating trial design, rather than quickly implementing trials and discovering safe and effective products in time to fight the epidemic"[16(p.47)]. Both randomized and non-randomized trials were discussed at the time and in the report. Since ethical and logistical concerns were raised regarding randomization, single-arm studies with historical controls were discussed as an alternative. However, the authors of the NAM report ultimately conclude that: "Randomized controlled trials are the most reliable way to identify the relative benefits and risks of investigational products, and, except when the rare circumstances detailed in Box 2-5 are applicable, every effort should be made to implement them during epidemics."[16(p.75)]

¶¶¶ Raoult, in an open letter to a French newspaper, described the scientific method as a "moral dictatorship" and methodologists as "methodology freaks".[84] He insisted that "we must get rid of mathematicians [whom he earlier described as methodologists], [who are] meteorologists in this area." In his letter, he relied on the parachute paradigm[85] to condemn the conduct of RCTs during health emergencies, arguing that the use of placebos and control groups is not ethical in such situations. Meyer, in a response published in the same newspaper, argued that the parachute paradigm does not hold in the case of HCQ: "this example is not valid: the statistical method is only used when there is obvious uncertainty about the answer, and not when the laws of physics are sufficient to predict the result with a negligible margin of error."[82] [authors' translation].

**** Concerns about randomization, control groups, and placebos are frequently raised during health emergencies. The NAM report mentions that such a controversy occurred during the 2014-2016 Ebola outbreak: some argued that "communities would not accept a randomized controlled trial because it would 'deny a new experimental treatment to some participants'"[16(p.51)]. Others stated that "trials 'should not include a placebo: exposed and vulnerable people in Ebola-affected and low-resource settings should not be led to think they are either being treated or protected when they are not'".[16(p.65)] Others, yet, argued that randomization, controls and placebos "would be acceptable to the community if public health leaders were 'to articulate the rationale for conducting scientifically valid trials, to work closely with local health authorities, and to engage community leaders'"[16(p.51)]. In light of these conflicting views, the authors determined that RCTs were ethical and that "[the above] considerations do not warrant the a priori rejection of the use of a placebo but rather should be taken into consideration within the specific context of a trial."[16(p.65)] The 2016 *WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* seems to agree with this conclusion, recommending that: "In clinical trials, the appropriateness of features such as randomization, placebo controls, blinding or masking should be determined on a case-by-case basis, with attention to both the scientific validity of the data and the acceptability of the methodology to the community from which participants will be drawn."[5(p.33)]

†††† Wittich and colleagues[87] note that prescriptions of off-label drugs represent 21% of all prescriptions in the US and 36.2% of all ICU prescriptions. Despite the fact that this practice is widespread, a study conducted by Cummings showed that two-thirds of patients advocate for the banishment of off-label drug use.[89]

‡‡‡‡ Kalil argues that "in addition to the risk of harming patients without the possibility to even detect the magnitude of harm, the administration of off-label drug use, compassionate drug use, and uncontrolled studies during a pandemic also could discourage patients and clinicians from participating in RCTs, hampering any knowledge that could be gained about the effects of the drug being tested"[90(p.E2)]. When an investigational drug is prescribed under an off-label or compassionate use, adverse events are rarely reported in a systematic manner to the scientific community and knowledge about the efficacy or potential harms of said investigational treatment cannot be generated.

§§§§ These seven principles were summarized and adapted from sect. 9 (p. 35-37) of the *WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (2016).[5]

¶¶¶¶ These critiques of the RECOVERY trial raise the question of whether a negative trial (ie, one that reveals no benefit of the intervention) can ever produce findings that are considered conclusive. Critics can bring into question many aspects of a clinical trial (eg, patient population, dosage regimen, clinical outcomes), as was the case with trials of HCQ. While the question of falsifiability in clinical medicine is interesting, it is beyond the scope of this paper.

***** This decision is explained as follows in the RECOVERY protocol: "the loading dose in RECOVERY is twice the normal dose for treating malaria. However, this dose has been selected based on the available data of the IC_{50} for SARS-CoV-2. The objective is to reach plasma concentrations that are inhibitory to the virus as soon as safely possible. The plasma concentrations that will result are at the higher end of those encountered during steady state treatment of rheumatoid arthritis. Given the significant mortality in patients hospitalized with COVID-19, this dose is felt to be justified."[94(p.22-23)]

††††† In the case of RECOVERY, the research findings may, at best, be generalizable to a population of severely ill patients. However, given the three-stage nature of COVID-19, HCQ should be tested in a population of patients who are still in the early stages of the disease (viral phase). Therefore, the results of RECOVERY are not generalizable to the population that would be the target of a HCQ treatment (ie, patients who are still in the viral phase).

‡‡‡‡‡ The 4CE Consortium is a grouping of 96 international hospitals that gathered and analysed Electronic Health Records data (using the i2b2 and OMOP platforms) to "inform doctors, epidemiologists and the public about COVID-19 patients with data acquired through the health care process."[105] The report cited here analyses aggregate data from 27 927 COVID-19 patients. The authors "deliberately aggregated the data to expedite the institutional review board (IRB) process at each institution [...]. This thereby constrained [their] analyses to count, rather than patient-level, data."[104(p.13)] The authors acknowledge this limitation as well as the limited amount of diagnosis code data available and issues with data harmonization across sites. They state that "the limits of [their] data collection method, where [the] results are not tied to the patient level and can be associated across populations, highlights the need for caution with any conclusion [...]."[104(p.13)]

§§§§§ The lack of academic recognition when sharing clinical data is made explicit in the report by Abramowitz and colleagues (2018).[107] The authors mention that researchers "are reticent to hand over data for

publication without recognition. [...] One problem impeding this recognition was that the names of those people who have laboured to produce data are not visible to their users."[107(p.65)]. Section V(F) "Key barriers and facilitators to data sharing" of this document further develop this argument. In the *WHO consultation on Data and Results Sharing During Public Health Emergencies* (2015),[108] sects. 1.4 and 1.5 examine the issue of recognition and data ownership. The authors and interviewees suggest that a "cultural" change in "academic reward structures"[108(p.19)] is needed. However, how this should be implemented in practice remains unclear.

¶¶¶¶¶ *Adaptive Designs for Clinical Trials of Drugs and Biologics FDA Guidance for Industry* (2019)[119] provides guidance on how adaptive trials ought to be designed and conducted. It is important to note, however, that "there is [currently] no explicit and transparent review process for APTs [adaptive platform trials], and therefore no mechanism for standardized evaluation across different national and international oversight and review bodies."[118(p.801)] Section 5 of this FDA document outlines all the adaptions that can be added to an adaptive platform trial (adaptations to sample size, patient population, treatment arm selection, patient allocation, endpoint selection).

****** Goozner[122] and others[120] note that making modifications based on an interim analysis of the data increases the probability of Type I errors (or false positives).

†††††† This problem may arise, depending on how the trial is designed and what inclusion criteria are used. Das and Lo carried an analysis of the I-SPY 2 TRIAL (an adaptive platform breast cancer trial) and emphasize that population drift could have been a concern and a limitation in the trial.[120(p.170)]

‡‡‡‡‡‡ Results for the corticosteroid arm of the REMAP-CAP trial were published in *JAMA* on September 2, 2020.[126] This treatment arm was halted after results from other trials were published. Primary results for the HCQ arm should be released in December 2021, and full study results should be published in June 2022.[127]

§§§§§§ In the video, Peter Horby (RECOVERY trial co-chair) articulates the three main goals of the RECOVERY trial: (1) to generate the best evidence as fast as possible, (2) to protect patients, (3) to protect the healthcare system so that the staff is not overburdened with too much administrative duties.[125]

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. World Health Organisation. *A Coordinated Global Research Roadmap: 2019 Novel Coronavirus*. https://www.who.int/publications/m/item/a-coordinated-global-research-roadmap. Geneva: WHO R&D Blue Print; 2020. Accessed December 19, 2020.
2. Chan JF, Kok K. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect*. 2020;9(1):221-236. https://doi.org/10.1080/22221751.2020.1719902.
3. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565-574. https://doi.org/10.1016/S0140-6736(20)30251-8.
4. Wilder-Smith A, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? *Lancet Infect Dis*. 2020;20(5):e102-e107. https://doi.org/10.1016/S1473-3099(20)30129-8.
5. WHO. *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks*. Geneva: WHO Press. https://apps.who.int/iris/handle/10665/250580. 2016. Accessed December 19, 2020.
6. Lurie N, Manolio T, Patterson AP, Collins F, Frieden T. Research as a part of public health emergency response. *N Engl J Med*. 2013;368(13):1251-1255. https://doi.org/10.1056/NEJMsb1209510.
7. Bedford J, Farrar J, Ihekweazu C, Kang G, Koopmans M, Nkengasong J. A new twenty-first century science for effective epidemic response. *Nature*. 2019;575(7781):130-136. https://doi.org/10.1038/s41586-019-1717-y.
8. WHO. *An R&D Blueprint for Action to Prevent Epidemics: Plan of Action*. http://www.who.int/csr/research-and-development/r_d_blueprint_plan_of_action.pdf?ua=1. Geneva: WHO R&D Blue Print; 2016. Accessed December 19, 2020
9. Xu X, Ong YK, Wang DY. Role of adjunctive treatment strategies in COVID-19 and a review of international and national clinical guidelines. *Mil Med Res*. 2020;7(1):22. https://doi.org/10.1186/s40779-020-00251-x.
10. Angus DC. Optimizing the trade-off between learning and doing in a pandemic. *JAMA*. 2020;323(19):1895-1896. https://doi.org/10.1001/jama.2020.4984.
11. REMAP-CAP. Pandemic preparedness—REMAP-CAP trial. https://www.remapcap.org/pandemic-preparedness. Accessed January 16, 2021.
12. Cosgriff CV, Ebner DK, Celi LA. Data sharing in the era of COVID-19. *Lancet Digit Heal*. 2020;2(5):e224. https://doi.org/10.1016/S2589-7500(20)30082-0.
13. Smith MJ, Upshur REG, Emanuel EJ. Publication ethics during public health emergencies such as the COVID-19 pandemic. *Am J Public Health*. 2020;110(7):e1-e2. https://doi.org/10.2105/ajph.2020.305686.
14. Glasziou PP, Sanders S, Hoffmann T. Waste in covid-19 research. *BMJ*. 2020;369:m1847. https://doi.org/10.1136/bmj.m1847.
15. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet*. 2009;374(9683):86-89. https://doi.org/10.1016/S0140-6736(09)60329-9.
16. Keusch G, McAdam K, Cuff PA, Mancher M, Busta E, National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Global Health, Board on Health Sciences Policy, Committee on Clinical Trials During the 2014-2015 Ebola Outbreak. *Integrating Clinical research into epidemic response the Ebola experience*. washington, DC: The National Academies Press; 2017.
17. Muller MP, McGeer A, Straus SE, Hawryluck L, Clinical Trials GWL. Novel pathogens: lessons learned from SARS. *Emerg Infect Dis*. 2004;10(3):389-394. https://doi.org/10.3201/eid1003.030702.
18. Edwards KM, Kochhar S. Ethics of conducting Clinical research in an outbreak setting. *Annu Rev Virol*. 2020;7(1):1-20. https://doi.org/10.1146/annurev-virology-013120-013123.
19. Baigrie B, Mercuri M. Relevance, validity, and evidential reasoning in Clinical practice. *J Eval Clin Pract*. 2020;26:1341-1343.
20. Sacristán JA. Clinical research and medical care: towards effective and complete integration. *BMC Med Res Methodol*. 2015;15(1):1-7. https://doi.org/10.1186/1471-2288-15-4.
21. WHO. WHO R&D Blueprint: Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection. https://extranet.who.int/iris/restricted/handle/10665/330680. 2020. Accessed December 19, 2020.
22. WHO. *WHO R&D Blueprint Novel Coronavirus: WHO Working Group—Therapeutics Prioritization for COVID-19*. Geneva: WHO Press. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwi9-4-Lh5rtAhU4GFkFHVT-Ch

EQFjACegQIAhAC&url=https%3A%2F%2Fwww.who.int%2Fdocs%2Fdefault-source%2Fblue-print%2Fwho-working-group-therapeutics-prioritization.pdf%3Fsfvrsn%3D151f64d8_1%26download%3Dtrue&usg=AOvVaw2qVcxxU34UgQSBIdzB-yY4. 2020. Accessed December 19, 2020.

23. WHO. *WHO R & D blueprint COVID-19 experimental treatments*. Geneva: WHO Press. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiz3Ybeh5rtAhUkF1kFHZ4xA44QFjABegQIBxAC&url=https%3A%2F%2Fwww.who.int%2Fdocs%2Fdefault-source%2Fblue-print%2Fcovid-classification-of-treatment-types-rev.pdf%3Fsfvrsn%3D4993afd6_1%26download%3Dtrue&usg=AOvVaw0rpKbzYt5XmCL4Gj31w0wV. Accessed December 19, 2020. - 2020.
24. WHO. COVID-19 Living Research Map. https://www.covid-nma.com/dataviz/. 2020. Accessed January 16, 2021.
25. WHO. Ethical standards for research during public health emergencies: Distilling existing guidance to support COVID-19 R&D. https://apps.who.int/iris/handle/10665/331507. 2020. Accessed December 19, 2020.
26. Tansey CM, Herridge MS, Heslegrave RJ, Lavery JV. A framework for research ethics review during public emergencies. *CMAJ*. 2010;182(14):1533-1537. https://doi.org/10.1503/cmaj.090976.
27. Smith M, Upshur R, Smith M, Upshur R. Pandemic disease, public health, and ethics. *The Oxford Handbook of Public Health Ethics*. New York, NY: Oxford University Press; ; 2019:796-811. https://doi.org/10.1093/oxfordhb/9780190245191.013.69.
28. INSERM. La science pour la santé. Covid-19: Essai Discovery, point d'étape au 7 mai 2020. science pour la santé. 2020. https://www.inserm.fr/actualites-et-evenements/actualites/covid-19-essai-discovery-point-etape-7-mai-2020. Accessed December 19, 2020.
29. SMART IRB. SMART IRB: National IRB Reliance Initiative https://smartirb.org/. Accessed December 19, 2020.
30. NIH. Trial Innovation Network. https://ncats.nih.gov/ctsa/projects/network. 2018. Accessed December 19, 2020.
31. COVID-19 CP. COVID-19 collaboration platform. https://covidcp.org/faq/. 2020. Accessed December 19, 2020.
32. Global Citizen. Ask an expert: why are there so many COVID-19 vaccines – and is it better to have more? *GAVI the Vaccine Alliance*. 2020. https://www.gavi.org/vaccineswork/ask-expert-why-are-there-so-many-covid-19-vaccines-and-it-better-have-more. 2020. Accessed January 6, 2021.
33. UN News. UN health chief announces global "solidarity trial" to jumpstart search for COVID-19 treatment. https://news.un.org/en/story/2020/03/1059722. 2020. Accessed December 19, 2020.
34. UPMC. 2020. Led global effort fast tracks testing of COVID-19 therapies. https://www.upmc.com/media/news/040920-innovative-clinical-trials. Accessed December 19, 2020.
35. Alexander PE, Debono VB, Mammen MJ, et al. COVID-19 coronavirus research has overall low methodological quality thus far: case in point for chloroquine/hydroxychloroquine. *J Clin Epidemiol*. 2020;123:120-126. https://doi.org/10.1016/j.jclinepi.2020.04.016.
36. Kim AHJ, Sparks JA, Liew JW, et al. A rush to judgment? Rapid reporting and dissemination of results and its consequences regarding the use of hydroxychloroquine for COVID-19. *Ann Intern Med*. 2020;172(12):819-821. https://doi.org/10.7326/m20-1223.
37. Sattui SE, Liew JW, Graef ER, et al. Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19. *Expert Rev Clin Immunol*. 2020;16(7):659-666. https://doi.org/10.1080/1744666X.2020.1792778.
38. WHO. Coronavirus disease (COVID-19): Hydroxychloroquine; 2020. https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-hydroxychloroquine. Accessed November 22, 2020.
39. FDA. Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and. 2020. Accessed November 22, 2020.
40. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72-73. https://doi.org/10.5582/BST.2020.01047.
41. Patel TK, Barvaliya M, Kevadiya BD, Patel PB, Bhalla HL. Does adding of hydroxychloroquine to the standard care provide any benefit in reducing the mortality among COVID-19 patients?: A systematic review. *J Neuroimmune Pharmacol*. 2020;15(3):350-358. https://doi.org/10.1007/s11481-020-09930-x.
42. Suranagi UD, Rehan HS, Goyal N. Review of current evidence of hydroxychloroquine in pharmacotherapy of COVID-19. medRxiv; 2020. doi: https://doi.org/10.1101/2020.04.16.20068205.
43. Cochrane Response. *Targeted update: safety and efficacy of hydroxychloroquine or chloroquine for treatment of COVID-19*. London, UK: The Cochrane Collaboration; 2020:1–18. https://www.who.int/publications/m/item/targeted-update-safety-and-efficacy-of-hydroxychloroquine-or-chloroquine-for-treatment-of-covid-19. Accessed November 22, 2020.
44. Hôpitaux Universitaires de Genève, Département de Médecine Aigüe. Chloroquine, hydroxychloroquine et COVID-19: évaluation pharmacologique. https://www.hug.ch/sites/interhug/files/structures/coronavirus/documents/hydroxy-chloroquine-et-covid-19.pdf. 2020. Accessed December 19, 2020.
45. Chowdhury MS, Rathod J, Gernsheimer J. A rapid systematic review of clinical trials utilizing chloroquine and hydroxychloroquine as a treatment for COVID-19. *Acad Emerg Med*. 2020;27(6):493-504. https://doi.org/10.1111/acem.14005.
46. Bansal P, Goyal A, Cusick A, et al. Hydroxychloroquine: a comprehensive review and its controversial role in coronavirus disease 2019. *Ann Med*. 2020;53(1):117-134. https://doi.org/10.1080/07853890.2020.1839959.
47. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;10594956(1):1–6. https://doi.org/10.1016/j.ijantimicag.2020.105949.
48. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv; 2020;7. doi:https://doi.org/10.1101/.20040758
49. Gautret P, Lagier J, Parola P, Hoang VT. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study Philippe. *Travel Med Infect Dis*. 2020;34:101663. https://doi.org/10.1016/j.tmaid.2020.101663.
50. Davido B, Lansaman T, Bessis S, et al. Hydroxychloroquine plus azithromycin: a potential interest in reducing in-hospital morbidity due to COVID-19 pneumonia (HI-ZY-COVID)? medRxiv; 2020. doi: https://doi.org/10.1101/2020.05.05.20088757.
51. Huang M, Al E. Preliminary evidence from a multicenter prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19. *Natl Sci Rev*. 2020;7(9):1428–1436. https://doi.org/10.1093/nsr/nwaa113.
52. Ahmad I, Alam M, Saadi R, Mahmud S, Saadi E. Doxycycline and hydroxychloroquine as treatment for high-riskCOVID-19 patients: experience from case series of 54 patients in long-term care facilities. medRxiv; 2020. https://doi.org/10.1101/2020.05.18.20066902.
53. Yu B, Wang DW, Li C. Hydroxychloroquine application is associated with a decreased mortality in critically ill patients with COVID-19. medRxiv; 2020. doi:https://doi.org/10.1101/2020.04.27.20073379
54. de Novales F, et al. Early hydroxychloroquine is associated with anincrease of survival in COVID-19 patients: an obser-vational study. Preprints; 2020:1–37. doi:https://doi.org/10.20944/preprints202005.0057.v1

55. Million M, Al E. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis*. 2020;35:101738. https://doi.org/10.1016/j.tmaid.2020.101861.
56. Kim MS, Jang S-W, Park Y-K, et al. Treatment response to hydroxychloroquine, lopinavir/ritonavir, and antibiotics for moderate COVID 19: A first report on the pharmacological outcomes from South Korea; 2020. doi:https://doi.org/10.1101/2020.05.13.20094193
57. Chen L, Zhang Z, Fu J, et al. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study; 2020. doi:https://doi.org/10.1101/.20136093.
58. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis*. 2020;97:396-403. https://doi.org/10.1016/j.ijid.2020.06.099.
59. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2020;49(2):215-219. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03.
60. Molina J et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect*. 2020;50(4):384. https://doi.org/10.1016/j.medmal.2020.03.006.
61. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. *Med*. 2020;1:114-127. https://doi.org/10.1016/j.medj.2020.06.001.
62. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med*. 2020;382(25):2411-2418. https://doi.org/10.1056/NEJMoa2012410.
63. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020;323(24):2493-2502. https://doi.org/10.1001/jama.2020.8630.
64. Tang W, Al E. Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open–label, randomized, controlled trial running. *BJM*. 2020;369:m1849. https://doi.org/10.1136/bmj.m1849.
65. Mahévas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ*. 2020;369:m1844. https://doi.org/10.1136/bmj.m1844.
66. Singh S, Khan A, Chowdhry M, et al. Outcomes of hydroxychloroquine treatment among hospitalized COVID-19 patients in the United States- real-world evidence from a we acknowledge the West Virginia Clinical and translational science institute to provide us access, and training to the TriNETX. medRxiv; 2020. doi:https://doi.org/10.1101/2020.05.12.20099028.
67. Ip A, Berry DA, Hansen E, et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients-an observational study. *PLoS One*. 2020;15:1-19. https://doi.org/10.1371/journal.pone.0237693.
68. Paccoud O et al. Compassionate use of hydroxychloroquine in clinicalpractice for patients with mild to severe COVID-19 ina French university hospital. *Clin Infect Dis*. 2020;1-14. https://doi.org/10.1093/cid/ciaa791.
69. Faico-Filho KS, Conte DD, Souza Luna LK, Carvalho JMA, Perosa AHS, Bellei N. Effect of hydroxychloroquine on SARS-CoV-2 viral load in patients with COVID-19; 2020. doi:https://doi.org/10.1101/2020.06.16.20133066
70. Sbidian E et al. Hydroxychloroquinewith or without azithromycin and in-hospital mortalityor discharge in patients hospitalized for COVID-19 infec-tion: a cohort study of 4,642 in-patients in France. medRxiv; 2020:1–23. doi:https://doi.org/10.1101/2020.06.16.20132597.
71. Lecronier M, Beurton A, Burrel S, et al. Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis. *Crit Care*. 2020;24(1):1-9. https://doi.org/10.1186/s13054-020-03117-9.
72. RECOVERY. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med*. 2020;383(21):2030-2040. https://doi.org/10.1056/nejmoa2022926.
73. Mitjà O, Corbacho-Monné M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. *Clin Infect Dis*. 2020; 1-9. https://doi.org/10.1093/cid/ciaa1009.
74. Chen C-P, Lin Y-C, Chen T-C, et al. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate Coronavirus disease 2019 (COVID-19). *PLos One*. 2020;2019:1-14. https://doi.org/10.1101/.20148841.
75. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med*. 2020;173(8):623-631. https://doi.org/10.7326/M20-4207.
76. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020;3(4):e208857. https://doi.org/10.1001/jamanetworkopen.2020.8857.
77. Barbosa J et al. Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: a quasi-randomized comparative study. *NEJM*. 2020;1–15. https://aslm.org/wp-content/uploads/2020/06/1589740749-NEJM_Clinical-Outcomes-of-Hydroxychlorquine-in-Patients-with-COVID19.pdf?x10839. Accessed November 22, 2020.
78. Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet*. 2020;6736(20):1-10. https://doi.org/10.1016/S0140-6736(20)31180-6.
79. Mallat J, Hamed F, Balkis M, et al. Hydroxychloroquine is associated with slower viral clearance in clinical COVID-19 patients with mild to moderate disease: A retrospective study. 2020:1–21.doi:10.1101/2020.04.27.20082180
80. Funck-Brentano C, Salem JE. Chloroquine or hydroxychloroquine for COVID-19: why might they be hazardous? *Lancet*. 2020;6736(20):1016-1017. https://doi.org/10.1016/S0140-6736(20)31174-0.
81. London AJ, Kimmelman J. Against pandemic research exceptionalism. *Science*. 2020;368(6490):eabc1731. https://doi.org/10.1126/science.abc1731.
82. Meyer N. On ne peut pas décider de l'utilité d'un traitement sur une intuition. *Le Monde*. 2020. https://www.lemonde.fr/idees/article/2020/03/27/on-ne-peut-pas-decider-de-l-utilite-d-un-traitement-sur-une-intuition_6034699_3232.html Accessed November 22, 2020.
83. Trump D. https://twitter.com/realdonaldtrump/status/1241367239900778501. Accessed November 22, 2020 2020
84. Raoult D. Le médecin peut et doit réfléchir comme un médecin, et non pas comme un méthodologiste; 2020. https://www.lemonde.fr/idees/article/2020/03/25/didier-raoult-le-medecin-peut-et-doit-reflechir-comme-un-medecin-et-non-pas-comme-un-methodologiste_6034436_3232.html. Accessed November 22, 2020.
85. Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *Br Med J*. 2003;327(7429):1459-1461. https://doi.org/10.1136/bmj.327.7429.1459.

86. Adebamowo C, Bah-Sow O, Binka F, et al. Randomised controlled trials for Ebola: practical and ethical issues. *Lancet*. 2014;384(9952):1423-1424. https://doi.org/10.1016/S0140-6736(14)61734-7.
87. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc*. 2012;87(10):982-990. https://doi.org/10.1016/j.mayocp.2012.04.017.
88. Radley D, Finkelstein S, Stafford R. Off-label prescribing among office-based physicians. *Arch Intern Med*. 2006;166(9):1021-1026. https://doi.org/10.1001/archinte.166.9.1021.
89. Cummings J, Harris Interactive US. *Adults Ambivalent about the Risks and Benefits of off-Label Prescription Drug Use*. Rochester, NY: Harris Interactive Inc.; 2006.
90. Kalil AC. Treating COVID-19 off-label drug use, compassionate use and randomized Clinical Trials during pandemics. *JAMA*. 2020;375(15):1448-1456. https://doi.org/10.1001/jama.2020.4742.
91. Caplan AL, Upshur R. Panic prescribing has become omnipresent during the COVID-19 pandemic. *J Clin Invest*. 2020;130(6):2752-2753. https://doi.org/10.1172/JCI139562.
92. RECOVERY. Statistical Analysis Plan RECOVERY; 2020. https://www.recoverytrial.net/files/recovery-sap-v1-0-09_06_20.pdf. Accessed November 22, 2020.
93. RECOVERY. Definition and derivation of baseline characteristics and outcomes; 2020. https://www.recoverytrial.net/files/recovery-outcomes-definitions-v1-0.pdf. Accessed November 22, 2020.
94. RECOVERY. Randomised evaluation of Covid-19 therapy (recovery); 2020. https://www.recoverytrial.net/files/recovery-protocol-v10-1-2020-11-01.pdf. Accessed November 22, 2020.
95. RECOVERY. Statement from the Chief Investigators of the RECOVERY Trial on hydroxychloroquine; June 5, 2020. https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf. Accessed November 22, 2020.
96. FDA. Hydroxychloroquine fact sheet for health care providers; 2020. https://www.fda.gov/media/136538/download. Accessed November 22, 2020.
97. Siddiqi H, Mehra M. COVID-19 illness in native and immunosuppressed states. *J Heart Lung Transplant*. 2020;39(5):405–407. https://doi.org/10.1016/j.healun.2020.03.012.
98. Angus DC. Fusing randomized trials with big data: the key to self-learning health care systems? *JAMA*. 2015;314(8):767-768. https://doi.org/10.1001/jama.2015.7762.
99. Lovelace B, Feuer, W. World Health Organization resumes coronavirus trial on malaria drug hydroxychloroquine after examining safety concerns; 2020. https://www.cnbc.com/2020/06/03/world-health-organization-resumes-coronavirus-trial-on-malaria-drug-hydroxychloroquine-after-safety-concerns.html. Accessed November 22, 2020.
100. Ministre de la Santé et des Solidarités. Avis du Haut Conseil à la Santé Publique relatif à l'utilisation de l'hydroxycholoroquine dans le Covid-19; 2020. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwj19a3TjprtAhVyFFkFHbIVCx8QFjABegQIAxAC&url=https%3A%2F%2Fwww.hcsp.fr%2FExplore.cgi%2FTelecharger%3FNomFichier%3Dhcspa20200524_covidutilidelhydro.pdf&usg=AOvVaw1xB96b0EfNosvBX5iIIWPV. Accessed November 22, 2020.
101. Watson J. A (Longish) post-publication review of the most recent observational study in COVID19 patients treated with (hydroxy) chloroquine. This is retrospective analysis of an international registry with 96,000 hospitalised patients in 6 continents; 2020. https://twitter.com/jwato_watson/status/1264793409618935809. Accessed November 22, 2020.
102. Waston J, Al. E. Open letter to MR Mehra, SS Desai, F Ruschitzka, and AN Patel and to Richard Horton (editor of The Lancet); 2020. https://zenodo.org/record/3862789#.X7x1SVnCpI0. Accessed November 22, 2020.
103. Mehra MR, Ruschitzka F, Patel AN. Retraction—hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet*. 2020;395(10240):1820. https://doi.org/10.1016/S0140-6736(20)31324-6.
104. Brat GA, Weber GM, Gehlenborg N, et al. International Electronic Health Record-Derived COVID-19 Clinical Course Profile: The 4CE Consortium; 2020. doi: https://doi.org/10.1101/.20059691.
105. 4CE. Consortium for clinical characterization of COVID-19 by EHR; 2020. https://covidclinical.net/. Accessed November 22, 2020.
106. El EK, Rodgers S, Malin B. Anonymising and sharing individual patient data. *BMJ*. 2015;350 1–6. https://doi.org/10.1136/bmj.h1139.
107. Abramowitz S. Data sharing in public health emergencies: Anthropological and historical perspectives on data sharing during the 2014–2016 Ebola epidemic and the 2016 yellow fever epidemic; 2018:124.
108. WHO. WHO consultation on data and results sharing during public health emergencies. Background briefing; 2015. http://www.who.int/medicines/ebola-treatment/background_briefing_on_data_results_sharing_during_phes.pdf. Accessed November 22, 2020.
109. Komorowski M, Kraemer MUG, Brownstein JS. Sharing patient-level real-time COVID-19 data. *Lancet Digit Heal*. 2020;2(7):e345. https://doi.org/10.1016/S2589-7500(20)30132-1.
110. Dean NE, Gsell PS, Brookmeyer R, et al. Creating a framework for conducting randomized clinical trials during disease outbreaks. *N Engl J Med*. 2020;382(14):1366-1369. https://doi.org/10.1056/NEJMsb1905390.
111. Cook D, Marshall J, Fowler R. Critical illness in patients with COVID 19 mounting an effective clinical and research response. *JAMA*. 2020;323(16):1973-1975. https://doi.org/10.1001/jama.2020.5775.
112. REMAP-CAP. REMAP-CAP randomized, embedded, multifactorial, adaptive platform trial for community-acquired pneumonia (REMAP-CAP): Pandemic appendix to the core protocol; 2020. https://static1.squarespace.com/static/5cde3c7d9a69340001d79ffe/t/5f1bb6657fbac53ab4d79938/1595651697549/REMAP-CAP+-+PAtC+-+V2.0+-+18+May+2020_WM.pdf. Accessed November 22, 2020.
113. CAPTIC. The REMAP-CAP trial; 2020. https://www.captic.ca/the-remap-cap-trial. Accessed November 22, 2020.
114. Angus DC, Berry S, Lewis RJ, et al. The randomized embedded multifactorial adaptive platform for community-acquired pneumonia (REMAP-CAP) study: rationale and design. *Ann Am Thorac Soc*. 2020;17(7):879–891. https://doi.org/10.1513/annalsats.202003-192sd.
115. REMAP-CAP. REMAP-CAP: Core protocol; 2019. https://static1.squarespace.com/static/5cde3c7d9a69340001d79ffe/t/5e82b62eda9c1c714065efc0/1585624649154/REMAP-CAP+Core+Protocol+V3+-+10+July+2019_WM.pdf. Accessed November 22, 2020.
116. REMAP-CAP. Domain-specific appendix: COVID-19 Antiviral therapy; 2020. https://static1.squarespace.com/static/5cde3c7d9a69340001d79ffe/t/5ea3fd83f222897b8d528195/1587805583231/REMAP-CAP+-+COVID-19+Antiviral+Domain-Specific+Appendix+V2.0+-+01+April+2020_WM.pdf. Accessed November 22, 2020.
117. REMAP-CAP. REMAP-CAP appendix to core protocol: statistical analysis appendix; 2019. https://static1.squarespace.com/static/5cde3c7d9a69340001d79ffe/t/5e82b68a143343364b38c10c/1585624721568/REMAP-CAP+Statistical+Analysis+Appendix+V3+-+24+August+2019_WM.pdf. Accessed November 22, 2020.
118. Angus DC, Alexander BM, Berry S, et al. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov*. 2019;18(10):797-807. https://doi.org/10.1038/s41573-019-0034-3.
119. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), . *Adaptive Designs for Clinical Trials of Drugs and Biologics FDA Guidance for*

Industry. Silver Spring, MD: FDA. 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry. Accessed November 22, 2020.
120. Das S, Lo AW. Re-inventing drug development: a case study of the I-SPY 2 breast cancer clinical trials program. *Contemp Clin Trials*. 2017;62:168-174. https://doi.org/10.1016/j.cct.2017.09.002.
121. Hey SP, Kimmelman J. Are outcome-adaptive allocation trials ethical? *Clin Trials*. 2015;12(2):102-106. https://doi.org/10.1177/1740774514563583.
122. Goozner M. Controversy trails adaptive clinical trials. *J Natl Cancer Inst*. 2012;104(18):1347-1348. https://doi.org/10.1093/jnci/djs404.
123. Meagher KM, Cummins NW, Bharucha AE, Badley AD, Chlan LL, Wright RS. COVID-19 ethics and research. *Mayo Clin Proc*. 2020;95(6):1119-1123. https://doi.org/10.1016/j.mayocp.2020.04.019.
124. Rojek AM, Horby PW. Modernising epidemic science: enabling patient-centred research during epidemics. *BMC Med*. 2016;14(1):1-7. https://doi.org/10.1186/s12916-016-0760-x.
125. Horby P. RECOVERY trial—Randomised evaluation of COVID-19 therapy; 2020. https://www.recoverytrial.net/. Accessed November 22, 2020.
126. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. 2020;324(13):1317–1329.doi:https://doi.org/10.1001/jama.2020.17022
127. REMAP-CAP Hydroxychloroquine; n.d.. https://www.lifespan.io/road-maps/the-covid-19-roadmap/remap-cap-hydroxychloroquine. Accessed November 22, 2020

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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