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An ethics framework for consolidating and prioritizing COVID-19 clinical trials

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Abstract

Given the dearth of established safe and effective interventions to respond to COVID-19, there is an urgent ethical imperative to conduct meaningful clinical research. The good news is that interventions to be tested are not in short supply. Unfortunately, the human and material resources needed to conduct these trials are finite. It is essential that trials be robust and meet enrollment targets and that lower-quality studies not be permitted to displace higher-quality studies, delaying answers to critical questions. Yet, with few exceptions, existing research review bodies and processes are not designed to ensure these conditions are satisfied. To meet this challenge, we offer guidance for research institutions about how to ethically consolidate and prioritize COVID-19 clinical trials, while recognizing that consolidation and prioritization should also take place upstream (among manufacturers and funders) and at a higher level (e.g. nationally). In our proposed three-stage process, trials must first meet threshold criteria. Those that do are evaluated in a second stage to determine whether the institution has sufficient capacity to support all proposed trials. If it does not, the third stage entails evaluating studies against two additional sets of comparative prioritization criteria: those specific to the study and those that aim to advance diversification of an institution's research portfolio. To implement these criteria fairly, we propose that research institutions form COVID-19 research prioritization committees. We briefly discuss some important attributes of these committees, drawing on the authors' experiences at our respective institutions. Although we focus on clinical trials of COVID-19 therapeutics, our guidance should prove useful for other kinds of COVID-19 research, as well as non-pandemic research, which can raise similar challenges due to the scarcity of research resources.

Keywords

COVID-19, coronavirus, research ethics, clinical trials, prioritization, triage

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Introduction

Given the dearth of established safe and effective interventions to respond to COVID-19, there is an urgent ethical imperative to conduct rigorous and meaningful clinical research.[1–3] Fortunately, there are many promising interventions to test. Unfortunately, it is possible to have too much of a good thing, including trials accelerating at a rate that institutional and global research capacity cannot support.[4–6] Not all COVID-19 studies can be pursued simultaneously—and some should perhaps not proceed at all—even if, considered in isolation, they would be approvable by an Institutional Review Board (IRB). Although the number of COVID-19 cases unfortunately continues to grow, especially in the United States, those who qualify for and are willing to participate in particular clinical trials comprise a limited pool at any particular site and cannot, for scientific and practical reasons, participate in an unlimited number of trials.[7] Resources needed to safely and responsibly conduct these trials—clinical staff time, personal protective equipment, freezers, mobile devices, lab time, information technology and data analytics staff time, and others—are scarce and may be needed to support clinical care and important non-COVID-19 trials.[8] Investigators, research staff, IRB members and staff, research grants and contracts personnel, institutional privacy and information security staff, custodial staff, and others also have limited capacity.

Thoughtful and deliberate approaches to institutional research priority setting are needed independently of pandemic-related challenges, but are particularly pronounced at present. Without a process for appropriately consolidating and prioritizing trials, trials will likely duplicate effort and fail to meet enrollment targets and less valuable, but more quickly fielded studies will crowd out higher-priority studies.[9–11] Existing research oversight bodies, such as IRBs, Research Ethics Boards, and scientific review committees, typically consider studies case-by-case. They generally do not evaluate them in context or comparatively to determine whether some might be combined to create efficiencies or to assess which would make the best use of limited resources.[12,13] Especially in a pandemic, this approach will almost certainly fail to achieve optimal results. Although there have been some efforts to respond to priority-setting challenges, such as the review committees required by comprehensive cancer centers funded by the National Cancer Institute[14] and similar committees tasked with prioritizing which trials the institution will field in certain other disease areas,[15] these are rare outside oncology.

Ideally, coordination and prioritization of trials would occur upstream (e.g. among manufacturers[16] and funders) and at a higher level than the individual institution (i.e. regionally, nationally, or internationally). In some jurisdictions, where a national health system facilitates coordination of COVID-19 research, important trials have been able to complete. For example, a single adaptive platform trial in the United Kingdom—RECOVERY—is responsible for three of the most robust and clinically actionable conclusions to date about COVID-19 therapeutics.[17–19]

In the United States and elsewhere, however, coordination has been lacking. This is not entirely surprising: incentives are likely misaligned, in particular due to competition for both academic credit and local/regional patient share. Leaders may resist sharing or ceding decision-making power to others (especially competitors) and may be reluctant to share business-sensitive information that might be relevant to frank trial prioritization discussions. Whatever the reason, the result has been a large number of trials accompanied by a dearth of answers to critical research questions.[6,20] Too many trials are duplicative (including continued pursuit of interventions that available evidence indicates should be abandoned), not robustly designed, or underpowered such that they are unlikely to be informative.[6,21,22] As of late June 2020, of all participants enrolled in one of 1200 COVID-19 trials registered on clinicaltrials.gov, an astonishing 35% were enrolled in a study of just one intervention: chloroquine or its derivative, hydroxychloroquine. And across all COVID-19 trials, 39% sought to or did enroll 100 or fewer participants.[6] By January 2021, the number of registered trials (2533) had more than doubled, with little reason to believe that problems of duplication, power, and prioritization have been addressed.[23] A private–public partnership that leverages existing clinical trial networks to test industry products, Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV),[24,25] is welcome. But participation in most of ACTIV's trials precludes participation in others, and with finite patient-participants (and other resource constraints), institutions must still decide which of these trials to field. Moreover, institutions face decisions about investigator-initiated, institution-funded trials.

In light of these challenges, we offer guidance for individual health systems, academic medical centers, and other institutions about how to ethically consolidate and prioritize COVID-19 clinical trials. First, we describe a three-stage process of consolidating and prioritizing COVID-19 clinical trials. The little guidance that exists about prioritizing clinical trials tends to focus on criteria such as robustness and feasibility. These are clearly important considerations that we too include. However, we also address the importance of conducting research that addresses clinical needs across the life span, across disease stages, and across diverse sociodemographic groups, including those—especially Black, Latinx, and Indigenous people—who have been disproportionately affected by COVID-19. We further emphasize the importance of evaluating not only individual trials but also how these trials fit into an

institution's broader COVID-19 clinical research portfolio. Second, we recommend that each research institution creates a COVID-19 Research Prioritization Committee in order to apply our substantive criteria to proposed trials.

The goal of our proposal is a fair, transparent process for avoiding research that will consume time and finite resources without resolving urgent research questions.[20] Finite research resources are, of course, not a problem limited to pandemics, and our guidance may be helpful for prioritizing other types of research. However, the urgency of discovering effective means of responding to the COVID-19 pandemic and the sheer volume of proposed trials make this problem acute. Although we focus on drug trials, many of these recommendations are also applicable to other types of COVID-19 research, including trials of important non-pharmaceutical interventions and non-trial studies, where even less coordination appears to exist.

Three-stage evaluation

Institutions should consider proposed COVID-19 trials in three stages (Figure 1). First, each trial must meet four *threshold criteria*. Second, if all threshold criteria are satisfied, *institutional capacity* to carry out the work should be assessed. When institutional resources and prospective participants are sufficient to accommodate all trials meeting threshold criteria, then all may proceed.

However, when institutional capacity is insufficient to support all proposed studies meeting threshold criteria, those studies should move to a third stage of consideration, in which they are prioritized on the basis of *study-specific criteria and of criteria relevant to the diversity of an institution's research portfolio* to determine which should proceed first. Lower priority studies should be delayed until institutional resources can support them and should not be considered to have a fixed position on a "waiting list"; they must be continually assessed against current and proposed research trials.

Given the importance of ensuring optimal use of finite resources, institutions should also consider pausing or ending active trials if they are not close to completing enrollment and a new trial competing for the same resources has *substantially* higher priority, given what is currently known about each trial's likely impact. If institutions pilot this practice, they should use a high bar when taking this step and would also have a responsibility to inform sponsors and participants in advance, given that stopping the trial would void their respective investments in it.

Stage one: threshold criteria

At the first stage of review, a trial should meet the following threshold criteria assessing whether it represents at least a *minimally* adequate use of resources. Trials that reach the minimal threshold may be higher or lower quality; comparative assessments are made at Stage Three.

Social value. Like any trial, COVID-19 trials should be allowed to proceed only if they address unanswered

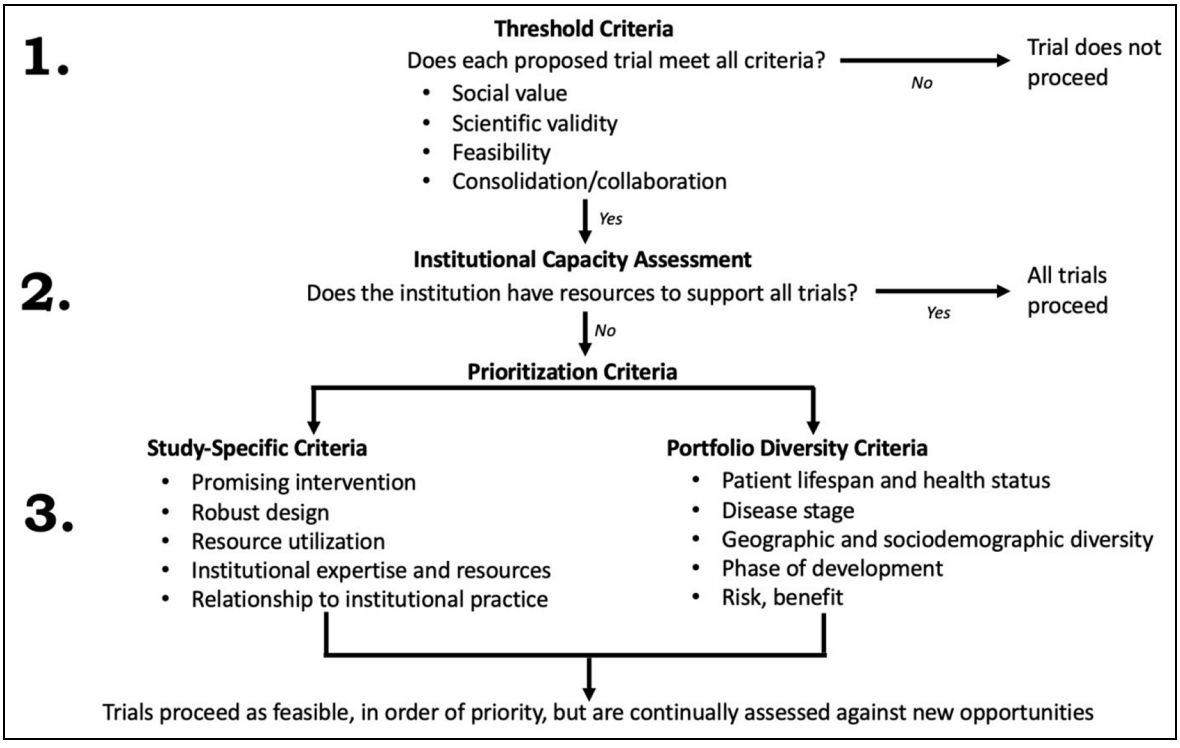

Figure 1. Three stages of COVID-19 trial consolidation and prioritization.

questions of at least some importance to stakeholders, especially patients.

Scientific validity. Trials must also be adequately designed and powered to answer socially valuable questions.

Feasibility. As with any research, COVID-19 trials should be allowed to proceed only if the institution has the human and other resources to field them, such that there is a reasonable likelihood of meeting enrollment targets and answering the question posed.

Consolidation/collaboration. To conserve resources, accelerate science, and facilitate better-powered studies, proposed trials that are sufficiently similar to other proposals or ongoing research should not advance to Stage Two, but should instead be consolidated. Within an institution, investigators proposing similar trials should be expected either to collaborate or differentiate their projects. Investigators proposing trials similar to those underway outside the institution should be encouraged to join those existing efforts, when possible, or to make a compelling case to the contrary (e.g. that their proposed design is superior, the population or environment is meaningfully different, or the proposed trial is more likely to reach its enrollment target or to do so faster). Institutions should also consider platform trials, which conserve resources by comparing multiple interventions against a shared control group.[26] Although we acknowledge that this approach is in tension with the often-competitive nature of academia, scientific progress must be paramount, especially during a pandemic. To address the professional needs of researchers, institutions should reward participation in team science and otherwise make accommodations for pandemic circumstances.

Stage two: institutional capacity assessment

Next, an institution must determine whether it can simultaneously field all trials that satisfy threshold criteria. This determination requires a realistic, granular assessment of each trial's requirements and of an institution's research capacity, including participants, research staff, and material resources. When determining research capacity, institutions should consider not only those trial opportunities that have already been proposed by internal or external investigators or sponsors, in a reactive sense, but also those the institution might proactively seek to initiate or join.

Stage three: prioritization criteria

When several trials meet the initial threshold criteria but cannot all proceed due to resource constraints, they must move on to the final stage—prioritization. At this stage, trials should be assessed against two additional sets of criteria: those that are study-specific and those that consider the diversity of an institution's portfolio.

Study-specific prioritization criteria evaluate whether a proposed study is more or less worth pursuing, relative to the costs of doing so and to other trials that are being or could be pursued. Although there is overlap between these criteria and the threshold criteria described above, the aim at this stage is not to determine minimal acceptability, but rather comparative strength.

Prioritizing the highest quality trials must be balanced with ensuring adequate coverage—at the institution and elsewhere—with regard to important categories of trials, such as those that address different populations (e.g. different ages, disease severity, comorbidities, or socially determined risk factors) or kinds of interventions. To avoid potential gaps, *portfolio diversity criteria* are collectively designed to promote access to the opportunity to participate for all of the patients an institution cares for (a concern about fair opportunity and burden sharing), to promote the study of COVID-19 in all types of patients who suffer from or are at risk for it (a concern about fair inclusion to ensure generalizability), and to balance the likelihood and timing of successful outcomes against the impact of the intervention.[27]

Ideally, upstream coordination and prioritization would ensure a diversified global portfolio of trials fielded at the institutions to which they are best suited. In the absence of such coordination, institutions should do their best to track trends in regional, national, and international COVID-19 trials and to consider how the trials they choose can contribute to answering a diverse range of research questions. In seeking to fill any gaps in the global trial portfolio, institutions should, however, consider their own comparative strengths and weaknesses in fielding certain kinds of trials. If there are no gaps the institution is well-positioned to fill, it should seek to achieve diversity in its own trial portfolio. Where diversification at a regional, national, or international level is out of reach, a commitment by each institution to field internally diverse trials is most likely to result in a globally diverse trial portfolio.

Study-specific prioritization criteria

Promising intervention. Although all trials must have the potential to contribute socially useful knowledge, some interventions have greater expected net benefit than others. That is, trials should be prioritized that are (1) more *likely* to result in a safe and effective intervention and/or (2) hypothesized to have a greater *magnitude* of impact on human welfare. The ideal trial is relatively low risk to participants (e.g. because it involves a repurposed drug with a well-known safety profile),

relatively high benefit (e.g. hypothesized to prevent or cure COVID-19 rather than mitigate symptoms or speed time to recovery), and relatively likely to succeed (e.g. based on the results of preclinical studies or early phase human trials, the agent's mechanism of action, or its performance against similar viruses[28,29]).

Robust design. Some designs increase the likelihood that a study will reliably answer a valuable research question. Robustness may be understood largely in terms of familiar hallmarks such as inclusion of a randomized control group, blinding, and use of validated instruments and endpoint measures. Robustness may also depend on study objectives and real-world applicability. Trials that evaluate clinically meaningful hypotheses and endpoints should score highly on this criterion. The experience and expertise of the study team should also be weighed.

Resource utilization. The more a trial would burden institutional resources, the more it must be justified by strong performance on other study-specific and/or portfolio criteria, since its relative burden on those resources will tend to crowd out other trials.

Institutional expertise and resources. Some trials are best conducted at specific institutions due to special clinical or research expertise, facilities, or patient populations. Those institutions can maximize the benefits of research by participating in such trials, since other institutions will be less suitable substitutes. Where institutions lack relevant expertise but have other relevant resources, such as a large clinical base of COVID-19 patients, collaboration is the best path forward. To the extent that different institutions have different strengths, this approach also promotes diversity within the wider research portfolio.

Relationship to institutional clinical practice. Given the current state of evidence regarding COVID-19 interventions, clinicians have adopted treatment regimens without strong evidentiary foundations—sometimes justifiably, such as the use of prone positioning without knowing precisely what timing is optimal, and sometimes not, such as widespread off-label use of hydroxychloroquine or convalescent plasma outside of a trial. Although COVID-19 Research Prioritization Committees (described below) may not control the practice of medicine at their institution, they have the opportunity to prioritize trials that will evaluate such institutional practices to inform decisions about whether they should be continued or stopped. The resources required for such trials are not trivial, but the marginal effort of studying what an institution is already inclined to do is likely to be modest compared to pursuing trials of interventions that would not otherwise be offered to an institution's patients.

Portfolio diversity criteria

Patient life stage and risk factors. COVID-19 affects people differently who are at different life stages,[30–32] who have comorbidities,[33] and who face different socially determined risk factors (often because they are members of disadvantaged racial and ethnic groups).[34–37] As a result, institutions should aim to field trials that cover the lifespan, including children, pregnant people, and the elderly, as well as trials that address the needs of those with chronic conditions and those facing socially determined risk factors.

Disease stage. Although trials that seek to help the sickest COVID-19 patients are critical, the costs to patients and society of even asymptomatic and mild to moderate forms of the disease are substantial and poorly understood. A balanced portfolio will therefore include both therapeutic trials that collectively reflect the spectrum of disease stage and prevention trials. Institutions can help foster such a portfolio by selecting trials that would be fielded in different patient encounter settings, such as intensive care units, other inpatient settings, and outpatient settings.

Geographic and sociodemographic diversity. Some health care systems have multiple campuses, but significant research capacity at only a few. To the extent that some trials offer the prospect of clinical benefit to participants, it is important that as many of health care systems' patients as possible (and, in some trials, its health care workers and other staff) have the opportunity to participate. Spreading trials across a system also helps ensure that the burdens of research are not unjustly concentrated on some groups.[27] Institutions therefore should attempt to widely extend research opportunities, perhaps by prioritizing trials that are "lighter lifts" and can be fielded at campuses with less research capacity. This is especially important because COVID-19 disproportionately affects some racial and ethnic groups[34–37] that face structural discrimination and may be concentrated in certain geographic regions.

Phase of development. Institutions may be tempted to prioritize Phase III trials, given that as many as 75% and 85% of Phase III infectious disease drug and vaccine trials, respectively, test interventions that are ultimately approved.[38] Yet if every institution fielded only Phase III trials, no one would field the earlier phase trials on which Phase III trials necessary build. Conversely, some institutions may be tempted by academic incentives to prioritize early phase trials initiated by their own investigators. If every institution took this approach, critical Phase III trials would never complete. Good citizenship in the research community requires institutions to seek to contribute to the full product development pipeline (with the caveat, reflected by the institutional expertise and resources

criterion above, that some institutions are especially well or poorly poised to field different trial phases).

Risk, benefit. Although in general, institutions should prioritize trials with greater expected net benefit (see the promising intervention criterion above), that benefit may be high because of likelihood, magnitude, or both. If an institution selects trials primarily based on magnitude of benefit, rather than likelihood, it may yield no successes, while displacing trials that are "surer bets," but with modest expected benefits. Similarly, if an institution focuses primarily on likelihood of benefit, it may yield modest successes while failing to pursue studies with greater potential impact. Accordingly, a balanced portfolio would contain some trials whose relatively high expected benefit is driven by high magnitude of benefit and some whose relatively high expected benefit is driven by high probability of success.

The oversight process

Many health systems, academic medical centers, and other facilities engaged in COVID-19 research—including ours—have created committees to consolidate and prioritize proposed COVID-19 trials.[39] These committees are likely to best maximize coordination when established at an institution's highest relevant level (e.g. one committee at the level of a health system, not one at each of its campuses).

Considering the types of questions likely to arise, committees should include clinical trialists, biostatisticians, research ethicists, and clinicians from infectious disease, critical care, emergency medicine, and research nursing. They should also include representatives from—or lines of communications to—each team that manages finite research resources and has an understanding of the burden that each proposed study would place on that resource. For the sake of efficiency, institutions might consider establishing subcommittees that lead review or assessment at different stages of the prioritization process. Because (sub)committees often must meet frequently and on short notice, it may be challenging to include patient or community representatives; we encourage institutions nevertheless to look for opportunities to solicit and incorporate patient perspectives, including about the kinds of research burdens they are willing to assume and the research questions and outcomes they find meaningful.

To the extent possible, the COVID-19 research prioritization process should occur prior to IRB, grants office, and other institutional reviews to avoid wasting those important resources. We note that the criteria used and tasks performed by these other bodies are distinct from the criteria we propose here (e.g. IRB assessment of acceptable risk); these processes are not substitutes for one another.

It might be efficient to review some proposals at the exploratory stage; trials that do not pass threshold criteria or fare well on prioritization criteria need not be developed further. Fielded trials should be periodically re-reviewed against other opportunities to ensure they remain a good use of resources.

Since prioritization committees have not been subjected to empirical assessment, many details of committee membership and process can reasonably vary across institutions as they try different models. For instance, some of our institutions assess proposed trials against each Stage Three prioritization criterion quantitatively—such as on a 1–5 scale—while others have taken a qualitative approach. Quantitative approaches will likely facilitate clearer comparisons between trials, which are especially important the more proposed trials a committee simultaneously considers. In addition, the more experience the committee gains with such ratings, the easier and more consistent the ratings are likely to become.

Because this form of research oversight will be new to many investigators and has implications for which experimental interventions patients will be able to access, research prioritization committees should have the clear support of both research and clinical leadership. The committee's purpose and process should be transparent to all stakeholders, committee members should commit to fair application of the framework and to managing conflicts of interests, and the committee should have access—via membership or reporting lines—to leaders tasked with shaping the organization's strategic response to the pandemic.

As with other forms of research review, some might object that the process we propose will inevitably delay the initiation of some clinical trials.[14] In our experience, an efficient committee that meets regularly—and, critically, whose discussions are guided by criteria such as those offered here—can make sound decisions within days (or shorter). In the long run, this prioritization process can save time and resources by ensuring that a comprehensive portfolio of high-quality, feasible COVID-19 research is conducted.[40] Quickly fielding an abundance of trials that fail to adequately recruit and answer questions, that exclude important populations, or that are disproportionally concentrated on certain interventions—as has been the case in the pandemic to date[6]—will do far more to waste scarce resources and set back scientific progress.

Conclusion

We have focused on COVID-19 drug trials, but other kinds of COVID-19 research—for example, trials of non-pharmaceutical interventions[41] and epidemiological, behavioral, health services, qualitative, and genomic research—are also important and in need of similar consolidation and prioritization. In particular, research to identify and intervene on racial, ethnic, and other

disparities in COVID-19 outcomes is sorely needed.[36] In addition, as precedents in cancer[14] and other areas of clinical research show,[15] the need to consolidate and prioritize research is not limited to pandemics. Our criteria add to existing guidance, which tends to focus narrowly on scientific merit rather than criteria designed to ensure fairness and justice. Nevertheless, as with other research review and oversight processes, COVID-19 research prioritization committees should themselves be studied to ensure that they are achieving their goals, to identify burdens (e.g. in addition to delays, consolidation and prioritization might have a disproportionate impact on early career investigators), to ensure that committees' benefits are worth their costs, and to identify aspects that can be improved.[42]

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