

# Deprioritization of Ongoing Clinical Trials

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**ABSTRACT** To be ethical, clinical trials must exhibit a favorable risk-benefit balance at the time of their initiation. However, in some cases, the expected value of a study decreases while the study is ongoing, due to developments outside of the study itself, such as findings from other studies or an otherwise shifting evidence base. While such situations are acknowledged in the research community, they have not received sufficient attention, given the high costs of uninformative studies, both in material and human capital. In addition, the Covid-19 pandemic has exposed serious shortcomings with current approaches to monitoring studies for continued relevance and value. In this article, with reference to a case study from the Covid-19 pandemic, we identify and describe the importance and challenge of ensuring that clinical trials continue to exhibit scientific relevance and value once initiated. We explore the ethical dynamics of these situations and identify unresolved issues. While more empirical work is needed to ensure that proposed solutions to the issues are evidence based, we offer some provisional considerations that amount to a framework for approaching these challenging situations.

**KEYWORDS** clinical trials, risk-benefit balance, scientific value, internal validity, institutional review board (IRB), data monitoring committee (DMC), research ethics

Bierer, B. E., D. A. Zarin, and L. Gelinas, "Deprioritization of Ongoing Clinical Trials," *Ethics & Human Research* 45, no. 5 (2023): 27-33, DOI: 10.1002/eahr.500180

Clinical trials should be initiated only when the value of the knowledge they can be expected to produce justifies their risks and burdens to participants. Sometimes, however, the scientific value of a study changes as it unfolds, based on evidence internal or external to the trial itself, that renders the research duplicative or uninformative or otherwise impacts its risk-benefit balance for the worse. This phenomenon is a particular concern when the standard of care changes frequently, such as it does in oncology, and is particularly acute with new diseases and rapidly changing evidence bases. For example, as of May 9, 2021, ClinicalTrials.gov listed 234 interventional studies of hydroxychloroquine (HCQ) for Covid-19. Of those, a total of 97 trials were actively recruiting ( $n = 60$ ), yet to begin recruiting ( $n = 32$ ), or enrolling by invitation ( $n = 5$ ) at a time when there was broad consensus that HCQ lacked efficacy for this use.<sup>1</sup> The World Health Orga-

nization<sup>2</sup> and the United Kingdom's Medicines and Healthcare Products Regulatory Agency<sup>3</sup> had already foreclosed continued investigation of the drug, the U.S. Food and Drug Administration had withdrawn its emergency-use authorization,<sup>4</sup> and the European Medicines Agency had issued warnings of its safety risks.<sup>5</sup>

## SCOPE OF THE CURRENT SYSTEM OF TRIAL OVERSIGHT

Clinical trials are generally reviewed and approved by an institutional review board (IRB) following an assessment of the potential benefits, risks, and burdens of the proposed research, along with an evaluation of the scientific integrity and its anticipated social value.<sup>6</sup> There are well-known ethical and scientific problems associated with asking human volunteers to participate in clinical trials that are unlikely to provide scientific value (uninformative trials).<sup>7</sup> Despite this awareness,

it is well-established that the current system(s) of research oversight does not systematically prevent the initiation of such trials, leading to “research waste” that includes exposure of thousands of volunteers each year to research activities that are unlikely to lead to any scientific advances.<sup>8</sup> Proposals for addressing this problem have not substantially changed the behavior of academic medical centers or research funders.<sup>9</sup>

Similarly, IRBs, data monitoring committees (DMCs), and other oversight bodies have experience monitoring ongoing clinical trials and making termination decisions when the emerging results from within the trial show little or no justification for trial continuation. Those considerations relate to safety, when accumulating evidence suggests that risks to participants outweigh the benefits; benefit, when an interim analysis reveals, by predetermined criteria, the superiority of one interventional arm, rendering continuation of the inferior arm unethical; futility, when an interim analysis suggests that a statistically significant difference between two arms of a trial is unlikely to be achieved; and feasibility, when a trial is not likely to be completed for a number of reasons, including poor accrual, logistics, lack of funding, investigator unavailability, or commercial business decisions.<sup>10</sup> While one may raise questions about the ethics or scientific implications of particular trial termination decisions, as well as the standards that should be used for recommending trial termination, there does appear to be widespread agreement that some trials should be terminated for these reasons.

### **MONITORING DATA EXTERNAL TO TRIALS: A LIMITATION OF CURRENT OVERSIGHT**

**B**y contrast, the problem of identifying and acting on information external to an index trial—data that might render a previously informative trial now uninformative or otherwise problematic—has received insufficient attention. We are not aware of processes, standards, or systems for monitoring the landscape of evolving evidence for information that might alter the likely informativeness or feasibility of an ongoing clinical trial. This question is particularly acute when the therapeutic landscape—consisting of scientific insight, clinical practice, and the evidence base generally—is rapidly changing. It is unclear whose responsibility it is to determine whether, in the context of other ongoing

and recently completed trials, the relevant literature, or external sources of evidence generally, the potential incremental value of trial continuation is worth the potential risk to current or future participants. It is also unclear what criteria should be used to make these decisions and how potentially competing considerations should be weighed.

What might be warranted for studies whose risk-benefit balance is put into question on the basis of emerging external evidence ranges from no action at all to changes to informed consent for new and/or ongoing participants, to various types of deprioritization (including pausing enrollment and/or intervention[s] or allowing enrollment to proceed but in a way that makes full accrual less likely, for example, by offering the deprioritized study to patients only after other studies have been declined), to, ultimately, trial termination. Decisions about whether and how to deprioritize—or terminate—ongoing trials will impact participants and other stakeholders differently (see table 1). While the research community is familiar with the implications of pausing or terminating studies on patients and other stakeholders, it lacks a framework for rigorous assessment of the types and levels of emerging external evidence that would justify specific forms of trial deprioritization or termination.<sup>11</sup>

More generally, who has the responsibility, resources, authority, and expertise needed to reassess the potential scientific value and continued clinical equipoise of ongoing studies, at a time when the body of evidence could be evolving? Such decisions would require nuanced expert evaluation and a principled framework for evaluation, given potential subtle differences in the target population, eligibility criteria, study design, drug dosage and comparators, and outcome measures, as well as the potentially appropriate role for studies intended to replicate (or refute) prior studies. Here we identify some of the basic issues involved with the review and deprioritization or termination of ongoing trials based on evidence external to an index trial. We focus first on the challenge of determining scientific value as science and practice evolve, comment on certain dependencies that could render evaluation and judgment easier, and then consider the impact of any decision on participants and the public.

**Table 1.**  
**Monitoring Value of Ongoing Clinical Trials: Framework for Review**

**Periodic assessment**

- Importance and risk-benefit considerations
  - Has the question been sufficiently resolved since the initiation of the trial?
  - Is there still adequate scientific value to be gained from the current trial?
    - Is there new knowledge about the study intervention(s) that modifies the risk-benefit analysis?
    - Is there new knowledge about the comparator that modifies either the risk-benefit analysis or power calculations?
    - Have other sources of information rendered the question irrelevant?
    - Is there new knowledge or evidence that an alternative intervention (i.e., one not used in the index trial) has been shown to be effective and that could render the index trial moot (e.g., an intervention shown to be superior to an active control that would render moot an index trial designed as a noninferiority study)?
- Design
  - Has any data or information about the index-trial intervention(s), either active or comparator, emerged from other trials testing the same intervention(s) that could lead to a change in the predicted event rates and/or power estimate for the index study?
  - Is there new information that could reduce the value or efficiency of or trust in the outcome measures (e.g., data on the correlation of a biological surrogate with change in disease progression)?
  - Is there any new information on an important subpopulation that may require study-design changes or redesign?
- Feasibility
  - Are there any changes impacting likely enrollment or rendering trial feasibility less likely?
    - Have trials with overlapping eligibility criteria been initiated that might compete for the same participants in the same geography?
    - Has there been a change in the availability of any of the experimental interventions? (For example, have any of them received marketing approval for another indication, and could this lead to off-label prescribing?)
    - Has new information about comparator intervention(s) rendered the trial less desirable?
    - Have interventions other than those evaluated in the index trial and that might be appealing to potential participants gained marketing approval or availability? (For example, the approval of Covid-19 vaccines may make new vaccine trials more difficult.)
    - Has publicly available information about the condition or intervention(s) under study emerged (e.g., through news reports or other media) that might change participant willingness to enroll in the trial?

**Potential actions based on periodic review and impact**

- No change: Trial proceeds as planned.
- Deprioritization
  - Changes to recruitment or other processes that are predicted to result in slower accrual are made. (For example, a deprioritized trial is offered only after other trials with similar eligibility criteria have been offered first.)
  - There is no direct impact on participants already enrolled, but informing them of the diminished chance of scientific benefit may be ethically advisable or required.
  - There is a lower likelihood of trial completion and generalizable knowledge necessitating more frequent monitoring.

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Table 1.

**Monitoring Value of Ongoing Clinical Trials: Framework for Review** (continued from previous page)

- Pause recruitment and enrollment of new participants.\*
  - Make no change for participants already enrolled, or provide information to or reconsent participants already enrolled, as needed (e.g., concerning diminished chance of scientific benefit, emergence of safety concerns, and/or the like.)
  - Delay (if temporary) or preclude (if permanent) recruitment and enrollment of new participants if there is a reduced possibility of trial completion and a reduced possibility of generalizable knowledge.
- Pause enrollment AND stop interventions for participants already enrolled.\*
  - Provide outreach and information to current study participants.
    - Disclose safety considerations.
  - Consider pausing current care or transitioning care, as necessary.
  - Provide information to or reconsent participants already enrolled, as needed.
- Study termination: Permanently stop recruitment and all interventions.
  - Provide outreach and information to current study participants.
    - Disclose safety considerations.
  - Assist participants with transition.

\* This can be a temporary or permanent decision.

### IMPORTANCE OF DETERMINING CONTINUED SCIENTIFIC VALUE

We start from the presumption that initiation of a trial is typically based on a determination that it reaches some threshold of scientific value and that the design has sufficient internal validity to support valuable conclusions. These determinations would—or should—be undertaken by investigators, research sponsors, and IRBs and include a review of the current state of knowledge, of results of completed trials and similar ongoing studies, and of a description of the new knowledge anticipated to result from the index trial. After a study is initiated, investigators, sponsors, and IRBs are expected to monitor the study, evaluate safety reports, and conduct interim and continuing reviews. Importantly, data monitoring plans, and DMCs if constituted, would guide the review of accumulating data from the trial, and such review would include processes for deciding about discontinuation based on emerging evidence (for example, about safety, efficacy, futility, or low accrual).

Can we apply similar considerations to decisions based on data external to the trial? For example, the feasibility, appropriateness, or value of an index trial could be affected by regulatory approval of a competitive or superior product or a change in the standard of care (e.g., such that the comparator arm is no longer deemed to be ethical or of scientific interest). In such situations, several options in addition to outright trial termination

could be considered. A decision to pause a trial, to allow participant reconsent with the new information; to amend the trial, to accommodate new knowledge; or to deprioritize the trial, based on diminished relevance of the comparator or emergence of a potential new intervention, for instance, may be a more fitting response to emerging evidence. In some cases, participants may wish to continue in a study even if the standard of care has changed or another intervention has gained approval. This carries some ethical weight—to override this preference in the face of participants' informed willingness to continue may constitute an objectionable form of paternalism. A more ethical approach may be to use a form of deprioritization that permits continued participation rather than outright termination; if doing so would be safe, this alternative approach should be considered.

### CHALLENGES IN DETERMINING SCIENTIFIC VALUE WHEN THE LANDSCAPE CHANGES

As a trial proceeds, systematic monitoring of the knowledge landscape is essential to ensure that relevant new information can be incorporated into decisions about continuing, changing, or stopping a trial. In the setting of an evolving evidence base and practice, such as during the Covid-19 pandemic, however, assessments of scientific value can be challenging.<sup>12</sup> First, determining whether a proposed trial is duplicative, that is, whether it is asking a question that has already been

answered with sufficient certainty, requires knowing about the status of other, similar trials. But understanding what constitutes a “similar” trial or just how similar another trial must be to render the index trial uninformative are substantive and difficult questions. Such assessments depend on multiple factors. These include the demographics of the participant populations as determined by the trials’ respective eligibility criteria (including stage and severity of the condition or disease), study design, drug doses and comparators, outcome measures, and other parameters; all of these must be known to assess the degree of similarity or overlap. Second, continued assessment of ongoing studies should consider data emerging from other studies that are under way. There are many sources of data about both ongoing and completed trials that might vary in their completeness and accuracy. The traditional process of relying entirely on peer-reviewed literature has proven insufficient, as more information is available through other venues, sometimes in a much more timely and complete manner (e.g., ClinicalTrials.gov and preprint servers). Clinical trial stakeholders, and specifically the sponsors and investigators, maintain a responsibility to review such sources and assess the current evidence base systematically. A landscape analysis (i.e., a review of completed and ongoing studies of relevance to the index trial) should take place both prior to initiation of the study, to ensure the results the index trial aims to deliver will be sufficiently meaningful, and at regular intervals as it unfolds, to ensure its continued relevance and determine, in a statistically meaningful way, whether continued participant accrual is worthwhile.

In general, approaches to evaluating ongoing studies based on external evidence should parallel the more familiar process of assessing studies for continuation and termination based on evidence internal to the trial. Entities responsible for monitoring and making these determinations should ask these questions: How many additional participants would need to be enrolled, with what predictive effect size, to result in a meaningful—and potentially actionable—result, given what we now know or have reason to believe considering the external evidence? In addition, what additional or revised information should be included in the informed consent form? Holding trials to a high standard in this regard need not discount the value of replication. However,

even the value of replication depends on factors external to the trial itself. If the index study is launched or continued with the goal of replicating a result and another study succeeds at replicating the same result while the index study is still ongoing, that replication may undercut the rationale for continuing the index study. Moreover, the existence of other, similar trials in a geographical region may impact study feasibility, given limits on the number of willing and eligible participants.

### RESPONSIBILITY FOR MONITORING THE EXTERNAL LANDSCAPE

Investigators and sponsors bear a responsibility for proposing trials that test genuinely unsettled hypotheses and ask questions whose answers will fill real gaps in knowledge, relative to the present state of research, and for including in protocols enough information to permit IRBs and review bodies to ensure that this con-

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## Who has the responsibility, resources, authority, and expertise needed to reassess the potential scientific value and continued clinical equipoise of ongoing studies, at a time when the body of evidence could be evolving?

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dition is met at initial review.<sup>13</sup> Once trials are initiated, DMCs (when constituted), investigators, and sponsors should, at set intervals, review both data internal to the trial as well as developments external to it and be willing to make recommendations about continuation on both types of factors. Similarly, IRBs should strive to consider how developments external to the trial bear on its potential informativeness and value at the time of continuing review or more regularly, as the situation demands. When information is rapidly evolving, the IRB is empowered to request that investigators and sponsors summarize the study data and external developments to date and either defend continuation of the trial as proposed or amend the study. If the IRB is concerned that the emergence of external data renders the



risk-benefit balance untenable, it will often be advisable for them to engage in dialogue about their concerns with the investigator, sponsor, and/or DMC before taking unilateral action, as the latter may have access to information that the IRB lacks or relevant expertise to aid in these assessments.

The proposed deliberative process would have a secondary value, particularly for trials of approved products that are being tested for novel indications (e.g., HCQ for Covid-19). These trials are often small and underpowered, investigating identical or similar treatments in the absence of common data standards, and often with marginally different endpoints,<sup>14</sup> rendering meta-analysis challenging. The likelihood of a type 1 error, the rejection of a true null hypothesis or “false positive,” will increase with the number of small, underpowered trials. The expectation that trials will be compared against similar or overlapping studies by DMCs and IRBs—and deprioritized or terminated based on the review of that analysis—may provoke scientific collaboration and larger, multisite trials.

### NECESSITY OF TIMELY INFORMATION

The review of new or ongoing trials for scientific importance depends upon the availability of timely information. Registration of clinical trials affords an important measure of transparency and serves as a public record that a trial exists with key protocol details. Results reporting is equally essential but needs to be more rapid, especially during public health emergencies. As mentioned earlier, of the 234 HCQ trials for Covid-19 registered on ClinicalTrials.gov as of May 2021, only 9 (7 completed, 2 terminated) had results reported in ClinicalTrials.gov. One year later, as of May 8, 2022, of 177 registered HCQ trials for Covid-19 infection that were completed, terminated, suspended, or withdrawn, only 28 had reported results. Federal rules require results for most drug studies to be posted within one year of the primary completion date, though many trials are eligible for an extension of up to two years. However, results could be posted more promptly if investigators elected to do so. The rules themselves also allow the secretary of the Department of Health and Human Services to require the posting of results much more quickly in times of a public health emergency.<sup>15</sup> Certainly, the Covid-19 pandemic seems like

such a time. The willingness of sponsors and investigators to make results, as well as detailed protocols and other information, available as early as possible would be encouraged if the consequence of data availability resulted in less competition and greater collaboration. In this context, both preservation of commercial interests and systems to apportion academic recognition and credit for data sharing<sup>16</sup> and collaboration would need to be considered.

### CONSEQUENCES TO PARTICIPANTS AND THE PUBLIC

The urgency to deprioritize or terminate a clinical trial that will not contribute scientific value rests on the principle that it is unethical to expose individuals to risk in the absence of potential benefit, where benefit is defined, at least in part, as generalized knowledge. There is also value in parsimony concerning and conservation of human and other resources. But deprioritizing a clinical trial is not without consequence. Notification and explanation to current participants, provisions for follow-up for potential adverse events, consideration of participants’ continued access to medication or treatment, and referral to ongoing follow-up care are all necessary. While these responsibilities do not differ from those incurred whenever a trial is stopped, the importance of explaining to the participant, a person who volunteered on the basis of their anticipated contribution to scientific knowledge, why the trial terminated prior to its anticipated end cannot be underestimated. This transparency and the directive to ensure that trials are informative may contribute to public confidence in the relevance, importance, and public value of ongoing trials, itself a constructive and worthy consideration. ♦

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## ACKNOWLEDGMENT

This work was supported by a Greenwall Foundation Making a Difference award.

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