Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 ARTICLES

Achieving effective informed oversight by DMCs in COVID clinical trials

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Abstract

Best practices of data monitoring committees (DMCs) in randomized clinical trials are well established. Independent oversight provided by DMCs is particularly important in trials conducted in public health emergencies, such as in HIV/AIDS or coronavirus epidemics. Special considerations are needed to enable DMCs to effectively address novel circumstances they face in such settings. In the COVID-19 pandemic, these include the remarkable speed in which data regarding benefits and risks of interventions are accumulated. DMCs must hold frequent virtual meetings, using state-of-the-art communication software that protects against risk for security breaches. Data capture and DMC reports should be focused on the most informative measures about benefits and risks. Because numerous clinical trials are being concurrently conducted in the COVID-19 setting, often addressing closely related scientific questions, structures for DMC oversight should be efficient and adequately informative. When these concurrently conducted trials are evaluating related regimens in related clinical settings, often individually underpowered for safety and having separate DMCs, processes should be implemented enabling these DMCs to share with each other emerging confidential evidence to better assess risks and benefits. Ideally a single DMC would monitor a portfolio of clinical trials or a trial with multiple arms, such as a platform trial.

Keywords: Data monitoring committee; Clinical trials; Coronavirus; COVID-19; Interim analyses

Over the past 5 decades, the process of monitoring ongoing randomized clinical trials (RCTs) by means of an independent data monitoring committee (DMC) for safety and benefit has evolved [1,2]. In March of 2020, the World Health Organization (WHO) declared COVID-19 disease to be a pandemic and numerous trials began soon thereafter to provide timely evaluations of vaccines and therapeutics. This article discusses challenges that the COVID-19 trials bring to the DMC process, influenced by the speed at which the epidemic is spreading, patients are being recruited, and outcome data for benefit and risk are accumulating. The independent oversight provided by DMCs is perhaps even more important in trials for extreme emergencies such as the HIV/AIDS or coronavirus epidemics.

There are many variations to the organizational structure of randomized clinical trials but most have similar components; a sponsor/funder, a steering committee or executive committee, a data coordinating center, a statistical center, clinical sites for participant recruitment, various laboratories needed for participant assessment, perhaps adjudication committees to classify clinical events, and a DMC [1−5] This basic structure has been in place and used successfully for over 4 decades. There are many examples of such success in a variety of disease entities that have been shared [2].

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Dr DeMets is a consultant to the National Institutes of Health, the Food and Drug Administration and the pharmaceutical and medical device industry on the design, monitoring, and analysis of clinical trials. He receives compensation for serving on several industry sponsored data and safety monitoring committees including Astra Zeneca, AmgenAmgen, Actelion, Bristol Meyers Squib, DalCor, GSKGSK, MerckMerck, SanofiSanofi, Boston ScientificBoston Scientific, MedtronicMedtronic, Mesoblast, Intercept, Duke Clinical Research InstituteDuke Clinical Research Institute and Population Health ResearchHealth Research Institute of Hamilton. He holds no stock in any pharmaceutical or device company.

Dr. Fleming reported receiving personal fees from industry sponsors for service on Data Monitoring Committees, research support from the National Institutes of Health, and extensive interactions in coronavirus disease 2019 (COVID-19) research with the World Health Organization Research and Development Working Group.

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What is new?

Covid-19 is a new fast moving viral epidemic.

Key findings

- DMCs must be prepared to meet often with very focused data collection.

What this adds to what was known?

- Covid-19 trial DMCs have been able to adjust to new demands.

What are the implications?

- DMCs must simplify the process to meet the demands of time.

Based on the Helsinki agreements, trials should not continue longer than necessary to answer the questions they are designed to address [1]. Trials may be terminated because of overwhelming benefit, convincing evidence of harm or lack of benefit, or logistical problems that cannot be corrected. To accomplish their mission of safeguarding participant interests while enhancing trial integrity, the DMC meets periodically to review accumulating data on primary and secondary outcomes, safety, and quality of trial conduct. DMC members typically include those with expertise in clinical trials methods, biostatistics, the biology and clinical features of the disease, ethics, as well as expertise in the interventions being evaluated.

Although protocols describe the details of the trial, a DMC charter outlines the responsibilities of the DMC and a statistical analysis plan describes how the analyses of interim as well as final data are to be performed. The process of monitoring accumulating data is not algorithmic but requires the collective experience and expertise of the DMC members. Very often, the accumulating data present issues that were not anticipated in advance, requiring the DMC to adjust their focus and adapt their activity [1,2,6,7].

1. The AIDS epidemic

When the AIDS epidemic arrived in the mid to late 1980s, two clinical trials networks formed by the National Institutes of Health (NIH) were the AIDS Clinical Trials Group (ACTG) and the Community Program for Clinical Research in AIDS (CPCRA). These networks simultaneously conducted numerous clinical trials evaluating multiple interventions in a variety of populations. These two cooperative groups used a single DMC that followed the traditions of earlier clinical trials, yet important adjustments had to be made [6]. Traditionally, a DMC monitored one trial, and met 2−3 times year. By contrast, the ACTG/CPCRA DMC required 2-day meetings that were scheduled to be held every 3 months. The interim data analysis reports for each meeting and each trial had to be well structured with a uniform format to achieve an efficient review process.

The early phases of the AIDS epidemic in the mid-1980s motivated the initiation of a large number of clinical trials. These trials engaged an array of stakeholders, including patients, care givers and patient advocates, academic investigators, ethics committees, regulatory agencies and research sponsors such as the pharmaceutical industry, the NIH or private foundations. Transparency as to how each trial was progressing was a necessity. However, the emerging evidence about the effects of treatments on primary and secondary outcomes and on safety domains needed to be kept confidential until the results reliably answered the questions each trial was designed to address [8,9]. Maintaining confidentiality of accumulating interim results, a challenge given the number of interested stakeholders, was essential to ensuring the integrity of ongoing trials. To meet the legitimate needs of these stakeholders, this DMC needed to make changes in the structure of their meetings.

At the beginning of the meeting for each trial, a closed session was held to enable DMC members to discuss privately key elements of the emerging data and share concerns that had been identified from their review of each study's closed DMC report containing data by intervention groups for the key outcomes for benefit and safety. The concept of an open session following the initial closed session was created to allow the DMC to discuss nonconfidential data regarding quality of trial conduct issues with the sponsor and lead investigators. In these open sessions, the DMC could seek clarifications in a manner that did not unblind emerging evidence about treatment effects on efficacy or safety measures. In turn, the trial leaders and sponsors could raise issues with the DMC about which they had concerns. After this exchange in the open session, the DMC returned to a second closed session where the review of confidential information was completed, the insights from the open session were discussed, and the DMC then formulated its recommendations to the sponsor regarding trial continuation and approaches to enhance quality of trial conduct. The DMC meeting for each trial was completed with a debriefing session where the recommendations of the DMC were presented to the trial leaders and sponsors. These refinements for the format for DMC meetings are now part of DMC best practices [3,4].

2. The COVID-19 pandemic

With the arrival of the COVID-19 epidemic in early 2020, government and industry sponsors scrambled to launch clinical trials to evaluate interventions that might favorably impact COVID-19 disease, including products already approved for use in other indications and others being newly developed [10−13]. These trials have largely followed the traditional clinical trial structure, including the

use of DMCs that are guided by best practices based on decades of experiences [4]. From our initial experiences, there are some emerging challenges that DMCs will have to address to meet both ethical and scientific needs.

One immediate challenge is the speed of recruitment. Trials such as RECOVERY [13] and SOLIDARITY [13] have recruited thousands of patients within a few weeks as the pandemic spreads throughout the world. This means that DMCs need to meet with much greater frequency than the usual 2–3 meetings per year. In fact, they may need to meet every few weeks as data accumulate at an astounding rate, as in RECOVERY for example. Owing to the need for pandemic sheltering, in-person DMC meetings are not a realistic option. Communication software such as Zoom [14], Blue Jeans [15], or Webex [16], increasingly used in recent years, are now standard when conducting DMC meetings for COVID-19 trials. Many of these software platforms allow members to see each other on their laptop or computer screen, and to observe a presentation of data reports including tables and graphs. This allows DMC members to participate effectively in meetings while implementing social-distancing practices. Although this approach to holding DMC meetings appears to be working well, given the risk for security breaches created by external hackers, effective procedures must be in place in COVID-19 trials to protect the confidentiality of interim data and the DMC review process.

Given the corresponding acceleration in the rate of data generation, the process for data capture needs to be considerably simplified. COVID-19 trials probably should not use traditional case report forms that collect volumes of data for each patient, including adverse events, much of which is not even used [17]. Collecting and processing data beyond what is of integral importance to addressing study objectives is expensive and a burden to the patient and health care team. Social media provides one possible approach to patient recruitment as well as follow-up. Smart phones or tablets, already used in a variety of earlier trials, offer an important contribution if coronavirus trials focus on limited outcome variables of key interest such as virologically confirmed symptomatic COVID-19, hospitalization, ventilator use, survival, and adverse events of special interest.

In most pharmaceutical sponsored clinical trials, a common practice is to validate each entry in the case report form through onsite visits by a research associate from the sponsor or a contract organization. In settings where onsite clinical staff are extremely busy caring for critically ill patients with COVID-19 disease, they cannot afford to spend additional time with external data auditors. Furthermore, with COVID-19 social distancing and ‘‘stay at home’’ sheltering in place in these settings, such onsite visits often are not feasible or recommended. The electronic data capture software can perform some level of data checking and validation by applying basic statistical quality and consistency checks.

It is particularly important for trial leadership and the DMC to identify those adverse events that would be especially important in the assessment of the benefit-to-risk profile of an intervention. For the evaluation of vaccines and drugs during the COVID-19 pandemic, researchers and regulators need information on key ‘‘deal breaking’’ adverse events, such as those from unintended effects that would be life-threatening or result in irreversible morbidity/mortality. In turn, DMCs should determine the level of interim data that, while not being of the usual quality or validity, would still be adequate for their monitoring needs.

Achieving protocol-specified levels of adherence to randomly assigned treatments also is integral to trial integrity. When it would be particularly challenging for health care workers to consistently check adherence, supportive approaches such as use of electronic data capture implemented by the patient are needed to enhance adherence and monitor whether targeted levels have been achieved.

3. Communications between DMCs monitoring concurrent related clinical trials

There are a large number of COVID-19 trials underway, as confirmed by clintrials.gov [13]. Although the DMCs in place for these studies usually have responsibilities for monitoring a single clinical trial, some DMCs may monitor a portfolio of clinical trials or a trial with multiple arms. For example, in platform trials where interventions may be added or deleted with time as safety and efficacy results emerge, such as in the RECOVERY or SOLIDARITY trials, the efficiency and effectiveness of the monitoring process is enhanced when this is conducted by a single DMC.

An important consequence of the breadth and depth of the COVID-19 pandemic is that frequently multiple trials are being concurrently conducted evaluating related regimens in related clinical settings. When separate DMCs would be monitoring these concurrent trials evaluating closely related clinical questions, while DMCs usually do not discuss the emerging data outside of their committee, there could be important benefits if DMCs had the ability to share key insights with each other, such as unblinded information on adverse events by intervention group [18]. This would enable some of the beneficially broadened insights achieved in settings where sponsors have engaged a single DMC to monitor multiple concurrently conducted trials that are part of a clinical development program for a drug or biologic.

The value of sharing safety information between DMCs monitoring concurrently conducted related trials is clearly illustrated by the experience in the CPCRA #007 trial [19]. In that blinded trial comparing an AZT-alone control arm with two experimental arms, one with the addition of ddI and other with the addition of ddC, patients were randomized in an unblinded manner in equal

portions to the ''ddI side'' vs. the ''ddC side'', and then participants on each side were randomized in a blinded manner where two-thirds received the active experimental drug (i.e., ddI or ddC) and one-third received the placebo for that drug (1: see Example 5.10). At an interim analysis, the DMC noted 17 deaths in patients receiving ddI placebo vs. 2 deaths in the equal number of patients receiving ddC placebo. It was recognized this difference could be due to chance given the level of multiplicity associated with such exploratory analyses. Nevertheless, there still were substantive safety concerns about continuing a placebo that might be harmful. Fortunately, a nearly identically designed trial was being concurrently conducted in Europe, called the DELTA trial [20]. Without revealing the reasons for their request, the CPCRA #007 DMC sought permission from the study sponsors for the CPCRA #007 and DELTA trials to be able to share their DMC closed reports. Fortunately, that permission was granted. The DELTA trial revealed that there was not a similar imbalance in deaths between the placebo groups. That invaluable insight enabled the CPCRA #007 DMC to recommend continuation of the trial as designed, rather than recommending an alteration of trial conduct that would have meaningfully jeopardized the interpretation of this trial and others using the ddI placebo. The final results from CPCRA #007 revealed that the mortality differences between the two placebo arms were small and fully consistent with chance.

The WHO's R&D Working Group has pursued development of novel approaches using a secure portal to enable sharing of key safety data, and potentially efficacy data as well, on an ongoing basis between the DMCs monitoring concurrently conducted related trials. These trials are in pre-exposure prophylaxis, predominantly in health care workers, and in postexposure prophylaxis, predominantly in household exposures or nursing homes. Memoranda of Understanding between sponsors, investigators, and DMCs enable DMCs to have access to shared information that enhances their ability to protect study participants and trial integrity while ensuring that unblinded confidential information would only be accessible to the DMCs and to their independent statisticians who generate their DMC closed reports [21].

In the AIDS epidemic, the ACTG and CPCRA DMC monitored a portfolio of concurrently conducted clinical trials, often conducted in closely related settings. That approach, rather than having a series of separate DMCs in place for each trial, has been used for decades [1,6] in trials for AIDS and many other diseases. This sets a valuable precedent for a process that would enable DMCs to be better informed when making recommendations intended to address their mission [6]. The AIDS epidemic also motivated refinements to the format of DMC meetings, with open and closed sessions. These advances also have benefitted DMC process in broad settings, including in trials conducted during the early stages of the COVID-19 pandemic. In turn, as we continue pursuit of evidence-based medicine during this pandemic, while being guided by DMC best practices [4], we also should pursue insightful innovations when we are confronted with novel challenges. Efforts should be made to enable the conduct of properly powered trials that would provide timely and reliable answers to clinical questions of greatest clinical interest, such as whether interventions reduce the risks of death or major organ failure in hospitalized patients, and where DMCs monitoring these definitive trials would have insights about efficacy and safety during trial conduct to effectively address their monitoring responsibilities. To achieve this requires prospective efforts to increase collaborations on the international level between clinical trialists. The phrase currently being stated for the COVID-19 pandemic, ''we are all in this together'', is a motivation for greater cooperation across the COVID-19 clinical trial enterprise than ever before so the treatment and prevention strategies can be evaluated as rapidly and reliably as possible.

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