Data Safety Monitoring during Covid-19: *Keep On Keeping On*

Spring 2020: Much of the world seems frozen in place. Air travel has effectively ceased; businesses and schools have moved online. The exceptions are medicine, health care, and research, which not only have continued but seem more relevant than ever. Even as the pandemic has created the imperative for new treatments and a vaccine, countless clinical trials already in progress have still needed oversight.

In February 2020, I was serving on four data safety monitoring boards (DSMBs), monitoring about a dozen trials in total funded by the National Eye Institute or the National Heart, Lung, and Blood Institute. Some of these had been in progress for years; others were just getting off the ground. With the emergence of Covid-19, studies needed to quickly adapt because what it meant to protect study participants wasn't the same as it had been weeks earlier.[1] One of the primary roles of DSMBs is to evaluate interim data to ensure that participants aren't at additional risk by virtue of being randomized to a study arm found to have more risks or fewer benefits than other arms. Stopping a study early when it falls out of equipoise is the most monumental task a DSMB is charged to perform. The pandemic brought with it risks that changed many studies' risk-benefit calculus. In some cases, merely attending a visit to report symptoms, check progress, verify pill counts, or report adverse events posed additional risk. Participants in placebo arms are typically expected to experience little benefit, and certainly not greater harm, than participants in the active therapy group. Suddenly, participating in even the most innocuous placebo arm might result in unforeseen harm.

Some research sites were closed to all but urgent cases. DSMBs' primary responsibility is to protect research participants, but if data is compromised, then the benefit of the study will never outweigh the risks to participants. Thus, protecting the integrity of data collection was also foremost in the minds of DSMB members. Researchers, representatives from the National Institutes of Health, and DSMB members were in constant communication about trials already in progress. The studies could be grouped into three types.

The first were trials that were easily suspended. Resources at some sites—personal protective equipment and significant human resources—were at a premium. Many research sites suspended operations. Participants were reluctant to go to visits even at sites that were operating at full capacity, and, in many cases, participants were urged not to attend visits, for their own protection. Some studies that had not yet met their enrollment goals put recruitment on hold until continuation of the trials was more tenable. DSMBs were rapidly consulted about trials that could be suspended.

The second type of trials were those that were not suspended, but for which data collection could continue remotely or be pared down. For these, the DSMB had to work closely with investigators to determine if continuing research remotely would put participants at greater risk or compromise data collection. Some types of data collection were easily moved to a remote setting. For instance, a research assistant could call a participant to fill out the 50-item St. George's Respiratory Questionnaire over the phone. Pill counts could similarly be reported over the phone or could wait until shelter-in-place orders were lifted. In some cases, adverse-event data could be tallied over the phone. Other data collection, such as for a six-minute-walk test, proved more challenging. Data collection might be imperfect, but the loss of

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benefit in quality of data had to be weighed against the harms to participants and burden on local investigators.

The third type of trials were ancillary studies added to trials of new drugs or therapies that might have treatment potential for Covid-19. Might therapies that were already being tested prove efficacious against the virus? DSMBs hastily reviewed informed consent addenda, revised protocols, and mustered their expertise to assess risk-benefit ratios when there were significant unknowns.

From the avalanche of work, a few important lessons emerge.

Prioritize the protection of research subjects and primary endpoints; triage secondary endpoints. Some protocols' secondary endpoints—including myriad outcomes not necessarily connected to patients' priorities—read like a wish list. DSMBs occasionally found themselves delivering the bad news that some research couldn't move forward as planned. Researchers should be ready to abandon some secondary outcomes to focus on what really matters: protection of research participants in the quest to find treatments that will best serve cohorts in the future. Even without a pandemic, some secondary endpoints are luxury goods bought at the price of participants' time and exposure to risk.

Rethink risk-benefit ratios, especially in light of the fact that data collection visits now have added costs. Ethical research requires both that benefits exceed risks and that risks are minimized as much as possible. Covid-19 required everyone to make adjustments that maintain a positive risk-benefit ratio. This is something DSMBs should have been doing all along—overseeing collection of generalizable data that places the smallest burden on participants.

Work in close communication with researchers. The facts on the ground changed rapidly as a result of Covid-19. Sites that were doing fine were suddenly inundated; sites that initially thought they couldn't continue research were later able to get back on track. DSMBs are used to being in close communication with researchers—expedited reporting of serious adverse events (SAEs) requires that DSMBs are informed as soon as possible at the occurrence of an SAE that may disrupt equipoise. The pandemic deepened the importance of this close communication. Barbara Bierer, who directs the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard, noted, "Ethics committees are working overtime as researchers file requests to alter their clinical-trial plans in ways that minimize how often participants need to venture into the clinic."[2] All DSMBs should be set up to accommodate this rapid communication, even in the absence of the expectation of expedited SAE reporting.

Don't abandon your principles. Revised consent forms or procedures assembled by people who are under time pressure may omit elements of informed consent. Revised informed consent documents should include all essential information; new procedures in ancillary studies should match those in consent forms, and vice versa. Despite the global need to find treatments and a vaccine as quickly as possible, the responsibilities of DSMBs to protect human subjects shouldn't be compromised.[3] If it takes another few days for protections to be in place, the delay is worth it.

The long-term lesson is that DSMBs were already doing an important job, with the principles and skills to do that job even in the midst of the unforeseen. DSMBs are comprised of hand-selected experts who have the unique clinical, statistical, and ethical backgrounds to oversee randomized controlled trials at their most dangerous, when experimental treatments are given to brave volunteers. The ability to respond quickly and the practical wisdom to apply expertise to a new, emerging situation are what data safety monitoring is all about.

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1. All protocols were instructed to follow NIH Notice NOT-OD-20-087, "Guidance for NIH-funded Clinical Trials and Human Subjects Studies Affected by COVID-19," https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-087.html.

2. Quoted in Ledford, H., "Coronavirus Shuts Down Trials of Drugs for Multiple Other Diseases," *Nature* 580 (2020): 15-16.

3. Luo, Q., and T. Qin, "Managing Clinical Trials for Covid-19: The Importance of Ethics Committees," *BMJ* 369 (2020): m1369; Maschke, K. J., and M. K. Gusmano, "Ethics and Evidence in the Search for a Vaccine and Treatments for Covid-19," *Hastings Bioethics Forum*, April 15, 2020, https://www.thehastingscenter.org/ethics-and-evidence-in-the-search-for-a-vaccine-and-treatments-for-covid-19/.