COVID-19 and readjusting clinical trials

The COVID-19 pandemic has disrupted clinical trials worldwide, with long-lasting effects on medical science. Aaron van Dorn reports.

The COVID-19 pandemic has created massive disruptions to clinical trial research across the world. As in other aspects of life, the virus has severely affected the ability to conduct trials in safe and effective ways. This is especially true when considering that trials often deal with vulnerable populations who are most at risk from exposure to COVID-19. Thousands of trials have been suspended or stopped because of the difficulties in continuing under lockdown conditions, even as those restrictions have begun to ease in parts of the world. At the same time, the pandemic has seen an unprecedented reorientation in clinical trials research towards COVID-19. Both of those aspects—the disruption and the fast, effective readjustment to address a new challenge—ensure that the effects of the COVID-19 pandemic will be felt in clinical trials research long after the initial effects have faded.

Clinical trials have long been a premier method of testing and validating new drugs and therapies. New drug approval is predicated on successful trials into the safety and efficacy of new treatments. Trials can involve hundreds of different sites around the world, all with different conditions and facing different effects and government regulations on what is permissible. Once you start looking at the number of people involved in a clinical trial, the scope of the problem begins to seem daunting. In addition to researchers who formulate the protocol for the trial and work to secure funding (either from governments, foundations, pharmaceutical or device manufacturers, or a combination of the above), clinical trials include clinical caregivers and nurses who work with patients at clinical trial sites, postgraduate researchers, postdoctoral fellows, research scientists, and others who work on the analysis of data generated by the trial, some of whom may or may not interact with patients, but all of whom are essential to the final result.

Trials that were stopped, in many cases, were stopped from enrolling new patients. Patients who were already enrolled mostly continued to receive treatment as institutions and researchers worked to make changes to how care was provisioned to deal with the reality of COVID-19. Fergus Sweeney, head of clinical studies and manufacturing at the European Medicines Agency, told *The Lancet* that one of the key parts of their guidance has been physical distancing to protect patients and clinic staff, but ensuring the safety of patients in testing and treatment is also important. "If people can't come in to a clinic or their hospital at the usual, regular intervals, it may be that they need to be provided with a medication for a longer period of time, or indeed that medication is distributed to their home by a distributor", Sweeney said. To that end, many trials have shifted from the distribution of drugs at the trial site to direct-to-patient courier services, whereby trial drugs are distributed and administered to patients in their homes, eliminating the need for at-risk patients to visit trial sites. Many in-person visits for checkups and other aspects of trials were shifted to teleconferencing services. In March, 2020 (and revised again in July), the US Food and Drug Administration (FDA) also issued guidance on protecting patient safety during the COVID-19 pandemic. The FDA guidelines called on researchers and trial sponsors to "determine that the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial". The guidance also calls on investigators and sponsors to coordinate with institutional review

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For **info on current clinical trials** see https://clinicaltrials.gov/ct2/resources/trends

For **FDA guidance on clinical trial research under COVID-19** see https://www.fda.gov/media/136238/download

For **Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study** see **Articles** *Lancet* 2020; **395:** 361–69

For **Re-envisioning clinical trials during the COVID-19 pandemic** see https://www.healthaffairs.org/do/10.1377/hblog20200702.963588/full/

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boards and ethics committees on potential changes to protocol as early as possible. But for many patients who have turned to clinical trials as a last resort for cardiovascular conditions, who have cancer, or other life-threatening conditions, the eventual resumption of non-COVID-19 trials could come too late.

Physical distancing to protect patient and researcher safety has been one of the major disruptions to clinical trial research during COVID-19, but according to Kevin Sheth, chief of neurocritical care and emergency neurology at Yale University, CT, USA, and a principal investigator, many of these changes could have been made long ago. "Telemedicine technology has been around for 10, 15, 20 years", Sheth told *The Lancet*. "In many cases, the barriers to incorporating telemedicine more widely into clinical practice really have been in large part administrative and bureaucratic, having to do with cost and reimbursement—not because of some conceptual or technological limitation. The same is true in the clinical research world."

The effect of COVID-19 has been enormous, with thousands of trials—around 80% of non-COVID-19 trials—being stopped or interrupted, according to Michael Lauer, deputy director for extramural research at the US National Institutes of Health. But the effect extends beyond just trials. "There have also been tremendous disruptive effects on all biomedical research that is not directly related to COVID", Lauer told *The Lancet*. "Laboratories are closed. Communications have been shut down, conferences have been cancelled, supply chains for equipment have been lost, resources have been lost. There have been widespread financial losses within academic medical centres that have had spillover effects on their research operations." The effect has also been felt by those who conduct research. Many researchers were pulled away from working on clinical trials to work in emergency medical care, especially during the first months of the pandemic in places where the pandemic threatened to overwhelm critical care resources. The slowdown or cancellation of trials will have a disproportionate effect on early career researchers, and even those who can work from home—statisticians and epidemiologists—face the same difficulties that many have in balancing work and home life, which is especially true for those raising children, the effect of which still disproportionately falls on women.

The pandemic has been devastating around the world and has exposed some serious structural flaws in our response. But the clinical trial response is in part encouraging. Ongoing trials in many cases shifted and made alternative plans in conjunction with funders and institutions. New trials to begin to address COVID-19 were fast tracked and numerous existing inefficiencies were identified and streamlined. Research on COVID-19 is proceeding quickly, according to Lauer. "It is on full thrust. There's a tremendous amount of amazing work going on," Lauer said. "The rapidity with which new information, new data becomes available, new studies become published...is quite impressive. In some respects, it's like something that we've never seen." Since the emergence of COVID-19 in December, 2019, 2995 clinical trials related to COVID-19 have been registered with ClinicalTrials.gov.

The disruptions to patients, researchers, and institutions have been numerous, and will leave a lasting effect on research that was ongoing before the pandemic. "I think when they're presented in a couple of years from now, virtually every trial will have a footnote that says, well, X percentage of patients were enrolled and followed during this part of the pandemic", Sheth said, "and that'll be a part of the literature that we all incorporate and read." What the long-term effects on research will be is unclear. *Health Affairs* posted a blog that examined ways to maximise the utility of data collected by stopped trials and looked forward to ways to protect trials from similar disruptions in the future, such as decentralising trial locations out of a few major urban centres.

Clinical trials are an essential tool in medical research, but COVID-19 has exposed ways that their design, conduct, and reporting could be improved. The rapid design and launch of clinical trials designed to research COVID-19 has shown that certain aspects and practices of clinical trials could be improved, streamlined, or modernised in ways that would benefit patients, practitioners, and all research. In the future, it will be important for the conduct of research to incorporate those lessons to ensure the highest quality of research.

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