

VIEWPOINT

Preserving Clinical Trial Integrity During the Coronavirus Pandemic

Mary M. McDermott, MD

Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; and Deputy Editor, *JAMA*.

Anne B. Newman, MD, MPH

Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania.



Viewpoint

Randomized clinical trials provide the highest-quality evidence for identifying therapies to help people attain longer and healthier lives. As of March 2020, ClinicalTrials.gov listed 262 366 ongoing randomized clinical trials, including 146 420 trials studying drug or biologic interventions, 85 045 trials of behavioral interventions, and 61 351 trials of surgical or device interventions.¹ Suddenly, and quite dramatically, the coronavirus pandemic threatens the integrity of these clinical trials. The National Institutes of Health has advised investigators to consult with their institutional review boards and institutions about potential measures to protect participants and research staff. Responses from academic medical center and other research groups have varied from mandatory suspension of research involving human participants (except when this increases risk to participants) to relying on principal investigator discretion.

Coronavirus mitigation efforts include self-isolation and avoiding health care centers where symptomatic patients congregate for medical care and where randomized trials are typically conducted. Mitigation efforts interfere with all aspects of a successful clinical trial: efficient accrual and randomization, intervention

ing ongoing trials could help millions of people realize substantial, durable health benefits that will be important once the coronavirus pandemic ends. Therefore, efforts and resources should be dedicated to support continuing randomized trials using creative and thoughtful methods and proactive planning. Adapting protocols to facilitate continued intervention adherence, outcome measurement, and some aspects of recruitment for trials already underway is likely to have the greatest benefit for the most people.

The following solutions may minimize disruption and preserve integrity of ongoing randomized clinical trials, while ensuring participant health and safety. These recommendations consider that the coronavirus pandemic has confined many staff and most participants to their homes, unable to visit a medical center for clinical trial activities. Each trial is unique, and the suggestions below will not be applicable to all trials. For example, risks of clinical trial participation during the coronavirus pandemic are different for a patient with end-stage cancer, for whom the clinical trial provides the only hope of survival, than for a patient with peripheral artery disease enrolled in a trial of a novel exercise intervention. For all clinical trials, however, research staff should keep participants informed about the effects of the coronavirus pandemic on their trial participation. Participants should be informed of necessary changes in protocol and how this may affect the risk associated with study participation. For many randomized trials, communication from research staff is likely to help protect against dropout or nonadherence by reassuring participants that their trial involvement remains important, even during the pandemic.

The effects of the coronavirus pandemic on randomized trials hopefully will be short-lived, relative to the long-term benefits of these trials to millions of people who will continue to live with debilitating medical diseases after the crisis ends.

adherence and delivery, and outcome collection. Those most susceptible to severe consequences of coronavirus, older individuals and those with chronic disease, are commonly included in randomized trials designed to improve health in these vulnerable populations.

When considering the risks and benefits of continuing clinical trials during the pandemic, one approach is to discontinue randomized trials that do not provide an immediate clear benefit to enrolled participants. However, benefits of therapeutic interventions in randomized trials are unknown until the trial is completed. Ongoing trials have potential to benefit millions of people with debilitating chronic diseases long after the coronavirus pandemic has ended. Furthermore, discontinuing ongoing trials wastes previously invested resources and squanders the time and effort of participants who may have already completed the trial. In contrast, sustain-

Collection of outcome data requires thoughtful consideration. First, outcomes should be prioritized. The primary outcome has highest priority, whereas outcomes that are exploratory or not prespecified are more appropriate to eliminate temporarily. Second, alternative methods for measuring primary outcomes that cannot be collected in-person should be prepared and protocols modified to facilitate collection of alternative self-reported or medical record data that can be adjudicated as a surrogate for the primary outcome. Once the trial resumes, collection of both the original outcome and the surrogate "remote" data allows better understanding of how the self-reported or medical record data can best be used to impute an objective measure that temporarily was not attainable. For example, self-report and medical record data from participants could be used to impute a 400-m walk outcome.²

Corresponding

Author: Mary M. McDermott, MD, Department of Medicine, Feinberg School of Medicine, Northwestern University, 750 N Lake Shore Dr, 10th Floor, Chicago, IL 60611 (mdm608@northwestern.edu).

Third, outcomes that can be collected remotely (ie, self-administered outcomes or outcomes collected by telephone or online) should be continued. Fourth, questionnaires previously collected in person can be converted to telephone administration. Self-administered questionnaires previously collected at an in-person visit can be mailed. Fifth, when feasible and when safe, objective outcomes could be collected at home. Sixth, when a high-priority outcome cannot be obtained at home, such as a 6-minute walk test, which requires a 100-foot hallway, consideration can be given to outcome collection off-site, away from the medical center, where exposure to potentially infectious individuals is minimized. However, collecting data off-site depends on local mandates and will not be feasible when all individuals are advised to stay home.

Delivery of intervention requires thoughtful consideration, emphasizing safety and feasibility under coronavirus restrictions. Interventions that can be safely adhered to without leaving home should be continued. In addition, when safe to do so, it may be appropriate to continue interventions, such as medications, beyond the originally intended stop date. For example, a 6-month drug or behavioral intervention could be extended by an additional 2 or 3 months, so that follow-up testing can be carried out while the participant is still receiving the intervention once isolation restrictions are lifted. If it becomes necessary to temporarily discontinue the intervention when necessary monitoring cannot take place, the intervention could potentially be resumed once restrictions are removed, to preserve originally planned intervention duration and outcome measure timing as much as possible. Moreover, some interventions may require modification to accommodate the inability of participants to attend behavioral interventions requiring group visits or exercise sessions at a gym. A supervised exercise session could be temporarily converted to a home-based session with remote monitoring—for example, by telephone, telecommunication tools such as Skype, or the internet—if feasible and safe. Virtual interventions are additional alternatives.

Another consideration is how the intervention might interact with coronavirus infection and whether the study drug should be continued if a participant becomes ill with symptoms of coronavirus. Conceivably, some interventions could improve outcomes. For example, a trial testing efficacy of a therapy such as a statin might mitigate the cardiovascular consequences of an acute inflammatory state. If continuing the intervention becomes untenable, intention-to-treat methods are essential for understanding risks and protective factors for infection, illness, or recovery.

Additional considerations follow. First, while baseline in-person visits will not be possible during the pandemic, self-

isolation facilitates telephone eligibility screening by staff working from home, who may have few other study activities they can carry out. Potentially eligible participants who are identified should be encouraged to attend study visits later. Second, alternate contact information, including cell phone and email addresses for family members and friends (at least 3) should be requested in the event that contact is lost with the participant. Third, when study visits are essential, investigators may help participants avoid public transportation, or shared ride services, where risk of disease exposure may be greater. Instead, participants could travel in their own car or obtain a ride from a friend or study staff member. Fourth, when in-person visits are continued, participants should be advised of the potential risk of leaving their home and offered the opportunity to decline. These participants may be willing to resume participation after the pandemic.

Fifth, experienced staff conducting randomized trials may be at risk for lost wages, especially if they were temporary workers whose primary duties were in-person data collection or if they have childcare needs that prevent them from working. Providing work-from-home opportunities, such as making additional retention telephone calls, will help retain this valuable workforce. Sixth, the US Food and Drug Administration has released guidance with additional suggestions for continuing randomized trials during the coronavirus pandemic, emphasizing participant safety and the importance of maintaining clinical trial integrity as much as possible.³ Seventh, the clinical trial community should consider scaling back or placing selected trials on hold, if doing so does not substantially harm the trials, so that investigators and research personnel can shift from their own ongoing trials to work on urgent trials of interventions to address the coronavirus pandemic, such as trials of therapeutic interventions for coronavirus.

The senior editorial staff at *JAMA* recognize the importance of staff and patient safety during this pandemic. Clinical trials often have challenges; in this case, all changes because of the pandemic should be described in the Methods section when the manuscript is submitted for publication.

Clinical trials require years to design, fund, conduct, and complete but are essential for improving health and preventing disability. The effects of the coronavirus pandemic on randomized trials hopefully will be short-lived, relative to the long-term benefits of these trials to millions of people who will continue to live with debilitating medical diseases after the crisis ends. To maximize public health benefits, creativity and persistence are required, especially during these unprecedented and uncertain times.

ARTICLE INFORMATION

Published Online: March 25, 2020.
doi:10.1001/jama.2020.4689

Conflict of Interest Disclosures: Dr McDermott reported receiving grants from the National Heart, Lung, and Blood Institute, National Institute on Aging, American Heart Association, and Regeneron; financial support for intervention for clinical trials from Helixmith, Hershey, Chromadex, ArtAssist, and ReserveAge; and nonfinancial support from Mars Inc. Dr Newman reported no disclosures.

REFERENCES

1. Trends, charts, and maps. ClinicalTrials.gov. Accessed March 16, 2020. <https://clinicaltrials.gov/ct2/resources/trends>
2. Pahor M, Guralnik JM, Ambrosius WT, et al; LIFE Study Investigators. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA*. 2014;311(23):2387-2396. doi:10.1001/jama.2014.5616
3. FDA guidance on conduct of clinical trials of medical products during COVID-19 pandemic: guidance for industry, investigators, and institutional review boards. US Food and Drug Administration. Published March 2020. Accessed March 18, 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic>