VIEWPOINT

Conducting Clinical Research During the COVID-19 Pandemic
Protecting Scientific Integrity

Thomas R. Fleming, PhD
Department of Biostatistics, University of Washington, Seattle.

Dominic Labriola, PhD
Department of Biometrics and Data Sciences, Bristol Myers Squibb, Princeton, New Jersey.

Janet Wittes, PhD
Statistics Collaborative, Washington, DC.

The current novel coronavirus disease 2019 (COVID-19) pandemic has led to substantial changes in health risks, access to health care, and daily interactions. Through these and other challenges, the pandemic is affecting ongoing clinical trials that are evaluating interventions aimed at preventing or treating diseases other than COVID-19. Meaningful alterations to the implementation of protocol-specified procedures for adherence and retention of study participants, without careful consideration of the consequences to statistical analysis, can compromise the generalizability of clinical trial results about efficacy and safety of studied interventions in the postpandemic setting.

Recent guidance from the US Food and Drug Administration[1] urges sponsors of clinical trials to be "assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing the risks to trial integrity during the COVID-19 pandemic." To achieve these goals, trialists should identify activities that do not place study participants at increased risk of COVID-19 due to study-specific procedures. While ensuring safety, trials should achieve timely recruitment, proper adherence to protocol-specified procedures, high retention of participants, and proper statistical analyses to avoid undue loss of statistical power and increased risk of bias due to informative missing data. This Viewpoint discusses procedures that would "ensure the rights, safety and wellbeing of participants,"[2] while mitigating risks to trial integrity.

> Trialists should present and interpret the results of clinical trials objectively, explicitly recognizing both the strengths of the analyses and the uncertainties resulting from the pandemic.

Potentially Delaying or Pausing Enrollment

Trials may proceed essentially unchanged if enrolled participants can complete protocol procedures safely and thus contribute to important analyses. Sometimes, however, a wiser course is to delay initiation of enrollment in trials that have not yet started or to pause enrollment in ongoing trials, perhaps on a site-specific basis, until the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral burden in that setting is low. Later reinitiation of enrollment to achieve protocol-specified statistical power can begin after the study team judges that it can adequately manage risks of COVID-19. Such an approach is particularly important if concurrent illnesses, both directly and indirectly related to COVID-19, could confound the effect of study treatment on the main safety and efficacy outcomes.

Attaining Best Achievable Adherence to Study Interventions and High Levels of Retention

Careful attention to administration of study drugs is needed to reduce risk of bias from nonadherence to study products caused by the COVID-19 pandemic.[3] Ideally, adherence to study drugs should be consistent with levels clinically achievable in nonpandemic settings. Approaches to increasing adherence without increasing risk of SARS-CoV-2 infection could include enabling study medications to be taken at home by the patient,[4] having health care workers make home visits while wearing personal protective equipment, or enabling delivery of injections in clinical facilities capable of achieving adequate social distancing.

Methods that facilitate more complete data collection during the COVID-19 pandemic also are crucial to increasing the validity of assessments of efficacy and safety.[5,6] To prevent disruption of data collection, trialists should consider approaches such as electronic data capture implemented at home by the patient or caregiver, telemedicine, or telephone interviews.[4] Additional procedures that could increase the validity of critical outcome assessments include centralized data monitoring, digital technology, home nursing visits, or use of local instead of central laboratories. Some data, even though imperfectly collected, usually are more useful than no data.

If an outbreak of COVID-19 leads to interruption of delivery of the intervention and study assessments at a site, study staff should maintain contact with participants to enhance the likelihood of retention after the intensity of the outbreak has waned.

Study staff should maintain a list of patients whose participation in the trial has been adversely affected by COVID-19, along with the nature of those consequences. The list should capture the type of missing information, as well as the reasons. Insights about missingness may be used to enlighten modifications to the proposed modified statistical analyses. All changes to data collection should be discussed with clinicians, statisticians, operational staff, and data management teams and should be well documented.

Corresponding Author: Thomas R. Fleming, PhD, Department of Biostatistics, University of Washington, PO Box 357232, Seattle, WA 98195-7232 (tfleming@uw.edu).

Prespecifying Analyses to Address Effects of the Pandemic on Trial Integrity

The pandemic may lead to the need to revise the statistical methods planned for the trial's primary and secondary analyses. Individuals blinded to emerging trial data about efficacy and safety should identify and prespecify sensible revised approaches to analyses. In some cases, the primary analysis would exclude intermittent intervals of calendar time that meet prespecified site-specific criteria for severe disruption from the COVID-19 pandemic (eg, substantively reduced ability to deliver blinded study drug or to retain participants). In trials that were relatively near completion when severe disruption began, the study team (not the data monitoring committee) could decide to terminate the trial, thus sacrificing a small degree of statistical power in exchange for more interpretable inference. In other trials, the investigators could justify restarting enrollment after the period of severe disruption, enabling a trial to achieve its specified goals by successfully building on the prepandemic data.

A protocol amendment or revised statistical analysis plan could specify additional modifications to planned study procedures, patient populations, and statistical methods made in response to the pandemic. The reasons for these modifications should be clearly and completely presented and dated. The appropriate protocol review committee, established by the sponsor and the relevant regulatory authorities, should review and approve these changes. The institutional review boards should be informed of operational changes to the protocol. Database lock should occur only after all of these steps are completed and the data quality is confirmed. These changes should be detailed in the Methods section of the research report, and any protocol amendment should be submitted to journals at the time of submission and highlighted in the cover letter.

Addressing Analytical Issues That Are Important in Protecting Trial Integrity

Valid statistical approaches should guide the presentation of results of clinical trials for which the conduct has been meaningfully influenced by the pandemic. For example, if data are collected during the period of severe disruption in a manner different from the approach originally planned, the analysis could stratify the data by method of collection.

Presentation of the results should focus on prespecified primary analyses of the primary and key secondary end points, as defined by the version of the statistical analysis plan that was in place when the database was locked. Sensitivity analyses, prespecified and post hoc, should be presented for these end points to assess the robustness of results. The analyses should address the influence of informative missingness and of deviations from protocol-specified levels of adherence. Descriptions of analyses should clearly delineate which of these irregularities were due to the COVID-19 pandemic.

Descriptive supportive analyses of treatment effects should present estimates and corresponding confidence intervals rather than *P* values. Traditional forest plots show estimated treatment effects across subgroups formed by baseline covariates; similar plots could explore the influence of the COVID-19 pandemic on trial results. For example, when prespecified primary analyses have excluded intermittent intervals of calendar time that meet prespecified criteria for severe disruption from the COVID-19 pandemic, forest plots could compare effects within and outside those intermittent intervals.

Trialists should present and interpret the results of clinical trials objectively, explicitly recognizing both the strengths of the analyses and the uncertainties resulting from the pandemic. The analyses should aim to make inferences relevant to the postpandemic period. If the COVID-19 pandemic has meaningfully compromised trial conduct, confirmatory trials to achieve targeted levels of reliability may be needed.

ARTICLE INFORMATION

Published Online: May 28, 2020. doi:10.1001/jama.2020.9286

Conflict of Interest Disclosures: Dr Fleming reported receiving support from the National Institutes of Health and Bristol Myers Squibb, and having extensive interactions in coronavirus disease 2019 (COVID-19) research with the World Health Organization Research and Development Working Group. Dr Labriola reported receiving support from Global Drug Development/Biometrics and Data Sciences of Bristol Myers Squibb. Dr Wittes reported that her employer (Statistics Collaborative) has contracts for statistical collaborations with many companies that have ongoing studies potentially affected by the COVID-19 pandemic.

REFERENCES

1. US Food and Drug Administration. FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards. March 2020 (updated May 14, 2020). US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, Oncology Center of Excellence, Office of Good Clinical Practice. Accessed May 21, 2020. Docket No. FDA-2020-D-1106. https://www.fda.gov/media/136238/download

2. European Medicines Agency. Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. European Medicines Agency. March 20, 2020 (updated April 28, 2020). Accessed May 21, 2020. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

3. Bauchner H, Fontanarosa PB. Randomized clinical trials and COVID-19: managing expectations. *JAMA*. Published online May 4, 2020. doi:10.1001/jama.2020.8115

4. McDermott MM, Newman AB. Preserving clinical trial integrity during the coronavirus pandemic. *JAMA*. Published online March 25, 2020. doi:10.1001/jama.2020.4689

5. Panel on Handling Missing Data in Clinical Trials, Committee on National Statistics, Division of Behavioral and Social Sciences and Education, National Research Council of the National Academies. *The Prevention and Treatment of Missing Data in Clinical Trials*. National Academies Press; 2010.

6. Fleming TR. Addressing missing data in clinical trials. *Ann Intern Med*. 2011;154(2):113-117. doi:10.7326/0003-4819-154-2-201101180-00010