Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency

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September 10, 2020

Nota Bene

- This talk **IS NOT** about the treatment or prevention of COVID-19.

- This talk **IS** about the impact of COVID-19 on clinical trials for regulatory purposes across all drugs.

Topics

- Overview of FDA efforts to address the impact of COVID-19 on clinical trials
- Specific statistical considerations
- Implications on future clinical research

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Coronavirus Disease 2019 (COVID-19)

COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders

Coronavirus Disease 2019 (COVID-19) Frequently Asked Questions

Preguntas frecuentes sobre la Enfermedad del Coronavirus 2019 (COVID-19)

Donate COVID-19 Plasma

Multilingual COVID-19 Resources

Coronavirus Disease 2019 (COVID-19)

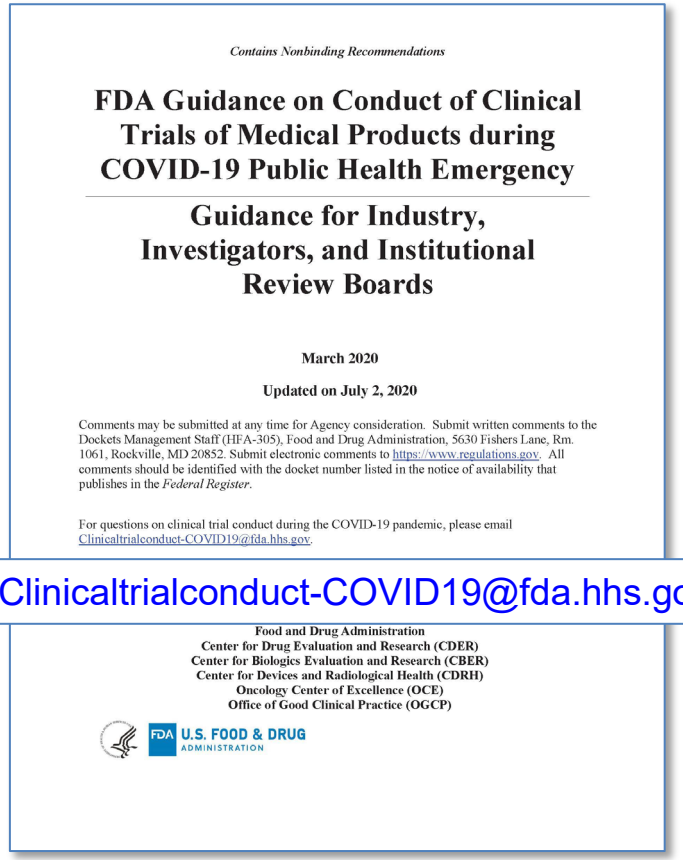
https://www.fda.gov/coronavirus

On this page:

COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders

Title	Guidance Type	Product Area	Date Posted
Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers	Final Guidance for Industry	Biologics Drugs	August 19, 2020
Temporary Policy for Manufacture of Alcohol for Incorporation Into Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)	Final Guidance for Industry	Drugs	August 7, 2020
Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)	Final Guidance for Industry	Drugs	August 7, 2020
Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency	Immediately in Effect Guidance for Industry	Drugs	August 7, 2020
Enforcement Policy for Viral Transport Media During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency	Final Guidance for Commercial Manufacturers, Clinical Laboratories, and FDA Staff	Medical Devices	July 20, 2020
FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (Updated July 2, 2020)	Final Guidance for Industry, Investigators, and Institutional Review Boards	Drugs Biologics Medical Devices	July 2, 2020
Development and Licensure of Vaccines to Prevent COVID-19	Final Guidance for Industry	Biologics	June 30, 2020

‘Conduct’ and ‘Statistical’ Guidances on Trials During COVID-19 Public Health Emergency



Contains Nonbinding Recommendations

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 on July 2, 2020

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

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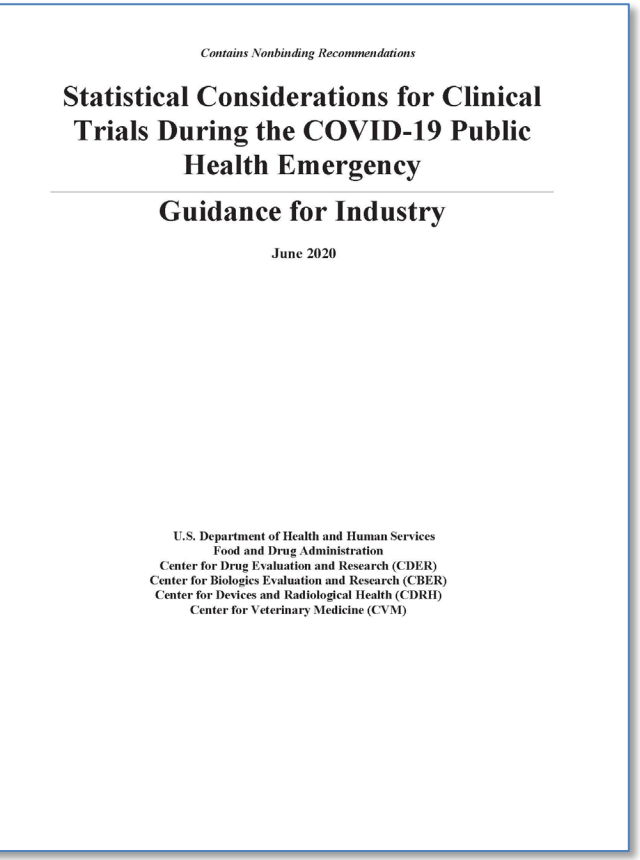
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

U.S. FOOD & DRUG ADMINISTRATION



Contains Nonbinding Recommendations

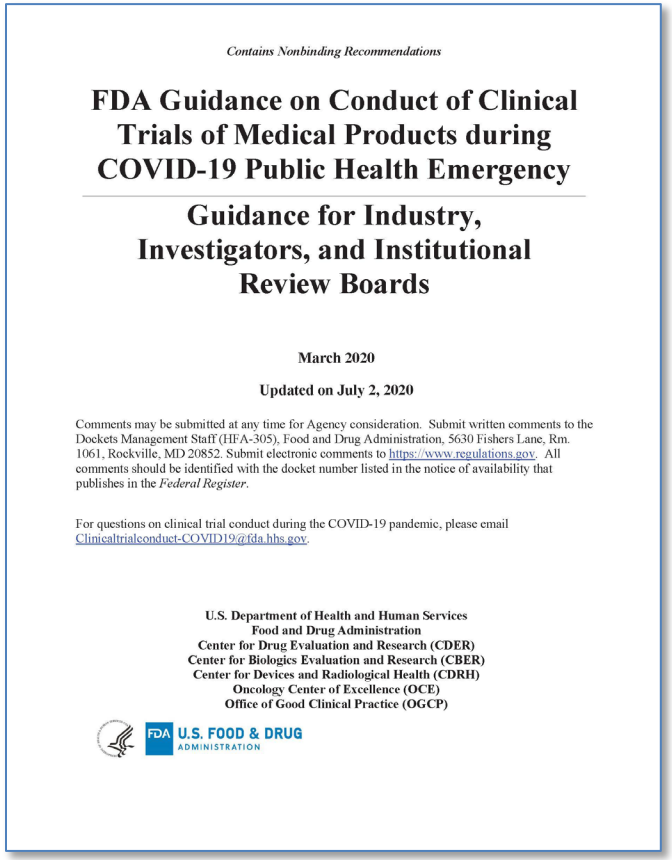
Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency

Guidance for Industry

June 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)

‘Conduct Guidance’



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FDA U.S. FOOD & DRUG ADMINISTRATION

Major themes in guidance:

- Participant safety paramount
- Appropriate flexibility while maintaining study integrity
- Pre-planning is important
- Training and technology
- Documentation
- Work with FDA review division

‘Conduct Guidance’

Appendix: Questions and Answers

Example of Q&A topics:

- Protocol amendments
- Remote assessments
- Remote site monitoring
- Safety reporting
- Access to investigational product
- Use of alternative labs

Submitting Questions or Comments to FDA

- Comment on guidances: www.regulations.gov
  - FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency
    Docket number: FDA 2020-D-1106
  - Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency
    Docket number: FDA-2020-D-1136
- For general questions on clinical trial conduct during the COVID 19 public health emergency, email Clinicaltrialconduct-COVID19@fda.hhs.gov

Topics

- Overview of FDA efforts to address the impact of COVID-19 on clinical trials
- Specific statistical considerations
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Overview

- COVID-19 has impacted clinical development and ongoing clinical trials across investigational product areas
- Goal is to help ensure that trials will provide interpretable findings with correct statistical quantification of uncertainty
- Engage the FDA review division for changes that may impact the statistical analysis of the primary and key secondary endpoints
- Outlines considerations for the statistical analysis of the primary and key secondary endpoints in a trial affected by COVID-19
  - Trial integrity
  - Trial mitigation and analysis strategies
- **NB: Participant safety is paramount**

Trial Integrity

- Sound scientific principles continue to apply
- Modifications to the analysis of the primary or key secondary endpoints should be reflected in an updated statistical analysis plan before locking the database and before any modifications to unblinded interim analyses.
- Trials should not be modified based on data that may introduce bias into the interpretation of trial findings (e.g., unplanned, unblinded interim analysis)
- Appropriate to consider summary information *pooled treatment arms* when considering the need to modify trials
  - Missing data, treatment discontinuations/interruptions, withdrawals from trial, site closures, etc.

Trial Mitigation & Analysis Strategies

- Specific information should be collected at the participant level for post-baseline events as they relate to COVID-19
  - This information may be incorporated into analytical strategies to address potential biases or for performing sensitivity analyses
- For blinded trials, a blinded power assessment may help inform decisions to terminate a trial prematurely and conduct the final analysis
- Stopping a trial earlier than planned or adding interim analyses may impact the statistical inference.
  - FDA reviewers will provide advice for specific cases.
- It may be possible to increase enrollment after the impact of COVID-19 has passed (and/or extend follow-up in an event-driven trial)

Trial Mitigation & Analysis Strategies (Missing Data)

- Addressing missing data is complex
- Example: Site closed for a period of time
  - Exclude all participants that were scheduled for an endpoint assessment during the site closure. Even participants who had previously dropped out.
- Other well-established methods rely on leveraging available participant information at baseline and post-baseline, including COVID-19-related information
- May have to extend trial or follow-up to account for missing data

Trial Mitigation & Analysis Strategies (Endpoints)

- Modifications to the definition and ascertainment of trial endpoints may be warranted
- Discuss proposed changes with the FDA review division
- Sensitivity analyses should explore the impact of the change
- Strategies
  - Replacing in-person endpoint ascertainment with remote ascertainment
  - Extending the protocol-defined window of time for performing the endpoint ascertainment or using an earlier or later planned ascertainment
  - For a composite endpoint, including additional and clinically relevant components or removing components that cannot be ascertained
  - For a binary endpoint that is based on a continuous or ordinal measurement, using the continuous or ordinal measurement as the endpoint

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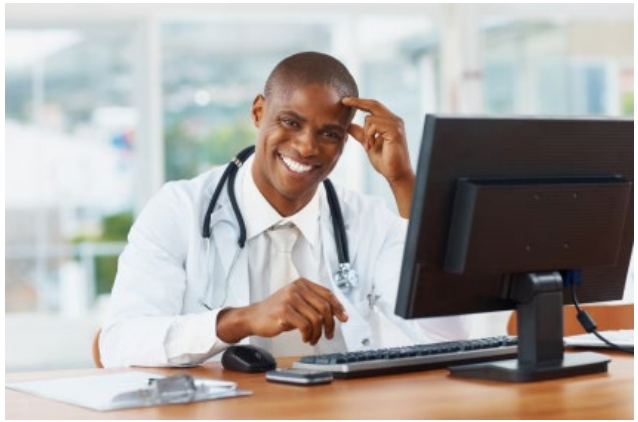
Technology Enabled Study Visits

- *Nearly half (43.5%) of Medicare primary care visits were provided via telehealth in April, compared with less than one percent before the PHE in February (0.1%)**
- *In a Clinical Trial Transformation Initiative (CTTI) survey of 62 stakeholders beginning of April, 85% reported transitioned to remote/virtual visits in > 1 ongoing trials***



* ASPE Issue Brief MEDICARE BENEFICIARY USE OF TELEHEALTH VISITS: EARLY DATA FROM THE START OF THE COVID-19 PANDEMIC, July 28, 2020

** Adapting Clinical Trials during COVID-19: Solutions for Switching to Remote & Virtual Visits, Webinar, CTTI

Decentralized Trials (DCTs)

- COVID-19 has necessitated rapid deployment of trial modifications consistent with Decentralized Trials (DCT)
- **What is a DCT?**
  - Some or all trial-related procedures and data acquisition performed at locations remote from the investigator
- **Some Notable Advantages:**
  - Decreased burden to patients
    - Decrease cost (missed work, childcare, travel, etc.)
  - Improved efficiencies for drug development
    - Potentially improve accrual speed
    - Potentially improve ability to enroll under-represented populations

Decentralized Trials: Potential Challenges

- **Remote efficacy and safety assessments**
  - Validation of digital health technology and remote assessment methods
  - Variability and missing data in remote assessment
- **Remote site monitoring**
  - Identification of trial conduct issues
- **Safety monitoring**
  - Identification and addressing participant safety issues
- **Regulatory**
  - Investigator responsibilities
  - Handling of investigational product
  - Etc.

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Thank You

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Statistical considerations in treatment and prevention trials for COVID-19

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Biopharmaceutical Applied Statistics Symposium
September 10, 2020

COVID-19: Developing Drugs and Biological Products for Treatment or Prevention

Guidance for Industry

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention

Outline of guidance recommendations

- Study population.
- Trial design and interim monitoring.
- Efficacy endpoints.
- Statistical analysis.

Study population

- A range of populations is appropriate for evaluation and may include outpatient, inpatient, or inpatient on mechanical ventilation populations.
- For treatment trials, sponsors should document diagnosis of COVID-19. Laboratory-confirmed disease is preferred.
- For treatment trials, FDA recommends that sponsors categorize the baseline severity of the enrolled population. The criteria used to describe baseline severity should incorporate objective measures.
- Clinical trials should include persons at high risk of complications such as the elderly, persons with underlying cardiovascular or respiratory disease, diabetes, chronic kidney disease, or other comorbidities, and immunocompromised persons (e.g., HIV-infected patients, organ transplant recipients, or patients receiving cancer chemotherapy).

Trial design

- FDA strongly recommends that drugs to treat or prevent COVID-19 be evaluated in randomized, placebo-controlled, double-blind clinical trials using a superiority design.
  - Background standard of care should be maintained in all treatment arms.
  - The standard of care is expected to change as additional information, such as from randomized controlled trials, emerges.

- Given the infection control concerns associated with COVID-19, sponsors should limit in-person data collection to those measurements intended to ensure safety and establish effectiveness or influence the benefit-risk assessment.

- The trial should be of sufficient duration to evaluate safety and effectiveness reliably (i.e., the duration should be adequate to capture the vast majority of COVID-19-related outcomes that are relevant for the population under study).

Trial design

- When there is compelling preclinical or preliminary clinical evidence, it may be appropriate to move directly to conduct a trial of sufficient size and appropriate design to provide substantial evidence of effectiveness and adequate characterization of safety.

- In instances where there is some but limited information supporting the potential for efficacy, approaches where an initial assessment of potential benefit can be made before enrolling a large number of subjects are appropriate.
  - Conducting an initial small, controlled trial to assess for drug activity (proof-of-concept) that suggests the potential for clinical benefit.
  - Conducting a trial that incorporates prospectively planned criteria to stop the trial for futility

Trial design

- FDA encourages sponsors to use an independent data monitoring committee (DMC) to ensure subject safety and trial integrity.

- FDA encourages sponsors to incorporate prospectively planned criteria to stop the trial for futility (lack of efficacy) or harm in any confirmatory trial.

- If a trial incorporates the possibility of early stopping for evidence of benefit or any adaptations to the sample size, dosing arms, or other design features, sponsors should prospectively plan the design in a manner to ensure control of the type I error rate and reliable treatment effect estimation. An independent committee, such as a DMC, should be tasked with providing any recommendations for early termination or design adaptations based on unblinded interim data.

- Well-motivated changes based on information external to the trial can be acceptable and sponsors are encouraged to discuss these changes with the FDA.

Efficacy endpoints

- The drug development program should evaluate the effect of the investigational drug relative to placebo on clinically meaningful aspects of the disease. The relevance and appropriateness of measures may depend on the population studied, the clinical setting, and/or baseline disease severity.

Efficacy endpoints

- In prevention trials, the primary endpoint should be the occurrence of laboratory-confirmed SARS-CoV-2 infection (with or without symptoms) or SARS-CoV-2 infection with symptoms (i.e., COVID-19) through a prespecified time point.

Efficacy endpoints

- In an outpatient treatment trial, examples of appropriate endpoints could be
  - Proportion of patients hospitalized by an appropriate time point (e.g., at least 28 days).
  - Time to sustained clinical recovery assessed over an appropriate duration.

Efficacy endpoints

- In a trial in severe and/or critical patients, examples of appropriate endpoints could be
  - All-cause mortality at an appropriate time point (e.g., at least 28 days).
  - Proportion of patients alive and free of respiratory failure at an appropriate time point (e.g., at least 28 days).
  - Clinical status at an appropriate time point assessed using an ordinal scale that incorporates multiple clinical outcomes of interest (e.g., death, mechanical ventilation) ordered by their clinical importance.
  - Time to sustained clinical recovery assessed over an appropriate duration.

Efficacy endpoints

- In phase 2 treatment trials, a virologic measure may be acceptable as a primary endpoint to support a phase 3 clinical endpoint study. However, virologic endpoints are not appropriate as primary endpoints in a phase 3 trial because there is no established predictive relationship between magnitude and timing of viral reductions and the extent of clinical benefit of how a patient feels, functions, or survives.

Statistical analysis

- The primary efficacy analysis should be conducted in an intention-to-treat population, defined as all randomized subjects.

- The primary efficacy analysis should be prespecified in the protocol.

- To the extent possible, sponsors should justify their assumptions in sample size calculations. The sample size should be large enough to provide a reliable answer to the safety and efficacy questions the trial is meant to address.

Statistical analysis

- Examples of analytic approaches for the primary efficacy analysis include:
  - Binary outcome analysis: each person is classified as having a successful or an unsuccessful outcome, with a difference in proportions used to compare treatment arms.
  - Ordinal outcome analysis: options include a proportional odds approach, a rank-based approach, and an approach to compare means with a score or weight assigned to each category. Any of these approaches should be supplemented by analyses communicating how treatment impacts different categories of the scale.
  - Time-to-event analysis: use of a proportional hazards model or log-rank test should be supplemented by a display of Kaplan-Meier curves in each treatment group.

Statistical analysis

- To improve the precision of treatment effect estimation and inference, sponsors should consider adjusting for prespecified prognostic baseline covariates (e.g., age, baseline severity, comorbidities) in the primary efficacy analysis and should propose methods of covariate adjustment.

- If a treatment trial enrolls a mixture of patients with different baseline severity levels, sponsors should conduct subgroup or interaction analyses by baseline severity to assess for differential treatment effects.

Statistical analysis

- The trial should aim to minimize missing data. The protocol should distinguish between discontinuation from the study drug and withdrawal from study assessments. Sponsors should encourage subjects who discontinue therapy to remain in the study and to continue follow-up for key outcomes. Virtual follow-up is acceptable if appropriate, and the aim should be to record vital status for all subjects.

- For the primary analyses, death should not be considered a form of missing data or censoring. Death should be incorporated into the endpoint as a highly unfavorable possible outcome. For primary endpoints other than all-cause mortality, a treatment effect could be driven by non-mortality components (e.g., hospitalization) despite increased mortality on drug. Therefore, analyses of all-cause mortality will be important regardless of the selected primary endpoint.