Conducting Clinical Trials During the COVID-19 Public Health Emergency

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Description & Objectives

The focus of this session is on *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*

- **Provide overview of FDA activities related to COVID-19**
- **Explain purpose and content of FDA Guidance on Conduct of Clinical Trials**
- **Invite feedback in the form of comments to inform possible updates**

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:

FDA COVID-19 Activities

- Review of numerous pre-market (IND) submissions
- Expanded access for investigational drugs
- Guidance available for industry, investigators, and institutional review boards related to COVID-19
- Outreach, listening sessions, soliciting feedback
- Emergency Use Authorization issued for:
  - ventilators, respiratory protective devices, in vitro diagnostics for COVID-19 detection/diagnosis, and other devices
  - anti-malaria drugs for treatment of certain hospitalized patients
- Convey up-to-date information to the public

Coronavirus Treatment Accelerator Program (CTAP)

- **Immediately upon receipt, triaged requests from developers and scientists seeking to develop or evaluate new drug and biologic therapies, getting the right FDA staff in touch with them and the work to get studies going fast**
- **Provide ultra-rapid protocol review – within 24 hours of submission, in some cases**
- **Review of individual patient expanded access requests around-the-clock, and generally within hours**

Snapshot for Developing Therapeutics

(as of April 20, 2020)

- 72 active trials of therapeutic agents
- 211 development programs for therapeutic agents in the planning stages

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap

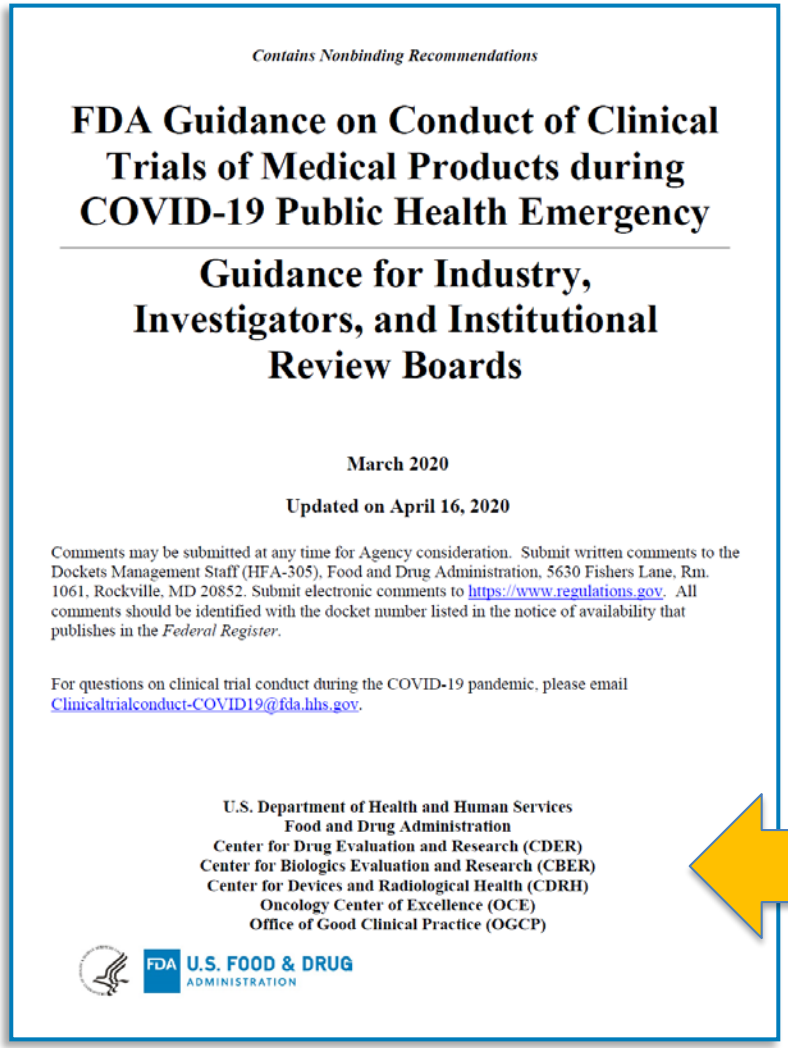
Title	Guidance Type	Product Area	Date Posted
Enforcement Policy for Imaging Systems During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency	Final Guidance for Industry and FDA Staff	Medical Devices	April 23, 2020
Enforcement Policy for Non-Invasive Fetal and Maternal Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency	Final Guidance for Industry and FDA Staff	Medical Devices	April 23, 2020
Temporary Policy Regarding Accredited Third-Party Certification Program Onsite Observation and Certificate Duration Requirements During the COVID-19 Public Health Emergency	Final Guidance for Industry	Food & Beverages	April 22, 2020
Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency	Final Guidance for Industry	Drugs	April 22, 2020
Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency Guidance for Industry	Final Guidance for Industry	Drugs	April 20, 2020
Policy for the Temporary Use of Portable Cryogenic Containers Not in Compliance With 21 CFR 211.94(e)(1) For Oxygen and Nitrogen During the COVID-19 Public Health Emergency	Final Guidance for Industry	Drugs	April 20, 2020
Enforcement Policy for Telethermographic Systems During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency	Final Guidance for Industry and FDA Staff	Medical Devices	April 16, 2020
FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency	Final Guidance for Industry, Investigators, and Institutional Review Boards	Drugs Biologics Medical Devices	April 16, 2020
Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency	Final Guidance for Industry	Drugs	April 16, 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	April 15, 2020

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

Examples of Topics Include:

- **Conduct of Clinical Trials**
- Temporary policy for certain risk evaluation and mitigation strategies (REMS) requirements
- Remote monitoring of patient-monitoring devices
- Enforcement policies for personal protective equipment (PPE), sterilizers and disinfectant, and ventilators
- Manufacture of alcohol-based hand sanitizers
- Temporary policy for compounding of certain drugs for hospitalized patients by outsourcing facilities
- Nutrition labeling, food supplier audit requirements
- Alternative procedures for blood and blood components
- Conduct and review of drug development for animals

*Access to FDA 'COVID' guidances: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders



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 April 16, 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.

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)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Guidance on *Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*

- **Initial release date: March 18, 2020**
- **Most recent update: April 16, 2020**

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

- After *Introduction* and *Background* sections, details provided in *Discussion* section, *Additional Resources* section, *Question & Answer* appendix
- *Question & Answer* appendix updated based on major issues and inquiries received in COVID-19 mailbox: Clinicaltrialconduct-COVID19@fda.hhs.gov
- Latest update April 16, 2020, includes new Q&A on obtaining informed consent from patients unable to travel to the trial site, remote performance outcome (PerfO) assessments, remote site monitoring, shipping of investigational product, and other topics

Conduct of Clinical Trials Guidance: Core Principles

- Safety of trial participants is the core focus of all recommendations
  - "*Ensuring the safety of trial participants is paramount*" is the first consideration mentioned in Conduct of Clinical Trials Guidance
  - Focus also on protecting trial integrity and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance
- Provides guidance on issues expected to be encountered and/or mentioned in inquiries to COVID-19 mailbox
- For specific questions that depend on factors such as the study population, type of investigational product, or trial endpoint, contact the appropriate FDA review division

Key Considerations for Continuing or Initiating Clinical Trials

Sponsors, in consultation with clinical investigators, Institutional Review Boards (IRBs)/ Institutional Ethics Committees (IECs), and, if applicable Data Monitoring Committees, should assess whether the protection of a participant's safety, welfare, and rights is best preserved by continuing a study participant in the trial as per protocol or by discontinuing the administration or use of the investigational product or even participation in the trial

Considerations include:

- **Whether COVID-19-related limitations on protocol implementation pose new safety risks to participants, and whether those risks can be mitigated by amending study processes/procedures**

Key Considerations for Continuing or Initiating Clinical Trials (2)

- **Availability of investigators/sub-investigators to oversee trial and adequately monitor safety risks**
- **Availability/ability of sufficient clinical trial staff, supplies, and technological tools**
- **Continued operations of, and ability to communicate with IRB/ Institutional Ethics Committee and, if applicable, Data Monitoring Committee (DMC)**
- **Feasibility of trial conduct in light of any COVID-19 public health measures implemented**
- **Important to consider DMC (if established) assessment of any modifications of trial conduct**

Considerations for Ongoing Trials

- **"Safety is paramount":** Modifications to trials should assure participant safety
- **Potential of alternative procedures for safety assessments:** Consider using technologies to facilitate remote data collection and monitoring, e.g., video conferences, local laboratory
- **Protocol modifications to eliminate apparent immediate hazards to participants may be implemented before IRB/FDA approval** (reporting required afterward)
- **Secure delivery of investigational product (IP):** Alternative delivery methods can be explored, such as for IP that are normally self administered
  - If decision made to discontinue the investigational product, may still need additional monitoring
- **COVID-19 screening as a part of health care** does not need to be reported as a protocol amendment, unless data will become part of the research objective(s)

Considerations: Efficacy Endpoints

- **Appropriate FDA review division should be consulted for protocol modifications related to collection of efficacy endpoints**
  - **Note: safety of participants may necessitate missed/altered assessments, even before consultation**
- **If an efficacy endpoint is not collected due to COVID-19, the reason for failing to collect the endpoint should be documented**

Remote Outcome Assessments

- Certain performance outcome assessments (PerfO) and interview-based clinician reported outcome (ClinRO) assessments may be feasible remotely
- Sponsors should:
  - consider if the remote technology is appropriate for the type of clinical data capture
  - consider the need to compare in-person and remote assessments if only some outcome assessments will be captured remotely
  - adequately prepare investigators
  - develop procedures for participant technical support

Considerations: Data-Related Issues

- **If changes to the protocol require amendments to data management and/or statistical analysis plan (SAP), considerations include:**
  - **documenting the context when missing data or censoring occur**
  - **consulting with FDA review division prior to making changes to data management/SAP**
  - **for prespecified analyses, determine how deviations related to COVID-19 will be handled, and document this *prior* to locking database**

Investigational Product Continuation

- **The decision of whether to continue the investigational product is different than continuing treatment**
  - **The risks and benefits of investigational products are still being assessed**
- **Nonetheless, decision to discontinue investigational product may be complex and should consider issues including:**
  - **Seriousness of the disease/condition**
  - **Reasonable alternatives and risks in changing**
  - **Apparent clinical benefit**

Investigational Products Administered at Home

- **Home delivery may be appropriate for self-administered investigational products**
- **Assure that during delivery, the drug is kept under appropriate storage conditions and there are systems put in place to maintain product accountability**
- **If home delivery is for only a limited number of trial participants, this can be done under "protocol deviations"**
- **If home delivery is more extensive, this should be described in an IND amendment**

Investigational Products Requiring Infusion

- **Due to the complexity and potential safety considerations with products delivered by infusion, consultation with the FDA review division on alternative plans is generally recommended**
- **Need to have appropriately trained personnel at the alternative site**
- **Storage and handling of products that are shipped to alternative sites may be more complex**
- **Accountability requirements must be addressed and documented**

Continuing Investigational Products Locally

- Potential for continuing investigational product administration by a participant's local provider
- Considerations
  - Is the local provider experienced with the drug or drug class?
  - Is the local infusion center experienced?
  - Can the IP be shipped to the local health care provider?
  - If commercially available, is it possible to procure locally?
    - Reimbursement for locally procured product acceptable

Continuing Investigational Products Locally

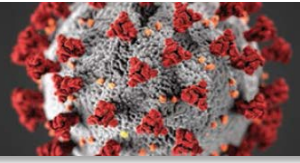
- **When is a local provider considered a sub-investigator and added to Form FDA 1572?**
  - **If administering the drug in a manner that does not differ from their normal clinical practice, would not be a sub-investigator**
  - **If performing research procedures or assessments that represent a direct and significant contribution to clinical data (e.g., performing a procedure that is unique to the study), then a sub-investigator**

Informing FDA - Amendments

- Protocol deviations are generally reported to FDA in clinical study reports
- Global changes to study conduct should generally be reported as a protocol amendment
- During the rapidly evolving circumstances of a pandemic, a sequence of changes may be needed, and consolidating several protocol modifications in a single protocol amendment would be acceptable but should be done expeditiously
- Specific guidance provided on changes to device trials and "5-day notification"
- Flag amendments as related to COVID-19
  - PROTOCOL AMENDMENT – COVID-19 for drugs/biologics
  - CHANGE IN PROTOCOL SUPPLEMENT – COVID-19, or NOTICE OF IDE CHANGE – COVID-19 for devices

Interacting with FDA

- Review division Regulatory Project Managers are the primary point of contact for communications between a sponsor and FDA
- For devices, the lead reviewer is the primary point of contact for communication
- FDA and sponsors use various communication methods to focus discussions to exchange information and resolve issues efficiently
- FDA staff try to response to sponsor questions promptly while balancing competing obligations
- For more information, see FDA guidance Best Practices for Communication between IND Sponsors and FDA During Drug Development

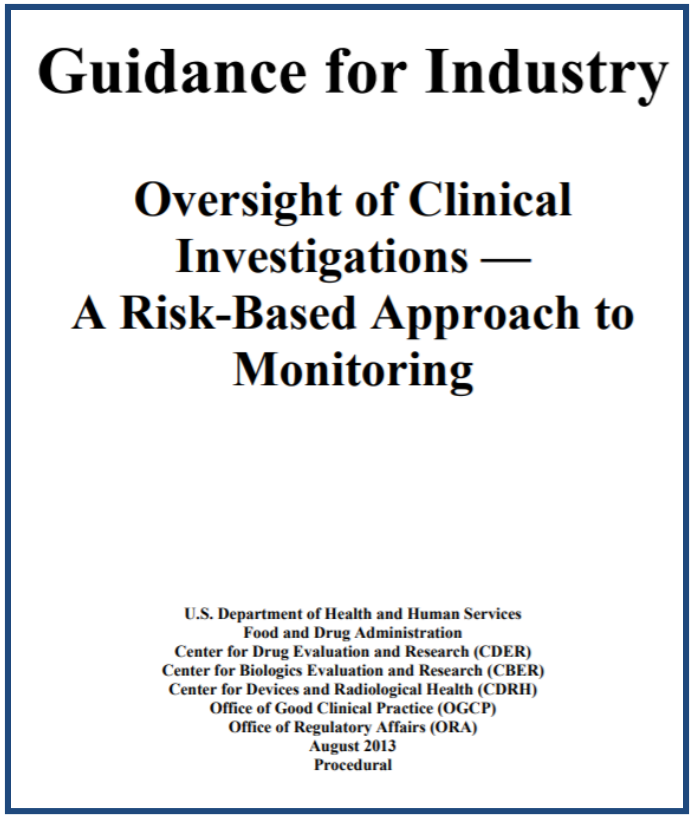


Informed Consent from Patients in Isolation

- **Consider electronic informed consent if available***
- **If consent cannot be obtained electronically, consider these steps:**
  - **Provide consent form to patient from a healthcare worker who has entered the room**
  - **If direct communication with patient is not possible, investigator (or designee) can arrange a three-way phone or video call with patient, an impartial witness, and (if desired and feasible) additional persons as requested by the patient**
  - **A standard process for such calls should be used that involves a series of steps for confirmation (see Guidance for details)**
  - **If the consent document cannot be collected from the patient's location, options include attestation by witness or photo of the signed informed consent document**

*Use of Electronic Informed Consent Questions and Answers

Monitoring Clinical Conduct



Risk-based monitoring, including the appropriate use of centralized monitoring and reliance on technological advances (e.g., e-mail, webcasts, online training modules), can meet statutory and regulatory requirements under appropriate circumstances

Access: https://www.fda.gov/media/116754/download

On-Site Remote Monitoring During COVID 19

- If planned on-site monitoring is not possible, consider a risk-based approach to prioritize sites for remote monitoring
- Should focus on critical study site data
- Remote review of medical records and other documents normally reviewed at site may be explored
  - Secure remote viewing portal
  - Uploading of certified copies to a repository with appropriate security controls

Document, Document, Document

- Sponsors should document COVID-19 contingency measures and how they impact the trial, as well as impacts at the individual participant level
- FDA anticipates there will be many protocol deviations that may lead to missing data, capture of data outside of protocol defined windows, and other changes
- Document now so that clinical study reports can capture:
  - listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier, and by investigational site, along with a description of how the individual's participation was altered

Summary: COVID-19 and Clinical Trials

- **First priority is safety of trial participants**
- **Trial modifications should address safety and seek to maintain trial integrity; FDA is being flexible where appropriate**
- **Consider options for remote assessments and alternative delivery of investigational product, when appropriate**
- **Important to document COVID-19 related protocol deviations and missing data**
- **Contact FDA Review Divisions for specific questions about clinical trials when related to efficacy endpoints, changes in statistical analysis plans, or other key aspects of trial**

Submitting Questions or Comments to FDA

- **Comment on the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency at www.regulations.gov (Docket number FDA 2020-D-1106)**

- **For general questions on clinical trial conduct during the COVID 19 public health emergency, email Clinicaltrialconduct-COVID19@fda.hhs.gov**

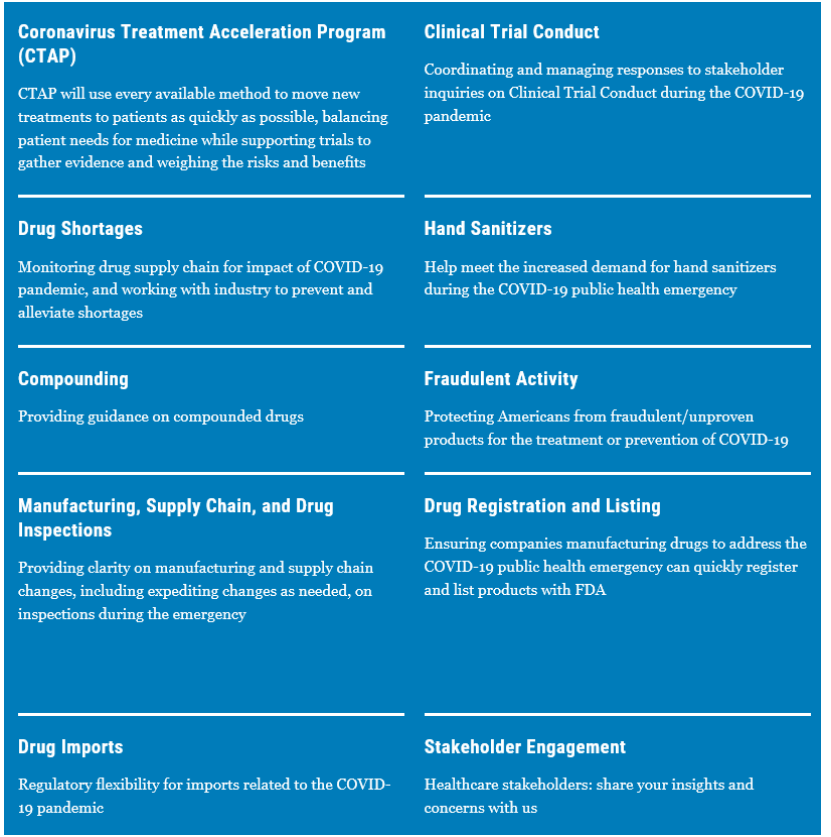
Submitting Questions or Comments to FDA (2)

- **For review division-specific questions, contact:**
  - **CDER:** https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs
  - **CBER:** https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/contacts-center-biologics-evaluation-research-cber#indcont
  - **CDRH:** https://www.fda.gov/about-fda/cdrh-offices/cdrh-management-directory-organization

FDA COVID-19 Online Resources

FDA:
- Coronavirus Disease 2019
- COVID-19-Related Guidance Documents

CDER:
- COVID-19 | Drugs
- Coronavirus Treatment Acceleration Program (CTAP)
- Clinical Trial Conduct During the COVID-19 Pandemic
- Drug Shortages Response | COVID-19
- Hand Sanitizers | COVID-19
- Compounding Activities | COVID-19
- Fraudulent Activity
- Manufacturing, Supply Chain, and Drug Inspections
- Registration and Listing
- Import of Drugs for Potential COVID-19 Treatment
- Stakeholder Engagement | COVID-19



FDA COVID-19 Online Resources (cont'd)

CBER:
- Letter to Sponsors, Applicants and Regulated Entities on COVID-19
- Recommendations for Investigational COVID-19 Convalescent Plasma
- Updated Instructions for Submitting Lot Release Samples and Protocols for CBER-regulated Products During the COVID-19 Pandemic

CDRH:
- Medical Devices and the COVID-19 Pandemic
- In Vitro Diagnostic Tests
- Personal Protective Equipment (PPE)
- Ventilators
- FDA Emergency Response Activities Related to Medical Devices
  - Emergency Use Authorizations (EUAs)
  - Guidance Documents

FDA COVID-19 Online Resources for Patients

- Coronavirus Disease 2019 (COVID-19) Resources for Patients
- COVID-19 Frequently Asked Questions (FAQs)
  - Frequently Asked Questions
  - Preguntas más frecuentes acerca de la Enfermedad del Coronavirus 2019 (COVID-19)
- Donate COVID-19 Plasma
- Coronavirus (COVID-19) Update: Blood Donations

Acknowledgments

- To all of the health care workers caring for patients
- To the research participants, sponsors, investigators and trial staff working to find new cures

Questions and Contact Information

Questions about clinical trial conduct during the COVID-19 public health emergency can be emailed to: Clinicaltrialconduct-COVID19@fda.hhs.gov

Conducting Clinical Trials During the COVID-19 Public Health Emergency: Question & Answer Session

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Center for Drug Evaluation and Research
US Food and Drug Administration

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