Best Practices for Conducting Trials During the COVID-19 Pandemic

BACKGROUND

The COVID-19 pandemic has turned our world upside down. In the clinical trials community, nearly every aspect of research is experiencing unprecedented disruptions. As a leading public-private partnership, the Clinical Trials Transformation Initiative (CTTI) is taking on several efforts to help the clinical trials ecosystem adapt and move forward despite these new challenges. This document* outlines those initiatives and resulting best practices for researchers conducting clinical trials during the COVID-19 pandemic.

GATHERING EXPERIENCES AND BEST PRACTICES ACROSS THE ECOSYSTEM

Clinical trials have been disrupted by COVID-19 and the safety measures enacted to limit the spread of the disease. A report from Medidata showed an 83% decrease in new patients entering trials in China in February 2020 compared to February 2019. The United States experienced a 62% decrease in the first half of March 2020, and similar trends have been seen in other countries. The U.S. Food and Drug Administration released guidance on March 18, 2020 (updated on March 27 and April 2, 2020), "to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic." The European Medicines Agency (EMA), Medicines & Healthcare Products Regulatory Agency, and Office for Human Research Protections (OHRP) released similar guidance documents.

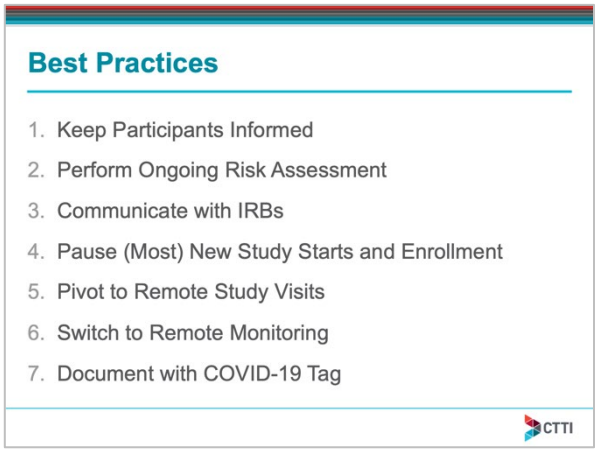
In the first of many COVID-19–related activities, CTTI launched a public survey on March 23 requesting feedback about experiences and best practices in the context of the FDA guidance on the conduct of clinical trials of medical products during the pandemic. The survey was distributed via email to CTTI member organizations and contacts, via posts on Twitter and LinkedIn, and by redistribution from trade, media, and other organizations. Fifty-five responses were received in four days. Those responses were collated and presented along with shared experiences from a patient representative, academic medical center, and independent institutional review board (IRB) on a CTTI-hosted webinar on March 31.

**CTTI will regularly update this document to incorporate learnings and findings from ongoing COVID-19-related webinars and other efforts.*

SEVEN BEST PRACTICES FOR CONDUCTING TRIALS DURING THE COVID-19 PANDEMIC

By collating insights from across the clinical trials ecosystem, CTTI identified seven best practices for conducting clinical trials during the COVID-19 pandemic.

The following section further details the findings from CTTI's survey and expands on points highlighted during its corresponding webinar.



1. Keep Participants Informed

- FDA guidance states, "It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them."

> "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."
>
> From *Preserving Clinical Trial Integrity During the Coronavirus Pandemic.* *JAMA* March 25, 2020. doi:10.1001/jama.2020.4689

- Need for a plan, process, and decision making
  - Plan should include who informs participants, when, how?
  - Resources for consistent, evidence-based information
  - Essential information at patient level
    Study delays, suspended procedures, clinic closings
    Transitions to remote, digital or home-based visits
  - Support, training necessary for digital tools, monitoring, home data collection
- Patient organizations can assist in reviewing modifications, broader outreach, guidance
- CTTI Recommendations: technical support (training) for digital tools, home collection (CTTI Optimizing Mobile Clinical Trials by Engaging Patients and Sites)

- Important considerations for participants during this time: Consider patient perspective of "safety" and ability to participate in context of pandemic
  - Continuously evaluating; daily prioritizing urgent needs (food, shelter, finances, family)
  - Patient, partners, children may all be sharing devices needed for remote visits
  - Fear and anxiety are common
    Baseline fear of living with life-threatening illness can turn to terror
    Heightened "safety" warnings aimed at "high-risk, especially vulnerable"
    Preexisting conditions, heart and respiratory ailments, diabetes, elderly
    Health care shortages: physicians, nurses, supplies
    Enforcing of self-isolation and home quarantine in impacted areas; travel restrictions
    Worry about added risks to loved ones and caregivers if exposed
  - Sense of urgency about disease
    My disease is progressing as research stalls
    Am I "essential"? Is my treatment? Is my trial?
    We've been waiting for this trial for months, years. How quickly can it resume?
    What happens to my participation if the trial doesn't resume?
    What can I do now?

2. Perform Ongoing Risk-Benefit Assessment

- Priority is safety of patients and research personnel over data integrity concerns
- Follow country, local, and institution rules and restrictions in place due to the virus
- Avoid interference or burden on clinical care
- Communication is very important
  - Site and participants: inform patient and determine interest and ability in continued participation
  - Between sponsor, site, IRB
    What changes are intended by sponsor?
    Logistical changes at site level
  - Sponsor communication with FDA/regulatory authorities
- Risk-benefit assessment is required for all studies at organization
  - Develop recruitment plan based on risk assessment that minimizes patient exposure, both for initial recruitment and subsequent visits
  - Determine which study activities can be performed remotely
  - Some organizations have instituted a tier system based on potential direct benefit of the research to research participants (NIH Collaboratory March 20 Grand Rounds)
    High benefit to patients
    Enrollment and study visits continue in person
    Convert as many study activities as possible to virtual, home

Examples include oncology, amyotrophic lateral sclerosis (ALS), and other areas where intervention is the only treatment option or one of limited treatment options

Screening for COVID-19 symptoms prior to and at visits

Moderate potential benefit

Pause enrollment

Convert to virtual/phone visits as much as possible

Limited potential benefit

Pause enrollment

Convert all visits to phone/virtual, or pause/stop visits

- Workforce adjustment
  - Telework for study personnel where possible, making sure they take everything home they need
  - Divide study team and adjust which work occurs on-site and off-site
  - Work with IT to set up network access (including electronic health records) from home computers or provide property passes to take laptops home
  - Reminder to study personnel to be mindful of surroundings, e.g., turn off any smart speakers
- For more information: See FDA Guidance, page 10: "What are some of the key factors that a sponsor should consider when deciding whether to suspend or continue an ongoing study or to initiate a new study during the COVID-19 pandemic?"

3. Communicate with IRB/IEC and Regulatory Authorities

- "Ensuring the safety of trial participants is paramount." (FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Pandemic)
- Tremendous strain on all involved
  - Sites: diversion to clinical care; remote staff; inaccessible participants
  - IRBs: institutional IRBs may shift staff, members to COVID-19 support; independent IRBs shift to remote work
  - Sponsors: measures to maintain/salvage studies under circumstances
- Goal of IRBs: provide reliable support in order to maintain research that is ethical, valid, compliant
  - Unprecedented volume of changes to ongoing research
  - Most common changes

    Elimination/reduction in frequency of study visits

    Shift from on-site to telemedicine, home health care

    Collection of labs offsite

    Changes to drug delivery: direct ship, delivery by site staff

    Other changes that do not require IRB approval
- When is IRB review required?

- Regulations expect prospective review and approval
- Regulations allow immediate changes when in best interest

  Each IRB shall…"(a) Follow written procedures for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects." (21 CFR 56.108(a)(4))

  "Investigators may implement changes to approved research prior to IRB review and approval, if the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.108(a)(3)(iii) under the 2018 Requirements and 45 CFR 46.103(b)(4)(iii) under the pre-2018 Requirements)."
- IRBs interpreting in light of COVID-19 context

  Check with your IRB to determine timeline for reporting changes to the IRB
- IRBs can and should be nimble and efficient when managing such changes

- Considerations for informed consent
  - Frequent question: Do changes require "re-consent"?
  - Secretary's Advisory Committee on Human Research Protections (SACHRP): "When there is a need to present participants with new information, IRBs should encourage use of the least burdensome approach for the participant."
  - "Re-consent" not a regulatory term
  - New information can be presented in different formats

    Revised consent document

    Addendum to consent

    Memo or other communication to subjects

    Orally by phone or in person
- Document all changes

4. Pause (Most) New Study Starts and Enrollment

- Determine which studies to pause enrollment and study starts based on risk-benefit assessment
- For global studies, adopt a country- and region-specific approach to pauses and restarts
- Language is important for existing patients
  - In most cases, paused enrollment does not mean patient participation is over
  - See section *1. Keep Participants Informed* above

5. Pivot to Remote Study Visits

- Important to collect data by other methods where possible
- Questionnaires, adverse events, other questions asked at study visits can be obtained via telephone
- Refer immediate safety concerns to primary care provider or other care provider

- Use available resources: institutions, IRBs, and patient groups have advice, tools and experience to provide assistance
  - Check for approved telemedicine platforms, programs (OCR Guidance)
  - Investigate apps, noninvasive physical assessment devices
- Explore alternative distribution of investigational product
  - Send study drug directly to patient from site

    Check state board of pharmacy guidelines

    Package delivery services with signature

    Home health for parenteral products
- Alternative locations for safety assessments that cannot occur via telephone
  - Utilize less crowded family health centers or home health for patients to have blood draws, electrocardiograms, and imaging away from the hospital
- Delayed study visits and expanded collection windows can be instituted when it is not harmful to delay assessments and obtaining data remotely or by other methods is not feasible
- Document all changes made to visit, assessments, investigational product delivery

6. Switch to Remote Monitoring

- Onsite monitoring delayed or suspended during pandemic
- Implementation of remote, risk-based monitoring
  - Prioritization of safety assessments and primary outcome measures
- Ensure secure methods to allow for access of subject data for remote review
  - Restricted access accounts in electronic health record, use of Epic Anyconnect feature (or web-based virtual conferencing) to permit remote monitoring with sponsor agreement (limit monitor access to only enrolled subjects); may require update to contract
  - Staff access while working from home (see workforce adjustment above)
  - Secure file sharing
- Document all changes made to monitoring plan

7. Document Everything with COVID-19 Tag

- Many IRBs have created COVID-19–specific submission flag or process for amendments, questions, new studies
- Add COVID-19 to all documentation at patient and study levels
  - For reports to sponsor, IRB, and FDA when required
- Create standard template for recording items, such as missed assessments, with procedure for documenting and communicating (see appendix for example)

ADDITIONAL RESOURCES:

FDA guidance: https://www.fda.gov/media/136238/download

For further questions, for the FDA, on clinical trial conduct during the COVID-19 pandemic, email:

- Clinicaltrialconduct-COVID19@fda.hhs.gov

Contact information for FDA's review divisions is as follows:

- **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
- **CDRH**: https://www.fda.gov/about-fda/cdrh-offices/cdrh-management-directory-organization

EMA guidance: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

MHRA guidance: https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19

OHRP guidance: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/ohrp-guidance-on-covid-19/index.html

ABOUT THE CLINICAL TRIALS TRANSFORMATION INITIATIVE (CTTI)

The Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by Duke University and the U.S. Food and Drug Administration, seeks to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials. Bringing together organizations and individuals from across the enterprise—representing academia, clinical investigators, government and regulatory agencies, industry, institutional review boards, patient advocacy groups, and other groups—CTTI is transforming the clinical trials landscape by developing evidence-based solutions to clinical research challenges. Many regulatory agencies and organizations have applied CTTI's more than 20 existing recommendations, and associated resources, to make better clinical trials a reality. Learn more about CTTI projects, recommendations, and resources at www.ctti-clinicaltrials.org.