



# Best Practices for Conducting Trials during the COVID-19 Pandemic

Collating insights from across the clinical trials ecosystem, the [Clinical Trials Transformation Initiative](#) (CTTI) identified best practices for conducting clinical trials when the COVID-19 pandemic first hit.

This document details the findings from CTTI's surveys on ongoing trials during COVID-19 and expands on points highlighted during those corresponding webinars (see [Background](#) for more information).

◆◆◆BEST PRACTICES◆◆◆	
1	Keep Participants Informed
2	Perform Ongoing Risk-Benefit Assessment
3	Communicate with IRB/IEC and Regulatory Authorities
4	Adjust New Study Starts and Enrollment Based on Current Risks
5	Pivot to Remote Study Visits
6	Switch to Remote Monitoring
7	Be Flexible
8	Document Everything with COVID-19 Tag

## 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 communication plan, process, and decision making
  - Plan should include who informs participants, when, and how
  - Participants should be contacted to determine their interest and ability in continued participation
  - Provide resources for consistent, evidence-based information
  - Receiving some sort of communication may be more important than *how* it's received
  - Essential information at the patient level
    - Study delays, suspended procedures, clinic closings
    - What procedures are changing
    - Transitions to remote, digital or home-based visits
    - Procedures for in-person visits when required and/or when resumed
      - Requirements may change from visit to visit according to community COVID-19 cases and local alert levels
      - Research visits will follow health system/hospital procedures for symptom screening, COVID-19 testing before procedures, and visitation
    - If signature on revised informed consent or addendum is required due to changes
  - Provide support and training necessary for digital tools, monitoring, home data collection
    - CTTI Recommendations: technical support (training) for digital tools, home collection ([CTTI Optimizing Mobile Clinical Trials by Engaging Patients and Sites](#))
- ▶ Patient organizations can assist in reviewing modifications, broader outreach, and guidance
- ▶ Consider participant perspective of “safety” and ability to participate in context of pandemic along with concerns about trial being paused or stopped; be flexible and continually reassess patient needs
  - Patients are continuously evaluating and prioritizing urgent needs (food, shelter, finances, family)
  - Patient, partners, and children may all be sharing devices needed for remote visits; consider technology access and reliability issues
  - 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”
    - Many have preexisting conditions, heart and respiratory ailments, diabetes, are elderly, or immunocompromised

“Any communication at all would have been great, there just wasn’t any.”

“It would have been nice to receive an email about how the study plans to address in-person visits during the pandemic.”

- CTTI survey respondents

“Getting to the site with this pandemic makes me more worried of contacting COVID-19.”

- CTTI survey respondent

- Health care shortages of physicians, nurses, and supplies
  - Enforcing of self-isolation and home quarantine in impacted areas and 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 or even years. How quickly can it resume?
  - What happens to my participation if the trial doesn’t resume?
  - What can I do now?

“Because the trial was put on hold, my heart function is getting weaker. If I was in the trial, I would have an implantable device that would improve my heart function.”

- CTTI survey respondent

## 2. Perform Ongoing Risk-Benefit Assessment

- ▶ The priority is patient and research personnel safety over data integrity concerns
- ▶ Continuously monitor the situation to address participant and program needs
  - See important [participant considerations](#) above
  - Follow country, local, and institution rules and restrictions
    - Monitor public data to appreciate disease activity
  - Site considerations:
    - Avoid interference or burden on clinical care
    - Site burden and availability of study staff
      - Consider sites’ priorities - some sites may be prioritizing COVID-19 trials over non-COVID trials
      - Ability to safely perform activities at site (e.g. is clinic building open, is adequate personal protective equipment available)
      - Ability of site personnel to perform activities from their homes (e.g. is technology available, is training needed, childcare, privacy)
- ▶ Communication is very important as part of risk assessment
  - [Site communication with participants](#)
  - Between sponsor, site, and IRB
    - What changes are intended by the sponsor?
    - Logistical changes at site level
  - Sponsor communication with FDA/regulatory authorities
  - Make communication efficient, non-duplicative, and consistent
- ▶ Risk-benefit assessment is required for all studies at organization
  - Develop a recruitment plan based on risk assessment that minimizes participant and research personnel exposure, both for initial recruitment and subsequent visits
  - Some organizations have instituted a tier system for making decisions on how to conduct ongoing and new research ([NIH Collaboratory March 20 Grand Rounds](#))

Study Classification	Example Assessment	Example Modifications
<b>Tier 1</b> High Potential Direct Benefit to Research Participants	Risk of interrupting study treatment may be greater than risk of contracting virus (e.g. ALS, oncology studies)	<ul style="list-style-type: none"> <li>Enrollment and in-person visits continued with precautions</li> <li>Converted to virtual visits as much as possible</li> </ul>
<b>Tier 2</b> Moderate Potential Direct Benefit to Research Participants	Potential study benefit may or may not be greater than virus risk	<ul style="list-style-type: none"> <li>Enrollment initially paused, some resuming</li> <li>Continue virtual visits as much as possible</li> </ul>
<b>Tier 3</b> Limited potential direct benefit to research participants	Study intervention less critical to the health of participant compared to risk of contracting virus	<ul style="list-style-type: none"> <li>Paused enrollment, some resuming</li> <li>Continue virtual/phone visits</li> </ul>

— Maintain safety while minimizing risks to trial integrity

- Important to preserve time, invested resources, and effort of participants already enrolled or completed
  - Sponsors should leverage analytics
  - Utilize data analytics (i.e. public COVID-19 data on cases)
    - Overlay public data with manual/internal assessments to appreciate statistical impact of:
      - Missing assessments, missed doses, remote vs onsite visit
      - Run a statistical analysis to determine validity of remote data
    - If available, utilize DMC for assistance in making these assessments
  - Define critical data collection
    - What efficacy and safety assessments are most important? (indication dependent)
    - Can research blood draws or biopsies that are less critical to efficacy or safety be eliminated or delayed?
    - Aim to make more pragmatic and streamlined trial designs and operations in future studies
  - Ensure uninterrupted study drug dosing/study treatment
    - Assess feasibility of drug shipment
    - Consider stability of the product
    - Can it be shipped to the home?
    - Applicable regulations
- For more information: See [FDA Guidance](#) (Appendix: Questions and Answers Q1) “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 public health emergency?”

### 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](#))
- ▶ See [FDA Guidance and Appendix: Questions and Answers](#) for recommendations on when to consult the relevant FDA review division
- ▶ Tremendous strain on all involved
  - Sites: diversion to clinical care; remote staff; inaccessible participants; instituting safety measures as some studies resume
  - IRBs: institutional IRBs may shift staff, board 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, and 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 of research changes
  - 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
- COVID-19 screening procedures do not need to be reported to the IRB as an amendment to the protocol even if done during clinical study visits unless the sponsor is incorporating the data collected as part of a new research objective.
- ▶ 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” is not a regulatory term
  - New information can be presented in different formats (See [Section 5](#) for additional information about remote consent approach)
    - Revised consent document
    - Addendum to consent
    - Memo or other communication to subjects
    - Orally by phone or in person
- ▶ Document all changes, including communication with participant




#### **4. Adjust New Study Starts and Enrollment Based on Current Risks**

- ▶ Adopt a country- and region-specific approach to pauses and restarts in global studies; state- and region-specific approaches also required for U.S. sites
- ▶ Be prepared to adjust approaches with more or less limitations on in-person activities based on changes to country, local, and institution rules and restrictions
- ▶ Pausing enrollment and new study start up:
  - When shelter in place orders were/are in effect most new enrollment and study starts were paused
  - Language of communicating pause is important for existing patients
    - In most cases, paused enrollment does not mean patient participation is over
    - See [Section 1. Keep Participants Informed](#) above
- ▶ Resuming, or continuing, select in-person activities
  - Some studies with high potential benefit to participants or in areas minimally affected by COVID-19 were not stopped and have been operating with modifications and safety precautions
  - Some paused sites now feel comfortable resuming some on-site research
    - As availability of COVID-19 testing and adequate PPE has increased
    - As COVID-19 screening procedures have been developed and implemented
    - Contingent on local and statewide COVID-19 disease metrics
  - Continue to perform as many activities as possible over phone/video visits


- Inform participant of risks of visit and precautions taken to lower risks
- Example precautions before and during on-site visits
  - Pre-screening on phone day prior and day of visit – cancel if participant or staff not feeling well
  - COVID-19 testing before study inpatient admission or outpatient procedure
    - Follow requirements of institution where research is occurring
    - If considered routine care outside of research, COVID-19 testing is billed to health insurance and should not need IRB approval
  - On-site screening at the door on day of visit
    - Temperature screening for patient and visitor
    - COVID-19 screening survey, test if screening indicates
  - Mask required: participant and visitor are provided masks at the door and required to wear them
  - Site staff wear appropriate PPE
  - Frequent handwashing and disinfect surfaces between visits
  - Limit number of staff and patients on-site at one time
    - Reduce number of staff on-site; divide study team and adjust which work occurs on-site and off-site
    - Stagger participant visit times
    - At some sites, participants are asked to wait for appointments in their car and are called when time for visit.
    - Participants should confirm, and site staff should convey, institution's policies on visitors during study visits.
  - Practice distancing during visit, limit time in direct contact
  - Combine/schedule study visit with clinical visits where/when possible

## 5. Pivot to Remote Study Visits

### Best Practices & Words of Wisdom

 Site	 Industry	 Tech
Think ahead & create a plan	Evaluate which assessments can be done remotely	Deploy privacy compliant tech platforms
Test run the telehealth platforms	Use mobile HCPs & Local Labs (match to assessments)	Train pts/caregivers & sites on platform
Be flexible	Follow regulations: privacy/OCR, local, Ethics/IRB	Create an appropriate environment
Maintain clear & on-going communication	Be respectful of sites: this is not their only priority	Know how to handle system failures
	Run a stats analysis to determine validity of remote data	

As conveyed by 50% of respondents



- ▶ Consider objectives for switching to remote/virtual visits including:
  - Supporting study patients during COVID-19 pandemic and minimizing exposure risk
  - Maintaining study assessments for protocol compliance and trial integrity
    - Which study assessments should and can be transferred to remote/virtual?
    - Prioritize most critical assessments
  - Ensuring uninterrupted access to study drug or to non-drug intervention
  - Maintaining patient-physician engagements
- ▶ Determine which study activities can be performed remotely
  - Consider the indication. Is it feasible to conduct a disease assessment in a virtual manner?
  - Determine most appropriate method of performing activities
    - Video visits or telehealth
    - In-person activities at less crowded location - local provider, local labs, or home health
    - Telephone
    - Ensure that remote method is accessible to representative patient population



- See [FDA Guidance](#) (Appendix: Questions and Answers Q12) for additional considerations
- Maintain consistency as much as possible (see [FDA Guidance](#), Appendix: Questions and Answers Q12)
  - Perform remote assessments in a manner as similar as possible to those done in-person, while protecting trial participant safety and privacy
  - Maintain methods and conduct of remote assessments as consistent as possible across sites, trial participants, and visits to minimize variability in the data

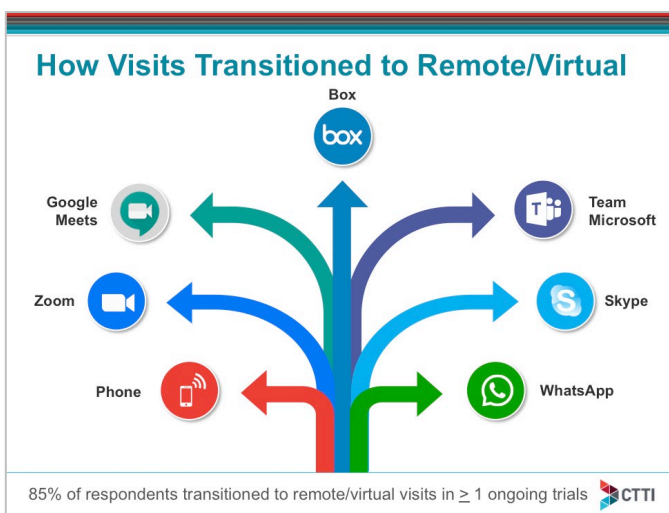
- Determine which parts of site visits can be transitioned to remote/virtual

- Remote screening by coordinators working from home via telephone or video conference
- Informed consent

- Methods for obtaining informed consent remotely are discussed in the FDA guidance, [Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency](#).
- The FDA MyStudies app is

[available to investigators](#) as a free platform to obtain informed consent securely from patients for eligible clinical trials when face-to-face contact is not possible or practical due to COVID-19 control measures

- Study visits via telehealth or mobile healthcare providers (HCPs)
  - Check for approved telemedicine platforms, programs ([OCR Guidance](#))
- Referring immediate safety concerns to primary care provider or other local care provider
- Alternatives for planned safety assessment and endpoint collection that cannot occur via telephone or video call
  - Use of less crowded family health centers or home health for patients to have blood draws, electrocardiograms, and imaging away from the hospital
  - Use of local laboratories for blood draws
  - Endpoint collection via wearable sensors, clinician reported outcomes, Patient Reported Outcomes, and online cognitive tests
  - Questionnaires, adverse events, and other questions asked at study visits can be obtained via telephone
- Alternative distributions of Investigational product (IMP) shipment
  - Check state board of pharmacy guidelines
  - Examples include:



“The interview part is now conducted over the phone and I pick up the medication curbside. It’s not a huge difference but it’s convenient.”

- CTTI survey respondent

- Send study drug directly to patient from site
  - Package delivery services with signature
  - Home health for delivery and administration of parenteral products
  - Pick up investigational product from site, or hospital's outpatient pharmacy
- ▶ 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
- ▶ Provide resources for site to successfully conduct additional/new study activities required:
  - Provide additional training on platforms used for remote visits
  - Assess if there is appropriate compensation for remote work
  - Ensure site staff are able to telework where possible
    - Take everything home that they need
    - Work with IT to set up network access (including to electronic health records) from home computers or provide property passes to take laptops home
  - Create consistent practices to facilitate appropriate documentation
  - Develop strategies to adapt to limited access to ancillary services (radiology, surgery, cardiology, laboratories, etc.)
  - Remind study personnel to be mindful of surroundings, e.g., turn off any smart speakers
- ▶ Provide training
  - Test run the telehealth platforms
  - Train patients/caregivers and sites on platform
  - Create an appropriate environment – be mindful of surroundings
  - Know how to handle system failures
- ▶ Choosing the most appropriate telehealth application
  - The appropriate application of telehealth is often study specific
  - Think about the patient in the setting and what resources are available to pivot to virtual (e.g. in dermatology setting do you need a higher resolution virtual platform?)  
Also, ensure that patient population has access to and is comfortable with the telehealth application selected
  - Review site infrastructure
    - Does the site have existing infrastructure to support remote study activities?
    - Does the study already have some remote features?
  - Use available resources: institutions, IRBs, and patient groups have advice, tools and experience to provide assistance
- ▶ Document all changes made to visit, assessments, investigational product delivery

## 6. Switch to Remote Monitoring

- ▶ Onsite monitoring was delayed or suspended during pandemic
- ▶ FDA provides [guidance](#) to help expand the availability and capability of non-invasive remote monitoring devices to facilitate patient monitoring during COVID-19
- ▶ For global studies be aware of changes to regulatory guidance as reopening may change temporary allowances (e.g. GDPR waivers in Europe)
- ▶ Implement remote, risk-based monitoring
  - Prioritization of safety assessments and primary outcome measures
  - Appreciate what really needs to be monitored
    - Use a risk-based monitoring approach
- ▶ 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 [provide resources](#) above)
  - Secure file sharing
- ▶ Document all changes made to monitoring plan

## 7. Be Flexible

- ▶ 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
- ▶ Realizing “remote” does not need to be all or nothing
  - A complete removal of brick and mortar is not necessarily needed; rather, for some instances, it may be worth considering how to keep care centered around the site and physician while supporting patients more at home
- ▶ Monitoring: Be flexible with visit completions
- ▶ Platforms:
  - Be willing to use different virtual platforms, that are “non-public facing”
    - Use HIPAA-compliant platforms, if possible
    - OCR encourages providers to notify patients that third-party applications that are not HIPAA compliant potentially introduce privacy risks, and providers should enable all available encryption and privacy modes when using such applications (see HHS’ [Notification of Enforcement Discretion for Telehealth Remote Communications During the COVID-19 Nationwide Public Health Emergency](#) for more information)

- Appreciate that some countries may require which modality to use based on data protection policies/requirements
- ▶ Assessments:
  - Utilize virtual (audio/video) or remote visits at an alternate site
  - Consider whether remote lab collections/assessments can be done at nearby facilities or mobile labs
  - Consider electronic completion of PRO, QOL, other questionnaires
- ▶ Enrollment: Consider remote screening when feasible
- ▶ Informed Consent:
  - Recognize that options exist when consenting remotely (e-consent versus video application to walk through a consent)

## 8. Document Everything with COVID-19 Tag

- ▶ Many IRBs and contracts departments have created COVID-19–specific submission flag or process for amendments, questions, and new studies
  - Example: Does this request involve data, services, technology or initiatives related to the COVID-19 pandemic?
- ▶ Add COVID-19 tag to all documentation at patient and study levels
  - For reports to sponsor, IRB, and FDA when required
  - Note how restrictions related to COVID-19 led to the changes in study conduct, duration of those changes, and which and how trial participants were impacted (see FDA Guidance for additional details)
- ▶ Create standard template for recording items, such as missed assessments, with procedure for documenting and communicating

## BACKGROUND

The COVID-19 pandemic has turned our world upside down. In the clinical trials community, unprecedented disruptions are affecting nearly every aspect of research. As a leading public-private partnership, the [Clinical Trials Transformation Initiative \(CTTI\)](#) is directing several efforts to help the clinical trials ecosystem adapt and move forward despite these new challenges. Information on all CTTI's COVID-19 activities and resources is available [here](#).

## GATHERING EXPERIENCES AND BEST PRACTICES ACROSS THE ECOSYSTEM

Clinical trials have been disrupted by COVID-19 and the safety measures enacted to limit its spread. A series of [reports from Medidata](#) has tracked the impact of COVID-19 on new patients entering trials in 2020 compared to 2019. The United States experienced 66% and 83% decreases in March and April 2020, with some recovery to -74% shown in May 2020. The U.S. Food and Drug Administration [released guidance](#) on March 18, 2020, and continues to post updates, “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 on experiences and best practices regarding the FDA guidance on the conduct of clinical trials for medical products during the pandemic. An additional survey was launched on April 29 requesting feedback about experiences switching to remote or virtual visits. Both surveys were distributed via email to CTTI member organizations and contacts, via posts on Twitter and LinkedIn, and by redistribution from trade, media, and other organizations. The survey responses were collated and presented along with experiences from key stakeholders on two CTTI-hosted webinars about [identifying best practices for conducting clinical trials](#), and [solutions for switching to remote and virtual visits](#), during the COVID-19 pandemic.

CTTI aims to continuously update this playbook, as needed, to reflect ongoing experiences and lessons learned as clinical trials advance. If you would like to suggest an update to this document, please [contact us](#).

## 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](mailto: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](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>

COVID-19 and Clinical Trials: The Medidata Perspective:  
<https://www.medidata.com/en/insight/covid-19-and-clinical-trials-the-medidata-perspective/>

WCG Resource Center: COVID-19 and Clinical Trial Operations:  
<https://www.wcgclinical.com/covid-19/>

AMA's Telehealth Implementation [Playbook](#)

CMS' [General Provider Telehealth and Telemedicine Tool Kit](#)

## 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](http://www.ctti-clinicaltrials.org).