



Best Practices for Designing High-Quality, Diverse COVID-19 Trials

Collating insights from across the clinical trials ecosystem, the Clinical Trials Transformation Initiative (CTTI) identified eight best practices for designing and conducting COVID-19 treatment clinical trials.

This document details the findings from CTTI's work and expands on points highlighted during corresponding webinars (see [Background](#) for more information). While these best practices, comments, and quotes are specific to COVID-19 trials, CTTI recommends that these principles should be used for all clinical trials, in line with CTTI [Quality by Design recommendations](#).

◆◆◆BEST PRACTICES◆◆◆	
1	Learn from the Past & What's Being Done Now
2	Make the Time to Design Right, but Move Quickly
3	Adequately Power Your Trial
4	Randomize Your Trial
5	Maintain Human Research Protections
6	Collaborate on Study Design
7	Engage & Enroll Racial & Ethnic Minorities
8	Use Core Set of Inclusion & Exclusion Criteria & Endpoints

1. Learn from the Past & What's Being Done Now

- ▶ History has shown that reliable, known scientific methods are key to effective treatments. Landmark trials in infectious diseases – including pulmonary tuberculosis, AIDS, and Ebola – provide lessons that can be applied to COVID-19 trials.
- ▶ Do your homework to see what research is already underway or has already been done.
- ▶ Do not design and conduct a duplicative trial unless you have valid scientific justification.

2. Make the Time to Design Right, but Move Quickly

- ▶ Conduct upfront planning so that strategies can efficiently be deployed across sites.
- ▶ Rigorously evaluate study design to verify that planned activities and data collection are essential.
 - Commit to rigorously questioning all aspects of trial design, plan data collection, and capitalize on those opportunities to streamline the trial so that focus remains on the important scientific questions at hand.

“Trials must be done during the pandemic if we’re going to make progress. This comes down fundamentally to meticulous planning, quality by design, integrating data collection efforts into the ordinary work flow & determining what constitutes an objective for future trials.”

- Janet Woodcock, FDA, CDER

3. Adequately Power Your Trial

- ▶ Ensure your sample size will be able to answer the question asked when designing your trial. If needed, get statistical support.
- ▶ Consider whether there are competing trials with similar participants and how that may affect sample size.
- ▶ Planning for under-sampling (under-enrollment) is an impediment to obtaining reliable evidence.

“Rapid streamlined and robust clinical development processes offer the best hope of identifying the vaccines and therapeutic interventions that will give the most help to people all over the world in combating the COVID-19 pandemic.”

- Fergus Sweeney, EMA

The FDA conducted an analysis of all registered COVID-19 therapeutic trials globally and found [only 5% of experimental trial arms were designed to create actionable results](#) (randomized and adequately powered). Many of the trials had poor actual or planned enrollment.

4. Randomize Your Trial

- ▶ In an infectious disease with a wide range of outcomes that is straining the healthcare system, and where the standard of care may change over time and by region, it is particularly important to have a concurrent control group generated by randomization with which to make reliable comparisons.

[ICH E-10](#): It is well documented that untreated historical-control groups tend to have worse outcomes than an apparently similarly chosen control group in a randomized study, possibly reflecting a selection bias.

5. Maintain Human Research Protections

- ▶ Include provisions to protect trial participants through safety monitoring (e.g., consider use of a DMC).
- ▶ Consider the ethics of conducting trials that are unlikely to enroll enough patients to answer the scientific question.
- ▶ Only conclude efficacy based on sound evidence like randomization.
- ▶ Use a single IRB of record (sIRB) to streamline the process of IRB review and amendments, maintain uniform informed consent language, and reduce administrative burden on individual sites.
- ▶ Provide additional support (a “sIRB liaison” or “site start up concierge”) for inexperienced sites to navigate research training requirements and the sIRB process.

6. Collaborate on Study Design

- ▶ Sites and sponsors should collaborate and coordinate across all stakeholders to ensure a feasible protocol and avoid problems during trials.
- ▶ Diverse patients should be engaged as equal partners at the table early and often throughout the design and implementation of COVID-19 clinical trials. Specific strategies include involving patients in protocol development and in Steering Committee meetings
- ▶ Consider the health care context in which the trial will be conducted.
- ▶ Consider master protocol designs for all severities of COVID-19.

The [RECOVERY trial](#) used a coordinated approach, using a single regulatory agency (MHRA), a single Ethics Committee (IRB) that covers the whole country, and common contract with all the hospitals. They also prioritized resources:

- Chief Medical Officer: clinical trial enrollment is part of delivering clinical care
 - National Institute for Health Research Clinical Research Network: mobilized research nurses at every hospital
 - Department of Health: procured & supplied treatment
 - NHS Digital: access to linked national health data from multiple sources
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7. Engage & Enroll Racial & Ethnic Minorities

- ▶ Executive leadership within sponsors must commit to and reinforce strategies to engage diverse patient populations in COVID-19 clinical trials.
- ▶ Make a financial commitment.
- ▶ Protect upfront planning efforts to develop effective inclusion strategies.
- ▶ Evaluate strategies across trials and course-correct, as needed.
- ▶ Provide additional resources to healthcare organizations that serve as safety net hospitals and clinics for underserved patient populations, as they are likely to be especially overburdened.
- ▶ Identify trusted voices – partner with community organizations and leaders to disseminate information and build trust in clinical research.
- ▶ Proactively identify and respond to patients concerns (e.g. risk of exposure to COVID-19, safety of IMPs, privacy and confidentiality).
- ▶ Build reciprocal, long-term relations with community stakeholders.
- ▶ Actively challenge disinformation about COVID-19 and related treatments and prophylactics.

“ There is no “one-size-fits” all approach to overcoming these barriers in recruitment. The focus really must be on the patient and engaging them in trial design, logistics, recruitment....”

- Anand Shah, FDA, OC

[Northwell Health](#) proactively collected data about race, ethnicity, geography, and preferred language for 1,100 participants enrolled in seven clinical trials across 13 hospitals. This data allowed Northwell Health to closely monitor the accrual of diverse patient populations and plan ahead for diverse patient enrollment in out-patient vaccine trials.

8. Align on a Core Set of Inclusion & Exclusion Criteria & Endpoints

- ▶ Have a standardized inclusion/exclusion and outcome/metrics set for every disease phase (i.e., preventive, outpatient, inpatient, ICU);
- ▶ Make sure eligibility criteria are:
 - Unambiguous.
 - Consistent across for every disease phase.
 - Not unnecessarily restrictive.
- ▶ Outcomes should be:
 - Similarly captured across all trials and then used to model and compare across trials.
 - Simple and readily measured avoiding fancy laboratory facilities or tests that are not widely available.
 - Relevant across the spectrum of disease severity from patients who did not even have the disease to those who have died from the disease.

- Reflect understanding of the epidemiology of COVID-19 infection and to reflect patient and family priorities.
- Applicable in low-, middle-, and upper-income countries.

The [Comet Initiative](#) in the United Kingdom champions the notion of collecting a small set of core outcome data across all trials, regardless of what the primary or secondary outcomes for the particular trial are. Each trial would collect these core outcome measures so that there would be commonality across trials and the pooling and synthesis of data might be expedited.

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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. This playbook captures efforts focused on COVID-19 clinical trials.

In April 2020, CTTI conducted an analysis of COVID-19 treatment trials in ClinicalTrials.gov and convened experts and other key stakeholders to discuss best practices for designing these

types of trials via [a webinar](#) on April 23, 2020. In May, CTTI launched a public survey requesting feedback on experiences and best practices on how to engage racial and ethnic minority patient populations in COVID-19 clinical trials in several ways – 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 via another CTTI-hosted [webinar](#) on June 18.

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](#). Information on all of CTTI's COVID-19 activities and resources is available [here](#).

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.