



WORLDWIDE
CLINICAL TRIALS

COVID-19 CLINICAL TRIALS:

A Guidebook for Trial Design and Study Conduct

The COVID-19 pandemic has challenged the research world to think differently about the conduct of global clinical trials. Research has rapidly evolved to “virtual” environments, forcing sponsors and clinical research organizations (CROs) to think differently about the way in which clinical trials are approached in the areas of site selection, study start-up, patient recruitment, monitoring, safety oversight, and data integrity.

The information contained within this document may be useful to teams conducting or planning COVID-19 clinical studies at any phase.

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COVID-19 Clinical Trial Design and Conduct Guidebook Introduction

The global COVID-19 pandemic has prompted an unprecedented adjustment to the world of clinical trial development, review and approval timelines, visit management, investigational product supply chains, and reporting requirements.

As sponsors, investigators, and the CROs that support them come to terms with the clinical and operational concerns facing those hoping to conduct COVID-19-related research, Worldwide Clinical Trials has collected its “lessons learned” and expert input based on its ongoing experiences in trial development for COVID-19 studies.

This guidebook aims to provide other research organizations and related entities with valuable insight into effective study planning and execution in these extraordinary times.



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Worldwide Clinical Trials experts from functional Scientific Solutions, study design, operations, patient recruitment, and safety and regulatory teams built this guide to support the current COVID-19 trials we have underway and to advance global progress against the pandemic by facilitating thoughtful and productive research undertaken through other sponsors and CROs.

For more information, please review our COVID-19 resources at www.worldwide.com/covid-19-resources, or contact our experts through www.worldwide.com/contact-us/ to collaborate with us for customized support and research solutions.

DESIGNING STUDIES BASED ON DISEASE SEVERITY

Research is currently being undertaken across a broad spectrum of COVID-19 patients to include asymptomatic patients as well as those with acute respiratory distress syndrome (ARDS). Worldwide recommends tailoring the operational strategy to the severity of the patient population that the study is serving.



Mild or moderate cases are generally defined based on less severe clinical symptoms (fever, cough, discomfort, labored breathing) with no evidence of pneumonia and typically not requiring admission to the Intensive Care Unit (ICU).



Severe cases have typically been defined as development of ARDS, organ failure, or other symptoms severe enough to require ICU admission.

Severity-specific considerations may involve adjusting the frequency of visits required, investigator burden for laboratory samples or safety monitoring, patient record/reporting burden for outcome measures, accommodation of at-home or isolation-specific needs, and variation in patient medical history requirements. Additional adaptations should be considered for patient populations in mild/moderate versus severe disease categories—and what to do if a patient transitions from one group to the other during the study—for each of the sections in this guidebook.

Feasibility Assessments

As clinical trials make increasing use of virtual visits, technology-facilitated assessment tools, remote monitoring and local vendor laboratory services, geographic planning and site-specific characteristics become increasingly instrumental to the conduct and success of COVID-19 studies. By conducting thorough feasibility assessments prior to study launch, sponsors and CROs can ensure that COVID-19 trials are prepared for both likely and unlikely contingencies that may arise as the pandemic progresses.

Geographic Considerations

The geographic regions and clinical investigator sites utilized in COVID-19 trials are highly dependent upon the patient population and whether the sponsor is researching hypotheses regarding preventive measures, diagnostics, or treatment of the disease, as well as the mechanism of action of the compound under study.

Worldwide recommends leveraging a broad range of technologies to support predictive analytics to assist study teams in the selection of geographical regions (countries and states) best suited to patient populations.

For example, the graphic below demonstrates how digital tools can help track COVID-19 population hotspots and guide decision-making in site selection globally to ensure that any study undertaken in a given region (even down to localities in some areas) will have a sufficiently sized COVID-19 population to fulfill recruitment goals.

Figure 1. Predictive analytics and reliable global epidemiologic data combine to enable smart and up-to-date trial planning.

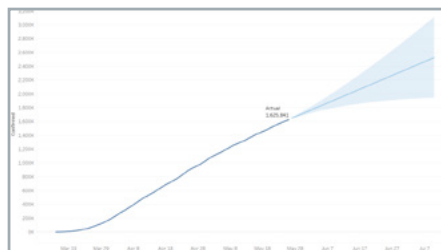
Local Laboratories

Many COVID-19 studies will require the use of local laboratories due to time requirements for testing and turnaround, especially in cases of severe disease, where fast results are essential to maintaining adequate standards of patient care.

To prepare for a range of potential COVID-19-related studies, consider developing a list of local labs or networks with local and regional laboratory hubs that have the capacity and the existing quality assurance and infrastructure to quickly scale up for clinical trial work. Mapping areas with sufficient laboratory support may facilitate site selection in advance of clinical investigator and site capability review.

Applying Powerful Analytics to Real-Time COVID-19 Data

- Geographic hotspots
- Estimates of future COVID-19 confirmed cases
- Country, state/province, and local level when available
- Daily updates
- Sources: WHO, CDC, ECDC, NHC, DXY, 1point3acres, Worldometers.info, BNO, state and national government health departments, and local media reports.



Site and Investigator Assessment

COVID-19 patients are seen by many different physicians, nurses, specialists, respiratory therapists, and residents who change daily depending upon hospital demands. Worldwide has experienced the best results when studies are driven by advanced trial management techniques, inclusive of a highly qualified team of top-notch, preferred vendor partners from global studies to coordinate study efforts among the various staff in the emergency departments, ICUs, wards, and technical services. This helps streamline study procedures and data collection while minimizing confusion and protocol deviations.

Even without vendor support, coordination and communication pathways at the site level must be established during feasibility checks. This helps ensure the site has a plan and an actionable method for conducting necessary study actions even under hectic circumstances.

Site Capability Assessment

These questions should help clinical trial teams identify regions and sites that are equipped to perform a study's required operations. These examples do not represent every possible way to assess sites and should be supplemented by study-specific questions:



What is the standard of care in different geographic regions?

- Will access to ventilators, personal protective equipment, trained healthcare providers, palliative care, etc., differ? If so, how might that impact study validity or ethical requirements?



How will the clinical investigator maintain oversight of the study?

- What qualifications and experience are required per the protocol?
- Is the site sufficiently staffed to enable study-specific oversight, or would additional research requirements reduce the standard of care the site can offer all patients?



Does this research facility support home healthcare activities when patients need to be seen at home?

- Will access to in-home staff visits or virtual visits be supportable in terms of staffing, technology, patient access to internet or telephone, etc.?



What are the regional requirements for enrollment when it cannot be done on site?

- Will differences among regional regulatory body requirements impact eligibility and enrollment consistency across study sites, and if so, is the impact likely to be systematic and meaningful?



Are patients being treated at a standard ICU (as opposed to ad hoc/quarantine centers) and do they have access to proper ventilators?

- How might site permanency impact staff and equipment resources, as well as competition for care and resources among study participants and non-participants?
- What are the site set-up, staff, and laboratory capabilities if the site is not a standard ICU? For example, where is the nearest hospital and ICU with ventilators? Is emergency transport planning in place and available for rapid use?



Are there competent local labs available for sample processing in cases where central labs are not feasible?

- Is the desired local laboratory able to follow quality standards and accommodate an increased sample volume to ensure streamlined sample processing for the study?



What is the average hospital stay for COVID-19 subjects depending on severity of the disease?

- How does the selected site compare in terms of expected average lengths of stay for patients with severe disease, and does the site's current performance raise concerns about its ability to accommodate research reporting burdens and a standardized study protocol?



Clinical Investigator Identification

It is critical that CRO partners have the ability to gather information in a central location for investigators that have expressed interest in participating in COVID-19 trials. Collecting the following information (tailored per your study-specific needs) may help identify a pool of investigators with many of the resources and experiences required for COVID-19 studies and allow faster site selection.

- 1 **All applicable contact information**
- 2 **Population accessible to investigator**
 - Mild/moderate COVID-19 patients
 - Severe COVID-19 patients
 - Post-COVID-19 patients
 - Adequate COVID-19 patient population available for study participation
- 3 **Investigational products/devices supportable at their facility**
 - Biologic agents such as antibodies and recombinant proteins
 - Anti-viral drugs
 - Anti-inflammatory drugs
 - Vaccine
 - Device
 - Diagnostic testing
 - Other
- 4 **Accessible resources and equipment**
 - Access to EMR
 - Access to ICU with ventilators
 - Personal protective equipment (PPE) available (N95 masks, gloves, etc.)
 - Consider study-specific requirements to ask investigators regarding quality and quantity of PPE. For example, are enough gloves available to change for each patient assessment? Are home-made cloth masks permissible PPE for staff?
 - Social distancing of beds available
- 5 **Training/expertise**
 - COVID-19 training
 - Infectious disease controls
 - Investigator qualifications, in good clinical practice (GCP) and infectious disease
- 6 **Informed consent support resources**
 - 24/7 availability of research staff to obtain informed consent forms from patients or family
 - Ability to obtain alternate methods of informed consent (e.g., e-consent, mobile/remote consent, phone consent, verbal consent, representative/agent consent)
 - Site standard operating procedures (SOPs) in place to obtain alternate methods of informed consent
- 7 **Ethics committees**
 - SOP for obtaining informed consent in emergent situations
 - Timeline for approval for COVID-19 studies
 - 1-2 business days
 - 3-5 business days
 - 5-10 business days
- 8 **Study start-up timeline**
 - Ability to activate within 2-4 weeks
 - No expedited start-up timeline available or unpredictable/unknown

Investigational Product

In the fast-paced drug development and clinical trial initiation environment COVID-19 has created, investigational product (IP) quality, management, and safety review cannot be compromised. Drug accountability is crucial for monitoring patient compliance and ensuring clinical trial data integrity.

The current clinical landscape may call for delayed or remote drug accountability processes to accommodate staff and resource limitations. Key questions must be addressed for proper IP management—with due adjustments to comply with regulatory requirements and patient safety safeguards—as performing drug accountability after the fact is a considerable risk both for patients and approval processes.

In addition to timing and accountability concerns, supply chain considerations and resource constraints may further impact the IP situation for certain studies. Consider the following in your IP-related feasibility assessments and protocol design:

- 1** | Where is the IP manufactured, sourced, and imported from, and how might resource constraints or supply chain interruptions in those areas affect product availability for all sites?
 - Is there a back-up facility or process in place for IP production and transport in case of unplanned interruptions?
 - Can you develop contingency plans for each stage of the supply chain?
- 2** | How will you ensure control of IP transport, both to sites and direct to home-based or quarantined patients?
- 3** | How will IP accountability be done (receipt, accountability, destruction, return, etc.)?
- 3** | Can the site coordinator manage IP accountability and send documentation to the internal clinical research associate for source data review (SDR) until source data verification (SDV) can be safely completed?
- 4** | Who will administer the IP and how (e.g., only the clinical investigator, or delegated study coordinators as well, by mouth, etc.)?
- 5** | How will IP storage, transport, and administration characteristics impact the feasibility assessments and requirements for sites, staff, local labs, and investigators?



Completing thorough feasibility assessments during study design and protocol planning phases can dramatically reduce the number of interruptions and delays a development program experiences. By conducting assessments that go one step beyond typical feasibility reviews to customize evaluations according to COVID-19-specific concerns, thoughtful preparation will set programs up for success.

Study Start-Up

Accelerated timelines and the international rush to identify vaccines, therapies, and additional natural history data on COVID-19 have resulted in expedited review accommodations by many regulatory bodies and trial oversight organizations. In many cases, COVID-19 studies currently take priority over review of studies in other indications. For example, Worldwide has witnessed Food and Drug Administration (FDA) investigational new drug (IND) application review timelines for COVID-19 trials to be as little as two business days. Likewise, central and local institutional review board (IRB) review timelines are also greatly expedited and may feature similar timelines.

At least in the short-term, sponsors can expect accelerated start-up timelines for COVID-19 work from:

- Regulatory bodies such as the FDA and EMA
- Review committees such as local and centralized IRBs
- Agencies and CROs supporting sponsors in clinical development programs
- Many local sites and research centers

While processes are expedited, study design requirements and ethical safeguards are still rigorous, making preparation, documentation, and compliance essential.

Regulatory Approval

FDA

The FDA has made a commitment to provide timely guidance and review supporting research and response efforts related to COVID-19. They have issued a guidance document on the conduct of trials investigating medical products during the pandemic, acknowledging the impact of the pandemic on typical processes while assuring the public that quality and good clinical practice will not be sacrificed for the sake of speed. In addition, the document provides recommendations and information to help guide expectations for other clinical research efforts underway during the pandemic.

European Medicines Agency (EMA)

The EMA has also announced its support for the submission of large, multinational trial protocols for the investigation of new treatments for COVID-19, also committing to expediting the development and approval of related treatments and vaccines. In addition, they have released related information supporting the continued commitment to existing clinical studies and drug development programs underway.

Sponsors are encouraged to consider the submission of COVID-19-related medicine applications for an accelerated Voluntary Harmonization Procedure (VHP) assessment when possible. Advanced contact with the agency (by emailing ncov@ema.europa.eu) can help CROs or sponsors determine whether a VHP is appropriate and may minimize delays during the review process. The EMA is currently waiving its fee for scientific advice and has expedited their response procedure.

Vendors and Sites

Once clinical investigator sites have been identified, CROs can expedite clinical trial agreements and budget agreements with selected sites, often completing start-up paperwork in 3-5 business days for COVID-19 trials. Sponsor and CRO collaboration can help modify agreement requirements that enable swifter contracting.

Training Requirements

After required reviews and formal site/vendor start-up agreements, sites and vendors must be properly trained and onboarded. Although many sites may have experience with infectious disease protocols, there are some elements of site and staff training specific to COVID-19 and related studies that should receive particular attention during the start-up procedures.



Project Team Assignment

Teams within Worldwide are dedicated to specific therapeutic areas of focus. Depending on the population of focus, the therapeutic specialty teams are then trained on the specifics related to the COVID-19 patient population and the unique operational requirements required when working with these types of studies.

Ensure that CRO-based functional teams are specifically educated in the impact that COVID-19 will have on their population so that they are equipped to apply their expertise to a new or altered study focus. This should be supplemented by thorough training in infectious disease trial design, protocol elements, and safety practices.



Investigator Brochures

In addition to the standard content available in investigator brochures, clinical staff and relevant vendors should have access to safety, mechanism of action, and prior testing or preclinical data that will help inform their participation. Elements specific to COVID-19 that have impacted study design, mechanism of action, preclinical results or IP effects in other populations, reporting requirements, or exceptions for testing and location of visits should be spelled out explicitly. This will help clinical participants understand not only how the protocol is similar to other studies they have conducted but also how it may differ and what disease-specific alterations they may encounter. FDA recommends that sponsors also prepare COVID-19-specific Investigator Brochures for drugs originally designed for other indications (example: cancer, autoimmune disease, pulmonary fibrosis) that are being repurposed for treatment of COVID-19.



Site COVID-19 Training

Sites and vendors should receive standardized COVID-19 education to ensure consistent disease-related knowledge across the project team, including study nurses and coordinators as feasible. Key elements for training may include topics such as:

- Known COVID-19 epidemiology
- Infectious disease management
- Safety practices and use of adequate personal protective equipment
- IP-specific protocols
- Remote monitoring practices (especially for CRAs)
- Protocol-specific considerations
- Resource management related to staff, ventilators, supportive medications, and PPE
- Answering patient and family questions
- Current best clinical practices for this evolving field
- Vendor-specific considerations, such as transport or sample processing needs germane to the protocol



By facilitating swift review processes and ensuring the entire study team is trained appropriately, study standardization is improved and the study can begin on an accelerated timeline, with no sacrifice in the quality of preparation.

Informed Consent

Due to the urgent and unpredictable nature of infectious disease admissions and complications, sites must be prepared for informed consent processes to take place at any time of the day or night, requiring study staff to be trained for all shifts. In studies dealing with severe COVID-19 cases, time pressures with critically ill patients affect the consent and enrollment process, and some patients may not be in a position to consent. Sites need clear, written procedures following local regulations for emergency consenting and legally authorized representatives if the patient is unable to provide informed consent.

Worldwide has experience working within a virtual environment when obtaining informed consent and utilizes trusted vendors to support us with these efforts. However, it should be noted that every country is different in its guidelines and ability to utilize e-consents and electronic documentation systems. Regional regulatory teams in global CRO networks can often provide country-specific guidance to maintain informed consent compliance.

Worldwide has extensive experience in the development of concise, efficient, and patient-focused informed consent documents, tailored to the needs of urgent and unpredictable consent situations. Abridged information sheets, separate or integrated, can be offered in addition to full, legally compliant informed consent documents. This aids with patient understanding, recruitment, and study procedure compliance.

FDA Guidance Related to Informed Consent

The FDA has provided specific guidance for cases of isolated patients in order to address infection control policies that prohibit removal of documents signed by a patient from their hospital room. Although written consent is still ideal, electronic methods of informed consent are considered acceptable and desirable to avoid concerns over infection control. When e-consent processes are not possible, standardized video conference procedures can be conducted, in which the patient is provided with a consent form, reviews it on the conference call and verbally confirms their willingness to participate. A witness must be on the call, and the patient must still sign their copy of the form.

Documentation of this informed consent can include attestations by witnesses and the investigator or a photograph of the signed document, together with attestation by the person submitting the form for study records, describing how it was obtained and what it is. In all possible cases, a copy of consent forms should enter the patient's trial source documents with notations on how it was obtained and the circumstances; if the original was not retained, you must provide the reasons for its absence and disposal (e.g., contamination).

If the patient is unable to provide informed consent and they have a legally authorized representative, this representative must provide consent in the patient's stead.



More detailed guidance on acceptable informed consent procedures for COVID-19 studies is provided in the FDA's *Guidance on the Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency*.

EMA Guidance for Informed Consent

In all cases, the EMA maintains that the informed consent procedure must be compliant with the trial protocol as well as with EU and national rules. While national approaches to exact consent procedures differ, regional advice should be sought to ensure that consent documentation that cannot leave the isolation room can be alternatively documented sufficiently for trial requirements. When physical records are not possible, oral consent in the presence of an impartial witness will usually suffice, provided the witness then signs and dates the informed consent document and the investigator records how the witness was selected. If possible, trial participants should submit a proper signed consent form later, when contamination danger has passed.

Legal representative consent is required for minors and participants who lack capacity to consent due to the severity of their illness (if allowable regionally). In all cases, the circumstances surrounding consent and alternative consent documentation should be recorded. All trials must comply with local consent regulations in the areas of participating sites.

Patient Recruitment and Retention

As with any clinical trial, patient recruitment and retention plans should be tailored to the sponsor, investigator, and—most importantly—the patient. In a time when the general public is frightened of contracting the disease, anxious about entering shared spaces or encountering people with the infection, and hoping for a vaccine or cure, clinical research programs must do everything possible to provide as much information and support to both investigative sites and patients alike.

Considerations for patient recruitment and retention—which in normal times are regarded as advanced when they take into account patient burden—must now also address the burden placed on research staff and study sites that must administer the procedures and facilitate follow-up in addition to caring for other patients in their units.

Beyond procedural burden and the reality of facilities with limited staff and equipment resources, trial designers must also consider how COVID-19 creates new demands on study eligibility, difficulty obtaining medical histories for emergent or unresponsive patients, challenges for informed consent processes, unique patient support and family education needs, shifting requirements for visit locations, and long-term follow-up challenges. With careful advanced planning and by learning from past studies conducted in emergent, highly infectious, or non-competent populations, many strategies can be adopted and transformed to meet the needs of modern COVID-19 research.

Eligibility Criteria and Related Considerations

Careful design of COVID-19 trials must not only enable the study to capture the most appropriate patients but must also safeguard data integrity and protect the trial against design flaws that may make its findings inconclusive or uninterpretable.

In the development of inclusion and exclusion criteria for your trials, consider some of the following concerns that may impact study design or affect implementation of common eligibility criteria:

- 1** | **How will COVID-19 diagnosis be confirmed?**
 - a. What tests are acceptable and available?
 - b. What is the turnaround time for COVID-19 test results, and does this vary by site?
- 2** | **How will healthy controls be monitored for infection to avoid confounding, while simultaneously minimizing their risk of contracting the illness?**
 - a. What qualifies as standard care for placebo-treated or control populations?
- 3** | **What is the target age of the patient population?**
 - a. Should the study target or avoid the most vulnerable populations?
 - b. For observation studies, healthy controls, and asymptomatic populations, how will age groups be best divided?
- 4** | **Are additional laboratory specimens required?**
 - a. How are common exclusionary laboratory parameters affected by COVID-19 infection or related illnesses?
- 5** | **When and where will eligibility be assessed—in the hospital, en route, in the ICU, at home?**
 - a. How will this vary over the time-course of the study?
 - b. What assumptions must be made to enable rapid treatment in cases where test results are not yet confirmed?
 - c. Must patients have a certain level of at-home connectivity for remote interactions?
- 6** | **What comorbidities are allowed?**
 - a. How will allowed comorbidities affect the ability to interpret IP efficacy as well as result generalizability?
- 7** | **What concurrent medications are permissible?**
 - a. How might common classes of medications impact IP efficacy from a pharmacodynamic standpoint?
 - b. Which drugs are most likely to interact negatively with the IP?
 - c. What ethical considerations come into play regarding concomitant medications for patients in high-risk COVID-19 groups, such as the elderly?
- 8** | **Will compassionate/emergency use criteria be proposed, and, if so, when do patients qualify?**
- 9** | **How will missing medical histories be dealt with for purposes of consent, enrollment, randomization, and treatment?**
- 10** | **What patient characteristics are most important for dose-finding studies, and how might criteria change after initial safety studies are complete?**

Patient Recruitment

Patients may be seen at testing facilities, such as clinics, pharmacies, community hubs, or drive-through tents, as well as in their own homes. This wide range of access points may either help or hinder recruitment efforts, depending on the network's preparation for diverse recruitment locations and visit or sample collection coordination, with many local points of patient interaction potentially rolling up to a single study site.

In some cases, clinicians may have the option to consent, screen, and enroll patients through remote access. While virtual-ready site locations can provide access to a greater patient pool in a venue that increases and improves patient comfort and convenience, the new nature of many of these recruitment venues and less controlled settings for study processes can also result in poorly standardized patient-investigator interactions, dramatically varied participant experiences, and opportunities for quality control concerns.

Consider these tips for improving patient recruitment for COVID-19 studies while ensuring standardized study information and consent procedures:



Provide local testing sites with study information that outlines available clinical trials when a patient tests positive for COVID-19.

- Information and promotional collateral, such as website, branding, and social media messaging, should be provided to investigative sites to enable effective recruitment.



Sites should be required, and financially supported, to conduct pre-screening of patients, as opposed to doing chart review.

- Patients that fail pre-screening may still be retained or engaged by having them register for the website/app; should their status change, they will be contacted or able to obtain additional screenings through the site.
- If the study and review boards allow, patients should have the ability to give their consent via electronic methods (e-consent) on the study recruitment webpage.



Develop trial-specific information accessible via a dedicated phone number or a study-specific recruitment website.

- The website can contain a pre-screener and access to a live clinician via a TeleVisit appointment (or through similar video chat software, provided patient privacy and healthcare law compliance can be assured) to ascertain if the patient qualifies for the study.
- This website can also be accessed by a family member and should contain vital study information that can be updated as necessary.



Develop a list of approved support vendors for patient recruitment and retention, to facilitate swift initiation for new studies using trusted consultants.

- Ensure that vendors on the pre-approved list have the desired e-consent, website/app, network, and distance learning capabilities required to facilitate rapid recruitment and ongoing digital support for study retention, even for studies that may be almost entirely remote.

Patient Retention

After baseline visits, the ongoing study period creates challenges for high-quality data collection. To secure patient participation for the duration of the study, CROs must take additional steps to maintain close contact with patients. There are several opportunities to improve retention and facilitate ongoing participation:

1

Providing IP delivery to the home, or to centers conducting laboratory testing for periodic assessments, can make it convenient for patients to continue complying.

- 2** | Regular telehealth visits to ease the burden on sites and offer a streamlined way to replace retention-boosting face-to-face communication affordably and efficiently. This approach also enables isolated or quarantined patients to participate without placing others at risk.
 - Telehealth can be used for virtually all studies with visits or follow-up taking place outside of the ICU. The patient and their family/caregiver can be onboarded prior to discharge from the hospital or enrollment center; visits post-discharge can be conducted via telemedicine.
- 3** | When possible, wearable devices with Bluetooth-enabled uploading technology can be used to monitor health data points or manage compliance. Virtual diaries and study apps offer additional touchpoint options that can engage patients from a distance.
- 4** | Standard retention strategies should not be overlooked just because of the current focus on new technologies and pandemic urgency. Traditional retention approaches include simple but sincere thank-you notes, acknowledgement for patients completing certain study milestones, nominal compensation when allowable, and periodic updates on study progress or results.

Post-Discharge Follow-up

Even in the best of circumstances, follow-up can create challenges for study staff, data quality, and compliance. This is complicated by the possibility that patients may have enrolled during stays in hospitals far from where they live, due to a rural home or a overwhelmed local hospital system. Even for those in close proximity to a study site, patients most likely to get severe COVID-19 tend to have considerable comorbidities and are often in poor health. Strategies to limit follow-up data collection, where possible, to phone calls may be implemented to mitigate risk of reinfection for both patients and investigators. To secure patient participation for the duration of the study, study coordinators must take additional steps to maintain close contact with patients once they leave the hospital, such as:

- Provide patients or their caregivers with a take-home information packet related to the study and the remaining follow-up contact they can expect.
- Increase documentation requirements for contact methods, such as by requesting secondary and tertiary contact information.
- Request contact information for the patient's primary care physicians or other physicians they see regularly, for cases in which study staff are unable to contact the patient.

Keeping Families and Caregivers Informed

Patient retention is often heavily influenced by the commitment of family members or caregivers. By providing a patient's key circle with up-to-date study information, continued patient participation may be encouraged and facilitated even without direct contact with study staff.

Materials and websites created for these tangential audiences must also receive IRB approval. In all cases, trial materials should communicate information on study purpose and its basic design.



As in all patient-facing communications, it is critical for family-focused materials to consider health literacy standards. Content should be written at an easily understood level, with images, charts, videos, and other graphic-oriented elements used to improve understanding.



All digital communications should be optimized for mobile devices. Considerations include content with fast access or downloadability as well as likely user familiarity with the overall look and feel of digital tools.

Trial Monitoring

Many monitoring requirements—be they for compliance, safety and risk reporting, or data management—do not disappear for COVID-19 trials. However, they may be adapted or forced into more remote or creative processes. Organizations that are experienced in remote monitoring, centralized reporting systems, and virtual data management may find themselves ahead of the curve in adopting COVID-19-friendly protocols.

Electronic solutions should enable remote review of electronic medical records, electronic data capture and related ePROs, as well as query resolution and data entry at the site. Studies will require dedicated solutions for HIPAA-compliant screen sharing and document processing. Solutions should support transmission of redacted subject source documentation, such as records or study notes, to the CRO's clinical research associates. Email and phone can be used to communicate frequently regarding subject safety, data integrity, and site staff support.

Site Monitoring

Regardless of the patient subtype the study may target, today's clinical research landscape is heavily dependent upon tools and technologies that support operating in a virtual environment. Remote monitoring can offer continuity of interaction with CRAs, promote social distancing regulation conformation, and even reduce monitoring costs by removing the expense of frequent site visits. When onsite monitoring is necessary, CRA assignments should be limited to local regions or states so that the CRA can drive to the site and avoid high-risk travel arrangements that may require subsequent quarantine measures.

Tips for facilitating successful remote monitoring include:



Train CRA teams on remote monitoring and how it impacts their relationship with sites as well as their reporting and documentation roles.



Use regular video conferencing with sites to build rapport, review site capabilities, and adjust logistics for trial success as necessary.



Ensure that monitors understand trial-specific outcomes and study variables they are required to monitor remotely and provide standards for obtaining the required information remotely through acceptable documentation procedures. These vary based on primary and secondary outcomes as well as the type of compound under study (vaccines, biologics, etc.).

Medical Monitoring

Patient safety is at the forefront of conducting any clinical trial, and COVID-19 trials are no exception. COVID-19-specific monitoring challenges may include:



Patients presenting with severe COVID-19 are typically seen in the ICU, where sites may experience a shortage of staff due to the unpredictability of workload (volume of patients presenting at a given time), as well as shortage of hospital beds and ventilators. This can compromise patient care as well as study monitoring and protocol compliance capabilities.



The clinical presentation and comorbidities of these patients require risk diagnosis and quick therapeutic intervention. Pre-existing conditions, medical history, and concomitant medications can easily be missed or, in the case of patients presenting without full competency or consciousness, be completely unknown.



Heavy data collection, monitoring, and reporting requirements may overburden some sites, which can reduce data quality and negatively impact patient care for study participants and other patients in the ICU. Areas with limited resources—even if they have large eligible patient populations—may not be desirable sites for studies.



Round-the-clock medical monitoring must be the default approach for COVID-19 studies, unless the protocol does not require stringent medical monitoring due to the nature of the IP under study or the severity of cases being treated.

Medical monitors will require access to the investigator brochure in order to understand the IP's mechanism of action, expected adverse events (AEs), and potential unexpected serious AEs. Because many IPs under investigation for COVID-19 treatment were originally developed for different therapeutic indications, it is critical that medical monitors receive a full safety background briefing for the compound.

Medical monitors for studies should be in frequent communication with the sponsor's medical monitor. This is especially important if a patient has a complication in the ICU and the compound was being developed for another indication. This helps medical monitors determine whether a complication may be expected due to the drug interaction from the compound, especially in the absence of prior safety data for COVID-related conditions.

Safety Reporting

COVID-19 knowledge is evolving rapidly. SAE and AE reporting are part of the effort to identify the efficacy of a procedure or compound under study and cannot be lessened or disregarded in the rush to conduct and complete trials. Safety reporting requirements depend heavily on the phase of research, the expected risk profile for an IP, the research setting, and the population under study.

Phase 2 COVID-19 Studies

When possible, sponsors should conduct research at permanent sites versus temporary care centers. In the ICU setting, rigorous safety data will likely be captured in the process of normal patient care and monitoring. However, consider avoiding “hotbed” cities that are overburdened, and approach research centers outside of these cities that can reliably capture AEs thoroughly and appropriately for patients at any level of disease severity.

Phase 3 COVID-19 Studies

As patient volume requirements expand for Phase 3 studies, and as additional safety data emerges from earlier-phase trials, it is more reasonable to consider selecting locations within heavily active COVID-19 regions. However, thorough consideration should still be given to specific site burden and even the time of year, which may further reduce resources as ventilators and ICU beds are in demand for patients with other seasonal viruses. Trials taking place in home healthcare settings and temporary facilities may also be considered but must also ensure that full safety reporting is not compromised.

FDA and EMA Guidance on Safety Reporting During COVID-19

Sponsors are expected to continue safety reporting in adherence to FDA, EU, and national legal frameworks. When protocol visits are reduced or postponed, and in all cases of planned protocol touchpoints, it is important that the investigator continue collecting AE information from the participant. This may require additional or alternative means, such as phone calls, e-diaries, or virtual check-ins.

Any changes to safety monitoring protocols or adjustments to data collection must be thoroughly documented. When these changes are anticipated, it is best to contact regulatory agencies in advance to discuss the most acceptable way to adjust safety reporting.

Risk Assessment

When designing a COVID-19 protocol, study teams may be able to identify safety risks and anticipate monitoring difficulties. Consider the following issues in pre-trial design approaches that may help mitigate risk and improve data collection by enabling adequate monitoring procedures to be in place from the beginning:

- 1** | Conduct a thorough Protocol Risk Assessment prior to first-subject-in to identify risks, both in protocol conduct and safety.
- 2** | Consider burden on research sites and how it may periodically change over the course of the study. What are alternative protocols or minimum emergency procedures/data collection you can pre-plan for times when resource constraints prevent ideal monitoring?
- 3** | Can the sponsor provide support via home healthcare nurses to reduce site burden and improve patient safety?
- 4** | How will the study deal with patients lost to follow-up?
- 5** | How will staff obtain medical history data when patients are brought in via ambulance, with no family to validate medical history?
- 6** | How will the protocol stratify groups without known medical history, and what additional monitoring may be necessary for these patients?
- 7** | How will expected and unexpected AE information or IP-specific risks be communicated to study sites?
- 8** | How will safety monitoring differ by level of disease severity, location of site, or nature of the IP?
- 9** | How might additional social distancing or isolation regulations affect planned site or medical monitoring procedures?

Data Management and Statistical Analysis

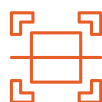
Clinical sites that are working with the COVID-19 patient population are already overwhelmed. It is imperative that CROs and sponsors plan data collection and management requirements that do not burden sites any more than necessary for safety and statistical data to meet regulatory requirements. Furthermore, electronic data collection is both good practice and essential to the safe and efficient conduct of clinical trials.

Data Recording and Management

Tips for COVID-19 trial data collection and management include:



Collect only data that is absolutely necessary; omit “nice-to-have” data.



Facilitate data entry by allowing sites to scan lab reports for central data entry on their behalf.



Ensure that the CRO, vendors, and sponsor teams are committed to expedited turnaround times for trial queries and data review points.



Minimize contamination risk for study staff and data analysts by implementing a cleaning procedure for shared tablets. If possible, utilize an electronic data entry system that enables investigators and study staff to use their own devices.



Utilize electronic trial filing systems to standardize data entry and ensure electronic back-up of patient-specific data.



Make data cutoffs clear and communicate data entry deadlines to sites in advance.



Perform a live walkthrough of the electronic case reporting system to save time and answer potential site questions before they become concerns.



Offer site-specific support for locations struggling to meet data entry requirements due to fluctuating site burden for clinical care.



Consider what can be tracked centrally rather than locally (for example, viral load). When it is possible to remove burden from local study sites and labs to a less-overwhelmed central review process, do so.

Statistical Analysis

Once a protocol is finalized, the statistical analysis plan (SAP) can be developed. In many cases, the expedition of COVID-19 studies has led to accelerated phase advancement, requiring even Phase 2 studies to include statistical analyses more common in Phase 1 studies. This allows faster advancement of studies without compromising data analysis. In order for this to work, however, statistical vendors or teams must commit to turnaround of fast topline result delivery (for example, within 1 week). This facilitates faster decision-making regarding continuation of a trial and provides enough data to determine whether adjustments may be required for more successful future protocol procedures.

Additional considerations to improve SAP efficiency, protect staff health, and safeguard statistical validity of COVID-19 studies include:

- 1 | Utilize a uniform platform for data systems to minimize complexity for investigators and site staff performing data entry.
- 2 | Optimize speed of data transport and the process for setting up technology systems by using vendors with existing speed-based procedures in place.
- 3 | Provide thorough training via remote e-learning to ensure proper site understanding of data requirements.
- 4 | Schedule a dry run of the Table, Figure, and Listing data analysis plans well in advance.

Conclusion

COVID-19 has forced a change in ongoing clinical trials and demanded the development of new ways to operationalize clinical trials moving forward. Many previously avant-garde practices in clinical trial design and execution—such as e-consent forms, remote monitoring, and single-system digitized trial documentation—have now become the gold standard for COVID-19-era studies. It is likely that many practices adopted during these extraordinary times will permanently change the world of clinical research.

At Worldwide, we've taken a step-by-step approach to offset any negative impacts of COVID-19 on clinical trial operations and become a proactive leader in the development of COVID-19 studies to minimize disruption and speed progress in search of a vaccine or therapy.

It is our hope that this guidebook will be informative and serve as a practical tool for improving and streamlining the process of initiating and successfully maintaining COVID-19 clinical trials in these uncertain times. For trials requiring study rescue services or for sponsors preparing to design and launch a new program, consider Worldwide.



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Worldwide Clinical Trials, at your service. *Whether we're refining study operation approaches or innovating solutions to adapt to unforeseen shifts in supply or site resources, Worldwide has the agility and adaptability to keep your project moving forward.*

[Talk to a Worldwide expert today](#) to ensure your clinical trial is designed intelligently and managed with the flexibility and expertise that COVID-19-era studies demand.