

Perspective

Clinical trial visits in the age of COVID-19: implementation of research participant safety measures

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Received: 03 October 2020

Accepted: 05 December 2020

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ABSTRACT

The COVID-19 pandemic is having a major impact on how current clinical trials are being conducted in the United States. Researchers have experienced the effects of COVID-19 through the halting and delaying of clinical trials, the lack of personal protection equipment (PPE), the closing of clinical sites, and a decrease in participant recruitment. Many clinical trials will have more missing data because of a participant's inability to attend in-person visits, discontinuation of trial activities, or interruption of time-sensitive study collection data due to COVID-19. All of these events affect the data quality of trials. Government agencies such as the Food and Drug Administration (FDA), centers for disease control and prevention (CDC), and National Institutes Of Health (NIH) have issued recommendations for investigators conducting clinical trials to combat the spread of COVID-19 and to maintain data integrity. Institutions sponsoring clinical trials have also provided guidelines to continue, modify, or pause research studies that are essential to ensure participant and research team safety. Key recommendations include implementing telehealth appointments, wearing a protective mask and face shield, quarantining for 14 days if exposed to COVID-19 or having travelled, and, if possible, maintaining a 6-foot distance. It is also recommended that investigators implement COVID-19 screening questionnaires prior to and during on-site visits. This includes participants and research personnel completing a temperature check and questionnaire screen before in-person data collection. This article will discuss the challenges encountered by researchers conducting clinical trials and provide resources and examples to assist investigators during the COVID-19 pandemic.

Keywords: COVID-19, Clinical trials, Patient safety recommendations

INTRODUCTION

The coronavirus disease of 2019 (COVID-19) was named a global pandemic by the World Health Organization (WHO) as of March 2020.¹ The source of COVID-19 was first discovered in China in December 2019 as a novel virus later termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 has been identified as a virus in the same family (*Coronaviridae*) and genus (β -CoV) as middle east respiratory syndrome coronavirus (MERS-CoV) of 2012 and SARS-CoV of

2002.² Though these three viruses contain large positive single stranded ribonucleic acid (RNA) and share similar genetic characteristics, SARS-CoV-2 has been revealed to be more transmittable and less pathogenetic than either MERS-CoV or SARS-CoV.^{2,3} The transmission of SARS-CoV-2 from human-to-human can be carried out through respiratory droplets, direct human contact, or indirect contact through contaminated objects.^{1,2} The wide spread of SARS-CoV-2 and the increasing cases of COVID-19 have led to challenges for ongoing clinical trials.⁴

Participants in clinical trials should be screened for common symptoms of COVID-19 that include fever, cough, dyspnea, fatigue, muscle pain, and diarrhea. COVID-19 has presented in a broad range of patients from asymptomatic individuals, to those with moderate symptoms, and to those with severe symptoms that may lead to death.^{1,3} Diagnostic testing has been developed for the detection of viral infection by reverse transcription polymerase chain reaction (RT-PCR) by using nasopharyngeal or oropharyngeal swab samples.⁵ There are currently three vaccines against SARS-CoV-2 approved for emergency use by the Food and Drug Administration (FDA) that are available to the public and multiple vaccine clinical trials are underway. Other COVID-19 clinical trials are investigating the use of antiviral drugs such as remdesivir and chloroquine/hydroxychloroquine, convalescent plasma, and antibiotics.^{1,5} Since there is no standard treatment for COVID-19, preventive measures such as social distancing, mandatory masking, and telemedicine have been initiated in order to reduce the spread of the virus that has affected the way clinical trials are conducted.⁶⁻⁸

Investigators of clinical trials are left with difficult decisions to continue, modify, or even momentarily stop the study due to COVID-19. Researchers should decide whether or not a clinical trial should continue based upon participant safety, the benefit-risk assessment, local and national regulations, and availability of personnel and research sites.^{9,10} Investigators will also need to consider how COVID-19 may affect the data collected from modified protocols, the efficacy of the treatment or device being tested, and patient safety outcomes when on treatment.⁴ In this review, we summarize the challenges encountered by clinical trials due to COVID-19 and highlight important research participant safety recommendations for clinical trials provided by the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), U. S. FDA, and our own institutional guidance from the University of Kansas Medical Center (KUMC).

CHALLENGES

The COVID-19 pandemic has created a multitude of barriers for clinical trials to sustain their typical functions. These have included complete suspension of research activities at clinical sites, stay-at-home orders preventing staff and participants from traveling to clinics, supply chain disruption, increased supply costs, staffing difficulties due to illness or virus exposures requiring extended quarantine, decreased participant pools from canceled hospital and clinic visits, participant noncompliance or fear of leaving home, mental and physical health concerns, lack of appropriate personal protective equipment (PPE), lack of appropriate cleaning and sanitation supplies, and navigating frequently changing regulatory guidelines.^{10,11}

One of the first challenges researchers faced as the pandemic progressed was a halt to research operations at most facilities in the U.S. The temporary suspension of research activities allowed time to implement additional safety measures and obtain required supplies.¹²

With an increasing proportion of the population either infected with the coronavirus or having a close exposure to an infected person, many businesses have been unable to stay fully staffed to maintain operations at a normal level. Local municipalities and some states instituted mandatory stay-at-home orders for residents and nonessential businesses.¹³ This has led to decreased production, shipping delays, and in some cases increased costs for supplies. Increased demand for products such as disinfectants, cleaning supplies, face masks, respirators, face shields, gloves, and medical gowns also made it difficult to procure the required cleaning and safety equipment needed to resume clinical research operations.¹⁴ Some investigators have had to search for new suppliers, borrow from colleagues, or partner with local organizations and businesses to obtain supplies. Such issues require a careful analysis of the study budget when considering orders of new supplies and those that have increased in price.

Research participant recruitment and retention has been another challenge for investigators during the pandemic. As hospitals and clinics canceled elective procedures and routine office visits or allowed for only telehealth communications, clinical researchers were left without the typical source of patients on site to engage in studies. Recruitment methods and informed consent were changed to primarily telehealth engagements until patients began returning to the hospital clinics.¹⁵ Investigators needed to address research participants' new apprehensions about being in a study that involves clinical research visits with the concerns for COVID-19. Some individuals continue to be reluctant to leave home for nonessential activities, while others are seeking reassurance that their health and safety are protected when participating in the study.¹⁶ By having a specific safety plan before continuing research operations, participants' worried about catching the virus during the research study can be advised of all the extra steps the staff are implementing to prevent the spread of the virus and assured by these procedures.

Of utmost concern for investigators is ensuring research participant safety at this time of increased risk of exposure to a novel virus. Those studying vulnerable populations that are highly susceptible to a severe reaction to the coronavirus have an even greater challenge to protect those individuals when they visit a research clinic. It requires careful planning and review of all regulatory authority guidelines to prepare for continuing research efforts, accounting for all possible points of exposure while a subject is on site participating in research activities. The current COVID-19 specific guidance from the FDA, CDC, NIH, and KUMC are summarized below.

FEDERAL SAFETY PROTOCOL RECOMMENDATIONS FOR COVID-19

In March of 2020, the FDA issued guidelines on the conduct of clinical trials during the COVID-19 pandemic, and institutes within the NIH provided additional guidance.¹⁷ These guidelines provided greater flexibility to the patient and the caregiver so that they could more easily participate in clinical trials during the pandemic. Safety guidelines were developed to protect both the participants and the research team during a clinical trial to prevent the spread of COVID-19.⁷ Investigators used creative methods such as obtaining consents from subjects by mail to reduce exposure to COVID-19. Investigators were allowed to implement accommodations to maintain continuity of care for their patients who were being treated during trials. If a clinical trial site's policies and practices varied from the guidance, researchers were encouraged to contact the funding agency to determine the actual plan.

U.S. government resources are available online for all researchers to review. The two main web sites are: coronavirus.gov (<https://www.coronavirus.gov>), and government response to coronavirus, COVID-19 (<https://www.usa.gov/coronavirus>). The first website is sponsored by the CDC, Federal Emergency Management Agency (FEMA), and the White House. On this website there is important information on how to prepare and protect researchers from COVID-19 and what to do if they become ill. The second website includes the top U. S. government websites for COVID-19 information. For researchers, the links to information on COVID-19 health and safety are helpful depending on the population that is being investigated. For instance, if the clinical trial concerns aging, the website related to COVID-19 and community living for older adults would provide information concerning the increased risk of residents of long-term care facilities and how to prevent exposure to COVID-19.

The CDC has specific COVID-19 infection control guidance for healthcare professionals that should be reviewed by researchers conducting clinical trials.¹⁸ These guidelines have many categories from using PPE to guidelines for hand hygiene. Table 1 is a list of the topics reviewed on the CDC website related to COVID-19 infection control and each of these topics has numerous subcategories for more detailed information.¹⁸ For researchers conducting a clinical trial, reviewing infection control guidance, PPE supplies, and potential exposure at work would be essential before collecting data in person.

Another important resource for researchers conducting clinical trials is the NIH COVID-19 website.⁷ This site provides the latest information related to public health from the CDC and research from NIH. There is a comprehensive list of all clinical trials currently from three sites - clinicaltrials.gov: federally funded clinical studies related to COVID-19; WHO Trial Registry Network: COVID-19 studies from the International Clinical Trials

Registry Platform (ICTRP) database; and NIH: COVID-19 treatment guidelines. Since COVID-19 pandemic is an emerging, rapidly changing situation, the NIH website is an excellent location for researchers who need to keep up to date. A researcher can sign up to get COVID-19 updates from NIH as well as specific NIH director's blog posts.

INSTITUTIONAL GUIDANCE FROM THE UNIVERSITY OF KANSAS MEDICAL CENTER

Phases

To mitigate the spread of SARS-CoV-2, University of Kansas Medical Center (KUMC) followed the guidelines of the CDC, state of Kansas, and local agencies and provided essential institutional guidance for clinical research throughout the following phases during the COVID-19 pandemic: shelter-in-place phase; and phases one, two, and three in the Ad Astra: a plan to reopen Kansas.¹⁹

General guidelines and travel guidelines

On 17 March 2020, following the declaration of the COVID-19 pandemic, the KUMC campus was depopulated and all the employees were asked to work from home to allow for social distancing. The KUMC Office of the Vice Chancellor for research issued 60-day temporary restrictions on human subject research to minimize the risk of spreading SARS-CoV-2 through interactions with human participants. All nonessential research activities that required personnel to be on campus were suspended, including closure of the basic research laboratories and suspension of new enrollment for clinical studies that require direct person-to-person interactions that did not offer direct therapeutic benefits to study subjects. In-person interactions were discontinued unless study procedures were modified to use alternative methods for data collection. Clinical studies that offered therapeutic benefit (drugs or devices) to study participants were continued; however alternative plans for study visits were considered. Essential research activities were defined as: critical, long-term studies that would have to be repeated if interrupted or if time-sensitive data collection were to be impacted; caring for animals, cell lines, or other perishable organisms; and maintaining equipment that cannot be shut down temporarily.²⁰ Safety plans were developed, and modifications to the study protocols were approved by the Institutional Review Board (IRB) to ensure the health and safety of research personnel and participants. In addition, a travel restriction policy was initiated, and all domestic and international business-related travel and attendance at meetings and conferences was immediately discontinued. Personal travel was strongly discouraged, and a 14-day quarantine was mandated for traveling to high-risk areas.

When Kansas entered phase one of the Ad Astra plan, KUMC began preparing to open basic research laboratories and reboot clinical research. Aligned with the infection control guidelines from the CDC, Kansas

Department of Health and Environment (KDHE), and Wyandotte County Health Department, the KUMC general guidelines for COVID-19 prevention in research laboratories and clinical research were released on 01 May 2020, and included research personnel safety, patient safety, and operating a safe laboratory/research facility.^{6,21} Each research team developed specific safety plans before approval to reopen was granted. All research employees were required to review the guidelines and complete “returning to campus safely” training prior to their return.

Research personnel are now required to check their temperature daily, wear a surgical mask, maintain social distancing, minimize time around other people, handwash frequently, sanitize workspace surface areas before and after each use, and stay home if experiencing any COVID-19 related symptoms.

For clinical research, investigators are encouraged to conduct all visits by telemedicine if possible. Depending on the level of risk, guidance for use of PPE for research participant interactions was provided. For example, for low-risk procedures such as a blood draw or questionnaires, surgical mask, face shield, and gloves are required for research personnel and a surgical mask is required for the participant. For moderate risk procedures such as spirometry, nasopharyngeal swab, or interaction with a COVID-positive patient after recovery/quarantine period, droplet precautions using surgical mask, gloves, eye protection and gown are required. For high risk procedures such as sputum induction, bronchoscopy, or interaction with a COVID-positive patient during active infection, aerosol-generating procedure precautions are required - using N95 mask or powered air purifying respirator (PAPR), gloves, eye protection, gown and the visit must be conducted in a negative pressure room.

Participant and research staff safety

The health and safety of subjects and the research team involved in clinical research is of the utmost importance during the COVID-19 pandemic. In addition to the safety measures discussed above, it is mandated that subjects and research members be actively screened for temperature, travel history, COVID-19 related symptoms, and close contact with any COVID-19 positive persons on the day before and on the day of the study visit. Visitor restrictions are implemented; no guests are allowed during the study visit unless the participant is disabled. All the study participants are required to wear a surgical mask during the visit. Procedures are in place in the event that a positive COVID-19 case is reported on-site. The rooms where the study visits are conducted must be appropriately decontaminated after each visit, including all working surfaces, door handles, faucets, and instruments.

After careful analysis of each entity’s new requirements to prevent transmission of COVID-19 among research staff and participants, a written procedure specific to our clinical trial protocol was prepared to account for all staff and participant safety measures necessary for in-person clinical research activities with high-risk individuals. In

addition, a safety procedure checklist was created for use during study visits to ensure that all staff follow the set protocol throughout each clinical trial visit. The study manager is responsible for seeing that each item is accounted for as tests are administered (Annexure 1).

To prevent those who are ill from coming to the research center, a COVID-19 symptom screening assessment was developed. A script for pre-screening research participants via telephone is used the day before their study visit as well as an in-person screening questionnaire when they arrive at the clinical research center. In addition to the questionnaire, a body temperature evaluation occurs at the building entrance, and participants are provided with a surgical mask and hand sanitizer. Likewise, all staff complete the symptom screening questionnaire the day before and day of meeting with any research participants. In the event that a participant or staff member is positive for any symptoms or exposures, they are asked to quarantine at home or return home if discovered while on site (Annexure 2).

Table 1: CDC website topics available for researchers related to COVID-19^a.

Testing
Clinical Care
Infection Control Guidance
Optimize PPE Supply
Potential Exposure at Work
First Responder Guidance
Preparedness Tools
Guidance for U.S. Facilities
Framework for Non-Covid-19 Care
Guidance for Non-U.S Facilities
Veterinary Clinics

^aCDC (August 16, 2020). Information for Healthcare Professionals about Coronavirus.¹⁸

CONCLUSION

During this COVID-19 pandemic, assuring the safety and health of study participants and the research team is imperative when conducting clinical trials. It is important to follow and implement governmental, state, local, and institutional guidelines in order to prevent the spread of the virus, despite the difficulty of keeping abreast of all the regulations. This article provides helpful suggestions and recommendations to investigators conducting clinical trials during this pandemic to ensure a safe environment, prevent the spread of the virus, and still conduct a successful clinical trial.

Funding: The study was funded by the Department of Health and Human Services, National Institutes of Health, National Institute on Aging, Grant Number: 1R01AG054486-01A1. Trial registration: ClinicalTrials.gov Identifier: NCT03133793
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Krueger KJ, Rahman F, Shen Q, Hiebert JB, Pierce JD. Clinical trial visits in the age of COVID-19: implementation of research participant safety measures. *Int J Clin Trials* 2021;8(2):167-73.

ANNEXURE 1

Clinical trial COVID-19 safety checklist

Day prior to scheduled visit

- Study team members monitor their body temperature (must be <100.4 F).
- Study team members complete Covid-19 symptom screening questionnaire.
- Call study participant for appointment reminder and complete Covid-19 symptom screening questions.
- Save a copy of all screening questionnaires in a secure location.

At clinical trial site: prior to participant arrival

- Study team members bring the minimum necessary items into the building to prevent contamination of personal belongings.
- Study team members screened for body temperature and symptoms at entry checkpoint.
- Study team members complete Covid-19 symptom screening questionnaire.
- Study team members wear appropriate PPE: gloves, face mask, eye protection, lab coat or other covering.
- Sanitize all contact surfaces in exam room prior to bringing in study equipment and supplies: tables, chairs, stools, counters, bed, door handles, cabinet handles, faucet handles, light switch.
- Check for and secure an adequate supply of gloves and sanitizing wipes in exam room.
- Set up equipment and materials for study participant.
- Wait for the participant to arrive at the front door and administer Covid-19 screening questionnaire after they pass the body temperature checkpoint. (If positive symptoms or temperature, send them home and advise them to contact their primary care provider)

At clinical trial site: during study visit

- Provide a face mask for the participant to wear during the study visit.
- Use gloves for all procedures, changing gloves between tasks and when entering/exiting exam room.
- Wash hands before donning gloves using appropriate handwashing procedure.
- Wash hands after removing gloves using appropriate handwashing procedure.
- Sanitize all surfaces between participant appointments.
- Place all Covid-19 symptom screening questionnaires in a secure location.

At clinical trial site: after participant departure

- Sanitize all procedure room surfaces and equipment, then secure equipment in storage.
- Continue to wear face mask and clean gloves until exiting the building.

After exiting the building

- Remove face mask and gloves at personal vehicle once away from other people, dispose of PPE.
- Use sanitizing wipes and/or hand sanitizer to clean hands after removing PPE.
- Once home, leave shoes at the door, remove clothing for laundering, and wash hands and shower.
- Continue following public health best practices as advised, including wearing a face mask in public, physical distancing, frequent handwashing, and general wellness practices.

ANNEXURE 2

COVID-19 clinical trial screening form

Participant Name: _____ **Participant ID:** _____

Study ID: _____ **Date:** _____

Staff Member Completing Screening Form: _____

Ask participants if they are experiencing any of the following symptoms related to COVID-19:

Symptom	Yes	No	If yes, describe
Fever (≥ 100.4 F)			
Cough			
Chills or shaking			
Shortness of breath			
Difficulty breathing			
Fatigue			
Muscle pain or body aches			
Weakness			
Headache			
Loss of taste or smell			
Sore throat			
Congestion or runny nose			
Nausea or vomiting			
Diarrhea			
Skin/Vascular rash on extremities			
Persistent pain or pressure in the chest			

	Yes	No
Have you been in close contact with a person known to have coronavirus?		
Have you traveled in the last 30 days? If yes, describe below the location, mode of travel, and dates.		

Additional Information: _____

Is the research participant permitted to come to their scheduled clinical study visit? (Circle One) **YES / NO**