



# COVID-19's Impact on Clinical Research

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## Key Findings

- Research activities were paused in the beginning of the COVID-19 pandemic, which allowed the integrity of clinical trials to be maintained due to regulatory agencies implementing appropriate and timely guidance documents.
- Research regulatory agencies, such as the Food and Drug Administration (FDA), released more than 70 guidance documents related to conducting clinical research during the COVID-19 pandemic and continues to update these periodically.
- Guidance documents released cover a variety of topics and select audiences (i.e., sponsors, investigators, and sites).

## Introduction

The World Health Organization (WHO) classified COVID-19 as a global pandemic on March 11, 2020.<sup>1</sup> The immediate result was to prompt research regulatory bodies to act fast and deliver effective regulations and guidance documents to support clinical research and the continuation of clinical trials.

The COVID-19 pandemic disrupted numerous clinical trials in the beginning of 2020 mainly because data collection activities were suspended.<sup>2</sup> In March 2020, a survey conducted in the United States concluded that roughly 39% of US clinical research sites were expecting patients to be less likely to enroll in new clinical research studies.<sup>3</sup> Thus, the pandemic prompted clinical trials to change how study activities were completed and created a need for new clinical trials focused on the COVID-19 pandemic.<sup>4</sup>

Regulatory intervention would be required to correctly implement and address the changes needed. Clinical research-related regulatory authorities, such as the Food and Drug Administration (FDA), began to provide guidance documents that applied both to the COVID-19 pandemic and to future pandemics or epidemics.<sup>5</sup> Therefore, elements of clinical trials such as study startups, study visits, protocols, and end points would require alterations to best fit the new regulations.<sup>6</sup> By pausing research activities at the beginning of the pandemic, study personnel were able to maintain the integrity of clinical trials by allowing sufficient time for federal agencies (FDA and Office of Human Research Protections [OHRP]) and institutional review boards (IRBs) to provide updated guidance documents.<sup>7,8</sup>

**Methods**

First, we searched through the US clinical research-related regulatory agency websites related to COVID-19, specifically OHRP and FDA. Through filtering and selective search terms, we narrowed the search to relevant articles associated with the research question at hand. Frequently used terminology across all avenues of search engines included: “clinical research and COVID-19,” “research guidelines during COVID-19,” and “COVID-19 guidances.” Next, we used Campbell University’s Library ONE Search and ProQuest databases to obtain additional published information from medical journals and published documents. Search terms used in One Search included “COVID-19 regulations AND Clinical Research,” “SARS-COV2 AND regulatory guidelines AND clinical research,” and “research guidelines during COVID-19/ SARS-COV2.” Last, to provide a personal touch to this data, we interviewed a regulatory coordinator to get an inside perspective on how COVID-19 affected daily work at the site level. This methods search was conducted in Fall of 2020. See Table 1 for reference.

**Table 1. Key search terms**

Source	Search Terms	Results
ONE Search	COVID-19 regulations AND Clinical Research Filter: journals	170
ONE Search	research guidelines during COVID-19 Filter: 2019–2020, Government Documents	118
ONE Search	SARS-COV 2 AND Regulatory Guidelines AND Clinical Research Filter: journals	4
ONE Search	research guidelines during SARS-COV2 Filter: 2019–2020, Government Documents	1

**Results**

**History**

The COVID-19 virus began to spread throughout the People’s Republic of China in December 2019 and eventually became a pandemic by early 2020.<sup>9</sup> Multiple social restrictions were put in place globally to slow the progression of the viral outbreak; these included quarantine, social distancing, and use of face masks.<sup>10</sup> The United States implemented the same restrictions once they became aware of the effects of COVID-19.<sup>10</sup> The purpose of the restrictions is to slow the spread of COVID-19 thus flattening the curve of infection overall.<sup>11</sup> History has shown that reducing contact with other individuals during a time of mass infection limits the spread of viruses such as the 2009 H1N1 influenza.<sup>12</sup>

The COVID-19 pandemic inevitably affected the healthcare industry, including facilities that conduct clinical research.

Unfortunately, the COVID-19 pandemic disrupted over 350,000 clinical research trials.<sup>13,14</sup> For example, US health care systems implemented guidance to protect patients and health care professionals from contracting COVID-19. Conduct of research in a safe environment is very important to clinical research sites, so site study personnel had to change procedures and protocols to continue research in a safe and feasible way for everyone.

At the research site level, in a brief interview with a clinical research regulatory coordinator on September 16, 2020, the regulatory coordinator noted additional challenges for sites based in North Carolina that arose when the Governor of North Carolina created the initial Executive Order 116, which “[declared] a state of emergency and [began] the work from the home ordinance.”<sup>15</sup> Consequently, most study personnel experienced shorter hours in the office and increased workloads because of protocol deviations and the onboarding of additional COVID-19-related clinical research trials. The interviewee describes the complications she faced, including an inability to access certain documents from her personal computer to complete her tasks when she worked from home rather than in the office. Such obstacles caused office work such as “filing, obtaining wet signatures, and recording protocol deviations” to be delayed, thus creating more work when getting back into the office. The transition of research during a pandemic was difficult for all study personnel, yet research has continued despite the challenges.

Two years later and still in a pandemic, clinical research sites are experiencing increased workload, staffing shortages, and recruitment issues. Most sites continue the traditional style of research, while other sites have decided to implement new practices, such as digital filing or remote office work, to avoid initial challenges that they had experienced at the beginning of the pandemic. Recruitment and retention have decreased for on-site research continuously throughout the COVID-19 pandemic for several reasons, including vaccination requirements and travel restrictions. However, some sites have alleviated restraints on recruitment by offering televisits to study patients. All the challenges faced during this pandemic have helped research move toward the future in a more safe and flexible manner for patients, families of patients, caregivers of patients, and study personnel.

**Development of Guidance Documents for Clinical Research by the FDA and OHRP**

The FDA quickly realized that the COVID-19 pandemic would affect all aspects of clinical research.<sup>16</sup> In the attempt to reduce the challenges that clinical research is facing, the FDA and OHRP gave many directions by developing or revising existing guidance documents for clinical researchers.<sup>16</sup>

The title 45 Code of Federal Regulations (CFR) part 46 and OHRP's "Effects of Disasters on Human Research Protections Programs" are two documents released before the COVID-19 pandemic and are important documents that highlight the need for developing relevant guidance documents for clinical research throughout a health emergency like the COVID-19 pandemic.<sup>17</sup> Both documents serve to protect research subjects by minimizing risk.

The FDA continuously updates all relevant guidance documents that were originally released in March 2020 under section 319(f) of the Public Health Service Act by the Department of Health and Human Services.<sup>7</sup> For example, the FDA published the guidance document, "FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency" in 2020 and updated it in 2021.<sup>7</sup> By the end of 2021, the FDA had released more than 70 guidance documents dedicated solely to COVID-19 research.<sup>18</sup> The FDA explained that the new guidance documents releases were issued to address the COVID-19 public health emergency.<sup>18</sup> Additionally, the FDA clarified that these documents represent the agency's present thinking for temporary policies to be enforced immediately upon release.<sup>18</sup> The documents are meant to reflect the protection of human subjects and health care professionals while also ensuring that research should continue safely and effectively.<sup>18</sup>

The more than 70 topics of the "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders" include but are not limited to sponsor and industry, IRBs, investigators and health care professionals, good laboratory practices, and good manufacturing practices.<sup>18</sup> Before the guidance documents were released, most study-related visits were restricted and subject enrollment was halted.<sup>19</sup> The FDA outlined considerations to assist sponsors in assuring the safety of the subject, maintaining good clinical practice and minimizing the risks to clinical trial integrity to ensure clinical trials continue providing high-quality data and efficacy.<sup>16</sup> For example, the FDA expected unavoidable protocol deviations likely caused by COVID-19; therefore, the FDA recommended sponsors evaluate alternative methods for assessments, such as making telephone contacts, holding virtual visits, and offering additional virtual safety monitoring for those clinical trial patients who may no longer have access to investigational products or the investigational site.<sup>16</sup>

The OHRP provides specific guidance to cover non-FDA-regulated clinical trials and emphasizes the importance of the new FDA instructions for FDA-approved studies.<sup>17</sup> The OHRP released an announcement on April 8, 2020, clarifying general questions that may arise and describing scenarios for which an IRB's approval is necessary for COVID-19-related changes.<sup>17</sup>

However, the 2020 guidance documents did not limit an entity's IRB the ability to request or require certain changes that were related to COVID-19. For instance, a large hospital's local IRB could require COVID-19 health questionnaires to be completed for patients, staff, and study monitors. The question of how to move research forward in a pandemic slowly dissipated as the regulatory agencies began developing these informative guidance documents.

The importance of the FDA and OHRP collaboration is mainly that the regulatory agencies constantly work together to protect humans and ensure their safety at all times. In short, the new federal guidance documents gave clinical research the proper support for the continuation of clinical trials at the site level.<sup>16,17</sup> FDA and OHRP are still developing guidance documents for clinical research during the COVID-19 pandemic to help with various restrictions while maintaining adequate protection of study patients and personnel.

### Implications

#### Policy Changes in Action

The COVID-19 public emergency placed a brief pause on or closed clinical and pre-clinical research studies because of the lack of understanding of effects of the COVID-19 virus on humans and the unknown surrounding effects on research. Study patients and personnel depended on guidance documents released by the regulatory agencies as they directly affected study personnel workload and patient experience. Quickly, everyone had to learn to adapt to a new order of operations in health care ranging from vaccine and mask mandates to COVID-19 testing and new sanitation practices. In particular, the four highlighted FDA guidance documents in this paper were released during the COVID-19 pandemic and supported changes that affected study personnel and study patients.

The first FDA guidance of importance was the "Enforcement Policy for Face Masks, Barrier Face Coverings, Face Shields, Surgical Masks, and Respirators During the Coronavirus Disease (COVID-19) Public Health Emergency" (and its multiple revisions), which ensured the most accurate and up-to-date information would be available to patients, study personnel, and sponsors of pre-clinical and clinical trials. The newest revision of this guidance was released to increase the availability of masks to the general public when entering health care facilities during the COVID-19 public health emergency period (i.e., since 2020).<sup>20</sup> Before the COVID-19 pandemic, study patients or personnel were not required to wear a mask to enter facilities. Providing guidance that required the use of masks in health care facilities ensured all parties associated with research could feel protected from the virus and continue with the new research practices during the COVID-19 pandemic.



The second FDA guidance of importance was the “COVID-19 Public Health Emergency Policy on COVID-19-Related Sanitation Tunnels” guidance, which was released after the People’s Republic of China implemented tunnels that released a mist of disinfectant as people entered buildings. The purpose of this document was to mitigate significant concerns for human safety by discouraging clinical research sponsors from implementing a practice quickly adopted by other countries.<sup>21</sup>

Furthermore, COVID-19 exposure tests similar to influenza tests needed to be developed to identify COVID-19 infection early in hopes of minimizing the spread of the disease. Thus, the FDA released the “Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency,” which is the third guidance document of importance.<sup>22</sup> This guidance gave manufacturers clear instructions and guidelines according to good manufacturing practices to develop appropriate diagnostic tests. Without the guidance document published, inaccurate tests would have penetrated the US market and potentially wreaked havoc.

Additionally, study personnel and patients have been given the opportunity to get vaccinated against COVID-19 with Moderna, Pfizer, or Johnson & Johnson vaccines. The vaccines were approved under the FDA’s Emergency Use Authorization pathway under section 564 of the Food, Drug and Cosmetic Act. The document “Emergency Use Authorization for Vaccines to Prevent COVID-19”<sup>23</sup> explains information and data required for issuing the authorization to the manufacturers. By releasing this fourth document of importance detailing how vaccines could be approved for emergency use, the FDA enabled manufacturers to develop efficacious vaccines and deliver them to the public sooner than otherwise anticipated.

All four guidance documents that we highlight here are a small fraction of those that affected study patients and personnel during the COVID-19 pandemic. If the situations described above had not been addressed properly, the resulting gap could have affected clinical research negatively. Thus, these guidance documents served as a tool for continuing research amidst a pandemic.

### Future of Clinical Research

The longevity of clinical research depends on subject enrollment. For that reason, investigators need to find acceptable ways to maintain enrollment rates; one option is to increase awareness of clinical research.

The COVID-19 pandemic has compelled sponsors to expand their outreach for subject enrollment of marginalized people through decentralized clinical trials; these efforts ultimately broaden the research.<sup>24</sup> Decentralized clinical trials (DCTs) are

a newer form of nontraditional study design that use mobile health care providers and telemedicine.<sup>24</sup> DCTs have enabled a more accurate representation of study drug interaction in various populations and have increased enrollment rates.<sup>24</sup> For clinical research to be completely successful in implementing DCTs, the quality of visits would need to be exceptional and overall feasible from the perspectives of sponsors, study personnel, and study patients.

For example, the use of in-home visits in protocols for clinical trials to minimize risks for study patients while simultaneously producing a better participant experience and retention rate will be a future gold standard.<sup>3</sup> In-home study visits will limit exposure to COVID-19 and other airborne illnesses for study patients participating in research studies by not requiring on-site clinical visits, often hosted at hospitals or doctors’ offices, which are central hubs for airborne illnesses and germs.<sup>3</sup> Patient safety comes first and foremost in clinical research, and in-home visits can help make study patients feel safer and more comfortable.

Amid the pandemic, clinical trials have continued and have proved to be able to maintain the safety of study patients and the integrity of research successfully in these new or improved research techniques.<sup>8</sup>

### Summary

In 2020, all clinical research studies were forced to pause or close because of the COVID-19 pandemic.<sup>25</sup> Regulatory guidance documents were published to govern clinical research to ensure the safety of study patients and study personnel moving forward. New guidance documents from the FDA and other regulatory bodies initially made it harder for investigators to conduct clinical trials but eventually have become normalized as the pandemic continues and research resumes. To ensure research can move forward, clinical research has had to figure out how to protect clinical trial patients by implementing new practices such as televisits or remote data collection. Although new or revised guidance documents may incorporate stricter rules, their overarching goal is to protect study patients and personnel so that research can continue. Without the guidance documents that have been released to date, research might have been halted indefinitely, which in turn would have forestalled development of COVID-19 exposure tests and vaccines, both of which have had a great impact on the world.

### Conclusion

The purpose of this COVID-19 impact research brief is to shed light on the challenges clinical research faced during the COVID-19 pandemic and how the researchers and relevant federal agencies have handled these challenges. Governing

bodies regularly update research guidance documents as needed for clinical research to continue research during an unprecedented time. The effect of post-COVID-19 regulations and guidance documents will continue to shape clinical research. If another pandemic were to occur, clinical research will know how to evolve and move forward, learning from the experiences during the COVID-19 pandemic.

Thus, we conclude that these documents and advisory publications will allow the integrity and good clinical practices to stay intact and encourage positive change for the clinical research industry. We believe that the guidance documents should stay in place or be revised to reflect current social restrictions, but research, as we have shown, can continue if the current guidance documents and requirements remain unchanged. New guidance documents should continue to be implemented as long as such recommendations or policies continue to protect and support study personnel and patients. For example, the COVID-19 exposure trends are projected to continue to fluctuate over time as more people are tested. Thus, if people wish to continue to wear masks or be vaccinated post-pandemic to feel safe, then the research field should encourage such behaviors. Taking these precautionary steps would bolster recruitment efforts and ensure that clinical research continues. Additionally, giving study personnel avenues to work from home or on a hybrid schedule has provided relief for overworked personnel and should continue to be implemented as seen fit.

Finally, all these changes may be long term. Effects of these changes will be evident in the quality of the data that are collected from clinical trials during this time. If the integrity of the data has not been compromised, then these changes have helped clinical research by introducing a new safe standard of practice.

### References

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. 2020 Mar 11. Available from: <https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>
2. Ramsay L. COVID-19 trial disruptions total more than 1,100, study shows. 2020 May 18 [cited 2022 Aug 30]. Available from: <https://www.centerwatch.com/articles/24715-covid-19-trial-disruptions-total-more-than-1100-study-shows>
3. ICON Plc. Minimise the impact of COVID-19 on clinical trials with in-home clinical services. 2020 Apr 2 [cited 2022 Aug 30]. Available from: <https://iconplc.com/insights/blog/2020/04/02/minimise-the-impact-of-covid19-on-clinical-trials-by-considering-in-home-clinical-services/index.xml>
4. Sathian B, Asim M, Banerjee I, Pizarro AB, Roy B, van Teijlingen ER. Impact of COVID-19 on clinical trials and clinical research: A systematic review. *Nepal J Epidemiol* 2020 Sep;10(3):878–87. <https://doi.org/10.3126/nje.v10i3.31622>
5. Simpson S, Kaufmann MC, Glozman V, Chakrabarti A. Disease X: accelerating the development of medical countermeasures for the next pandemic. *Lancet Infect Dis* 2020 May;20(5):e108–15. [https://doi.org/10.1016/S1473-3099\(20\)30123-7](https://doi.org/10.1016/S1473-3099(20)30123-7)
6. van Dorn A. COVID-19 and readjusting clinical trials. *Lancet* 2020 Aug;396(10250):523–4. [https://doi.org/10.1016/S0140-6736\(20\)31787-6](https://doi.org/10.1016/S0140-6736(20)31787-6)
7. US Food and Drug Administration. FDA guidance on conduct of clinical trials of medical products during COVID-19 public health emergency. 2021 Aug. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency>
8. Fleming TR, Labriola D, Wittes J. Conducting clinical research during the COVID-19 pandemic: protecting scientific integrity. *JAMA* 2020 Jul;324(1):33–4. <https://doi.org/10.1001/jama.2020.9286>
9. AJMC. A timeline of COVID-19 developments in 2020. 2021 Jan 1. Available from: <https://www.ajmc.com/view/a-timeline-of-covid19-developments-in-2020>
10. Boccia S, Ricciardi W, Ioannidis JP. What other countries can learn from Italy during the COVID-19 pandemic. *JAMA Intern Med* 2020 Jul;180(7):927–8. <https://doi.org/10.1001/jamainternmed.2020.1447>
11. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ; COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet* 2020 Jun;395(10242):1973–87. [https://doi.org/10.1016/S0140-6736\(20\)31142-9](https://doi.org/10.1016/S0140-6736(20)31142-9)
12. Wang Q, Zhang T, Zhu H, Wang Y, Liu X, Bai G. Characteristics of and public health emergency responses to COVID-19 and H1N1 outbreaks: a case-comparison study. *Int J Environ Res Public Health* 2020 Jun;17(12):4409. <https://doi.org/10.3390/ijerph17124409>
13. Kent DG, Knapp DJ, Kannan N. Survey says: “COVID-19 lockdown hits young faculty and clinical trials”. *Stem Cell Reports* 2020 Jul;15(1):1–5. <https://doi.org/10.1016/j.stemcr.2020.06.010>
14. Clinicaltrials.gov. Trends, charts, and maps. 2019. Available from: <https://clinicaltrials.gov/ct2/resources/trends>
15. NC Governor Roy Cooper. Executive Order No. 116. 2020 Mar 10 [cited 2022 Aug 30]. Available from: <https://governor.nc.gov/documents/executive-order-no-116>

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16. US Food and Drug Administration. Coronavirus (COVID-19) update: FDA issues guidance for conducting clinical trials. 2020 Mar 27. Available from: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-guidance-conducting-clinical-trials>
17. Office for Human Research Protections. OHRP Guidance on Coronavirus. 2020 Apr 8. Available from: <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/ohrp-guidance-on-covid-19/index.html>
18. US Food and Drug Administration. COVID-19-related guidance documents for industry, FDA staff, and other stakeholders. 2022 Sep 27. Available from: <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>
19. Lupkin S. Coronavirus pandemic brings hundreds of U.S. clinical trials to a halt. 2020 Apr 11. Available from: <https://www.npr.org/sections/health-shots/2020/04/11/832210606/coronavirus-pandemic-brings-hundreds-of-u-s-clinical-trials-to-a-halt>
20. US Food and Drug Administration. Enforcement policy for face masks, barrier face coverings, face shields, surgical masks, and respirators during the Coronavirus Disease (COVID-19) public health emergency (revised). 2021 Sep 15. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-face-shields-surgical-masks-and-respirators-during-coronavirus-disease-covid-19>
21. US Food and Drug Administration. COVID-19 public health emergency policy on COVID-19-related sanitation tunnels. 2022 Feb 8. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-public-health-emergency-policy-covid-19-related-sanitation-tunnels>
22. US Food and Drug Administration. Policy for Coronavirus Disease-2019 tests during the public health emergency (revised). 2020 May 4. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-revised>
23. US Food and Drug Administration. Emergency use authorization for vaccines to prevent COVID-19. 2021 Feb 22. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19>
24. Plana D, Arfè A, Sinha MS. Re-envisioning clinical trials during the COVID-19 pandemic. *Health Affairs Forefront*. 2020 Jul 8. <https://doi.org/10.1377/forefront.20200702.963588>
25. ICON Plc. Post pandemic clinical trial strategies: how COVID-19 altered clinical trials forever and what's next. n.d. [cited 2022 Aug 30]. Available from: <https://iconplc.com/insights/blog/2020/08/05/post-pandemic-clinical-tr/index.xml>

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