

## VIEWPOINT

# Approaches to Continuing COVID-19-Related Clinical Research Practices After the Pandemic—Must Cinderella Leave the Ball?

**David E. Gerber, MD**  
Harold C. Simmons  
Comprehensive Cancer  
Center, The University  
of Texas Southwestern  
Medical Center, Dallas;  
and Peter O'Donnell Jr.  
School of Public Health,  
The University of Texas  
Southwestern Medical  
Center, Dallas.

**Elizabeth K. S.  
Barksdale, PhD**  
LUNGeVity Foundation,  
Chicago, Illinois.

**In January 2023**, the Biden administration announced its intent to end the COVID-19 public health emergency on May 11, 2023. The sunset of this declaration, in place since early 2020, has numerous implications. Among others, these include coverage of COVID-19 vaccines, tests, and treatments through Medicare and Medicaid; the expansion of Medicare- and Medicaid-covered telehealth visits beyond rural areas; state licensure requirements, which had been waived to facilitate interstate telehealth encounters; mandated 90-day prescription supplies through Medicare Part D; and public availability of COVID-19 countermeasures before formal approval by the US Food and Drug Administration (FDA). Critical to patients with cancer, clinicians, and researchers, components of the COVID-19 public health emergency also addressed the conduct and oversight of clinical trials.

Recognizing the unique challenges of COVID-19 to the practice of medicine and conduct of clinical trials—including quarantines, site closures, travel limitations, investigational product supply, and potential for staff and/or patient illness—the FDA and other agencies provided interim guidance on clinical research practices during the pandemic.<sup>1,2</sup> Suggested adjustments to conventional trial activities included remote informed consent, telephone or video visits, local (ie, near the patient's home) laboratory and imaging studies, delaying assessments, alternative sites for treatment administration, shipping oral study therapy directly to patients' homes, use of electronic signatures, and remote study monitoring. Taken together, these shifts arguably marked the greatest change to a long-standing status quo in recent memory.

Early studies have indicated that these profound changes are not only feasible, but may also be preferred over prior research practices.<sup>3,4</sup> Indeed, COVID-19-related adjustments to essential processes and data capture appear to have resulted in a more patient-centric approach to clinical trials.<sup>5</sup> Nevertheless, because these policies were originally linked to the COVID-19 public health emergency, their fate remains uncertain. The European Medicines Agency recently issued recommendations on decentralized trials after COVID-19.<sup>6</sup> In March 2023, the FDA announced that it would extend more than 20 COVID-19-related guidance documents (from among 72 total) 180 days after the expiration of the public health emergency, including guidance related to clinical trial conduct.<sup>7</sup>

While it is not known how the FDA might revise or further prolong this particular guidance beyond this time period, it is still possible to capitalize on the possibilities revealed and experience gained during what might

be considered a golden era in clinical research. This is because—although most of these adjustments were widely implemented for the first time during the COVID-19 pandemic—many had pre-existing regulatory support. As such, they may remain feasible well after the public health emergency ends, regardless of forthcoming regulatory decisions. Coupled with early and frequent communication with regulators as needed to clarify ambiguities, this information may help preserve these recent, welcome, and long-overdue innovations. To inform and empower investigators, sponsors, clinicians, and patients, herein we review relevant components of federal *regulation* (mandatory; designated by the symbol §, indicating a section of the Code of Federal Regulations) and *guidance* (the FDA's interpretation of regulations and their applicability to clinical research, which do not carry the force of law; designated by document titles).

## Remote Informed Consent

The FDA initially addressed the use of electronic informed consent in 2016, with additional guidance for industry issued in 2017. The FDA noted the following: (1) information may be presented in writing, through verbal dialog, or a combination of approaches; (2) consent may be written or oral; (3) documentation of consent must be signed and dated but does not have to be on paper or performed in person and/or at the study site; and (4) there must be a system for archiving consent documentation (regulation: §50.20, §50.27, §56.103[a], §56.111[a], and §312.62; guidance: "Use of Electronic Informed Consent in Clinical Investigations—Questions and Answers: Guidance for Institutional Review Boards, Investigators, and Sponsors" [2016] and "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under Part 11—Questions and Answers: Draft Guidance for Industry" [2017]).

## Remote Data Collection and Study Visits

Well before the COVID-19 pandemic, the FDA expressed support for including decentralized elements in clinical trials, though specific guidance has not yet been issued. Considerations include listing off-site laboratories and imaging centers on the FDA 1572 form, ensuring that these facilities meet regulatory requirements such as Clinical Laboratory Improvement Amendments, and complying with state and local policies regarding telemedicine for patients residing out of state (regulation: §493.1, §493.2, §493.3, and §493.25; guidance: "Frequently Asked Questions—Statement of Investigator (Form FDA 1572): Guidance for Sponsors, Clinical Investigators, and IRBs" [2010]).

**Corresponding  
Author:** David E.  
Gerber, MD, Harold C.  
Simmons  
Comprehensive Cancer  
Center, The University  
of Texas Southwestern  
Medical Center, 5323  
Harry Hines Blvd, Mail  
Code 8852, Dallas, TX  
75390-8852 (david.  
gerber@  
utsouthwestern.edu).

## Shipping Investigational Product

Requiring patients to pick up short-duration study drug prescriptions in person can pose a barrier to trial enrollment and retention. Home delivery of investigational product can be considered if sponsors detail study-specific plans for handling study therapy in the study protocol, including shipment, receipt, and method of disposal of unused study therapy. Sponsors and investigators must keep records of when, how much, and to whom study therapy is shipped. Additionally, investigators must ensure that study participants understand and comply with protocols for administration and disposal of study therapy and have appropriate resources for compliance (regulation: §312.57, §312.59, §312.60, and §312.62).

## Remote Study-Site Monitoring

Recognizing the potential costs and inefficiencies of serial in-person study monitoring by sponsor or contract research organization representatives, the FDA first issued guidance recommending consideration of remote study-site monitoring in 2013. Rationale for this approach included the availability of technological advances (such as webcasts) and evidence that certain data anomalies could be better recognized through central rather than on-site monitoring. Specific suggestions included using centralized (ie, remote) monitoring to supplement or reduce the frequency and extent of on-site monitoring, as well as focusing on-site monitoring by identifying higher-risk clinical sites (eg, those with data

anomalies or higher rates of errors, protocol violations, or drop-outs) (regulation: §312.50, §312.53[d], and §312.56[a]; guidance: "Oversight of Clinical Investigations—a Risk-Based Approach to Monitoring" [2013]).

The COVID-19 pandemic has left in its growing wake widespread illness, hundreds of thousands of deaths, and economic turmoil. At the same time, the worst global health crisis in more than a century has inspired tremendous advances, ranging from messenger RNA vaccine technology to widespread uptake of video-based communication. As a part of this revolution, patients and clinicians have also witnessed a major streamlining and simplification of clinical trials.

Until COVID-19, despite repeated calls to reform clinical trial design and operations, protocols were becoming increasingly complex.<sup>8</sup> Eligibility criteria were growing in number and stringency. Protocol-required procedures were also increasing, with mandated completion timelines remaining inflexible. As a result, cancer clinical trials frequently failed to meet enrollment targets, and lack of participant diversity limited generalizability of results. There is now proof that there can be another way. Armed with this experience and the understanding that key changes to clinical research conduct may be permissible regardless of pandemic status, sponsors, investigators, clinicians, and patients can continue to design, conduct, and participate in safe, informative, yet also highly feasible, trials. Maybe, just maybe, Cinderella does not have to leave the ball.

## ARTICLE INFORMATION

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