ASPE ASSISTANT SECRETARY FOR PLANNING AND EVALUATION
OFFICE OF SCIENCE & DATA POLICY

COMMENTARY

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Applying lessons learned from the COVID-19 pandemic to future clinical trials

Introduction

The COVID-19 pandemic had wide-reaching impacts on healthcare delivery and medicine, including the conduct of clinical trials. While in-person interactions were being curtailed to prevent spread of COVID-19, there was simultaneously a need to rapidly develop new medical products to test, treat, and prevent COVID-19. Clinical trials unrelated to COVID-19 had to quickly adapt to unprecedented challenges, which resulted in the rapid and widespread deployment of innovative strategies to continue existing studies and initiate development of products to respond to the COVID-19 pandemic.

In 2023, the Office of the Assistant Secretary for Planning and Evaluation (ASPE) launched a research project to understand the impacts of COVID-19 on the clinical trial enterprise and identify key lessons learned. This project included an environmental scan of the peer-reviewed and gray literature from 2020 to 2023 as well as a series of interviews with experts in clinical trial design, clinical trial operations, decentralized clinical trials, digital health technologies, clinical trial diversity, and regulatory oversight and evaluation. The methods and results from this project are described in detail in the full report, available at https://aspe.hhs.gov/reports/covid19-clinical-trial-impacts. This ASPE commentary provides a summary of some of the key lessons learned in the context of two domains: 1) preparing for and conducting clinical trials during a pandemic; and 2) strategies to streamline the everyday conduct of clinical trials.

Lessons learned: Preparing for and conducting trials during a pandemic

The rapid development of safe and effective COVID-19 therapeutics and vaccines highlighted a range of successful clinical trial strategies for conducting trials during a pandemic or other public health emergency. Key among these approaches were widespread adoption of decentralized clinical trial elements and the incorporation of technology into clinical trials (see Chapter 4 of the report). Experts noted that trials that were able to pivot to alternate locations for site visits, incorporate digital health technologies, videoconferencing, and other decentralized elements experienced the least disruption due to the onset of the COVID-19 pandemic. Those trials that already incorporated these types of flexibilities into their design were particularly resilient – suggesting that more widespread contingency planning could make the clinical trial enterprise more resilient in the event of future public health emergencies. Furthermore, the literature and interviews highlighted that innovative approaches to patient recruitment, including enrollment at non-traditional facilities such as pharmacies and using social media and text messaging to reach potential participants, helped trial sponsors recruit more quickly and from more diverse populations.

In addition to incorporating decentralized elements and digital health technologies, many COVID-19 product trials successfully implemented unique trial designs and statistical approaches to achieve more robust trial results in less time (see Chapter 5 of the report). These included adaptive platform trials, in which multiple products are tested as part of a common protocol and products can be added or removed as evidence

accumulates, and the use of Bayesian statistics, a statistical approach for learning from evidence as it accumulates, for analyzing trial data. Although these approaches were not new at the onset of the COVID-19 pandemic, they were implemented at a much larger scale than at any point to date. One expert estimated that four adaptive platform trials generated approximately 90% of the evidence for recommended COVID-19 therapeutics. Clinical trialists interviewed for the report also observed time savings and reductions in the number of participants needed for statistical analysis when using adaptive designs, particularly when employing Bayesian statistical approaches. However, despite these benefits, the majority of adaptive platform trials were conducted outside of the U.S. during COVID-19, suggesting that there may be unique barriers or challenges with implementing these approaches within the U.S. healthcare system and clinical trial enterprise. In particular, experts suggested that the lack of integrated health care infrastructure in the U.S. posed a barrier to implementing adaptive platform trials – in other countries such as the United Kingdom, patients could be rapidly identified, enrolled, and randomized into trials using centralized electronic health records.

One of the key success stories highlighted by the experts interviewed for this project was the robust coordination between the U.S. Food and Drug Administration (FDA) and trial sponsors, which facilitated the implementation of strategies to allow clinical trials to safely continue during COVID-19 as well as supported the rapid development and regulatory review of COVID-19 products (see Chapter 8 of the report). Regulatory activities such as the rapid release of FDA guidances provided clarity, and regular communications with product sponsors, particularly vaccine developers, streamlined the development process. However, interviewees also noted that these successes were at the cost of "heroic" efforts by FDA staff, including round-the-clock work and shifting of priorities and staff, which would not be sustainable outside of a short-term emergency situation.

Our study also identified a number of opportunities to explore how pandemic preparedness could be improved within the clinical trial enterprise. Future work might explore the value, need, and cost of more widespread pandemic contingency planning in clinical trials for both trial sponsors and the healthcare system more generally. As noted above, innovative trial approaches such as adaptive platform trials were instrumental in generating evidence for COVID-19 therapeutics, but were generally used outside of the U.S. Examining ways in which these approaches might be adopted in the U.S., particularly in the event of a public health emergency, could further strengthen preparedness of the trial enterprise. This might include a more robust analysis of the costs and barriers of implementing such approaches within the U.S. medical system. Finally, interviewees noted that while FDA's response was highly effective, it was unsustainable outside of a short-term emergency context. Additional work may be needed to identify strategies that might further streamline oversight and review processes in the event of a public health emergency and reduce burden on regulators.

Lessons learned: Strategies to streamline everyday conduct of clinical trials

Many of the strategies implemented to streamline clinical trials during the COVID-19 pandemic have the potential to streamline product development outside of a pandemic scenario as well, either directly through the conduct of the trial itself or indirectly through more robust recruitment and retention of trial participants. Decentralized clinical trial elements and digital health technologies, while not new, emerged as one of the promising lessons learned from COVID-19 that should continue to be carried forward to all types of trials. Using decentralized clinical trial elements and digital health technologies has great potential to increase the reach of clinical trials to diverse populations around the country. Currently, patients are frequently limited in their ability to participate due to the need for travel to clinical trial sites and associated costs to patients such as transportation, missed work, or childcare needs. Decentralized approaches have the potential to significantly reduce these burdens as well as increase access to clinical trials for people who do not live near

academic medical centers or hospitals that represent traditional clinical trial sites. By reducing these barriers to participate in clinical trials, decentralized approaches can therefore increase patients' ability to participate.

Experts noted in the COVID-19 context that non-traditional and multi-channel recruitment approaches, including social media advertising, engagement of local pharmacies, and text messaging, augmented standard recruitment and were particularly suitable for enrolling underrepresented and underserved patients that may not have been reached through traditional channels. This also included making adjustments in real time if recruitment targets were not being met. These novel recruitment techniques are easily available to utilize in the context of everyday trials, and will give clinical trials that use them the ability to be more representative of the affected patient populations (see Chapter 6 of the report).

Trials conducted during the COVID-19 pandemic also highlighted the value of real-world evidence, defined as clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data (see Chapter 7 of the report). Real-world evidence can be particularly beneficial for certain patient populations or to evaluate therapies that are widely used for other indications. For example, pregnant women are rarely studied in everyday clinical trials due to concerns about effects on the developing fetus, even though this exclusion may not be evidence-based. However, real-world data helped to provide evidence for the safety of certain COVID-19 therapeutics for pregnant women – a population excluded from trials for these drugs and vaccines. Researchers also used electronic health records data to retrospectively identify repurposed drug candidates for treating COVID-19. However, experts observed that the collection of real-world evidence within the U.S. was limited by our fragmented medical data system – in contrast with other countries such as Israel or the United Kingdom, which were able to analyze real-world evidence at scale to evaluate COVID-19 therapeutics and the COVID-19 vaccines outside of clinical trial settings. Over the course of the COVID-19 pandemic, U.S. researchers were able to build tools to examine real-world evidence from U.S. hospital systems, such as the National COVID Cohort Collaborative Data Enclave, although these resources were limited by the types of organizations that chose to participate. Developing similar systems to generate and use real-world evidence outside of a pandemic scenario could be beneficial for studying the safety and efficacy of a wide range of medical products, particularly for patient populations excluded from trials.

Finally, as discussed above, COVID-19 product trials successfully employed trial strategies such as adaptive platform trials (see Chapter 5 of the report). This approach may also have value for development of products with traditionally challenging trial designs, such as antimicrobial drugs or products intended for use in patients with rare diseases, especially where multiple therapeutics are under development. The use of adaptive platform trials may allow sponsors to generate robust clinical trial evidence with fewer patients and at lower cost, which is especially critical in these underserved therapeutic areas, where future sales may be limited. However, widespread use of these strategies in everyday trials may be limited, particularly where sponsors do not benefit from head-to-head comparisons with competitor products.

Our study identified several gaps and areas for additional research when translating lessons learned from COVID-19 clinical trials to everyday clinical trials. Future work might endeavor to better understand costs, cost savings, and barriers to implement or utilize decentralized clinical trial elements, adaptive platform trial designs, digital health technologies, and real-world evidence. Such work could identify strategies to address barriers to implementation within the U.S. and inform future policy actions. Future studies might explore the types of products that might most benefit from these approaches. Finally, the COVID-19 pandemic demonstrated that taking innovative approaches in clinical trials can improve the diversity of research participants. Additional research is needed to identify the strategies that can most effectively be deployed in all types of trials to enhance diversity in trial participants.

Conclusions

COVID-19 had significant impacts on the conduct of clinical trials for all types of medical products. Here, we summarized some of the key takeaways from our research study on lessons learned for the clinical trial enterprise – focusing specifically on the ways in which this might inform future pandemic trials, preparedness for future public health emergencies, and everyday clinical trials. Our study identified a number of gaps and opportunities for additional research to apply these lessons learned to streamline all types of clinical trials as well as enhance the resiliency of the clinical trial enterprise against future public health emergencies. More detailed discussion of the environmental scan, expert interviews, and lessons learned is contained in the accompanying report.

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