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TRANSFORMATION OF THE CLINICAL TRIAL ENTERPRISE: LESSONS LEARNED FROM THE COVID-19 PANDEMIC

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1. REPORT SUMMARY

The COVID-19 pandemic disrupted clinical trials in early 2020 and created an urgent need for new diagnostics, therapeutics, and vaccines. The clinical trial community's response propelled greater use of new and existing tools, such as community outreach to increase the diversity of trial participants; decentralized patient monitoring and recruitment; innovative trial designs; real-world evidence (RWE) from point-of-care research; and collaboration between multiple federal agencies, industry, and academia.

This report summarizes research to reveal the impacts of the COVID-19 pandemic on the clinical trial enterprise, the innovations it engendered, and the implications for future pandemic preparedness as well as how to improve practices for all clinical trials.[1]

The research entailed a targeted literature review followed by interviews with experts from within the clinical trial enterprise. The research describes disruptions to clinical trials due to COVID-19 and specific impacts and lessons learned in six broad areas:

1. Decentralized clinical trials and digital health technologies
2. Platforms and statistical innovation in clinical trial design
3. Participant diversity drivers and infrastructure
4. RWE and the gap between clinical research and practice
5. Regulatory trial oversight and evaluation
6. General operational considerations

The COVID-19 pandemic led to widespread disruption of clinical trials and simultaneously necessitated the urgent conduct of trials for COVID-19 diagnostics, therapeutics, and vaccines. Most ongoing and pre-launch trials were interrupted to some extent by the COVID-19 pandemic, but those trials that allowed for research to take place in local clinics or even in participants' homes were more resilient. Chapter 2 explains the methods used to produce this report, and Chapter 3 summarizes the types of disruptions to clinical trials during the COVID-19 pandemic. Subsequent chapters explore specific ways in which clinical trials conducted during the COVID-19 pandemic mitigated these disruptions as well as the lessons learned for both pandemic-era and everyday clinical trials.

Chapter 4 describes the role of decentralized clinical trials (DCTs) and digital health technologies (DHTs) during the COVID-19 pandemic. DCTs and DHTs offer participant-centric approaches to clinical research that enable (more) remote participation, extending clinical research sites to community and even home settings. These approaches and tools can prove particularly impactful for enrolling underserved populations, including rural, socioeconomically disadvantaged, and mobility-limited people, as well as patients with rare or severe diseases. Beyond enrollment, COVID-19-era clinical trials demonstrated that appropriately decentralizing activities to community clinics can reduce participant barriers during treatment and monitoring. However, DCTs and DHTs are not necessarily appropriate or feasible for all

[1] For readability, this report summary does not include citations. Instead, these cites appear in each of the detailed themed sections, with corresponding references in the bibliography.

trials, and clarifications and reforms regarding reimbursement and state-specific medical licensing regulations for activities such as telemedicine might be necessary for non-emergency use in clinical research.

Chapter 5 describes the use of platforms and statistical innovation in clinical trial design during the COVID-19 pandemic. Platform trials, in which multiple products are evaluated simultaneously under a master protocol (among other features), proved effective at generating action-oriented evidence for COVID-19 candidate therapeutics. The variations among platforms showed that their use is not, however, a guarantee of speed and efficiency. Rather, platform design, governance, and technical infrastructure all appeared fundamental to platform performance. Bayesian adaptive trial designs in some cases generated comparable results faster and with fewer enrolled participants than frequentist designs. Although these strategies proved particularly effective during the COVID-19 pandemic, broader uptake of these innovative approaches may speed development and reduce costs for trials conducted outside of a pandemic scenario.

Chapter 6 discusses the impacts that COVID-19 disruptions and mitigation strategies had on the diversity of clinical trial participation. Historically, clinical trial participants have imperfectly represented the patient populations who are likely to use the medical products being studied. For COVID-19 vaccine and therapeutic trials, clinical trialists sought broad participation in COVID-19 vaccine and therapeutic trials using a wide range of non-traditional recruitment strategies, including social media, partnering with retail pharmacies, and engaging community leaders. The COVID-19 pandemic demonstrated that increased diversity can be achieved by explicitly planning diversity recruitment activities; without broader implementation of these approaches, however, diversity gaps will persist in future clinical trials.

Chapter 7 describes RWE and the gap between clinical research and practice. Highly fragmented medical data and information technology systems combined with a lack of embedded research capabilities in clinical care limited the use of RWE to identify effective clinical practices and candidate therapies early in the COVID-19 pandemic. As a result, the United States had to depend on evidence from other countries (the United Kingdom and Israel, among others) with more unified medical record systems, detailed public health surveillance, and embedded clinical research capabilities in their clinical care. Reducing health data fragmentation while simultaneously allowing access by researchers could improve clinical trials during normal contexts and prove critical to rapid response during pandemics.

Chapter 8 describes regulatory trial oversight and evaluation. Federal leadership, through coordination among government agencies and private organizations, proved critical for mitigating immediate impacts and galvanizing action for all trials during the period. The timely publication of clear guidance documents for the performance targets of COVID-19 vaccines especially helped the trials for those products. Clinical trial sponsors and their study sites described rapid and frequent guidance documents from the U.S. Food and Drug Administration as having enabled rapid restarts of existing trials and initiation of COVID-19 product trials. All future clinical trials can apply these regulatory lessons of

proactive guidance and policy communication, mutual education for collaborative innovation, and streamlining protocols to processes.

Finally, Chapter 9 presents additional operational approaches that were taken to streamline clinical trials during COVID-19. These include strategies to reduce start-up time, including simplified contracting, innovative recruitment approaches to both speed and diversify participation, and integrated data systems that expedited data collection, processing, and database lock. Many of these approaches could be implemented more broadly after the COVID-19 pandemic to accelerate clinical development for a wide range of product types. More generally, future clinical trial contingency planning should be robust, especially regarding personnel issues such as personal health protection, absentee rates from diversion or illness, and wellness management and exhaustion avoidance.

Although the literature and expert interviews documented a wide range of disruptions, mitigation strategies, and innovations in the clinical trial space during COVID-19, there is still very little known about the quantitative impacts on clinical trial costs, trial success, or other factors. In Chapter 10, the report concludes with areas for future quantitative research to understand the impact of the approaches taken during the COVID-19 pandemic.

2. METHODS

Over six months beginning in March 2023, an independent research team at Co-Bio Consulting, at the direction of the Office of the Assistant Secretary for Planning and Evaluation (ASPE), conducted a multiphase project designed to understand how the COVID-19 pandemic transformed the clinical trial enterprise. The team's qualitative research consisted of a literature review, interviews with high-level subject matter experts, and synthesis. The Co-Bio Consulting team prepared the report under contract with Mathematica with financial support and feedback from HHS. The Co-Bio Consulting team retained full editorial responsibility and any remaining errors are their own. The work focused on clinical trial developments, lessons learned, and forward-looking opportunities for U.S. policymakers.

Informed by a detailed literature review conducted in spring 2023,[2] the research team identified a set of themes that capture core areas of lessons learned from clinical trials during the COVID-19 pandemic. This document includes insights from this work, which was constructed as an overview of (primarily peer reviewed) published expert knowledge accumulated over the 38 months after the COVID-19 pandemic began.

While synthesizing the literature, the research team also developed a set of interview guides to use as qualitative survey instruments in a diversified set of interviews with people who had high-level experience and expertise in each of the following five areas: (1) clinical trial design (in particular, statistical innovation in clinical trials), (2) clinical trial operations, (3) decentralized clinical trials and digital health technologies in clinical trials, (4) clinical trial diversity, and (5) regulatory oversight and evaluation of clinical trials.

The goal of the expert interviews was to fill in gaps and augment the findings from the targeted literature scan. As such, the five interview guides were designed to elicit information on the lessons learned in the conduct of clinical trials and recommended strategies or practices that likely provide the most benefit (e.g., reduce costs or time or increase diversity) to the clinical trial enterprise. The guides were also meant to help gather information on the types of products for which these lessons learned are likely to be most applicable going forward.

All interview guides were approved by Health Media Lab IRB on May 22, 2023. The research team conducted all interviews via Zoom.

Experts were identified according to their experience with clinical trials during the COVID-19 pandemic, with multiple experts representing each major regulated COVID-19 product type (vaccines, drugs, and devices). The team identified interviewees via the literature review and through the principal

[2] To collect and aggregate information sources on the approach and strategies, including policy interventions, adopted in the clinical trial enterprise in response to the COVID-19 pandemic, the research team scanned the literature using a set of keywords selected with ASPE experts. The team performed keyword searches using LEXIS NEXIS, Google Scholar, and Google search engines from March to May 2023. The environmental scan was designed to capture lessons learned from clinical trials during COVID-19. For more detail on the literature scan and a full list of keywords, see Appendix C.

investigators' experience and network. Although the team interviewed each expert using only one of the interview guides, several had expertise in more than one product category. Among the final set of interviewees, 10 had experience with vaccine trials, 12 with therapeutic trials, and seven with diagnostic/device trials). In total, the team interviewed 24 experts, with each of the unique interview guides used for no more than seven experts.

The findings have some limitations based on this project's scope and design. The completion of this project from March to September 2023 means that the period of hindsight was only the 3 to 3.5 years after the onset of the COVID-19 pandemic. Further, the findings from the targeted literature review are necessarily limited to the top 20 pieces published by mid-2023 that met the keyword search phrases (see Appendix C), and many experts in the clinical trial enterprise might not publish the lessons they learned. The second phase of the study, the expert interviews, was designed to mitigate this potential source of bias by speaking with leaders in the field who were actively involved in clinical trial leadership during the pandemic. Although the expert interviews yielded new insights—a fact that is consistent with there still being gaps in the published literature—the number of such interviews conducted was limited to 24. Some latent insights were certainly missed because of the relatively small number of expert interviews. Further, because the interviews focused on senior organizational experts and principal investigators, the findings do not reflect insights from mid-level and operational clinical trial staff (e.g., clinical trial nurses, site monitors, phlebotomists, etc.) that were not shared with clinical trial leaders or shared by the interviewees.

3. DISRUPTIONS TO CLINICAL TRIALS DUE TO COVID-19

The COVID-19 pandemic disrupted operations for all clinical trial activities, from trial initiation and recruiting to execution, monitoring, and close-out. In many cases, these disruptions incentivized broad and swift adoption of innovative approaches.

Overall, in a direct year-over-year evaluation of clinical trials registered on ClinicalTrials.gov, 116 trials were suspended in 2019 compared with 769 trials in 2020 (Evidera, 2021). Among 300 global pharmaceutical companies, 75% of organizations paused site activation, and 50% paused recruitment at the beginning of the COVID-19 pandemic (Agrawal *et al.*, 2020).

In addition, travel restrictions, global consumable shortages, supply chain disruptions, and social distancing guidelines were obstacles to conducting clinical research during the pandemic. The realities of social distancing made it difficult for patients to travel to trial sites and for trialists to monitor patients in person and perform otherwise normal trial-related tasks.

This chapter summarizes the types of interruptions experienced due to COVID-19 and their consequences to the clinical trial enterprise, and it briefly introduces the overarching themes that will be discussed in subsequent chapters.

TYPES OF INTERRUPTIONS

Studies have reported a variety of clinical trial disruptions from COVID-19 that affected ongoing trials that were in-progress or preparing to launch at the outset of the pandemic as well as the initiation of trials for COVID-19 vaccines and therapeutics. For example, clinical trials for cancer therapeutics and cardiovascular medical devices reported broad reductions in enrollment during the first year of the pandemic (Unger, Xiao, *et al.*, 2021; Rymer *et al.*, 2022). The cancer studies reported 23% average enrollment reductions over the first year of the COVID-19 pandemic (Unger, Xiao, *et al.*, 2021), but in the cohort of cardiovascular device trials studied, over 80% were disrupted or not started because of mandated institutional shutdowns or patients' concerns related to interacting with the health system (Rymer *et al.*, 2022). Other investigations suggest that COVID-19 led to delays in patients receiving chronic condition care, which subsequently affected clinical trial enrollment during the first year of the COVID-19 pandemic (Pretzel *et al.*, 2022; Rose *et al.*, 2022). Clinical staffing, fatigue, and shortages contributed to interrupted clinical trial operations. One expert from the National Institutes of Health (NIH) said that staff exhaustion during the COVID-19 pandemic resulted in the organization forcing employees to take a rest from the office and sending them home.

Many clinical trialists interviewed discussed how clinical trials were halted or shifted because of the lack of resources during the early months of the COVID-19 pandemic and the overall lack of volunteers. At the same time, experts observed that resources from ongoing trials—in particular, trial staffing and some reviewers—were shifted to COVID-19-related clinical trials. These and other factors led to a roughly 10% absolute decrease in clinical trial starts in 2020 relative to 2019 and an even greater

decline compared with the steady year-over-year growth trendline observed in the years leading up to the COVID-19 pandemic (Lasch *et al.*, 2022; IQVIA, 2023).

Responding to the impacts of the COVID-19 pandemic on participant and staff safety, trial operations, and data quality, the U.S. Food and Drug Administration (FDA) issued a guidance document in March 2020 (updated August 2021) (U.S. FDA Conduct, 2021) recommending that sponsors consider delaying initiation of new trials and pausing or slowing enrollment in ongoing trials. In 2021, clinical trial starts surged again as many of the previous year's delayed trials launched belatedly (Lasch *et al.*, 2022; IQVIA, 2023).

The literature and expert interviews noted that trials early in the recruitment phase or those unable to pivot to virtual patient and site visits were among the most affected (Rymer *et al.*, 2022). In such instances, decentralized trial techniques were not feasible from a practical, financial, information technology (IT), or staff resourcing perspective. For example, a participant's physical presence might be necessary in cases such as those involving special patient populations or trials with complex interventions (e.g., cell therapies).

The literature also, however, highlighted examples of trials that were able to continue successfully by reducing in-person requirements. One primary-care-based diuretic point-of-care pragmatic trial that pivoted to remote follow-up sessions actually increased recruitment compared with pre-pandemic levels (Leatherman *et al.*, 2023), and an in-hospital trial for acute stroke that used similar strategies was able to maintain participant diversity and patient follow-up levels (Yamal *et al.*, 2021). Similarly, other trials in dementia and cancer obtained participant information by phone instead of in-person during this period while maintaining other pre-pandemic clinical trial management practices (Flores *et al.*, 2021; Heintz, Clouqueur, and Puopolo, 2021; Park *et al.*, 2022). An FDA official interviewed for this report emphasized that more resilient studies were more likely to rely on approaches such as electronically consenting patients, performing blood draws close to home, and conducting remote trial monitoring visits whenever possible (see Chapter 4, Decentralized clinical trials and digital health technologies).

Mitigation activities in clinical trial operations during the COVID-19 pandemic period increased costs, as many experts reported (though these are not yet well quantified at scale in the published literature), which might have affected trial success rates. Expert interviewees and the literature listed costs associated with additional resources needed to ensure that trial activities could continue safely (e.g., additional personal protective equipment), implement previously unplanned adoption and employment of decentralized approaches, and deploy digital health technologies (DHTs). In some cases, these activities rapidly drained trial budgets. Many conventional participant recruitment and retention channels were shuttered during the COVID-19 pandemic, forcing trialists, research organizations, and sponsors to pivot and amplifying the impact of initial disruptions.

One expert we interviewed further highlighted "unseen" challenges for specific clinical trial participant populations, sharing the anecdote of a working single mother whose child care closures compromised her availability to continue participating in a trial. Although widespread child care closures were

specific to the COVID-19 pandemic, this example highlights how existing barriers and challenges to clinical trial participation were exacerbated by the institutional decisions taken during the COVID-19 pandemic. Similarly, experts noted that existing structural and socioeconomic barriers to trial participation such as participants' physical disabilities and/or dependency on public transportation are likely to become even stronger hindrances to people's ability to participate in clinical research during a public health emergency (see Chapter 6, Participant diversity drivers and infrastructure).

Clinical trials involving therapies for COVID-19 encountered a unique set of disruptions, including competition with other COVID-19 therapeutic trials for participants, contracting delays, and slow institutional review board (IRB) and regulatory protocol reviews from thinly stretched agencies (Goossens *et al.*, 2022). FDA worked to help mitigate clinical trial interruptions early in the pandemic by rapidly issuing guidance documents on how to safely conduct trials (Turner, 2020) and increasing its consultations with sponsors. Experts broadly cited these guidance documents as beneficial and helpful as the basis for understanding how to best modify trial approaches when appropriate (see Chapter 8, Regulatory trial oversight and evaluation).

4. DECENTRALIZED CLINICAL TRIALS AND DIGITAL HEALTH TECHNOLOGIES

A decentralized clinical trial (DCT) is a clinical trial in which some or all trial-related activities occur at locations other than traditional clinical trial sites (e.g., enabling patients to participate from their homes or local health care facilities; U.S. FDA DCT, 2023). DCTs may use software applications and digital solutions, such as those categorized as DHTs by FDA (U.S. FDA DHT, 2023), to allow real-time data collection and remote patient monitoring. Boxes 1 and 2 provide additional information and examples of DCTs and DHTs.

Box 1: Decentralized clinical trials

A decentralized clinical trial (DCT) refers to a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites. In fully DCTs, all activities take place at locations other than traditional trial sites. These trial-related activities may take place at the homes of trial participants or in local health care facilities that are convenient for trial participants. In hybrid DCTs, some trial activities involve in-person visits by trial participants to traditional clinical trial sites, and other activities are conducted at locations other than traditional clinical trial sites, such as participants' homes. Potential advantages of DCTs include the following:

- *Ability to include patients in rural areas, patients from underprivileged geographies, or those with limited travel possibilities*
- *More flexibility for patients, which in turns leads to higher retention and better satisfaction with the trial participation*
- *Helps prevent missing data*
- *Can be performed at larger scale, spanning across centers and countries to enhance diversity and robustness of trials*

Source: U.S. Food and Drug Administration (U.S. FDA DCT, 2023)

Box 2: Digital health technologies

Digital health technologies (DHTs) offer many potential benefits in the development of medical products, including drugs. Advances in DHTs, including electronic sensors, computing platforms, and information technology, provide new opportunities to obtain clinical trial data directly from patients. Portable DHTs that may be worn, implanted, ingested, or placed in the environment allow real-time collection of data from trial participants in their homes or at locations remote from clinical trial sites. Potential advantages of these DHTs include the ability to do the following:

- *Make continuous or frequent measurements of clinical features*
- *Record or measure novel clinical features that could not be captured during traditional study visits*
- *Decentralize clinical trial activities by obtaining clinical data from study participants remotely*

Source: U.S. Food and Drug Administration (U.S. FDA DHT, 2023)

Despite considerable interest in DCTs over the past decade, before the COVID-19 pandemic, their application had remained limited to smaller studies or secondary measurements (Spinner, 2022). Only

a few trials were executed in a fully decentralized manner before the pandemic (Roehr, 2011; Ho *et al.*, 2017; Sommer *et al.*, 2018). The onset of the COVID-19 pandemic, together with the emergency constraints, social distancing requirements, travel restrictions, and shifts in the availability of hospital resources, created significant challenges for standard clinical trial operations, threatening closure of ongoing trials and delays in the new trial initiations (see Chapter 3, Disruptions to clinical trials due to COVID-19 for more detail). Under these circumstances, decentralized approaches and use of DHTs emerged as promising solutions to ensure continuity of ongoing trials and to enable initiation of new trials, including COVID-19 vaccine studies (Agrawal *et al.*, 2021; Lee *et al.*, 2021; Parkins, 2021; Aitken, Connelly and Leamy, 2022; Moore *et al.*, 2022). Box 3 presents some of the key opportunities created by DHTs in the space of clinical trials.

Box 3: Opportunities created by digital health technologies

Digital tools (e.g., mobile devices, mobile apps, remote monitoring devices, and online social engagement platforms) can be incorporated into study designs for some novel benefits, including the following:

- Improving trial participant recruitment and retention (speeding results, lowering costs for sponsors), including improving trial participant diversity
- Possibly improving trial participant retention, which may reduce missing data, shorten timelines, and improve data interpretability
- Enabling online-based informed consent
- Tracking adverse events
- Providing greater control, convenience, and comfort for participants by allowing them to contribute from home rather than traveling to a trial site, which can, in turn, increase engagement
- Possibly enabling continuous real-time data collection of endpoints (rather than periodic data collection during site visits)

Source: National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Drug Discovery, Development, and Translational Health (NAS *et al.*, 2019)

DCT and DHT Implementation during COVID-19

In March 2020, FDA released a guidance document regarding the conduct of clinical trials during the COVID-19 Public Health Emergency (Turner, 2020; U.S. FDA Conduct, 2021). This document provides practical advice for ensuring participants' safety, maintaining data integrity, and accounting for pandemic-related variability in trial protocols. It advocates for remote and decentralized trial methods, offering detailed considerations and recommendations for their implementation and integration into the study when appropriate. An expert on vaccine development pointed out that strong guidance documents from FDA early in the pandemic (Turner, 2020; U.S. FDA Conduct, 2021) helped many trials finish during COVID-19 pandemic and observed that some that did not follow recommendations struggled.

Two experts spoke of the challenges of referring to decentralized trials as a "separate category" of trials, instead emphasizing that decentralized *elements* and DHTs can be incorporated into a multitude of trials and trial designs to drive efficiencies and patient centricity. For example, even a fully inpatient trial might achieve more efficient and more patient-centric enrollment by designing an electronic informed consent (eIC) process that incorporates educational videos and interactive elements. Using these strategies to reduce on-site visits also benefits sponsors because of their high costs for clinical staff and significantly higher time burdens for participants.

Over the course of the COVID-19 pandemic, DCTs and DHTs saw effective use during various stages of the clinical trial. The implementation of these tools is described by trial stage below.

Trial recruitment, enrollment, and informed consent: Digital tools have long allowed patients to complete pre-screening, consultation, and informed consent through video-meetings or virtual platforms, but these approaches were leveraged more frequently during the COVID-19 pandemic. Although many non-COVID-related trials faced disruptions and delays in recruitment, those that had incorporated digital and decentralized strategies from the beginning were able to proceed and sometimes even benefit from the situation. For example, the "Intuition" study (ClinicalTrials.gov identifier: NCT05058950), an observational study using multimodal sensors to measure cognitive health in adults and detect mild cognitive impairment launched in January 2021, was designed to be remote and managed to recruit thousands of participants within the first three months. The surge in enrollment could be attributed, in part, to the COVID-19 pandemic because people who might have otherwise been involved in different studies opted to join the INSIGHT study. Other strategies to meet the patients where they are included the engagement of retail pharmacies, such as Pfizer's partnership with Walgreens to allow patients to conveniently enroll in the Paxlovid trial (ClinicalTrials.gov identifier: NCT05576662) while picking up their prescriptions (Grabenstein, 2022). These examples further underscore the importance of a patient-centric approach in increasing clinical trial participation.

Sponsors facilitated eIC through online portals, mobile apps, secured emails, or text messaging (Josan *et al.*, 2021; Lee *et al.*, 2021; U.S. FDA Conduct, 2021). These approaches were used to not only reach patients at their homes but also drive enrollment of intensive care unit patients, as non-clinical staff were frequently barred from entering patients' rooms or hospitals. The COVID-19 experience also highlighted the importance of a well-designed—often multimodal—eIC process, in which standard consent forms and language are enhanced by infographics, videos, links to learn more, Slack support groups, and multiple language options to improve patients' experience and comprehension. Independent experts cited better retention of information and higher patient satisfaction with the enhanced versions of consent procedures compared with the standard approach to decentralized/remote patient consenting of a 20-minute phone call. More importantly, enhanced forms of informed consent processes have been shown to empower people who were historically underrepresented in clinical studies, as witnessed in the All of Us study, which uses such approaches to enroll a group of participants that "reflects the diversity of the United States" (All of Us, 2020).

Treatment and monitoring: To minimize barriers to patient recruitment and participation, several experts highlighted the importance of patient-centric data collection; this includes accommodating participants by facilitating remote data collection outside the clinical setting. The experts saw this as a vital approach under all circumstances but particularly imperative during the COVID-19 pandemic, when patients could not or did not want to travel to clinical sites. The logistical challenges of conducting clinical trials amid a pandemic led to the adoption of several decentralized trial elements for clinical trial operations, often enhanced by DHTs. These include the following:

- **Telemedicine**, the remote delivery of health care services, played a crucial role in substituting in-person visits and ensuring the continuity of clinical trials during the pandemic. It encompassed various trial aspects, including virtual clinician visits, patient monitoring, symptom reporting, and virtual pill-taking (medication adherence monitoring through home delivery coupled with video conferencing software).

  Although telemedicine existed in the United States before COVID-19, its use was significantly constrained in clinical care delivery and research. These constraints included limited reimbursements, underdeveloped digital infrastructure, ambiguities in IRB jurisdiction (for some federally funded research), other regulatory variations across states, and restrictions on cross-state health professional licensing (Apostolaros *et al.*, 2020; Lee *et al.*, 2021)**.**

  To ease these barriers during the COVID-19 pandemic, the Centers for Medicare & Medicaid Services issued waivers to grant payment parity between telehealth and in-person care, and the Office for Civil Rights exercised enforcement discretion (and effectively halted the use of penalties) for use of technologies that did not comply with the Health Insurance Portability and Accountability Act (HIPAA) (e.g., Zoom, Skype, and FaceTime) to provide telehealth services (Baumann, MacArthur and Michalski, 2020; Shachar, Engel and Elwyn, 2020; De *et al.*, 2021; Schofield, 2021; HHS HIPAA, 2022). In addition, some states provided emergency licensing waivers, which alleviated the burden of cross-state licensure requirements (Federation of State Medical Boards, no date). Although these policies were not universally adopted across the United States, they expanded the deployment of telemedicine in clinical practice as well as in clinical trials—not only for research and care associated with COVID-19 but also for other diseases (Freedberg *et al.*, 2020; Hatcher-Martin *et al.*, 2020; HHS, 2020; De *et al.*, 2021; Josan *et al.*, 2021; Greenough *et al.*, 2022; Kaizer *et al.*, 2023).

  All the interviewed experts agreed that the COVID-19 pandemic demonstrated that many aspects of clinical trials can be effectively performed remotely—a belief long held by the DCT community but previously not widely adopted. The experts also agreed that, to harness the benefits of telemedicine for clinical trials outside of emergency situations, greater reimbursement parity and changes in cross-state licensing regulations are necessary, especially because many COVID-19 pandemic policies (at local, state, and national levels) have been reversed since the end of the federal public health emergency in May 2023.

- **Self-monitoring and at-home measurements:** During the COVID-19 pandemic, many sponsors opted to send measuring devices, such as blood pressure monitors, spirometry tools, or glucose monitoring devices, directly to patients' homes for self-monitoring to substitute for (some) in-person clinical site visits. Their use during the COVID-19 pandemic revealed that patients were capable of effectively using these at-home measuring devices. One expert referred to a PROGRESS study in which patients were offered an option of at-home visits or self-guided at-home testing to perform glucose monitoring. The vast majority (>90%) of the participants chose self-guided at-home testing, allowing the trial's leaders to shift some study coordinators' time to other work. The possibility of reducing at-home visits also creates potential for cost reduction and resource optimization. This trial includes a patient-centric approach that acknowledges the diverse range of patient preferences and comfort levels, fostering inclusivity regardless of participants' technological literacy.

  Certainly, activities such as neurological evaluation, neurocognitive or joint mobility assessment, and radiology scans require nuanced clinical judgment and expertise that patient-reported outcomes or at-home measurements cannot easily capture in the absence of a clinician. Moreover, concerns about the discrepancies between at-home and ambulatory clinic measurements remain. Still, it's possible some at-home measurements might capture data in the context of a patient's daily routines and natural behaviors, providing more true-to-life evidence on disease progression, symptoms, and side effects. Some discrepancies could be potentially reduced through telemedicine to supervise patients during the measurements. Others will inevitably remain, and ongoing research is necessary to validate at-home measurement tools and the measures they collect.

  Interviewed experts agreed that despite these uncertainties, there remains significant value in leveraging at-home measurements tools and that such approaches can and should be leveraged on an ongoing basis to substitute for select in-patient visits. A combination of ambulatory clinic and at-home measurements could be what one expert called the "goldilocks" solution, offering greater flexibility to patients and better accounting for real-world evidence (RWE) and maintaining oversight and the broad integrity of the trial's findings.

- **DHTs** were used for remote patient monitoring and data collection during the COVID-19 pandemic. For example, to monitor COVID-19 patient recovery or cardiac safety signals, some patients were allowed to use wearable devices and mattress sensors to track their vital signs such as heart rate, respiratory function, body temperature, sleep patterns, and movement. This continuous monitoring resulted in data reflecting the patient's everyday status and could alert health care professionals of new side effects and symptoms (Seltzer *et al.*, 2022; Von Preyss-Friedman *et al.*, 2022). Trials also employed custom mobile applications, such as a medication adherence app that reminded patients to take their medication, specified the dosage, tracked missed doses, and provided refill notifications (Dockendorf *et al.*, 2021; Volpi *et al.*, 2021). Other digital tools included symptom tracking apps and eJournals that recorded symptoms and

patients' experiences in real time, as opposed to the retrospective reporting normally collected in person during hospital visits (Drury and O'Connor, 2021; Houhamdi and Fournier, 2022; Pandit *et al.*, 2022). Although DHTs hold promise for clinical research, trials using DHTs must ensure that patients have prior training or digital proficiency when reporting their symptoms and validate their methods so that they can maintain the integrity of these measurements (Hashem *et al.*, 2020; Inan *et al.*, 2020)**.**

- **Trials leveraged local medical centers and mobile units** for interventions unsuitable for virtual conduct. In many trials, mobile units (e.g., phlebotomists) collected biological samples directly at patients' homes. For instance, the Healthy-Lung trial (ClinicalTrials.gov identifier: NCT04798664) accomplished two-thirds of its sample collections through mobile units, offering safer alternatives to on-site visits during the COVID-19 pandemic. An expert specializing in DCTs emphasized that despite the higher costs involved, the use of mobile units significantly simplifies patient participation in the trials and provides an additional tool to augment the diversity of participants.

  Clinical trial activities that required medical site visits, such as radiotherapy and imaging, were often conducted in collaboration with local medical centers (Izmailova, Ellis and Benko, 2020; Ali *et al.*, 2021; Anderson, 2021; Boughey *et al.*, 2021; De *et al.*, 2021; Park *et al.*, 2022). As with all multisite trials, this collaboration necessitated substantial harmonization of practices to address the variability in medical devices and protocols used across the health centers. Another innovation incorporated during the pandemic was allowing community pharmacists and local health centers to administer medications or delivering medication direct to patients (National Cancer Institute, 2020; Waterhouse *et al.*, 2020; McDermott and Newman, 2021; Sami *et al.*, 2021; Van Norman, 2021; Mohamed Ibrahim *et al.*, 2022; Pantasri, 2022; Kaizer *et al.*, 2023). Handling of medication outside of a centralized trial site requires additional oversight, detailed protocols, and close monitoring to ensure participants' compliance and drug stability and appropriate storage (e.g., temperature tracking). Precautionary measures also had to be implemented to prevent unauthorized medication access and to ensure timely refills to prevent study interruptions (National Cancer Institute, 2020; Van Norman, 2021). Beyond emergency conditions, involvement of local health centers and direct-to-patient delivery could serve to improve accessibility to clinical trials, benefiting patients from rural areas or those with limited travel possibilities.

With the conclusion of state public health emergency declarations beginning in 2021, and the federal public health emergency concluding in May 2023, certain regulatory waivers and flexibilities were reversed (Cox *et al.*, 2023; U.S. FDA Staff, 2023). For instance, some states discontinued cross-state licensing waivers (*Licensing across state lines*, no date), and the use of HIPAA-compliant technologies became a requirement for virtual patient encounters (HHS HIPAA, 2022; Cox *et al.*, 2023). Notably, certain platforms such as Zoom have updated their services to provide HIPAA-compliant solutions (Zoom, 2021; Alder, 2023). Significant aspects of telemedicine, such as payment parity, waiver of

geographic and location requirements, and the in-person visit requirement for initiating tele-behavioral health services, were extended until December 31, 2024 (U.S. FDA Staff, 2023; HHS Fact Sheet, 2023).

CONSIDERATIONS FOR SPECIAL POPULATIONS: LESSONS FROM ONCOLOGY AND RARE DISEASE TRIALS

Given the typical geographic dispersion of patients with rare diseases,[3] some trials of therapies for these conditions were already designed to incorporate decentralized elements before the COVID-19 pandemic. Interviewees and a 2023 study reported that these trials experienced fewer or less severe disruptions during COVID-19 (Miller and Miller Needleman, 2023). A 2020 McKinsey survey of 20 cell and gene therapy companies in Europe found that 55% of organizations paused site activations and enrollment visits (Loche *et al.*, 2020). Because of the inherent paucity of participants for rare disease trials, interventions to salvage trials and facilitate ongoing research were seen as particularly valuable. Companies used DHTs to collect data when possible, which helped trial leaders use other resources efficiently during the COVID-19 pandemic. In addition, an expert in the development of therapies for patients with rare diseases noted that there have long been numerous support programs to get patients to study sites, including travel grants for participants and families, but the funding for these programs and existing collaborations with patient advocacy groups were further expanded during the pandemic.

Oncology trials were dramatically impacted by COVID-19, with one analysis finding that 95% of clinical trials in the space were suspended at the beginning of the COVID-19 pandemic (Wilkinson, 2021). Of the trials that managed to navigate the COVID-19 period, many relied on tools facilitated by existing regulations and regulatory guidance documents, including eIC from participants, drawing blood close to the patients' homes (rather than at a central study site), and remote monitoring. All of these approaches were already allowed (CTTI, 2018; Florian, Forrest and Randall, 2018; Gottlieb, 2019; Rodriguez-Chavez, 2019) and sometimes incorporated into trials, but COVID-19 accelerated their adoption. Experts cited patient registries and community support groups across various disease spaces for their role in facilitating recruitment and creating a valuable online community for patients. Patients were able to use them to find needed information and resources and communicate with others who have the same diagnoses.

DIGITIZATION VERSUS DIGITAL TRANSFORMATION

Expert descriptions of DCTs in the first year of the pandemic emphasized unplanned augmentation of existing protocols with digital tools and "bolt-on solutions" to existing trials to enable (more) remote trials. These included activities such as replacing paper consent documents and in-person meetings with eIC and virtual visits. Experts noted, however, that simply digitizing existing processes and approaches might offer limited value and, in some cases, introduce more overhead work if they are not

[3] The Orphan Drug Act defines a rare disease as a disease or condition that affects fewer than 200,000 people in the United States.

implemented thoughtfully. An expert specializing in DCTs recounted a case in which the IRB required screenshots of all eICs in all languages, a task that necessitated 800 hours to complete and which, the expert noted, was not otherwise associated with any value-add for participants or the trial sponsor. Successful digitization of individual activities requires aligning all impacted parties, not just the direct users.

Digital transformation connects those individual innovations to broadly impact clinical trial experiences and quality. For example, experts underscored the value of making trials more participant-centric and also spoke of the importance of "giving something back" to participants, such as providing actionable data or education about their health. This reciprocity not only fosters trust but also empowers participants in their health care journey. For instance, the Johnson & Johnson–sponsored Heartline trial (ClinicalTrials.gov identifier: NCT04276441) included upfront education to the population with high prevalence of cardiac arrhythmia.

This approach allowed the entire cohort to learn and engage throughout the trial, leading to a better understanding of digital alerts and results, as pointed out by the study representative. This example stands in stark contrast to most traditional trials in which participants receive a few email updates about findings (often months after their own involvement) without tangible insights for the participants themselves. Creating value for trial participants can involve establishing social networks and communities (see Box 4), although doing so might risk sharing information that could compromise participant blinding. The pandemic demonstrated that these additional measures, which often involve minimal overhead compared with existing study procedures, can significantly enhance patients' adherence and satisfaction.

Box 4: Empowering participants and communities through clinical trials

The 4YouAndMe Trial
A clinical trial led by the 4YouAndMe nonprofit demonstrated an example of participant empowerment through clinical trials. The objective of the study was to determine the feasibility of COVID-19 detection before the onset of symptoms using continuous monitoring through smartwatches and aurora rings. The study recruited 1,200 nurses at intensive care units across the country; it took an innovative approach by building an entire community around the trial participants. The trial offered weekly touch points to further support the participants. The study representatives reported extraordinary adherence and positive attitude of participants toward the study involvement. The participants' positivity stemmed from the additional benefits of trial participation in the form of a social network. By fostering a sense of community, this clinical trial not only focused on the scientific objectives but also recognized the importance of participant experience and engagement. Although the community approach might not be suitable for all trials, an expert highlighted that communities already exist around rare diseases, and digital technology might provide new avenues to reach people and engage them in clinical trials. Source: (*4YouandMe*, no date) and expert interview

As another example of needing to link individual innovations and reduce the burden placed on trial sites as clinical trials become digitized, experts highlighted an increasing need to create integrated and standardized systems useful across multiple trials simultaneously. Many trials demand their own

technology stack, including devices, leading to site challenges with managing an overwhelming array of tools. One expert recalled a case involving a site reaching its saturation point of devices and technology, in which the site implored, "please don't give me another tablet!" Inclusion of bring-your -own-device options could alleviate some issues and improve efficiency in the context of a public health emergency and more broadly as mobile technology becomes more ubiquitous. For instance, the DETECT trial (ClinicalTrials.gov identifier: NCT04336020) managed to recruit 41,000 participants in four weeks using a bring-your-own-device approach. An expert familiar with this trial reported large time savings, saying they distributed devices only when needed (e.g., to include people who didn't have their own technology in underrepresented groups).

Box 5: The Michael J. Fox Foundation's virtual study demonstrates digital transformation

The opportunity created by digital technologies
People with and without Parkinson's disease were enrolled using The Michael J. Fox Foundation's Fox Trial Finder, a clinical trial matching tool. More than 160 participants from 39 sites spread across the country were enrolled in the study. Parkinson's disease is typically visually diagnosed. The virtual platform used in the study allowed investigators to visually examine Parkinson's disease status remotely via videoconferencing, without requiring participants to leave their homes. Furthermore, it allowed for wide geographic representation and enabled participation for those who previously had no means of doing so. In a follow-up evaluation of participants' experience, 90% of participants reported satisfaction with the trial, 80% reported they were more willing to participate in a similarly designed trial, and 85% reported they would be more able to participate if they could do so remotely. Source: (NAS *et al.*, 2019)

An expert well-versed in DHTs underscored that although these technologies have the potential to improve retention, their effectiveness hinges on smooth integration into patients' lives. Adopting a product-like mindset, which emphasizes functionality and a positive user experience, can prove transformative in this context. For instance, trials often require patients to navigate different gadgets, apps, and software, which can overwhelm some participants. Two experts separately suggested that a more streamlined and convenient user experience could be achieved through a unified platform that would offer multiple functionalities, including monitoring vital signals, medication reminders, appointment scheduling, and telemedicine consultations. Further, one expert noted that, for those suffering from conditions that already create daily stress and demand a high burden of ongoing management, such as long COVID-19 or multiple sclerosis, minimal interaction with DHTs and passive data collection (when possible) might be particularly valuable.

The COVID-19 pandemic subjected DCTs and DHTs to a crucial stress test, driving emergent innovations and prompting solutions that might not have been explored otherwise. Still, caution is necessary when assessing the lessons learned and cost implications of DCTs and DHTs from this period because they might not fully reflect the future landscape of these approaches and tools. The pandemic-induced transition to decentralized and digitized clinical trials was primarily driven by the urgent need to save trials from an ethical and new product development perspective rather than the result of

premeditated planning and design. This abrupt transition was often associated with substantial costs, often without adequate opportunities for return on investment. As one expert put it:

> *"The sudden change to DCT was hard. I'm not sure if we did it in the best way; we did in the fastest way. It was sort of retrofitting—good DCTs should be designed with decentralization in mind."*
>
> *- Expert on DCTs*

The experts on DCTs and DHTs and those from other backgrounds consistently agreed that DCTs and DHTs offer an opportunity to reimagine clinical trials to create a higher quality participant experience and generate better, more efficient evidence for sponsors. Such a digital transformation for clinical trials requires proactively designing the novel approaches into a connected trial protocol, from patient recruitment to patient-centric monitoring to database lock, to enhance overall participant experience, sponsors' outcomes and endpoints, regulatory review, and public acceptance. Of course, participant-centric trial design means considering many relevant patient preferences in any given setting. For example, some participants might not want trial personnel coming to their homes, and others might not be comfortable with technology. As such, experts highlighted that outside of the pandemic, during which DHTs and DCTs might have been the only way to keep trials going, these approaches should be seen as just some of many ways in which clinical trials can be made more inclusive and participant centric. Any deployment outside of a pandemic should be fit-for-purpose with respect to the study and the target participant population.

OPPORTUNITIES FOR THE FUTURE

Technology and decentralization played a pivotal role during the COVID-19 pandemic and are poised to become crucial tools for research during future public health emergencies and more broadly. Integrating DCT elements and DHTs into routine clinical trial procedures can substantially reduce emergency-related expenditures in the future.

The value demonstrated by DCTs and DHTs during the COVID-19 pandemic extends beyond emergency situations, as experts universally highlighted. Historically, clinical trial participation has been limited, with only 5% of the U.S. population participating in trials, and 70% living about two hours away from trial sites (Miseta, 2022). This challenge is compounded by dropout rates that can reach up to 30% (Miseta, 2022). Recognizing these hurdles, experts endorse DCTs and DHTs to bring clinical trials closer to participants and increase clinical trial enrollment rates (Agrawal *et al.*, 2021; Rogers *et al.*, 2022; Adesoye, Katz and Offodile, 2023).

This sentiment has spurred creative approaches, such as integration of retail pharmacies into the trial ecosystem (although one major player, CVS, has already left the business [Fierce Healthcare, 2023]).

Tailoring trial recommendations based on patient medication profiles and establishing connections during medication pickups—a strategy that proved fruitful during the pandemic—can drive efficiencies for sponsors and participants. Moreover, retail giants such as Walmart, with its widespread presence, offer an avenue to enhance trial visibility and extend outreach to a broader and more diverse patient base (see Chapter 6, Participant diversity drivers and infrastructure).

Engaging people who already use DHTs such as smartwatches could further streamline patient enrollment. An additional approach to improving data-gathering activities involves embedding trial-related information into contexts in which patients are already engaged, such as during blood donation. For example, researchers could add a simple targeted consent form into the existing forms, allowing patients to consent that a portion of their blood might be used for research. Such an approach could be introduced with minimal overhead. Experts further underscored the value of integrated electronic medical records. For instance, connecting clinical trials with diagnostic codes would allow clinicians to quickly suggest appropriate trials to qualifying patients, further increasing trial awareness and patient outreach.

The pandemic revealed that DCTs and DHTs can potentially include people who would otherwise remain excluded from trial participation, such as those from rural areas, from underprivileged regions, and with limited mobility or travel capabilities (Lee *et al.*, 2021; Noonan and Simmons, 2021; Sedhai *et al.*, 2021; Aitken, Connelly and Leamy, 2022). These technologies also represent opportunities for trials focused on rare diseases, in which localized patient clusters are typically absent (Moore *et al.*, 2022; Rogers *et al.*, 2022). Another novel opportunity involves including patients with severe conditions, such as severe Crohn's disease, who might be too ill to leave their homes and participate in traditional trials.

DCTs and DHTs are not universally appropriate solutions. They are often more suitable for later-phase trials (Osborne and Danheiser, 2023), for which safety profiles are better known, and for long-term studies and post-approval or post-market surveillance. Virtual patient visits might be inadequate for detecting certain symptoms and changes (Lee *et al.*, 2021). The accuracy of remote measurements, whether self or device-reported, will require validation for each measurement and setting (Lee *et al.*, 2021; Aitken, Connelly and Leamy, 2022; Osborne and Danheiser, 2023).

In some cases, DCTs might require higher upfront costs and investments in infrastructure, digital platforms, direct-to-patient medication delivery, and harmonization of protocols across local health centers (Aitken, Connelly and Leamy, 2022; Osborne and Danheiser, 2023). These costs might (or might not) be recouped through faster recruitment and higher retention rates as well as the reuse of software and tools for other trials. Another avenue for cost effectiveness is leveraging shared areas of interest across therapeutic domains. For instance, a therapeutic interest area such as nausea and vomiting holds relevance in gastroenterology and oncology. Identifying such cross-disciplinary points for reuse can justify investments in trial infrastructure and might increase the likelihood of success.

LESSONS LEARNED FOR DECENTRALIZED CLINICAL TRIALS AND DIGITAL HEALTH TECHNOLOGIES

The accumulated expert interviews and literature outcomes of the use of DCTs and DHTs catalyzed by the COVID-19 pandemic underscore that **DCTs and DHTs offer participant-centric approaches to clinical research and have the potential to reduce barriers to trial participation, enhance engagement, improve retention, and drive participants' satisfaction**. These lessons apply to therapeutics, vaccines, and diagnostics in pandemic and non-pandemic (normal) contexts.

Telemedicine or virtual visits, in which therapy assessments and interventions are carried out online or at home, could reduce pandemic disruptions for many trials, not just pandemic product trials. Remote models can lower costs, focus on individual family needs, and support equal access to evidence-based quality. Achieving telemedicine advantages in non-pandemic settings will necessitate clarifications of and some updates to reimbursement and state-specific medical licensing regulations.

Decentralization supports the extension of trial participation to underserved populations, including rural, socioeconomically disadvantaged, and mobility-limited people, as well as patients with rare or severe diseases. **At-home measurements can substitute for certain in-site visits**, improving patient flexibility, generating RWE, and concurrently reducing costs and study coordination workload.

Fit-for-purpose uses of DCTs in "meeting people where they are" proved effective at various stages of a trial, ranging from recruiting, to consent, to data collection. Utilizing social media, pharmacist referrals, and/or community ambassador involvement are just some of the decentralized approaches that can support clinical trials. As such, **DCTs and DHTs should be approached as tools to enhance the conduct of clinical trials, rather than distinct entities**. For example, eIC processes, supplemented with visuals and videos, improves information retention and patient satisfaction, while also strictly adhering to the goals of informed consent processes for research.

With respect to any future clinical trials and for pandemic preparedness, it will be important to draw on experiences with the use of decentralized approaches and DHTs during the COVID-19 pandemic. These approaches and tools proved vital to keeping many trials going during the COVID-19 pandemic, but were widely viewed as "retrofits" and in many cases they were costly to incorporate into trial designs after-the-fact. Vitally, **integration of situation-appropriate decentralized elements into clinical trials will result in building both the infrastructure and expertise needed for future pandemic resilience**. As a corollary: solutions that "bolt on" DHTs and decentralized elements to existing trials will fail to take advantage of the full promise of these tools and learnings from the COVID-19 pandemic.

5. PLATFORMS AND STATISTICAL INNOVATION IN CLINICAL TRIAL DESIGN

Because of the urgency to identify viable COVID-19 treatments, some clinical trials implemented previously underused approaches such as adaptive (often Bayesian) statistical analysis and platform frameworks. Key definitions are briefly provided here, with additional detail available in Appendix A.

UTILIZATION OF PLATFORMS AND STATISTICAL INNOVATION IN CLINICAL TRIAL DESIGN DURING COVID-19

Adaptive trial design, Bayesian statistical analysis, and platform trials helped accelerate the evaluation of multiple therapeutic candidates while also satisfying regulatory requirements for drug safety, characterization, and evaluation (Abani *et al.*, 2022; Butler *et al.*, 2023). A small number of platform trials evaluated individual agents against common (or shared) control arms (Lundgren *et al.*, 2021; Files *et al.*, 2022; McLeod *et al.*, 2023). These trials often also performed frequentist interim analyses, Bayesian statistical assessments, or both.

Although many conventional (i.e., single-product, frequentist) trials were rapidly established and enrolled hundreds of thousands of participants during the COVID-19 pandemic, novel trial designs—namely those with platform approaches or adaptive elements—comprised a comparatively small fraction of overall enrolled randomized controlled trial (RCT) subjects (LaVange *et al.*, 2021; Lundgren *et al.*, 2021; Files *et al.*, 2022; Higgins *et al.*, 2023; Naggie *et al.*, 2023). Despite the small number of participants enrolled in such trials, platform trials generated most of the evidence on effective COVID-19 therapeutics (ATTACC Investigators *et al.*, 2021; Gordon *et al.*, 2021; RECOVERY Collaborative Group *et al.*, 2021) and identified likely ineffective COVID-19 treatments (Naggie *et al.*, 2022; McCarthy *et al.*, 2023).

PLATFORM TRIALS

Platform trials are open-ended trials that occur under master protocols, facilitating the addition, evaluation, and elimination of trial arms/candidates without specifying timing parameters. Unlike a traditional RCT that tests a single intervention and typically ends (i.e., decommissions its trial operations, data collection, and associated infrastructure) when the study is complete, platform trials are RCTs that keep the trial active over longer periods via amendments to the master protocol while other sub-studies (trial arms) continue or have been completed. Unlike single-intervention-oriented trials, in which a drug is compared with standard care or a placebo, a platform trial is typically disease-centric, determining what therapy is optimal for a given indication or sub-population.

Platform experts have highlighted that the core advantage of the platform approach is that a product can be quickly added for testing through a modular amendment to an existing master protocol, resulting in more efficient trial initiation and execution within a broader ecosystem of ongoing clinical research. Platform trials have the potential to accelerate and streamline knowledge generation across indications and patient populations, but they are inherently more statistically and organizationally complex to set up and manage. Research suggests that, despite higher up-front costs and set-up times, platform trials might lead to an overall cost reduction for individual agent evidence generation (Park *et*

al., 2022). The prevailing biopharmaceutical research and development funding models, however, do not create strong incentives for more widespread platform trials (Park *et al.*, 2022), a sentiment echoed in expert interviews.

> *"From the scientific perspective, it is difficult to find trials where the platform is not useful."*
>
> - *Clinical trialist*

ADAPTIVE TRIAL DESIGN

Adaptive trial designs allow for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial. Adaptive trials build in flexibility as they use a design-review-adapt-conduct-analyze process rather than a traditional RCT process of design-conduct-analyze (Pallmann et al., 2018).

Adaptive trials may evaluate single agents or multiple agents in parallel (adaptive platform trial). For example, single agent designs involve one intervention (simplifying the assumptions or methods that can be used), and multiple agent designs assess multiple interventions (e.g., therapies) where the toxicity curve or other properties may not be well understood, defined, or both. Adaptive single-agent designs were used in COVID-19 studies earlier in the pandemic, whereas adaptive multi-agent platform trials were mostly employed in later COVID-19 pandemic stages after clinicians and researchers established the needed infrastructure (Butler *et al.*, 2021, 2023; Abani *et al.*, 2022).

During the COVID-19 pandemic, a subset of clinical trials simultaneously evaluated multiple therapeutics using adaptive platform trials to rapidly identify promising treatments for COVID-19, changing clinical management of COVID-19 worldwide (RECOVERY Collaborative Group *et al.*, 2021; Butler *et al.*, 2023). Investigators leveraged trial coordination resources, data collection frameworks, robust national data registries (when available), and public health infrastructure (Angus, Derde, *et al.*, 2020; RECOVERY Collaborative Group *et al.*, 2020; Griffiths *et al.*, 2021; LaVange *et al.*, 2021; Yu *et al.*, 2021; Reis *et al.*, 2022; Butler *et al.*, 2023). In one example, the U.K. RECOVERY platform trial randomized more than 48,496 COVID-19 patients to nine treatment groups with a single shared standard of care control group ([Abani *et al.*, 2022], Box 7). Platform trials also generated evidence that identified marginally efficacious or non-efficacious COVID-19 treatments, and, according to one interviewed platform expert, this evidence aided in the de-emphasis or removal of these treatments from standard of care guidelines. One expert noted that, from the thousands of registered COVID-19 trials, four platform trials generated about 90% of evidence for COVID-19 treatments recommended by FDA or clinical organizations. The literature provides no exact quantification of this impact.

In the literature on adaptive trials from before the COVID-19 pandemic, one evaluation compared conventional and adaptive protocols for 29 trials and found 62% of adaptive trials completed with time savings compared with non-adaptive designs. Overall, trials saved 56 days on average by employing an

adaptive approach (Lorch *et al.*, 2012). During the COVID-19 pandemic, new data on the efficiencies associated with adaptive platform trials emerged. In the REMAP-CAP trial, trialists stopped two arms, convalescent plasma and corticosteroids, early with only N = 2,011 and N = 403 participants enrolled (Angus, Derde, *et al.*, 2020; Higgins *et al.*, 2023). In the same adaptive platform trial, trialists enrolled the Interleukin-6 receptor antagonist arm to successful completion with 401 participants (REMAP-CAP Study Investigators, 2021). It is important to note that the REMAP-CAP investigators cited the RECOVERY results as the reason for their closing of these trial arms, demonstrating organizational adaptiveness to redirect resources to other sub-studies rather than to dogmatically add evidence to a resolved research question (*REMAP-CAP*, no date). Although both arms stopped, doing so helped liberate and redirect resources and participants to other viable candidate therapeutics and optimize COVID-19 patient treatment guidelines.

Trialists cited COVID-19 adaptive platform trials as more efficient per evaluated candidate product (operationally streamlined) and more informative per participant (fewer participants required to detect futility or a given effect size) compared with traditional fixed trial designs (Angus, Berry, *et al.*, 2020; Griffiths *et al.*, 2021; Yu *et al.*, 2021; Files *et al.*, 2022; Butler *et al.*, 2023; I-SPY COVID Consortium, 2023). In the case of the AGILE adaptive platform trial, investigators cite the seamless ability to expand their existing Phase I platform, where the compound's dose was established, into a Phase II to confirm efficacy of a promising compound (Griffiths *et al.*, 2021). One adaptive trial expert indicated adaptive platform trials offer a more efficient ecosystem, in which both negotiation and organization are performed upfront, which makes the conduct of specific trial arms highly efficient. This echoes comments from clinical trial operations experts, who cited aspects of standardization and upfront clarity as drivers of efficiency in clinical trials in other contexts.

Of note, most adaptive platform trials for COVID-19 products did not occur in the United States and did not evaluate compounds on the U.S. population. When asked about this geographical divide, platform trial experts indicated that the United States did not have the integrated health care infrastructure found in some other countries. For example, the U.K. RECOVERY trial identified and randomized patients using electronic health records (EHRs). Such integration enabled swift, efficient, large-scale randomization of patients into each of the treatment arms in parallel with real-time data collection from the EHR.

Adaptive trials, platform trials, or both can be used across all phases of research and through the evaluation of compounds across any context. There are specific upfront costs associated with adaptive platform trials, including data and IT infrastructure needs that typically far exceed those of a more traditional frequentist trial. For example, infrastructure is needed to isolate the results—both interim and final—from different arms of an adaptive platform trial. Different arms of a platform trial will often have different sponsors, which, for various reasons, do not want their data shared with other platform participants or are apprehensive about head-to-head comparisons of their product (e.g., a therapeutic) with that of others being tested on the same platform. Notably, in our environmental scan, no diagnostic technologies were evaluated using either of these trial design paradigms. Two different

experts in platform and adaptive trial design spoke to the catalytic effect that platforms necessitate all—seemingly disparate entities—to come together and trust each other.

For illustrative purposes, summary points of comparison between traditional frequentist trials and adaptive platform trials are available in Box 6.

Box 6: Traditional trials versus adaptive platform trials

Drawbacks of conventional (frequentist) randomized controlled trials	How does an adaptive platform trial address or improve on this?
● Typically only tests one therapy or has one treatment arm	● Multiple study arms envisioned from the start with a platform trial ● Multiple therapies can be tested in tandem
● Trial statistical experts cannot use data collected in the trial to inform the trial's ongoing activities	● Trial statistical experts can assess interim data at predetermined trial milestones for futility and to alter trial design while continuing the trial
● Potential mismatch with "precision" research, in which therapies are increasingly specific to patient subtypes	● Better able to evaluate disease subtype responses to therapies
● Requirement to pay fixed costs related to trial infrastructure for each additional RCT	● Can spread such fixed costs across multiple agents and (often a growing number of) trial arms
● Extensive delays related to start-up activities between trial phases are common	● Seamless trial designs allow products to flow through trial phases more quickly and accumulate statistical power

BAYESIAN STATISTICAL ANALYSIS

Bayesian analysis is an approach for learning from evidence as it accumulates. Bayesian statistical analysis incorporates prior knowledge about a treatment effect in its statistical inferences (McCreary *et al.,* 2022). In traditional (frequentist) clinical trials, statistical methods might use information from previous studies only at the design stage. Then, at the data analysis stage, the information from those previous studies is considered to be a complement to, but not part of, the formal analysis. In contrast, the Bayesian approach uses Bayes' theorem to formally combine prior information with current information on a quantity of interest. Bayesian approaches can reduce clinical trial sizes and enhance trial speed (Saville and Berry, 2016). A risk of Bayesian analysis is that studies of the same research question might generate different a priori probability distributions (patient population by therapy), resulting in distinct or even conflicting conclusions. Bayesian approaches have their own regulatory guidance document for planning, statistical analysis plans, and submissions compared with frequentist analysis, most of which was seen in the medical device space pre-COVID-19 (U.S. FDA Bayesian, 2018; U.S. FDA Adaptive, 2020; Ruberg *et al.,* 2023).

Adaptive study designs typically use Bayesian analysis to facilitate an agile trial process, allowing for the rapid evaluation of multiple hypotheses across varying indications and therapies, leading to more efficient futility analyses and identification of promising candidates and a dynamic shift for patient recruitment to accelerate evidence for those promising candidates. At least 80 COVID-19 clinical trial

publications include Bayesian analysis (World Health Organization, 2023). One example is the I-SPY COVID adaptive platform trial, which incorporates Bayesian stopping or graduation rules to efficiently halt ineffective candidates or to progress promising therapies (Files *et al.*, 2022). Stopping futile arms can save time, liberate resources, and decrease the number of patients who would otherwise have been enrolled in a futile trial arm. Researchers also used Bayesian survival regression models to model the hazard functions for the two events of interest: (1) recovery (treating death as a competing event) and (2) overall death from COVID-19. Bayesian proportional-hazard Weibull models simulate outcomes (i.e., the cause-specific hazard function for recovery, treating death before recovery as a competing event, as a function of study arm), and adjusted for baseline COVID-19 level at a given moment in the COVID-19 pandemic. Importantly, in such a study design, the control group is chosen from the same population as the investigational agent group, which, because of the potential of evolving real-time recovery and fatality rates in an ongoing pandemic, potentially enables more optimal control comparison as opposed to the alternatives (Files *et al.*, 2022).

In a direct comparison of Bayesian and frequentist interventional approaches, two trials evaluated the potential impact of therapeutic dosing of the anticoagulant Heparin on patients with COVID-19 rather than the standard of care, which used the typical lower doses of Heparin. In a collaborative effort between the REMAP-CAP, ATTACC, and ACTIV-4a platform trials (ATTACC Investigators *et al.*, 2021), randomization to Heparin began on April 21, 2020. After 276 days and 1,181 Heparin-treated patients, on January 22, 2021, the data and safety monitoring boards advised enrollment be discontinued for a planned adaptive analysis of data from 1,398 patients. The analysis revealed that the prespecified stopping criteria for superiority of a therapeutic-dose anticoagulation had been met. In contrast, in the HEP-COVID trial, which followed the classic RCT framework and frequentist statistical analysis, 130 patients were randomized to therapeutic dose Heparin between May 8, 2020, and May 14, 2021 (371 days) (Spyropoulos *et al.*, 2021). HEP-COVID, like the REMAP-CAP, ATTACC, and ACTIV-4A trials, found that in non-critically ill patients hospitalized with COVID-19, therapeutic dose anticoagulation with Heparin increased the probability of survival (ATTACC Investigators *et al.*, 2021). The Bayesian platform framework reached this conclusion in 74.4% of the time and with 9.1x the study participants of the RCT frequentist approach.

Other COVID-19 treatment trials maximized Bayesian primary analysis models to use previous enrollments in the standard-of-care arm of a trial to increase the precision of efficacy estimates, which allowed the trialists to declare futility with high precision because of low probability of a meaningful benefit of a given compound on time to recovery (ATTACC Investigators *et al.*, 2021). Employing a Bayesian approach allowed trialists to drop ineffective arms (in the case of both REMAP-CAP and RECOVERY, two arms) and to efficiently and quickly allocate limited trial resources to other interventions.

There is little to no publicly available quantitative evidence of cost savings based on Bayesian analyses (opposed to frequentist) through either simulations, controlled trials, or observational studies during the COVID-19 pandemic. Yet simulations conducted before the COVID-19 pandemic suggested adaptive Bayesian trials might require less than half the participants and time that traditional frequentist two-

arm trials require (Saville and Berry, 2016). Such trials also come with additional setup costs and unique needs that are not seen in other trials, such as the data and IT infrastructure needed to build firewalls between sponsors and trialists to manage protocol-compliant interim analyses and a much greater demand for computational power to run simulations. Future action could aim to quantify cost comparisons and other tradeoffs that are unique to Bayesian trials to direct future trial strategies.

> *"The COVID-19 pandemic was good for teaching us how platform trials can be successful and showing us that a Bayesian approach is probably the right way for the analytical approach."*
>
> - *Clinical trialist*

CASE STUDY: U.K. RECOVERY VERSUS U.S. NIH ACTIV ADAPTIVE PLATFORM TRIALS

Although there were several platform trials established during the COVID-19 pandemic, a comparison of the U.K. RECOVERY platform (Box 7) with the NIH ACTIV platform demonstrates that platform trials can differ in their speed and ability to enroll, which is highly correlated with the pre-pandemic medical information and clinical research infrastructure available to each. Both RECOVERY and NIH ACTIV evaluated aspirin and convalescent plasma as potential COVID-19 therapies.

For aspirin, the RECOVERY trial enrolled and dosed 7,351 participants in 140 days (November 1, 2020, to March 21, 2021) compared with 164 patients enrolled in 273 days (September 2020 to June 2021) in NIH ACTIV (Connors *et al.*, 2021; Abani *et al.*, 2022). It is important to note, however, that investigators stated that the NIH ACTIV trial arm for aspirin was stopped early because of an unanticipated low event (COVID-19) rate, to which the low enrollment might have contributed (Connors *et al.*, 2021). RECOVERY recruited 44.8x times more participants into its aspirin study in about half the time as compared with NIH-ACTIV.

For convalescent plasma, NIH ACTIV initiated three sub-studies assessing convalescent plasma, compared with a single RECOVERY sub-study. RECOVERY enrolled and dosed 5,795 patients in 232 days (May 28, 2020, to January 15, 2021) (Abani *et al.*, 2021). The first NIH ACTIV sub-study enrolled 468 patients in 346 days (April 17, 2020, to March 29, 2021) (Ortigoza *et al.*, 2022). The second NIH ACTIV sub-study, PassItOn, began only a week later, enrolling 438 patients in 438 days (April 24, 2020, to July 6, 2021) (Self *et al.*, 2022). The final NIH ACTIV sub-study, C3PO, was initiated five months later and enrolled 257 patients in 230 days (August 11, 2020, to March 29, 2021) (Korley *et al.*, 2021). Compared with the third NIH ACTIV convalescent plasma sub-study, RECOVERY enrolled 22.5x more participants in nearly the same number of recruiting days (232 versus 230). The other two NIH ACTIV convalescent plasma trials required 1.49x and 1.89x longer to each enroll only 8% of the number of participants that RECOVERY enrolled.

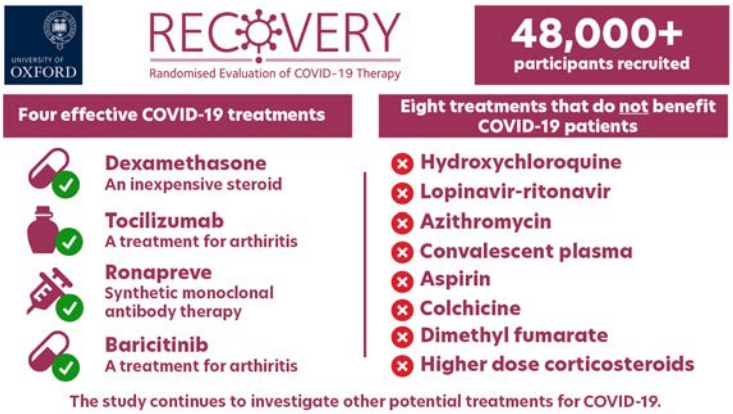
Although the NIH ACTIV sub-studies often began before their respective RECOVERY trial arms, RECOVERY enrolled far more patients in the same or fewer days. RECOVERY had the advantage of leveraging the U.K.'s National Health Service EHR across many care delivery sites for recruitment, whereas the NIH ACTIV trial relied on narrower network study sites each using their local patient identification capabilities.

U.K. platform trials leveraged existing integrated medical records as well as an infrastructure prepared for large, distributed clinical trials, often at the point of care. Researchers and federal agencies in the United States do not have the ability to pursue either of these options at present, despite public investments of billions of dollars of into health information exchanges, electronic medical records, and trial networks.

Box 7: RECOVERY demonstrates adaptive platform trial feasibility for COVID-19 therapies

Launched in 2020, the *Randomised Evaluation of COVID-19 Therapy* (RECOVERY) trial is an international adaptive, multi-arm platform, open label, randomized controlled, clinical trial established to identify treatments that might benefit people hospitalized with suspected or confirmed COVID-19. The study is being conducted by researchers at the University of Oxford, which acts as the sponsor for the research, working with doctors at many hospitals across the United Kingdom. Following its U.K. launch, the trial later expanded internationally to Ghana, India, Indonesia, Nepal, South Africa, and Vietnam (RECOVERY TRIAL, 2020).

Within two years of its establishment, RECOVERY had identified four effective treatments against COVID-19 as well as 10 treatments that do not benefit COVID-19 patients:



Source: RECOVERY trial website: https://www.recoverytrial.net/files/recovery-results_december-2022.png

As of July 2023, the RECOVERY trial was evaluating two additional suggested treatments for COVID-19 and three for influenza to discern whether they are more effective in helping people recover than the standard care that all patients receive (RECOVERY TRIAL, 2020). At the time of the report writing, RECOVERY had 190 active sites and had enrolled more than 48,564 participants into the trial.

Initial funding for the trial was provided by a grant to the University of Oxford from U.K. Research and Innovation and the National Institute for Health Research along with core funding provided by the National Institute for Health and Care Research (NIHR) Oxford Biomedical Research Centre, the Wellcome Trust, U.K.'s Department for International Development, Health Data Research U.K., the Medical Research Council Population Health Research Unit, National Institute for Health and Care Research Clinical Trials Unit support funding, and the Bill and Melinda Gates Foundation, which pledged more than $250 million to the global COVID-19 response, in particular to support African and South Asian countries to roll out detection, treatment, and isolation programs (RECOVERY TRIAL, 2020).

The RECOVERY Trial is registered at ISRCTN50189673
EU Clinical Trials Register: EudraCT 2020-001113-21
Clinical Trials.gov: NCT04381936

CHALLENGES AND OPPORTUNITIES FOR MORE WIDESPREAD ADOPTION OF ADAPTIVE AND PLATFORM TRIALS

Multiple experts spoke about the challenges of employing platform and adaptive trials under pandemic conditions. One expert said that, theoretically, platform approaches can work for every product, but creating the infrastructure, governance, and connections to regulators requires time to build multi-party alignment and then the operational capabilities. When these pieces were already in place,

platforms performed well. The lesson for future pandemics is that infectious disease platform trials should be operationally tested, already be operational at some level, and have capacity expansion plans in place to fulfill their potential for the future.

Experts identified multiple practical challenges to more widespread adoption of platform trials and adaptive trial designs, including the following:

- Platform trials require sponsors to commit their drug and vaccine development programs to standard outcomes metrics and comparisons that might diminish product distinctiveness. Tools such as verified IT solutions and regulatory guidance on best practices can only partially address sponsors' concerns regarding head-to-head comparisons between products on the same platform. Accepting the costs and benefits of this approach will require culture change, and commercial and operational risks may remain.
- Traditional publication processes are not designed to accommodate adaptive trial designs or platform trials and can be overly cumbersome for corresponding/lead author investigators. Authors generally have to repeatedly submit and review master protocol elements rather than leveraging platform trial commonality among sub-studies and arms.
- Adaptive and platform trial expertise among regulatory reviewers is needed across all FDA centers and divisions. Because these approaches have historically been adopted by some therapeutic areas more than others, not all FDA centers and divisions have built the expertise or implemented review strategies appropriate for these emerging clinical trial approaches.

Individual FDA guidance documents have recommended a set of practices for using adaptive or Bayesian statistics, establishing master protocols and platform trials, incorporating decentralized approaches into clinical protocols, and deploying DHTs in clinical development. Each provides significant clarity, and, in combination, they have facilitated successes such as the point-of-care REMAP trials, rapid diverse enrollment in COVID-19 vaccine trials, and the standing up of therapeutic platform trials such as NIH-ACTIV and, to a lesser extent, the U.K. RECOVERY platform trial. With ongoing leadership, especially to overcome organizational and business model inertia, positive innovative synergy in industry- and government-sponsored trials could continue.

Lessons Learned for Platforms and Statistical Innovation in Clinical Trial Design

During the COVID-19 pandemic, platform trials proved highly effective in generating actionable evidence for COVID-19 candidate therapeutics. Nevertheless, the speed and efficiency gains varied across platform types. Infrastructure differences, from governance to technical, have since emerged as important contributing factors to this variance.

Bayesian statistics demonstrated speed and power advantages compared with traditional designs for generating comparable results with fewer enrolled participants. In the future, the value of such efficiencies will be particularly salient in a pandemic setting, but they also can be realized in non-emergency settings as well. Against this backdrop, experts reported that **ongoing conversations and**

transparency between and among trialists and regulators enables implementing clinical trial design innovations. While generally true, pandemic circumstances exacerbate the need for dialogue and transparency and highlight the need for collaborative personnel cross-sharing to speed the process. In particular, because sponsors perceive risks in adopting innovative designs, regulatory guidance documents can partially address sponsor concerns; however commercial and operational risks may remain. **Accepting the risks of innovative designs and adopting these approaches more broadly will also require culture change among sponsors.** Aligning regulatory staff reviews and expertise with these innovative trial designs may also streamline the review process, particularly in urgent scenarios.

Looking ahead to future efforts to enable pandemic preparedness, infrastructure investments emerge as a key enabling factor. **Pandemic response requires pre-existing platform infrastructure** for both EHR access to support participant recruitment and endpoint tracking as well as clinical research infrastructure to generate the time-urgent evidence that public health emergencies need. The United Kingdom demonstrated the value and speed such capability can deliver—capabilities that were largely absent in the United States and time consuming to create, especially during a pandemic.

6. PARTICIPANT DIVERSITY DRIVERS AND INFRASTRUCTURE

Many, including FDA, have emphasized the importance of including diverse communities in clinical research—both in studies investigating the treatment and prevention of COVID-19 and in clinical trials more broadly (U.S. FDA Diversity, 2020). Achieving participant diversity across age, race, ethnicity, geography, biological sex, gender, disability status, and other characteristics is an ongoing challenge in clinical research because of several structural barriers. Still, experts emphasized that diverse participation is necessary to gain community trust, promote fairness, and generate evidence on whether treatments have varying effects on different populations (Lackland *et al.*, 2020; Jethwa, Wong and Abraham, 2021; Schwartz *et al.*, 2023).

IMPACT OF COVID-19 TRIAL DISRUPTIONS AND INNOVATIONS ON PARTICIPANT DIVERSITY

In interviews, experts said that clear recommendations from regulators on diversity requirements, such as those shared early in the COVID-19 pandemic, are necessary and will lead to more representative studies and generate benefits for a larger share of the population. Clinical trial participants should match the expected population of eligible patients for the condition and therapy. For example, although some trials, such as those for vaccines for COVID-19 should reflect the general adult population, others, such as those for therapies for sickle cell disease, should reflect the specific group of people who suffer from the target disease.

Research examining diversity in the set of clinical trials that investigated COVID-19 vaccines and therapeutics during the early years of the COVID-19 pandemic produced mixed results. Some studies reflect continuing diversity challenges: they have documented trials with racial and ethnic representation that are not reflective of the U.S. population and a lack of geographic heterogeneity (Pepperrell *et al.*, 2021; Khalil *et al.*, 2022; Xiao *et al.*, 2023). For example, in a study of eight U.S. vaccine trials, the percentage of white participants ranged from 79% to 92% (U.S. FDA - Trial Diversity, 2022) - all of which represent a higher share of whites than in the U.S. population overall. For example, in a phase 1 vaccine trial of an mRNA vaccine conducted in 2020, 89% of the participants were white (Jackson *et al.*, 2020). In addition, many trials did not publish demographic data, an omission that could indicate even greater disparities than those currently reported. Indeed, one study noted that "even when reported, 20% of studies did not follow the NIH's recommendation to report race and ethnicity as independent categories" (Pepperrell *et al.*, 2021; Xiao *et al.*, 2023). (See Appendix E Part II for a research feasibility demonstration for systematically considering clinical trial demographics.) As discussed below, however, the literature also identified several promising strategies to increase participant diversity identified and implemented during the COVID-19 pandemic.

APPROACHES TO IMPROVE PARTICIPANT DIVERSITY

Experts spoke about the need to improve communications more broadly. In particular, they emphasized that the standard legalistic participant consent process with its stilted communications materials and communication approaches could discourage underrepresented participants from

enrolling. One expert said that typical communication and consent approaches may be particularly intimidating for underrepresented populations and in the context of severe illness (e.g., oncology trials). Because of common misunderstandings, participants might not be aware that in many clinical trials—and certainly in settings such as oncology trials—that there is no "sugar pill." Rather, by participating in clinical trials, participants will be guaranteed the standard of care—a notion that the expert implied was not widely known. Quantitative research regarding cancer trials suggests that trialists do not offer participation to underrepresented populations as frequently, but, when given the opportunity, those populations participate at similar rates to other groups (Unger, Hershman, *et al.*, 2021).

Research has also suggested that efforts to improve diversity can succeed. Existing barriers remained a challenge for clinical trial enrollment of diverse populations after COVID-19 began. Such barriers include proximity to clinical trial site location, the vernacular and approaches used to recruit participants, and suitable compensation. One expert shared that although trialists can discuss diversity at length, emphasizing feasibility of participation might be the most important factor.

> *"Everything we can do to maximize the opportunity to participate for people regardless of their personal and demographic circumstances will be a win for the pace of approval, the internal validity, the diversity, generalizability, upholding of basic principles of fairness, the ability to rebuild considerable degradations in trust of the health care system."*
>
> - *Medical ethicist and epidemiologist*

Consequently, explicit efforts to increase diversity in trial enrollment during COVID-19 using DHTs and decentralized approaches might have contributed to better diversity enrollment outcomes. DCTs and DHTs extend the reach of clinical trials into the community or even individual homes. This, in turn, can help include populations that otherwise might not participate because of geographic, mobility, financial, or other barriers. One study showed that some remote trials during the COVID-19 pandemic were more geographically diverse (Stewart *et al.*, 2022). These more representative trials often involved strategies to increase and evaluate diversity throughout the multiple phases of the clinical research process, including community engagement; identification and removal of financial barriers to participation; creation of culturally tailored recruitment materials, which resulted in more racial and ethnic diversity among participants in COVID-19 vaccine trials; and use of virtual visits, remote technology, and local laboratories to reach more diverse communities and limit the financial and time burden on patients (Andrasik *et al.*, 2021; Stewart *et al.*, 2022; Castellon-Lopez *et al.*, 2023; Versavel *et al.*, 2023). Researchers and interviewed experts have emphasized that the best communication and outreach approach will vary by the targeted (sub-)population. For instance, the RADx® Underserved

Populations group found that barber shops and hair salons were highly influential in encouraging other types of COVID-19-related health decisions (Whanger *et al.*, 2022).

Heightened efforts to increase diversity in COVID-19 research succeeded in recruiting more diverse cohorts than ever before. One study showed that COVID-19 vaccine trials launched later in the COVID-19 pandemic enrolled Black, Indigenous, people of color participants at a faster rate because of existing networks and relationships, underscoring the value of maintaining community relationships (Andrasik *et al.*, 2021). One expert noted that in a COVID-19 vaccine trial, Moderna briefly paused enrollment to satisfy the diversity metrics established by FDA (U.S. FDA - Trial Diversity, 2022). Another expert mentioned that their employer, a large pharmaceutical company, was shifting its strategy to partner with fewer but more varied study sites in the hope of improving trial efficiency and trial participant diversity. Another trialist shared that they had eight weeks to recruit 40,000 participants, and, given such a short time frame, there is very little "course correction" that can be performed. The trialist said that, by recruiting through registries, they were able to understand the characteristics of the potential participant population (including comorbidities) and estimate the feasibility of achieving participant diversity targets. Leveraging patient registries also facilitated direct-to-patient interactions. The same trialist said that the approach has broad applicability beyond pandemics, whenever registries are available.

In contrast, regarding COVID-19 diagnostic evaluation, the environmental scan found that diversity did not appear to be a key priority in their characterization and performance validation (Lackland *et al.*, 2020; Jethwa, Wong and Abraham, 2021; Schwartz *et al.*, 2023).

THE CONNECTION BETWEEN TECHNOLOGY AND DIVERSITY

As described above, decentralized approaches to clinical trials and the technologies that support these approaches can increase participant diversity in trials. Yet, some studies warn that DHTs might widen clinical research disparities in practice because of the "digital divide" that disadvantaged communities often experience (Loucks *et al.*, 2021). One trialist countered that using text messaging in their clinical trials aided enrollment and trial execution for underrepresented populations, as most people have cell phones. Context-specific research, technical and informational support, and monitoring are likely necessary to ensure that digital strategies achieve their diversity aims for participants of clinical research.

A digital technology expert said that trialists must engage community representatives when designing clinical trials, adding that if trial leaders are not certain how to engage diverse communities, then the wrong people are in leadership positions. Another trialist discussed the unique challenges and opportunities associated with diverse recruitment, saying that the clinical trial community needs to think about new mechanisms for community engagement and creatively "going the last mile." This expert said that there is a Walmart within 10 miles of 90% of the entire U.S. population, a reach that no health system can match, which emphasizes the potential value of partnerships with retail pharmacies and similar retailers. Although the expert recognized that engaging all communities will demand

additional financial resources or entirely novel approaches to recruiting for and conducting clinical trials, the results will be better and maximally relevant. Furthermore, reluctance to adopt approaches that are known to improve recruiting and communications with minority audiences, such as text messaging and community outreach, will likely have a negative impact on a trial's ability to achieve its diversity goals. Several experts cited the value of using the Digital Medicine Society's tools and playbooks for trial diversity inclusion going forward (DiMe, 2023).

One expert gave the example of successful remote collection of bio-samples and patient-reported outcomes. The trial in question evaluated healthy lungs and provided participants with an option for mobile bio-sample collection. Although doing so was costlier, the expert emphasized that the costs made trial participation and participant retention easier, thereby supporting greater diversity. Further, once the COVID-19 pandemic occurred, patients avoided the clinic, and 67% of collection happened through mobile units.

Another expert cited the acceleration of web- or EHR-based tools to collect patient-reported outcomes with clinically and economically relevant measures. Indeed, experts spoke about the value of incorporating clinical trial recruitment technologies into the EHR more broadly—an approach with multiple possible advantages, one of which is establishing a constant pool of representative and diverse patients. (Other advantages of EHR-based recruitment are discussed above in the context of platform trials; see Chapter 5, Platforms and statistical innovation in clinical trial design.)

Lessons Learned for increasing participant diversity in clinical trials

The COVID-19 impacts on participant diversity cited above appear to apply equally well to pandemic and normal contexts across all products. **Explicitly including diversity recruitment activities into clinical trial plans is the core and consistent lesson emphasized**. How best to include diversity recruitment plans, which activities to select, and how to fund them remain unresolved. Planning for a diverse trial might also include employing registries and addressing barriers to participation, such as by providing financial compensation.

A second lesson emphasized by nearly all the literature and experts is that **recruiting diverse participants requires "meeting them where they are" geographically and culturally** (for example, at formal or informal community gathering locations—or simply in their own homes, workplaces, and other frequently visited locations—and through engaging trusted community leaders, whether secular, religious, tribal, or advocacy-oriented).

Techniques newly emphasized for recruiting general population participants such as **partnering with retail pharmacies, using decentralized trial approaches, and employing DHTs and social media to recruit and retain participants can also be tuned to ensure diversity**.

7. REAL-WORLD EVIDENCE AND THE GAP BETWEEN CLINICAL RESEARCH AND PRACTICE

FDA defines RWE as clinical evidence about the use and potential benefits or risks of a medical product derived from analysis of real-world data, such as data derived from DHTs or EHRs.

A 2023 study designed to provide a retrospective landscape analysis of how FDA used RWE in regulatory decisions before the COVID-19 pandemic found 34 instances of RWE submission between 1954 and 2020. The study found that 25% of cases were in the oncology setting, 18% in hematology, and 12% in neurology, and more than 50% of the products were intended for rare disease or pediatric populations (Mahendraratnam et al., 2022). These findings are consistent with RWE being used conservatively and primarily in situations in which evidence generation is otherwise difficult. Indeed, the authors conclude that "there is significant potential to further explore the role of [RWE] in regulatory effectiveness decision-making." Yet the authors' assert that the need remains for product regulators to "track, centralize, and make publicly available the scientific lessons learned from when [real-world data] is both accepted and rejected."

APPLICATIONS OF RWE DURING THE COVID-19 PANDEMIC

During the pandemic, researchers used RWE to accelerate the identification of various COVID-19 care improvements. For example, the Quebec Pregnancy Cohort was used to review the safety of hydroxychloroquine and chloroquine for pregnant women, an important population subset excluded from clinical trials (Bérard *et al.*, 2021). Researchers mined EHRs to evaluate COVID-19 treatment outcomes (Sidky *et al.*, 2023). In Spain, a retrospective cohort study sought repurposed drug candidates by analyzing COVID-19 patient survival after therapeutic use for other indications before COVID-19 hospitalization (Loucera *et al.*, 2022). Due to fragmented medical data and lack of embedded research capabilities in clinical care, the United States relied substantially on research findings from other countries—the United Kingdom and Israel, among others (RECOVERY, 2020; Pfizer, 2021)—to identify effective clinical practices and candidate therapies early in the COVID-19 pandemic.

Despite the challenges, some U.S. efforts achieved notable successes. The National COVID Cohort Collaborative Data Enclave managed by the National Center for Advancing Translational Sciences at NIH established a harmonized EHR data set of patients tested for COVID-19 in 65 health care institutions. The data platform facilitated online query, visualization, and statistical analyses across large and diverse patient populations to identify patterns relevant to clinical COVID-19 challenges (Sidky *et al.*, 2023). Machine learning techniques helped generate RWE regarding therapeutic efficacy in some settings (Bustos *et al.*, 2021).

The literature review did not reveal any research that quantified the impact of RWE on improving care during the COVID-19 pandemic. Some studies mentioned the missed opportunity for leveraging RWE to enable continuous learning about treatments beyond emergency authorization (Eichler *et al.*, 2022).

In interviews, experts primarily highlighted the value of real-world data and evidence as tools to augment, support, and build on evidence from clinical trials. Box 8 summarizes the types of real-world

data used during the COVID-19 pandemic cited in the literature and by the interviewed experts. One pharmaceutical industry executive gave the example of health care in Israel, where early and rapid vaccine rollout enabled rapid learning that informed decision making in the country and internationally (Pfizer, 2021). Such a dynamic real-time approach to generating and using RWE in the lead-up to the authorization or approval of a medical product stands in contrast to more typical practices, in which RWE is generated for pharmacovigilance and confirmatory evidence (e.g., via legacy registries and phase 4 trials).

Box 8: Types of real-world data used in clinical trials during the COVID-19 pandemic

- EHR data and patient outcomes: Real-world control arms in platform adaptive trials
- DCTs and digital biomarkers: Participant generated endpoints that could be measured in real-world settings (e.g., participants wearing/using DHTs to collect real time data)
- Patient or disease registries used as a historical control data source or a recruitment mechanism, especially for rare diseases
- Patient-reported outcomes, including from at-home use cases, or through social media or patient advocacy groups to direct trial strategy

Bringing clinical research and practice closer together: Opportunities and challenges

RWE can help unify clinical research and practice through iterative knowledge generation embedded in patient care. The COVID-19 pandemic spurred efforts such as REMAP-CAP, which integrated the clinical trial infrastructure with EHRs for near real-time prospective point-of-care randomized trials (Huang *et al.*, 2021). Multiple experts spoke about the value and urgency of bringing clinical care and clinical practice closer together, citing the value of such approaches during the COVID-19 pandemic (see, e.g., Box 7 above on the RECOVERY trial) as well as the promise of driving greater efficiencies well beyond the COVID-19 public health emergency. One clinical trial expert emphasized the disconnect between clinical research and patient care, saying that the history of clinical trials and the Belmont Report itself have led practitioners to think about these as "separate worlds." Still, the expert pointed out, no other industry separates new learnings from existing models so completely as does medicine. An expert suggested that the COVID-19 pandemic pushed clinicians to appreciate the promise of a more unified approach to medical research and practice.

Lessons Learned for RWE and the gap between clinical research and practice

Clinical trials during the COVID-19 pandemic demonstrated that RWE can rapidly inform clinical care and that real-world data can speed clinical trial recruiting. Yet **fragmented health IT and medical information limited the ability of U.S. clinical trials to leverage real-world data** in identifying potential trial participants, impeding patient recruitment, treatment, and monitoring. This then delayed RWE results to guide clinical practice in the use of existing therapeutics and prevented detailed product effect monitoring during emergency use with ongoing confirmatory trials. **Reducing health data fragmentation while simultaneously allowing access by researchers could improve clinical trials during normal contexts and prove critical to rapid response during pandemics**.

8. REGULATORY TRIAL OVERSIGHT AND EVALUATION

DESCRIPTION OF COVID-19 IMPACTS

The COVID-19 pandemic posed multiple challenges for the FDA and the clinical trialists for therapeutics and diagnostics who seek to meet regulatory requirements. Trials that were underway for non-COVID-19 products were interrupted with concomitant operational, statistical and compliance issues regarding how to continue without fully re-starting, and how to interpret the data from the interrupted protocols if they did so. New trials for COVID-19 products faced urgency to complete while also protecting participant and trialist safety as well as generating quality scientific results.

Based on the literature review and expert interviews, after an overview of pandemic regulatory activities, this section addresses:

- Trial and evidence generation influence
- Decision acceleration
- Regulatory coordination
- Regulatory resourcing

OVERVIEW OF PANDEMIC REGULATORY ACTIVITIES

FDA, the Centers for Disease Control and Prevention (CDC), NIH, and other government agencies navigated the challenges of COVID-19 by issuing guidance documents and adapting processes while working to fulfill their responsibilities during the public health emergency.

FDA alone issued 84 COVID-19 related guidance documents from 2020 to 2022 (U.S. FDA Industry, 2021; U.S. FDA Staff, 2023), with 16 of those issued (as final documents) already in March 2020 (U.S. FDA Industry, 2020) just five to eight weeks after HHS declared a public health emergency on January 31, 2020 (Azar, 2020). Of those 84 guidance documents, at least 21 directly addressed human clinical trials (See Appendix D for a list). One covered veterinary product clinical trials, which are out of scope for this report. At least another 10 addressed medical device regulatory modifications due to the COVID-19 pandemic that would not require usual validation, which might have otherwise required clinical trial or trial-like activities. Those 10 plus at least another 18 guidance documents might have had indirect impacts on clinical trials through their effects on availability or variability of medical devices or clinical supply of drug products for clinical trials.

FDA was able to rapidly develop and release (final) guidance by using its Good Guidance Practices, under which the "*…FDA will not seek public comment prior to implementing a guidance document if the agency determines that prior public participation is not feasible or appropriate"* (U.S. FDA Staff, 2023). FDA occasionally updated its guidance documents, as exemplified by one of the most relevant examples for this report, which was originally issued in March 2020 and updated in August 2021: Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (Turner, 2020).

This early guidance document set the tone for much of the FDA clinical trial response by doing the following:

- Emphasizing that "ensuring the safety of trial participants is paramount"
- Encouraging sponsors "to evaluate alternative methods for safety assessments" from phone to virtual and from local alternative sites to home visits
- Altering monitoring schedules
- Promoting early consultation for proactive protocol and statistical analysis plan changes because of COVID-19 circumstances
- Considering remote monitoring of clinical sites

With respect to other opportunities to simplify operations and improve the efficiency of interactions with regulators, one expert highlighted the ongoing value of remote meetings. Before the COVID-19 pandemic, face-to-face meetings had been the norm with FDA regulators, but since the COVID-19 pandemic, even advisory committee meetings have been taking place over Zoom. The expert saw this as a pandemic-era change that was born out of necessity but welcomed the persistence of remote meetings.

Whether remote or not, and despite the desire by many product developers to continue such intensive interactions, current regulatory capacity constraints would need to be eliminated before broadly rolling out such practices according to interviewees familiar with the area.

Beyond issuing guidance documents, the speed of the regulatory response and flexibility was perhaps best illustrated by Moderna Therapeutics launching the first human vaccine trials on March 17, 2020, with Pfizer/BioNTech expanding its own Phase 3 COVID-19 vaccine trial to 44,000 patients six months later on September 14, 2020, and Johnson & Johnson expanding its vaccine trial to 60,000 patients one week after that on September 21, 2020. This rapid start-up and enrollment of trials for the Moderna and Pfizer/BioNTech vaccines permitted assessment of interim results in November 2020 that supported FDA's Emergency Use Authorizations and CDC Advisory Committee on Immunization Practices recommendations for use in adults in December 2020 (CDC, 2023).

NIH's strategic response also impacted the clinical trials it sponsored implicitly via the studies it chose to sponsor as well as the detailed requirements and approvals they required for trials during the COVID-19 pandemic period (NIH Response, no date). For example, the ACTIV public-private partnership employed seven adaptive master protocols to reduce administrative burdens and rapidly advance (or slow) candidate therapies for therapeutic approaches such as immune modulators or repurposed drugs, settings (inpatient or outpatient), and modalities (monoclonal antibodies), among others (NIH Therapeutics, 2023). The master protocols established common outcomes and statistical analyses among other elements, which regulated the quality of potential evidence generated. Some interviewees suggested that relying on academic networks might have resulted in more elaborate, complex, lengthy, and expensive trial arms than would have been the case had the same approach been executed by experienced commercial firms.

TRIAL AND EVIDENCE GENERATION INFLUENCE

FDA-issued specific trial guidance documents: Clearly and publicly stating trial recommendations, especially regarding patient follow-up and required vaccine efficacy thresholds, helped sponsors design and complete meaningful trials that met the requirements of regulatory review. The urgency for action amidst uncertainty and even fear might have provided a context for the broad welcome that the rapidly released documents received in the clinical development community. To its credit, the FDA was explicit in its desire and processes to update the guidance documents as evidence evolved and then did so, thoughtfully balancing improvement with the risks of excessive volatility. As one interviewee said:

> *"During a pandemic…Make sure that you have rules that are known to all parties, in black-and-white, so people can't cheat. Large vaccine manufacturers knew what they needed to do. Those who didn't do that had problems."*
>
> - *Regulator*

Unfortunately, no quantitative or qualitative research studies were found addressing the impact of these actions.

Diagnostic early development: Diagnostic testing posed challenges early in the COVID-19 pandemic. Lessons learned included the need to balance assay validation, manufacturing certification, and intended uses of the assays. Early diagnostic test assays were challenged in clinical trial validation and manufacturing, which had follow-on impacts on therapeutic and vaccine product development trials. An accurate and consistent assay to screen participants and ascertain their outcomes fundamentally enables the generation of valid clinical evidence for therapeutic and vaccine products.

Responding to critical COVID-19 test shortages early in the COVID-19 pandemic, on February 29, 2020, FDA issued a policy that allowed laboratories certified to perform high complexity tests consistent with requirements under FDA's Clinical Laboratory Improvement Amendments to begin using tests immediately upon completion of their validation while recommending the labs submit the validation data with an Emergency Use Authorization request within 15 days (College of American Pathologists, 2020; U.S. FDA Expedite, 2020). Although this expanded rapid public health monitoring capacity at a critical time, it also overwhelmed FDA's ability to review submissions (Shuren, 2022) and led to the use of what became recognized as highly variable COVID-19 diagnostics (Younes *et al.*, 2020).

Diagnostic tests underlie the effective parallel clinical development of vaccines and therapeutics. Without reliable and available diagnostic tests, identifying and following patients to test an intervention's efficacy and safety is hindered or even infeasible.

> *"When every second counts, you cannot have ambiguity on the quality of these tests. [We] learned early on that one cannot develop a product without diagnosing whether the patient has the disease. You cannot start until you have a diagnostic you have confidence in…and we did not pay attention to having diagnostics that we could have faith in."*
>
> - *Contract research organization executive*

As a result, lessons have been learned for balancing timeliness and quality. FDA has expanded and clarified its policies for COVID-19 tests (U.S. FDA Test, 2022), which improve ongoing development for COVID-19 variants and provide a template for future pandemics. But FDA policy alone might not be sufficient. Avoiding similar outcomes in a future pandemic might require government specification and funding for diagnostic and assay development as well as direct government validation, such as the approaches South Korea used (U.S. FDA Korea, 2020; Terhune *et al.*, 2020). An expert interviewee in the United States further endorsed aspects of South Korea's approach, such as using high-quality laboratory-grade samples when samples are rare at the beginning of a pandemic as well as establishing contracts ahead of time for developing and supplying diagnostics, including manufacturing capacity.

Vaccine development consultation: Through Operation Warp Speed, FDA and companies developing potential vaccines had frequent, sometimes daily, communications that, combined with the guidance documents on COVID-19 vaccine development, provided rapid detailed feedback to vaccine developers. In turn, vaccine developers could present potential clinical development improvements and COVID-19 mitigation actions for regulatory consideration before full implementation. Engaging the highest biopharmaceutical executives (chief executive officers, chief research and development officers) with corresponding FDA officials enabled all their organizations to be bold, refine ideas quickly, and implement rapidly when appropriate during the COVID-19 public health emergency.

Reduce use of under-powered or poorly designed trials: Up to 95% of COVID-19 therapeutic trials did not generate evidence of sufficient resolution to inform FDA regulatory decision making for approval or denial (Bugin and Woodcock, 2021). Some, including a former NIH deputy director well before the COVID-19 pandemic in 2017, have called for NIH processes to eliminate "SCTs (small crappy trials)" (Wired, 2018; The Good Science Project, 2023). NIH officials have expressed support for such new recommendations proposed by the Clinical Trials Stewardship Task Force to the NIH Advisory Committee to the Director on June 9, 2023, but they have not yet announced a process or time frame for their adoption (Health Care Compliance Association, 2023; NIH Advisory, 2023). FDA currently possesses power to pause or halt trials due to safety concerns (U.S. FDA Safety, 2020). Some interviewees suggested that, at least during public health emergencies, FDA could be granted and the assertively exercise authority for pandemic products to halt trials and trial initiations identified as

uninformative to prevent disinformation that might emanate from such trials and because knowingly recruiting patients into uninformative trials is usually considered unethical.

Adaptive and platform trial reviews: Interviews suggested that the FDA initially struggled with reviewing the adaptive Bayesian interim and final analyses as well as the resultant seamless Phase 2/3 trials. Without additional resources and advanced tools, experts saw the labor-intensive FDA review of adaptive trials and master protocols as unsustainable outside of a public health emergency (see also Chapter 5, Platforms and statistical innovation in clinical trial design).

Essential data trials: Trials may collect multiple data elements that possess minimal value to the sponsor or FDA. The excess data might be collected out of an abundance of curiosity or caution, but the result is delay, expense, and perhaps barriers to trial expansion to broader community sites or use of home monitoring. One interviewee with direct experience said:

> *"FDA reviewers spend two weeks extra going through this excess data. It's not just collecting it [that takes time], but also the agency review."*
>
> *- Regulator*

In accordance with best practices, it is particularly important during pandemics that trials be designed in consultation with FDA to collect the minimal essential outcome data required to assess the efficacy and safety of the candidate product for the benefit all stakeholders (from patients to sponsors and funders).

Risk-based development streamlining: Development plans generally were tailored according to the anticipated effect sizes (efficacy), safety profile, and regimen of the candidate product. This was especially true during the COVID-19 public health emergency, during which implicit or explicit value-of-information and risk-based design choices were emphasized to simplify and speed clinical development. Well-characterized product types such as monoclonal antibodies were occasionally allowed to perform truncated Phase 1 safety studies to rapidly initiate adaptive Phase 2/3 trials. Another example was how the difficulty in obtaining non-human primates for non-clinical safety studies during the COVID-19 pandemic led to significant discussion between sponsors and regulators on alternative strategies. All such opportunities to reduce or eliminate activities required intensive interaction among the sponsors and FDA to align risk-benefit views regarding which streamlining opportunities were appropriate for each product indication.

Bioequivalence/biosimilar studies: Generic small molecule manufacturers and biosimilar biologic products must demonstrate either bioequivalence or biosimilarity, which are often accomplished through targeted clinical trials. Experts suggested that during a pandemic, regulators could more vigorously exercise their existing authority—or be given expanded authority—to speed provision of

reference product to potential generic and biosimilar manufacturers. Experts also suggested that FDA provide additional consultation to such firms to expedite authorization and therefore supply of urgently needed repurposed therapies.

DECISION ACCELERATION

COVID-19 vaccine development was condensed to seven months for select vaccine development programs to achieve Emergency Use Authorization and less than three years to complete Phase 2/3 trials for a traditional approval. Before COVID-19, the average novel vaccine development program required 9.8 years, with the acceleration attributed to novel trial sequencing techniques such as seamless adaptive trials and elimination of "between-trial white space" (Aitken, Connelly and Leamy, 2022). The regulatory actions described above strongly contributed to those successful vaccine trial sequences and "white space" reductions.

REGULATORY COORDINATION

Regulatory coordination successes and challenges emerged during the COVID-19 pandemic in inter- and intra-agency communications, data collection, and international regulatory coordination, particularly regarding reliance-based practices.

A notable success was the rapid communication to vaccine developers regarding the trial methods and desired vaccine performance thresholds (see above, Trial and evidence generation influence). This success required significant inter-agency coordination, which was occasionally difficult. For example, regulatory leaders noted disruptions to intragovernmental communications. The frequent turnover of members of the CDC COVID-19 response team (as frequently as every four to 12 weeks) proved to be a particular challenge for inter-agency collaboration and communication regarding COVID-19 therapeutic and diagnostic evidence requirements, which was eventually overcome. FDA and CDC built on this success and have further improved how they communicate to developers their combined vaccine requirements (CDC Vaccines, 2023).

Experts saw coordinated interaction among government agencies and private organizations as enablers of more efficient COVID-19 trials. The Operation Warp Speed task force was established to include multiple HHS and Department of Defense offices to support accelerated private sector clinical development activities, particularly in manufacturing (Shulkin David, no date; Slaoui and Hepburn, 2020; Winch *et al.*, 2021). Operation Warp Speed created efficiencies by consolidating multiagency decision making into a single governing group and leveraging expedited government mechanisms from Other Transaction Agreements (Adler, 2021; Dobriansky and O'Farrell, 2018) and the Defense Production Act for contracting to FDA Emergency Use Authorizations for regulatory authorizations (GAO, 2021).

Improved data collection and then sharing among agencies could aid in future pandemics and ongoing development of products that impact public health. For example, the United Kingdom and Nordic countries, with more connected population health and medical reporting, could better understand

COVID-19 spread, recruit participants into trials, and monitor the impact of emergency authorized products. It required up to two years for CDC to gather immunization data for reasons ranging from inadequately computerized processes to lack of legal authority that required negotiating data use agreements with many states (Dyer, 2020; Davis *et al.*, 2023; McPhillips, 2023). Even when collected, experts stated, and the literature supported, that the data could not provide timely, granular information regarding the characteristics of COVID-19 patient populations, such as biological sex, age, severity, and product usage (Galaitsi *et al.,* 2021, Harawa *et al.,* 2022). Such information could have informed everything from trial designs to post-authorization label refinement.

Internationally, FDA's interpretations of its confidentiality obligations to sponsors inhibited its ability to cooperate in global trial coordination, reviews, and reliance-based practices during the COVID-19 pandemic (World Health Organization, 2021; Lumpkin *et al.*, 2022). External experts suggested that FDA possesses greater statutory freedom to share information than it currently exercises. A reexamination of those obligations might enable greater collaboration and data sharing in future crises to benefit people in America and elsewhere.

REGULATORY RESOURCING

Many of the activities described above required additional regulatory effort from FDA, CDC, NIH and other involved agencies and task forces. During the COVID-19 pandemic, regulatory experts stated that these additional resources often came from activities such as diverting staff from other work on non-COVID-19 products and existing staff working extraordinary hours (late into the night or early mornings, over weekends and holidays, and not taking paid time off). Although heroic, such resourcing is not sustainable.

> *"I am very worried as we go back to our daily activities—nightmare that COVID-19 was—that we don't lose what we could learn from it going forward: How we could do clinical trials better, how we could be prepared to do them better in the intervening period, and how we could jump in more quickly if we have another pandemic."*
>
> - *Regulator*

Some process efficiencies, such as rolling reviews and team-based reviews, were also adopted and expanded in the mid to late periods of the public health emergency, but they did not eliminate the need for heroic and ultimately unsustainable working hours by many staff.

Resource constraints will require prioritizing which candidate products receive intensive regulatory attention and consultation, from early consultation through final review and release according to existing criteria and processes for programs including the pre-IND consultation program, the Breakthrough Therapy Designation, Priority Review, Accelerated Approval, and NIH-ACTIV platform

trial selection. Without greatly expanded staffing and processes, unfettered FDA interactions cannot become part of the post-pandemic "new normal."

Lessons Learned for regulatory trial oversight and evaluation

Experts **suggested that benefiting from clinical trial innovations** (platforms), statistical analyses (Bayesian), DCTs and DHTs, and novel preclinical approaches to mitigate non-human primate shortages **requires significant communication and mutual education between FDA and sponsors**. Building such connections and expertise benefits pandemic preparedness as well as non-pandemic drug development. In a pandemic, experts noted that **frequent consultation among senior leaders** of government and medical product (e.g., vaccine) developers aids alignment and rapid action and contributes to an increased likelihood of success.

Reducing data collection demands and regulators' data review demands through risk-based or value-of-information design to obtain the least information necessary to meet regulatory, payer, and patient/provider evidence needs can be an effective strategy to speed development in pandemic and non-pandemic contexts.

Rapid proactive guidance from regulators during an emergency minimizes disruption or complete loss of ongoing clinical trials as well as accelerated pandemic product development. Rapid issuance of clear clinical development guidance documents for each product type (e.g., vaccine, diagnostic device, or small-molecule or biologic therapeutic agent) galvanized researchers to pursue impactful product development, creatively and quickly. Similarly, expert developers recognized **rapid publication of joint CDC and FDA vaccine evidence standards and effect thresholds, with subsequent enforcement (via additional legislative authority for public health emergencies if need be)** of those standards by FDA—and by NIH and other federal agencies for the studies they fund—as critical to their success.

Robust validation for assays and diagnostics must be assured for all drug development programs, especially during a pandemic. Clinical diagnostics and assays for quantifying therapeutic effects are foundational to clinical trial recruitment, participant selection, randomization, and participant response measurement. **Building assay development and validation capabilities via cross training of FDA staff to create regulatory surge capacity** to review applications for infectious disease analyte specific reagents, laboratory-developed tests, and in-vitro diagnostics can help but may not alone resolve the issues under pandemic conditions. **Establishing FDA assay validation centers**, similar to South Korea's centralized approach, which is likely to be operated by contractors who guarantee capacity to do so under pandemic conditions, might further address the pandemic-specific assay and diagnostic challenges.

Heroic work can meet emergency needs but is not sustainable as a new normal as staff exhaustion and burn-out was observed by the experts. More **rapid de-prioritization of non-pandemic activities** with lower relative incremental net patient benefit, to provide adequate staffing for pandemic needs was also suggested for future pandemics. They also suggested using **team-based regulatory reviews** to spread workloads and increase process resilience.

9. GENERAL OPERATIONAL CONSIDERATIONS FOR CLINICAL TRIALS

As discussed in previous chapters, numerous operational innovations measurably mitigated COVID-19 impacts, accelerated urgent COVID-19 clinical development, or supported both. One expert recounted that accelerating COVID-19 vaccine trial initiation from (roughly) 300 to 100 days was only possible with meaningful changes to business practices, including pre-initiation consensus on collection tools and endpoints and highly streamlined reimbursement structures for clinical trial sites. This chapter discusses several specific operational considerations not included in the topics of the previous chapters.

Study planning: Several experts supported encouraging or even requiring pandemic contingency protocols for all clinical trials. These might include plans for protecting patients and personnel, such as increasing utilization of decentralized elements or DHTs, as well as plans for personnel diversion or exhaustion.

Study start-up: Launching a clinical trial involves coordinating several activities, including site selection, contracting and regulatory approval and alignment, and planning for participant recruitment. IQVIA reported that COVID-19 therapeutic trial start-up required only 1.5 months to initiate patient enrollment, an 83% reduction from the pre-pandemic 8.2-month benchmark (Aitken, Connelly and Leamy, 2022). This reduction in study start-up time has been attributed to features unique to the pandemic, including a pre-award site selection process that used models of participant density and diversity to identify sites with higher risk of severe disease, and dedicated start-up teams providing 24-hour virtual support for site document review to comply with country-specific regulations (Aitken, Connelly and Leamy, 2022). Of course, because COVID-19 was a common enough disease during the pandemic, potential participant identification was not a bottleneck for such trials. Notably, much of the evidence comes from trials associated with COVID-19 products themselves, which represent many of the most salient trials that were designed after the pandemic's onset and the release of FDA guidance documents. Other efficiencies highlighted by multiple interviewed experts came from streamlining study start-up processes across trials for COVID-19 products and other therapeutics. This involved implementing simplified protocols, such as using a central IRB process or a master protocol with amendments.

Another expert described streamlined institutional trial site contracting (e.g., via approaches including standardized rate cards, single IRBs, remote site monitoring) as helping to reduce trial timelines during the COVID-19 pandemic period. Traditional site contracting often necessitates lengthy and site-specific negotiations, as different centers have varying reimbursement rates for the same tasks (e.g., radiology scans, bloodwork, etc.). This issue was largely mitigated for COVID-19 products, however, through a "take-it-or-leave-it" strategy. Expert interviews highlighted how this simplified contracting helped start studies faster and felt that this type of standardization could drive further efficiencies beyond the COVID-19 pandemic. Of course, practical considerations need to be addressed (e.g., it may be desirable to geographically adjust standard reimbursement rates, as the Centers for Medicare & Medicaid Services does).

Trial recruitment: Patient recruitment for COVID-19 vaccine trials happened 52% faster and involved 80% larger and more diverse cohorts than previous vaccine trials, as reported by IQVIA (Aitken, Connelly and Leamy, 2022). During the pandemic, standard recruiting strategies were augmented by several innovative approaches. These included multichannel recruitment through social media advertising, emails, public awareness campaigns, referrals from local pharmacists, and involvement of ambassadors from local communities to target diverse subgroups (Sami *et al.*, 2021; Aitken, Connelly and Leamy, 2022; Mohamed Ibrahim *et al.*, 2022; Pantasri, 2022). For instance, the Pfizer/BioNTech vaccine trial (ClinicalTrials.gov Identifier: NCT04368728) recruited patients through social media and referrals from health care providers, while the ACTIV-2 Trial (ClinicalTrials.gov Identifier: NCT04518410) used targeted advertising to reach diverse populations, including adolescents and elderly people in the United States, European Union, and South Africa. The Healthy Lung trial (ClinicalTrials.gov Identifier: NCT04798664) (Kohn *et al.*, 2022), launched in 2021, recruited most of its patients via text messaging. One researcher involved in leading the study underscored that this approach was particularly suitable for enrolling underrepresented and underserved patients. This sentiment was more broadly echoed by another expert on patients' diversity in clinical trials, who further emphasizing that many people are hesitant to answer calls from unfamiliar numbers, particularly those with 800 prefixes.

Database lock and analysis: This process involves gathering, certifying, refining, and analyzing all data that clinical trials will submit to regulatory authorities. COVID-19 therapeutic trials achieved a 95% faster database lock than standard trials (Aitken, Connelly and Leamy, 2022) by leveraging direct data entry and electronic data capture systems. This eliminated the need for manual data entry and consequent verification (Ienca and Vayena, 2020; Kianersi *et al.*, 2021). In turn, this streamlined data collection and real-time data cleaning and, coupled with active involvement of all stakeholders, helped speed sponsors' decision making and further expedited the database lock process. The interviewed experts underscored that although these approaches were crucial during the pandemic, their benefits expand beyond emergency situations.

Lessons Learned for general operational considerations

Having **pandemic contingency plans in place** for clinical trials would likely reduce disruption of clinical research in a future pandemic scenario.

Steps to **streamline study start-up can greatly reduce time to develop new products during a pandemic.** Although this primarily applies to a pandemic scenario, streamlined processes such as simplified protocols and simplified trial site contracting are lessons learned that could be applied to all clinical trials.

Innovative, non-traditional trial recruitment strategies, such as use of social media, text messaging, and community ambassadors, may speed enrollment and help recruit more diverse participants in clinical trials. These lessons learned can be applied outside of the pandemic to improve recruitment for all clinical trials.

More widespread adoption of **direct data entry and electronic data capture systems** for all types of trials will help expedite the database lock process and reduce clinical trial costs.

10. TESTING THE LESSONS LEARNED: AREAS FOR FUTURE ANALYSIS

The literature review and expert experiences presented above are particularly well suited for documenting experiential and qualitative lessons learned. Future work could **quantitatively** explore some of the themes in this report at scale and potentially test hypotheses suggested by the findings. Examples include the following:

- **Examining use and impact of DHTs in registered clinical trials (in particular, by leveraging ClinicalTrials.gov)** such as in the example presented in Part I of Appendix E.

- **Documenting trends in clinical trial participant diversity**—for both COVID-19 products (e.g., vaccines and therapeutics) and non-COVID-19-related products (e.g., oncology therapies). Part II of Appendix E presents an example of how an algorithmic approach could support such an analysis at a larger scale. The results would support efforts to improve representativeness of clinical trials, improving confidence in their generalizability and reducing resistance among underrepresented populations to use the medical products.

- **Exploring clinical trial site diversity** among geographies (states; urban/rural) and settings (home, pharmacies, mobile clinic, community clinic/practice, hospital, etc.) and the impact on clinical trial speed, cost and diversity.

- **Quantifying the time, cost, and diversity impacts of individual (or combinations of) clinical trial innovations,** such as decentralized or DHT trial elements (e.g., text messaging, social media outreach, self- and home-monitoring), platform trials, adaptive trial designs, and community outreach efforts. Many of these approaches have not been rigorously evaluated by direct comparisons within or across trials or otherwise. NIH's All of Us Research Program, which includes decentralized and centralized recruitment cohorts, could provide an opportunity for such research.

- **Testing intersectional theme synergies** to differentiate relative contributing factors and their mutual reinforcement (synergy effects). For example, it might be valuable to explore the extent to which the use of decentralized approaches or specific tools such as text messaging or social media outreach affect the length of clinical trials or the likelihood that such trials fully enroll. Similarly, one could explore how the use of DHTs (or specific types of DHTs) correlates with trial diversity and representativeness.

- **Studying regulatory change propagation times** to understand the lags and impact of regulatory changes through the clinical trial enterprise. Because trials often take years, and trialist risk-avoidance reduces new method adoption, the time required to realize new regulatory opportunities for DCTs, DHTs, adaptive designs, and so on could be quite lengthy. There has

been little tracking of these adoption times or research regarding what factors or incentives affect those times.

Testing each of these elements would entail significant original research cost and time. Prioritizing only the most critical for field testing will be necessary, but some elements or topics can be explored using existing data sources. Appendix E presents preliminary data from two early feasibility analyses in greater detail.

11. CONCLUSIONS

The academic and gray literature, as well as the expert participants interviewed for this research, provided examples and insights of the way COVID-19 impacted clinical trials and lessons learned around six key areas:

1. Decentralized clinical trials and digital health technologies
2. Platforms and statistical innovation in clinical trial design
3. Participant diversity drivers and infrastructure
4. RWE and the gap between clinical research and practice
5. Regulatory trial oversight and evaluation
6. General operational considerations for clinical trials

Overall, Americans dramatically benefited from the combined impact of clinical trial innovations during the COVID-19 pandemic. For example, innovative approaches helped bring COVID-19 vaccines to market in fewer than nine months rather than the usual nine years—a more than ten-fold improvement in speed in service of public health and millions of lives. Although resourcing levels and clinical appropriateness might prevent replication of these approaches across all medical products all the time, the COVID-19 clinical development experiences showed what could be possible and pointed toward what further improvements might be made.

Despite these benefits, little quantitative evidence is yet available on the impact of specific practices on clinical trial time, cost, diversity, and success. Future research could support quantification of that impact; two possible approaches that demonstrate initial feasibility are described in Appendix E.

KEY LESSONS LEARNED

This report identifies a set of lessons learned for future policy and pandemic preparedness from each of these core thematic areas that includes the following recommendations for forward-looking policy:

1. **Pandemic disruptions in clinical trials can be mitigated through designed resilience and pre-planned rapid response.** Most ongoing and pre-launch trials were interrupted to some extent by the onset of the COVID-19 pandemic, but those using decentralized approaches were more resilient. Mitigating future clinical research disruptions may require combining contingency planning and rapid response.
2. **DCTs and DHTs can expand participation and reach of clinical research.** DCTs and DHTs allow clinical researchers to "meet people where they are" by offering participant-centric approaches to clinical research that enable (more) remote participation, extending clinical research sites to community and even home settings. This can prove particularly impactful for enrolling underserved populations. DCTs and DHTs should be approached as tools to enhance the conduct of clinical trials, rather than distinct entities. And while DHTs often have advantages, for some, clarifications and reforms regarding reimbursement and state-specific medical licensing regulations may be needed for non-emergency use in clinical research.

3. **Platform trials and innovative statistical trial designs were highly effective in generating actionable evidence during the pandemic and have potential to streamline development more broadly.** Platform trials and adaptive trials were a small portion of COVID-19 clinical trials, but they proved effective in generating actionable evidence for COVID-19 candidate therapeutics. Yet their speed and efficiency varied widely across platform types. Infrastructure differences, from governance to technical, appear to be important contributing factors to this variance. But sponsors perceive risks in adopting appropriate innovative designs. Regulatory guidance documents may partially address sponsor concerns, but commercial and operational risks will likely remain.
4. **Clinical trials conducted during the COVID-19 pandemic provide lessons for improving participant diversity in clinical research.** Innovative strategies for recruitment, such as social media, text messaging, and engaging community leaders proved successful in recruiting historically underrepresented populations. Explicitly including recruiting diversity into clinical trial plans is becoming a recognized best practice.
5. **The United States benefited from real-world data and RWE but struggled to create its own.** Highly fragmented medical data and IT systems combined with a lack of embedded research capabilities in clinical care made the United States dependent on others (the United Kingdom and Israel, among others) to identify effective clinical practices and candidate therapies during the COVID-19 pandemic.
6. **Regulatory leadership proved critical to COVID-19 clinical trial efforts.** Rapid issuance of clear clinical development guidance documents for each product type can galvanize researchers to pursue impactful product development, creatively and quickly. From adaptive trial designs to mitigating recruitment barriers to streamlining decision making, regulators showed that thoughtful crisis risk management can advance technical and organizational innovations by product sponsors that deliver outcomes previously believed impossible. However, heroic work can meet emergency needs but cannot become a new normal.

Incorporating and institutionalizing the lessons learned from clinical research during the COVID-19 pandemic requires a multi-modal and integrated approach to updating standard practices in clinical research going forward. Fully incorporating lessons learned will require more than institutional memory, reports, and playbooks. Process improvements (such as regular and increasing use of centralized and streamlined IRB processes) must be exercised, and capabilities need to be kept up to date or even newly created (such as clinical trial platforms and patient recruitment tools). This might be best accomplished not only by ensuring future pandemic readiness but also by actively encouraging the ongoing use of the best-practice innovations in ongoing non-pandemic clinical development whenever appropriate. Making some aspects of the changes adopted during the COVID-19 pandemic part of standard practice can increase the efficiency and impact of the clinical trial enterprise while simultaneously buffering the system against future disruptions.

12. APPENDIX A: DEFINITIONS

Adaptive trial: The FDA defines an adaptive design as one that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial. Adaptive designs can make conventional clinical trials more flexible by employing results generated in the trial to amend the trial's course in accordance with pre-specified parameters. Such adaptations to the trial's course may include stopping an arm early for safety or due to futility, terminating recruitment to an arm prematurely in the event of efficacy, or amendment of target sample size or allocation ratios.

Adaptive study designs often use Bayesian analysis (see below) to facilitate an agile trial process, allowing for the rapid evaluation of multiple hypotheses across varying indications and therapies, leading to more efficient futility analyses, identification of promising candidates, and the dynamic shifting of patient recruitment to accelerate evidence for those promising candidates.

Adaptive trials may evaluate single agents, or multiple agents in parallel. For example, single agent designs involve one candidate (simplifying the assumptions or methods that can be used), while multiple agent designs assess multiple therapies where the toxicity curve or other properties may not be well understood, defined, or both.

Bayesian Analysis: Bayesian statistics is an approach for learning from evidence as it accumulates. In traditional (frequentist) clinical trials, statistical methods may use information from previous studies only at the design stage. Then, at the data analysis stage, the information from those previous studies is considered as a complement to, but not part of, the formal analysis. In contrast, the Bayesian approach uses Bayes' Theorem to formally combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available. Bayesian analysis allows trialists to combine prior data about a given parameter with evidence from information contained in a new sample to guide the statistical inference process. A probability distribution for the parameter of interest must be specified from the outset. Bayesian frameworks can be applied to all models, including but not limited to exponential, logistic regression, proportional hazard Weibull, survival regression, and participant randomization.

Decentralized clinical trials (DCTs): The FDA defines DCTs as clinical trials where some or all of the trial-related activities occur at locations other than traditional clinical trial sites. In full DCTs, all activities take place at locations other than traditional trial sites. These trial-related activities may take place at the homes of trial participants or in local health care facilities that are convenient for trial participants. In hybrid DCTs, some trial activities involve in-person visits by trial participants to traditional clinical trial sites, and other activities are conducted at locations other than traditional clinical trial sites, such as participants' homes.

Digital health technologies (DHTs): Includes a wide range of products that are used in healthcare settings or have a medical purpose. FDA notes that these include electronic sensors, computing

platforms and information technology, which, in turn, provide new opportunities to obtain clinical trial data directly from patients. Portable DHTs that may be worn, implanted, ingested, or placed in the environment allow real-time collection of data from trial participants in their homes or at locations remote from clinical trial sites. The FDA definition of DHTs includes Software as a Medical Device (SaMD), Mobile Medical Applications (Mobile Apps), Wearable Devices or Telemedicine and Telehealth Platforms.

eIC: Electronic informed consent (often also referred to as “eConsent") involves electronic systems and processes that may employ (multiple) digital or electronic media sources to obtain informed consent for both HHS-regulated human subject research and FDA-regulated clinical investigations of medical products. This includes human drug and biological products, medical devices, and combinations thereof. FDA’s requirements for electronic records/electronic signatures, informed consent, and IRBs are set forth in 21 CFR parts 11, 50, and 56, respectively. HHS requirements regarding the protection of human subjects are set forth in 45 CFR part 46. The information presented to the subject, processes used for obtaining informed consent, and documentation of the eIC must meet the requirements of these and other applicable regulations.

Master protocol: FDA notes increased interest in expediting late-stage product development by developing trial designs that test multiple drugs and/or multiple subpopulations in parallel under a single protocol without a need to develop new protocols for every trial. The term master protocol is often used to describe trials with a variety of designs including umbrella, basket, or platform trials.

A master protocol typically has multiple sub-studies, which may have different objectives and involve coordinated efforts to evaluate one or more medical products in one or more disease subtypes within a broader study structure.

Platform trial: Platform trials are open ended trials that occur under master protocols (see below), facilitating the addition, evaluation, and elimination of trial arms/candidates without specifying timing parameters. Unlike intervention-oriented trials, where a drug is compared to standard care or a placebo, a platform trial is disease centric, determining what therapy is optimal for a given indication or sub-population. Platform trials can also flexibly amend the control or “standard of care” group as the study progresses. For example, when a platform trial reveals the efficacy of a candidate therapeutic to be superior to existing “standard of care,” said new candidate can be rolled out to benefit patients immediately and in turn become the new “standard of care” against which all new therapeutics are measured in the trial.

Real-world data: FDA defines real-world data as “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of real-world data include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status.”

Real-world evidence: FDA defines real-world evidence as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of [real-world data]." Real-world evidence can support clinical study design, inform clinical trial feasibility, and support regulatory risk-benefit assessments.

13. APPENDIX B: ACRONYMS

ASPE: Office of the Assistant Secretary for Planning and Evaluation
CDC: Centers for Disease Control and Prevention
DCT: decentralized clinical trial
DHT: digital health technology
eIC: electronic informed consent
EHR: electronic health record
ETP: eligible treatment population
FDA: U.S. Food and Drug Administration
HHS: U.S. Department Health and Human Services
ICMJE: International Committee of Medical Journal Editors
IT: information technology
IRB: institutional review board
NIH: National Institutes of Health
RCT: randomized controlled trial
RWE: real-world evidence

14. APPENDIX C: SEARCH TERMS FOR ENVIRONMENTAL SCAN

	Search Phrase
1	"clinical trial" + "COVID"
2	"adaptive trial" + "COVID"
3	"platform trial" + "COVID"
4	"diagnostic" + "COVID"
5	"vaccine" + "trial" + "COVID"
6	"clinical trial" + "COVID" + "diversity"
7	"clinical trial" + "COVID" + "innovation"
8	"clinical trial" + "COVID" + "delay"
9	"clinical trial" + "COVID" + "interrupt"
10	"clinical trial" + "COVID" + "wearables"
11	"virtual clinical trial" + "COVID"
12	"decentralized clinical trial" + "COVID"
13	"virtual clinical trial" + "COVID"
14	"clinical trial" + "COVID" + "telemedicine"
15	"covid" + "trial" + "lessons"
16	"COVID" + "clinical development" + "trends"
17	"COVID" + "clinical development" + "evolution"
18	"COVID" + "trial" + "platforms"
19	"COVID" + "trial" + "decentralization"
20	"COVID" + "trial" + "costs"
21	"COVID-19" + "vaccine" + "candidates" + "trial designs"
22	"Applying" + "COVID" + "trial" + “innovations"
23	"COVID" + "trial" + "acceleration"
24	"COVID" + "diagnostic" + "development" + "lessons"
25	“COVID” + “Therapeutics” + “Trials” + “Innovation”
25	"COVID” + “Therapeutics” + “Trials” + “Lessons”
26	“COVID” + “RWE” + "Trials" + “Innovation”
27	“COVID” + “Real-world evidence” + "Trials" + “Innovation”
27	“COVID” + “RWE” + "Trials" + “lessons”
28	“COVID” + “Telemedicine” + “Trials” + “Innovation”
29	“COVID” + “Telehealth” + “Trials” + “Innovation”
30	"COVID" + "trial" + "trends"
31	"COVID" + "trial" + "evolution"
31	"COVID" + "clinical development" + "lessons"

15. APPENDIX D: FDA COVID-19 RELATED GUIDANCE DOCUMENTS DIRECTLY REGARDING CLINICAL TRIALS

Below is a list of the 21 guidance documents directly related to clinical trials compiled from the FDA current and archived webpages entitled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders".

Title	Product Area	Date Posted
Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals	Drugs, Biologics	22-Mar-20
COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products	Drugs, Biologics	11-May-20
Supplements for Approved Premarket Approval (PMA) or Humanitarian Device Exemption (HDE) Submissions During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency	Biologics, Medical Devices	21-May-20
Effects of the COVID-19 Public Health Emergency on Formal Meetings and User Fee Applications — Questions and Answers	Drugs, Biologics	26-May-20
Institutional Review Board (IRB) Review of Individual Patient Expanded Access Requests for Investigational Drugs and Biological Products During the COVID-19 Public Health Emergency	Drugs, biologics	2-Jun-20
Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry	Drugs, Biologics, Animal & Veterinary, Medical Devices	16-Jun-20
Development and Licensure of Vaccines to Prevent COVID-19	Biologics	30-Jun-20
Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment	Drugs, Biologics	14-Sep-20
Effects of the COVID-19 Public Health Emergency on Formal Meetings and User Fee Applications for Medical Devices - Questions and Answers	Biologics, Medical Devices	22-Dec-20
COVID-19: Potency Assay Considerations for Monoclonal Antibodies and Other Therapeutic Proteins Targeting SARS-CoV-2 Infectivity	Drugs	13-Jan-21
Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency	Drugs	15-Jan-21
Investigational COVID-19 Convalescent Plasma	Biologics	11-Feb-21
Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests	Medical Devices	22-Feb-21

Title	Product Area	Date Posted
Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID 19 Public Health Emergency	Drugs	22-Feb-21
COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (Updated)	Drugs, Biologics	22-Feb-21
COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention	Drugs, Biologics	17-May-21
Emergency Use Authorization for Vaccines to Prevent COVID-19 (Updated)	Biologics	25-May-21
FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (Updated August 30, 2021)	Drugs, Biologics, Medical Devices	30-Aug-21
Development of Abbreviated New Drug Applications During the COVID-19 Pandemic – Questions and Answers Guidance for Industry	Drugs	8-Sep-21
Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised)	Medical Devices	15-Nov-21
Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease-2019 (COVID-19) Public Health Emergency (Revised)	Medical Devices	28-Oct-20

16. APPENDIX E: TESTING THE LESSONS LEARNED: FEASIBILITY DEMONSTRATIONS

PART I: ANALYZING THE USE OF DHTS IN REGISTERED CLINICAL TRIALS

As described above, DHTs received increased regulatory guidance and active use in clinical trials during the COVID-19 pandemic (U.S. FDA DHT, 2023). An early investigation of DHTs in clinical trials before and after the onset of the COVID-19 pandemic considered trials that launched in the 10 months prior to the COVID-19 pandemic onset (May 2019–February 2020) and compared them with trials launched during the 10 months following the acute lockdown phase of the COVID-19 pandemic (May 2020–February 2021) (Marra *et al.*, 2021). The study (Marra *et al.*, 2021) found that the use of "connected digital products" (a category which was defined nearly identically to FDA's definition of DHTs) increased by only 1.65 percentage points from the earlier to the later period—from 14.19% of all trials initiated in the 10 months prior to the COVID-19 pandemic onset to 15.84% of those started in the 10 months following ($p<0.01$). Notably, the authors found that the increase was observed "primarily in observational studies and non-industry funded trials and was driven entirely by connected digital product usage in trials for COVID-19," raising questions as to the lasting impact of DHTs in clinical trials.

It is important to examine longer-term trends, as previous research has demonstrated DHTs grew at a ~34% cumulative annual growth rate in the years from 2000 through 2018 (Marra *et al.,* 2021). The study (Marra *et al.*, 2021) considers only a brief period before and after the COVID-19 pandemic onset, which did not allow the study design to capture longer-term trends in the growth of DHTs in clinical trials. To address these two shortcomings, the authors piloted an exercise in which a significantly longer period of time—both before and after the COVID-19 pandemic onset—could be considered in detail. Below, the authors present two example analyses in which the use of DHTs are considered in registered clinical trials included in ClinicalTrials.gov from March of 2017 through the end of March of 2023.

In the first exhibit, aggregated trials are represented by the solid gray line: interventional (light blue), observational (royal blue), non-industry funded (dark pink), and industry funded trials (light pink), are also represented as separate lines. The period immediately after the COVID-19 pandemic onset (March-June 2020) is considered the "disruption" period, while the two-year period beginning in July 2020 is considered the "adaptation" period. The period thereafter, which followed the formal end of the public health emergency is labeled here as the "new normal" period.

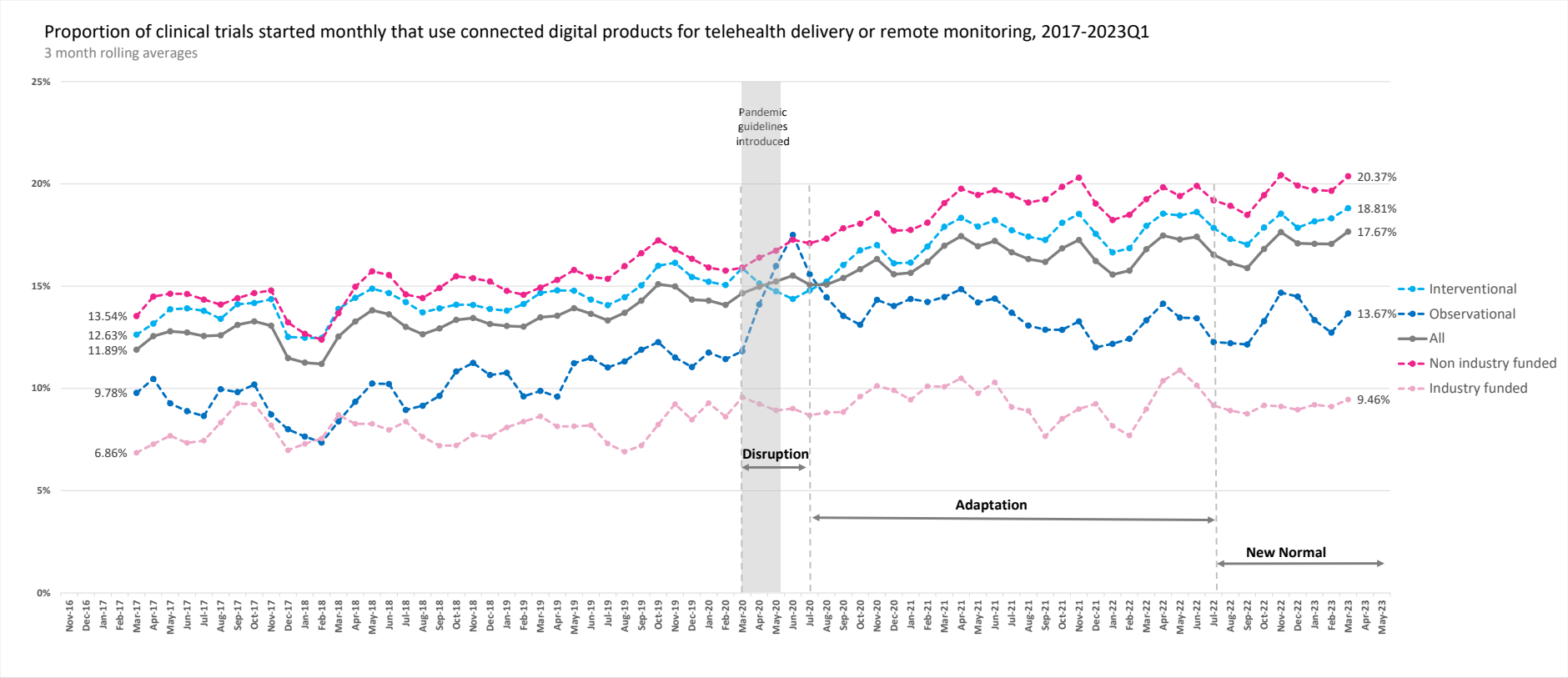


Exhibit 1: Proportion of clinical trials using DHT by month.

The second exhibit presents bar charts showing the same breakdowns by study sponsor type, where overall average shares of trials using DHTs are presented during the same time periods: the pre-pandemic (PP) period, the disruption (DR) period, the adaptation (AD) period, and the new normal (NN) period. In this exhibit, COVID-19 trials are in shades of orange, while non-COVID-19 trials are in shades of green.

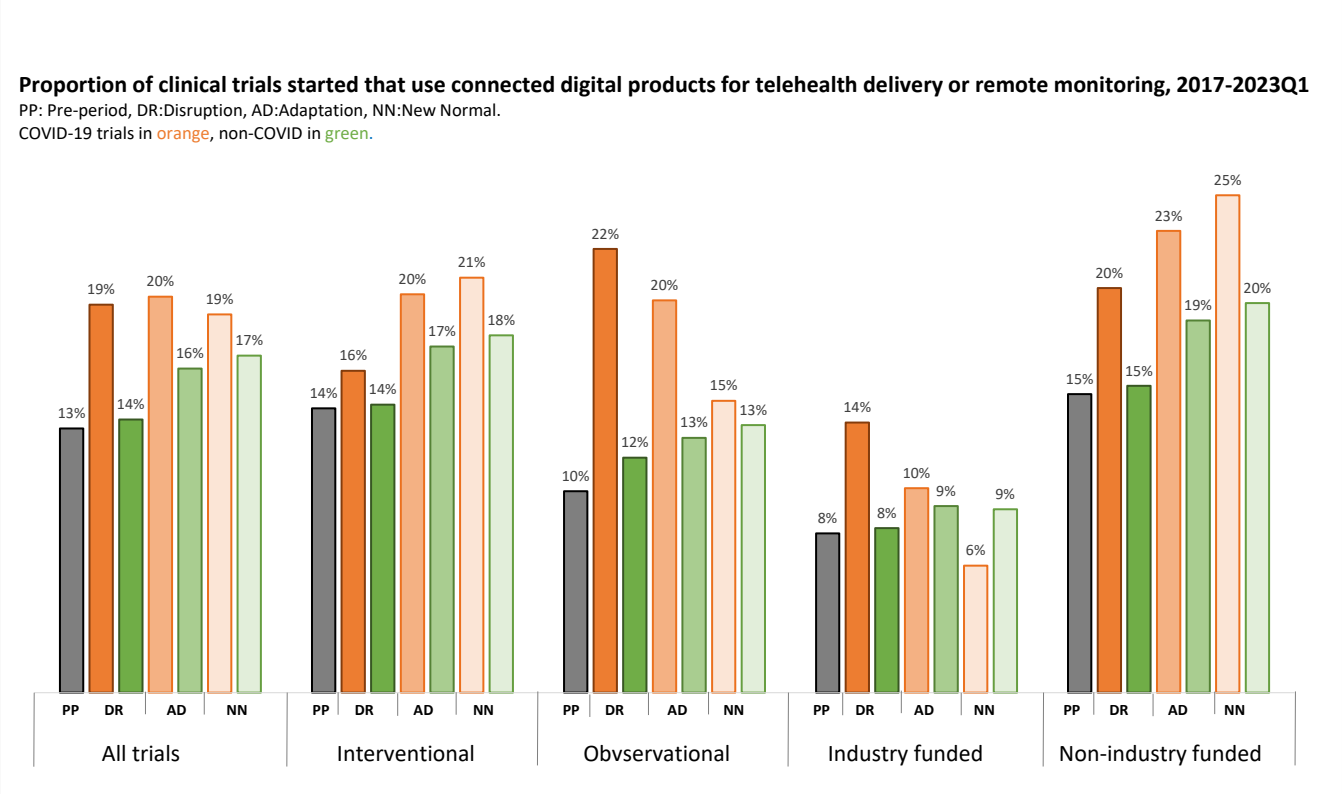


Exhibit 2: Proportion of clinical trials using DHT by COVID-19 pandemic period: pre-period; disruption period, adaptation period; new normal period.

Discussion of DHT analysis results. Sponsor reported DHT use saw an increase in the COVD-19 'adaptation' period on average and across most sponsor types. While too early for final conclusions, it appears that a leveling of DHT use in the "new normal" period may be occurring.

Industry reported DHT use remains approximately half that seen in non-industry sponsored trials. Industry sponsored trials also appear to have declined slightly from its peaks while non-industry use has sustained or even slightly increased DHT use in the "new normal" phase.

Clinicaltrials.gov data does not currently support analysis of potential causes for the "new normal" plateau. It may be that DHT use is now considered so normal that sponsors feel no need to call it out in their Clinicaltrials.gov reporting since the system does not contain dedicated fields for reporting DHT use. Or it may be that trialists view DHTs only as extraordinary measures for a crisis not applicable for ordinary times. Reasons may include the complexity, cost, planning effort of using DHTs or the belief that the risk of trial initiation delay outweighs potential benefits of DHT use. The momentum of

traditional trial processes and in-place supporting capability from staff to technology might also contribute to the stalled, and low-level, adoption of DHTs. Exploring such themes will likely require use of alternative methods (such as surveys), identification of alternative data sources, enhancement of ClinicalTrials.gov to formally collect DHT use data, or a combination of these or other approaches.

PART II: ANALYZING CLINICAL TRIAL DIVERSITY REPORTING AND REPRESENTATIVENESS AT SCALE

The eligible treatment population (ETP) to receive a drug or vaccine may differ from the clinical trial participants by demographic and non-demographic characteristics such as comorbidities, condition severity, pregnancy, and others. The FDA has encouraged clinical trialists to broaden the diversity of clinical trials to better match the most likely to be treated population (U.S. FDA Diversity, 2020).

The resistance exhibited by some populations that viewed themselves as underrepresented in the COVD-19 vaccine and therapy trials. Shearn and Krockow (2023) highlighted the importance of clinical trials representing the ETP. Quantitatively and systematically characterizing clinical trial diversity has not been done although some preliminary semi-quantitative scorecard analysis has been posted on medRxiv by the FDA (Fitzsimmons, Idris and Pemu, no date) and European pivotal trials have had some analysis (Smith, Botto and Getz, 2022)**.** Quantifying U.S. clinical trial diversity would enable better projections of representativeness, provide increased accountability, and may lead to reduced public hesitancy for new treatments as diversity demonstrably improves.

Clinical trial publications nearly universally now report their demographic characteristics in a "*Table 1"* included in each article published in a medical journal abiding by International Committee of Medical Journal Editors (ICMJE) standards (ICJME, no date). Table 1 demographics included in clinical trial publications describe the trial population participant by age, biological sex, race/ethnicity, and occasionally other descriptors the trialists deem relevant. It is typically left to the reader to calculate and decide whether the trial is representative of the likely to be treated patient population.

The common inclusion of "Table 1" in clinical trial publications enables a computer scalable extraction process that when coupled with natural language processing tools can generate a raw data set for curation and subsequent analysis of clinical trial participant diversity.

Table E1 below demonstrates the feasibility of such an approach on a test set of PubMed COVID-19 vaccine clinical trial articles. Structured "Table 1" demographic data were included in most papers (44 of 48; 92%) describing COVID-19 vaccine trials indexed in PubMed and reported in ClinicalTrials.gov. ClinicalTrials.gov registration is required for trials: included in FDA review applications; in select other FDA oversight circumstances; that are funded by the NIH; or that will be published in an ICMJE compliant journal (ICJME, no date; U.S. FDA Role, 2023).

Two thirds of demographic tables included in the pilot exercise presented contained race or ethnicity data at any level (30 of 44; 68%). The pilot exercise successfully extracted nearly all the demographic tables with race or ethnicity data (29 of 30; 97%). Scaling this study approach to all COVID-19 pandemic era trials of interest is feasible.

Table E1: COVID-19 vaccine trial articles with race or ethnicity

	n
PubMed Article having in Title: covid AND vaccine AND (safety OR efficacy OR immunogenicity)	713
with Text Availability equal to "Free Full Text"	615
with Article Type as "Clinical Trial"	65
with a corresponding ClinicalTrials.gov NCT ID	48
with a Table 1	44
that contains Race or Ethnicity	30
and that is scrapable via R	29

While biological sex reporting is highly standardized, age groupings have not been as standardized (especially for pediatric trials). In addition, only the largest race and ethnicity U.S. Census categories may be reported, as this example illustrates. Clinical trial utility for regulatory and clinical decision making, not merely systematic analysis, would be facilitated by a detailed clinical trial publication requirement.

Example diversity representativeness report for a single trial

Walsh and colleagues (2020) published the results of a 195 adult participant, Phase 1 trial NCT04368728 regarding the safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. Due to racial differences in the types of human leukocyte antigens (HLA), which play a critical role in the immune system response to viruses, and declining immune systems in older adults, understanding population representativeness is important for projecting trial results to the general population. Hepatitis C treatments (Thio *et al.*, 2001), transplant access (Pidala *et al.*, 2013), and COVID-19 susceptibility, severity, and mortality (Deb *et al.*, 2022) demonstrate this. Furthermore, eliminating poor vaccine candidates early eliminates large subsequent trials not just reducing cost but also reducing the competition for possibly scarce participants, research sites and clinical trialist staff as well as de-risking the portfolio of candidate products.

Table E2: Example "Table 1" race and ethnicity co-mingled reporting from COVID-19 vaccine trial NCT04368728

Race or Ethnicity	BNT162b1		BNT162b2		Total	% of Total
	18-55	65-85	18-55	65-85		
White (Non-Hispanic	49	41	37	45	172	88.2%
Black	2	1	3	0	6	3.1%
Asian	7	2	3	0	12	6.2%
Hispanic	2	1	2	0	5	2.6%
Total					**195**	100.0%

In the reported Table 1 for the clinical trial, the trial had the 195 participants self-report their race and ethnicity but did not have them distinguish between their race and their ethnicity. The resulting admixture is summarized in Table E2 in which the 5 Hispanic ethnicity participants do not report a separate race. For the following analysis we assumed that they were white Hispanic recognizing the possible error that some or all may have been from other races.

Table E3: Example "Table 1" race and ethnicity characteristics from COVID-19 vaccine trial NCT04368728

Race	n
White	177
Black or African American	6
Asian	12
American Indian/Alaskan Native	0
Native Hawaiian or Other Pacific Islander	0
Indigenous South American	0
Total	195

Ethnicity	n
Hispanic	5
Non-Hispanic White	172
Total	177

Demographic comparisons to the eligible treatment population of U.S. adults suggests substantial underrepresentation of Black and Hispanic participants in the study (Table E3). The clinical trial either did not recruit members from two census race groups (American Native/Alaskan Native and Native Hawaiian or Other Pacific Islander), or the authors grouped them into the three reported race categories without describing the method of doing so.

Adding summary statistics for the estimated eligible treatment population demographics and their percentage difference from the realized trial population would enhance transparency of the representativeness of any given trial. This would facilitate discussion of the generalizability of the trial results. This report's research team has piloted such an exercise (Table E4) which suggests that future research might feasibly explore diversity analysis at scale across large numbers of clinical trials.

Table: E4: Example race or ethnicity comparison for COVID-19 vaccine trial NCT04368728 and the target treatment population of U.S. adult populations

Race or Ethnicity	Trial (%)	US ETP Population (% ≥18)	Direct Difference (pp)	Relative Difference (%)
White (non-Hispanic)	88.2%	53.3%	34.9%	65.4%
Black	3.1%	12.0%	-8.9%	-74.4%

Race or Ethnicity	Trial (%)	US ETP Population (% ≥18)	Direct Difference (pp)	Relative Difference (%)
Asian	6.2%	6.1%	0.1%	0.9%
Hispanic	2.6%	10.8%	-8.2%	-76.2%
American Indian/Alaska Native alone		1.1%	-1.1%	-100.0%
Native Hawaiian or Pacific Islander alone		0.2%	-0.2%	-100.0%
Other race alone		7.7%	-7.7%	-100.0%
Two or more races		8.8%	-8.8%	-100.0%

*US population from Census "2020 Census Illuminates Racial and Ethnic Composition of the Country" (Figure 5): https://www.census.gov/library/stories/2021/08/improved-race-ethnicity-measures-reveal-united-states-population-much-more-multiracial.html
pp: percentage points

Although this example describes only a single study, it suggests that a more systematic diversity survey, perhaps with sub-analyses by study phase and product type (vaccine, therapeutic, and diagnostic) could further describe the clinical trial representativeness of the anticipated eligible treatment population and inform the relative effort level that might be required to close any systematic gaps.

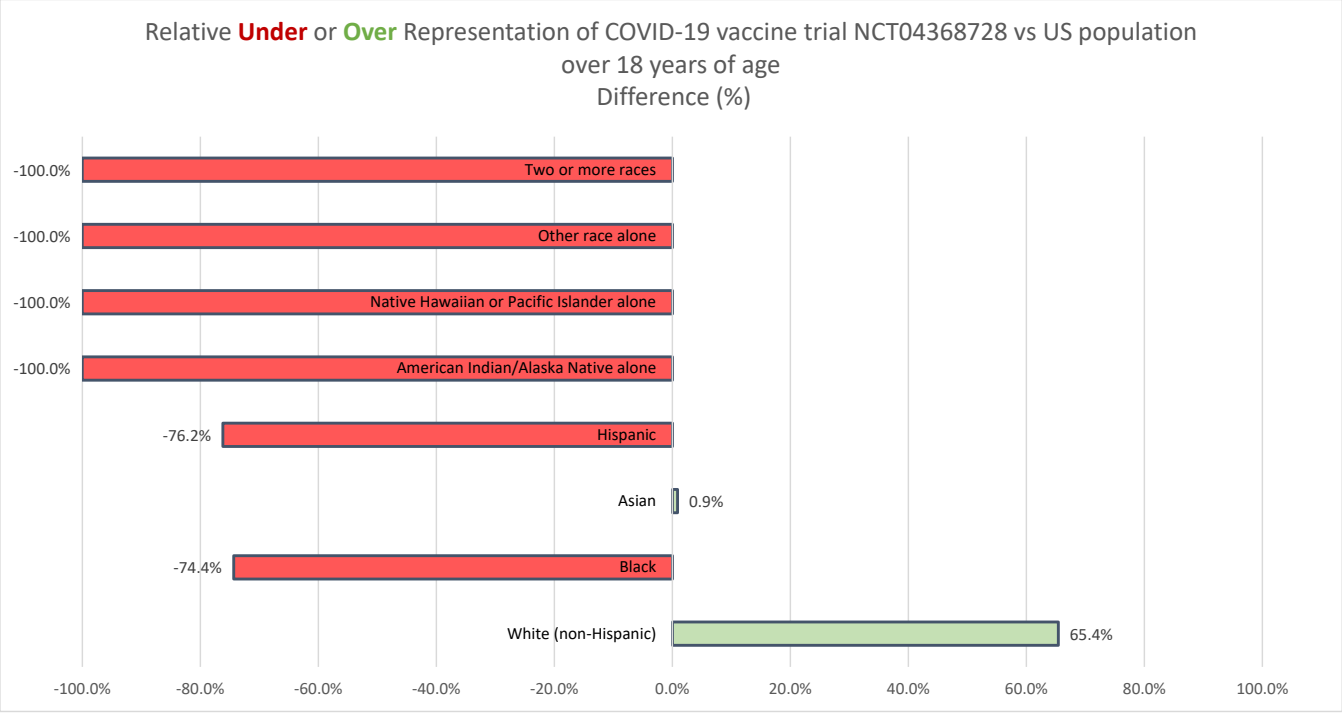


Exhibit 3: Under/over representativeness in an example COVID-19 clinical trial.

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