DCRI THINK TANKS

FROM INSIGHT TO ACTION

Durable Innovations in Clinical Trials and Regulatory Oversights From COVID-19: Emergence of a New Normal

July 28-29, 2021

EXECUTIVE SUMMARY

BACKGROUND

COVID-19 has disrupted clinical research in numerous ways. Reallocation of staff, suspension of recruitment activities, movement to virtual delivery of interventions, and other changes have required unprecedented adaptability of research teams. While efforts to streamline research conduct are not new, the pandemic has broadened awareness of existing inefficiencies and galvanized calls for change. The experiences of the past year offer a unique opportunity to learn where we have made the most progress and what barriers persist.

Identifying innovations with the greatest durability is critical, and 3 areas are ripe for examination. First, platform trials offer the opportunity to study multiple hypotheses concurrently but were infrequently used before the pandemic. The evidence generated by COVID-19 platform trials has improved patient outcomes around the world, yet acceptance of these novel designs faces substantial pre-existing barriers. Second, the promise of decentralized trials has been more fully realized due to limitations on in-person recruitment and data collection throughout the pandemic. However, longstanding obstacles may continue to frustrate implementation. Finally, COVID-19 has had major impacts on the way science is shared and understood. Balancing rapid evidence generation, robust study design, and integrity in interpretation is critical in the information age. The goal of this DCRI Think Tank was to identify key opportunities to accelerate innovation from the study design phase through study implementation and to rapid dissemination of results.

WELCOME AND OVERVIEW

Cohosts Emily O'Brien (Duke University) and Craig Lipset (Clinical Innovation Partners) welcomed the attendees and highlighted the 3 themes: platform trials, decentralized research, and dissemination of results.

INTRODUCTION: INNOVATIONS AND WHAT MADE THEM SO HARD TO STICK AND SCALE

Craig Lipset introduced the opening speaker, Badhri Srinivassan (Novartis).

Badhri Srinivassan reflected on the importance of paradoxes for driving innovation: "Durable innovations happen when contradicting forces meet to create paradoxes." For example, traditional clinical trials rely on site visits for monitoring, but the COVID-19 made site visits difficult or impossible. This paradox led to innovations and more widespread use of virtual site visits and remote assessments.

Badhri Srinivassan described 2 categories of innovation in clinical trials resulting from the COVID-19 pandemic: innovations in trial execution, and innovations in the clinical trials ecosystem. Innovations in execution include a shift toward virtual trials as the norm; the rise of the patient and research participant as a consumer; and the use of the "home as the new site." Innovations in the clinical trials ecosystem include investing in technology to build organizational resilience; anticipating disruptions and planning for the "just-in-case" instead of the "just-in-time"; and allowing practice to shape policy. During the pandemic, stakeholders have had to react quickly to ensure patient safety and trial integrity—showing what can be done in crisis situations and letting policy catch up. While practice should not always precede policy, this tension can stimulate good dialogue with policy makers about bringing practitioners' voices to the policy-making table.

Attendees further discussed the concept of home as the new site, overcoming established practices, and sustaining this innovation. Badhri Srinivassan noted that elements of the innovation can easily be sustained, such as home visits for blood pressure measurements. Widespread use of telehealth by clinicians and investigators is likely to continue. However, truly seeing the home as the new site by enabling measurements to happen in the home without home visits will require conversations with policy makers and industry sponsors to consider the benefits, understand the trade-offs, and change the standards. These innovations are not about abandoning the old to make room for the new, but rather to have more tools in the toolbox.

Attendees also discussed the implications for data integrity with the use of new modes of measurement. Badhri Srinivassan noted that technology and standards for data capture have matured. Researchers, sponsors, and regulators are all taking steps in the right direction. But they must begin to converge rather than continue as isolated actors for the innovations to be sustained.

SESSION I: PLATFORM TRIALS

Moderator Lesley Curtis (Duke University) introduced the session with a poll question about the key advantages and disadvantages of platform trials. Attendees highlighted the ability to incorporate multiple therapies and reduced costs as the greatest advantages. Attendees highlighted complexity as the main disadvantage.

Panelist Scott Berry (Berry Consultants) discussed the innovations offered by platform trials during the COVID-19 pandemic, noting that platform trials are faster and more efficient because the trial infrastructure does not have to be built from scratch for every study. He used the analogy of building a single football stadium that can host many games rather than building a new stadium for every game. Continuous adaptation is an advantage in platform trials rather than something to penalize. Barriers to platform trials were removed because of the urgency of the pandemic, and industry and regulators now increasingly accept this approach as useful. To communicate the value proposition and make the innovation durable, we should acknowledge that the first step in building the trial infrastructure (ie, building the football stadium) is expensive. In the COVID-19 pandemic, this cost was largely covered by government. In the future, other models could be considered, including platforms created with the help of patient groups, combined platforms created by pharmaceutical companies, and new models for CROs.

Panelist Daniel Millar (Janssen) offered an industry perspective on platform trials and master protocol studies. Master protocols offer value for all stakeholders. For patients, there is a higher probability of randomization to the most promising treatment and lower probability of assignment to placebo or usual care. For drug developers, there is a shorter time to answer questions, lower cost because of shared controls, and higher quality because of invested sites. For regulators, there is the benefit of advancing the most promising therapies more quickly. For investigators, these studies offer long-term research opportunities and match the most promising treatment to each patient. It will be important to understand what evidence is acceptable for regulators around the world; an exchange of case studies could be helpful. It will also be important to engage and educate stakeholders about benefits and costs, new roles, and the value proposition for each stakeholder group tailored to the drug development needs of the given disease area.

Panelist Lindsay McNair (WCG) shared a regulatory oversight perspective. Experience in the United Kingdom has demonstrated the importance of having a national infrastructure ready, whereas in the United States there were hundreds of small trials using resources and time with less coordination. For the regulatory oversight community, platform trials will require new models and approaches for writing and amending protocols and informed consent documents. An important change is that the FDA now recommends the use of a central IRB, which is imperative for platform trials. As Lesley Curtis noted, “Current systems support traditional trials, not platform trials.”

Panelist Abby Bronson (EdgeWise Therapeutics) offered a patient perspective. Using the example of building a platform trial for Duchenne muscular dystrophy, she noted that the number of patients is small and there are few studies available, which makes for slow enrollment. Patients want to avoid being assigned to a placebo and do not want to lose their eligibility to participate in future trials. Abby Bronson compared the experience of building a Duchenne platform trial with that of the HEALEY ALS platform trial. In the Duchenne muscular dystrophy effort, the work is led by patient advocates and funded by the patient community. There is little infrastructure in place (for example, there is no active clinical trial network), and the patient population is a pediatric population with a rare disease in which parents advocate

on behalf of their children. In comparison, the HEALEY ALS trial is led by an experienced clinical development and operations team with funding from community, academia, government, and private sources; the infrastructure includes an existing research consortium, a biorepository, and a culture of collaboration; and the patient population consists of adults with a rare disease who advocate for themselves. One lesson is that patient and community advocacy organizations are the most likely champions but have the least resources and know-how; challenging the status quo will require every stakeholder to understand the value of platforms trials and to leverage their respective strengths.

Attendees discussed how to "de-risk" the environment in order to foster more platform trials. Scott Berry noted the importance of identifying the risks and whose risks they are. Daniel Millar identified collaboration as a central challenge for the industry; individual companies can begin to de-risk by trying the approaches internally and taking what they learn into a larger consortium to scale it up. Lindsay observed that structures for conducting clinical trials are built on the traditional model: single protocol, single consent, everyone in the same study. With platform trials, a huge protocol must be reviewed as if is multiple protocols. The structures are not set up for this new model of clinical trial.

Attendee Rob Califf (Verily, Google Health) recollected that a model akin to platform trials was once being allowed and encouraged in acute coronary disease. As the approach expanded into other fields, bureaucratic requirements increased costs. This led stakeholders to rely on small trials with putative surrogate endpoints, the approach that seems to dominate today and that has become big business. To truly leverage the promise of platform trials, we must collectively acknowledge the constraints of the current ecosystem and actively collaborate to overcome barriers to change.

SESSION II: DECENTRALIZATION

Moderator Craig Lipset introduced the session.

Michelle Longmire (Medable) shared a perspective on telehealth. Decentralized clinical trials can improve access to investigational therapies. During the COVID-19 pandemic, Medable focused on implementing telemedicine in trials that were already underway, because of the urgent need to shift to virtual outcome assessment. Use of telemedicine has since become widespread, and pharmaceutical companies are investing to ensure they are prepared to meet future needs. Telehealth is becoming a routine solution for improving convenience and access for patients in clinical trials and in health care more broadly. When asked what can make these innovations durable, Michelle Longmire noted that physicians' widespread adoption of telemedicine and its integration into the point of care is encouraging. We knew patients wanted it; now the clinics can do it, and it has become mainstream.

Hassan Kadhim (Bristol-Myers Squibb) addressed implications of decentralization for data quality and governance. Data quality is foremost in study teams' minds when they consider moving to decentralized models. At a basic level, decentralized trials bring telemedicine, e-

consent, and electronical clinical outcome assessment (eCOA) directly to the patient. From this perspective, they are not much different from standard trials. For example, with consent in a traditional trial, we take measures to ensure proper data quality in the process conducted at the site. The considerations are the same when the process is conducted remotely, except that the introduction of telemedicine comes with e-consent. Likewise, clinical outcome assessment can be conducted from the clinic in the presence of a study team member or remotely via eCOA. The data quality considerations for collecting data directly from patients are generally similar. However, methods like wearables and other alternative data collection measures require considerations of impacts on primary or secondary outcome measurements. Pharma tends to introduce these in a nuanced way, collecting the information as secondary data not to be used for submissions, to mitigate risks for data quality. Governance questions come into play when, for example, a sponsor is deciding whether a decentralized trial will be conducted internally or outsourced to a CRO, or whether they will use a technology platform vendor.

Bray Patrick-Lake (Evidation) discussed the importance of building relationships with patients in ways that drive participation in research and health programs. Evidation's large patient member network enables longitudinal connections, deep phenotyping, precision recruitment, and use of patient-centered outcome measures. In an example of precision recruitment, they developed and implemented a machine learning algorithm to identify members at risk of COVID-19. Precision recruitment can support timely and efficient clinical trials by identifying the right people for the right trial, reducing recruitment and operations costs, and shortening cycle times. Direct connections to people outside the clinic, built on trust and value, can support rapid enrollment and retention of diverse populations. These connections, along with person-generated health data, can be used for phenotyping, hypothesis generation, testing of study communications, and better understanding of patients' experiences, leading to development of meaningful patient-centered outcome measures. Building relationships with patients early supports collection of higher-quality data and better engagement over time.

Patrick Gee (iAdvocate, Inc) stressed the importance of inclusion and access for underserved and underrepresented populations. These populations often have longstanding mistrust of health care and research institutions due to institutional biases and discriminatory practices. They also face a host of access barriers, including access to health care, health insurance, housing, food, transportation, childcare, and time off from work. Innovations in clinical trials that expand access and remove barriers are promising, but lack of access for these communities remains an important issue.

Isaac Rodriguez-Chavez (ICON) offered a regulatory perspective on decentralization. He stressed that good protocol design is critical for any clinical investigation and helps avoid problems later on. From a regulatory standpoint, the focus is less on technology and more on participant safety and data quality. It is important to understand the safety profile of the intervention and whether that intervention can be delivered in a decentralized way. Even if it cannot be, there may be ways to decentralize other aspects of the trial to reduce participant burden.

In response to poll questions, attendees identified patient convenience and the ability to reach a broader patient population as the leading advantages of decentralized trials. They identified the leading difficulties as monitoring trial execution and protocol adherence, as well as regulatory constraints.

Attendees discussed the acceptability of decentralization for regulatory agencies. Isaac Rodriguez-Chavez noted that the FDA is ahead of the pack in supporting these trials and that the European Medicines Agency has issued guidance for introducing elements of decentralization into traditional trials during the COVID-19 pandemic. There is a clear opportunity for regulatory harmonization, as long as there is primary focus on participant safety and data quality.

Attendees also discussed the responsibility to support sites and patients in decentralized trials. Creating more burden for sites is not an option, and patients cannot be expected to adapt to unfamiliar technologies without support and education. Bray Patrick-Lake noted that the Digital Medicine Society has started a new consortium, DATAcc, to improve digital technology inclusion, support diverse patient populations, and serve as a resource for CROs and other stakeholders. Support for patients depends on the population of interest. The greatest impact can come from working with a patient advisory group to test assumptions, meet basic needs, and understand the interests of the patients' communities.

DISCUSSION WITH HARLAN KRUMHOLZ ON RAPID DISSEMINATION

Josie Briggs (*Journal of the American Society of Nephrology*) facilitated a discussion with Harlan Krumholz (Yale University), who gave remarks about rapid dissemination of science.

Harlan Krumholz noted that our obligation to study participants is to finish and report the results, tell them the results, and provide context for the results.

The traditional model of dissemination through peer-reviewed medical journals is slow, expensive, incomplete, and inaccessible. Peer-reviewed literature represents only a subset of all the trials being conducted. Many completed trials go unreported or take a long time to be published. During the COVID-19 pandemic, many journals prepared for more rapid review but were inundated and have been less able to discriminate with regard to quality. Preprints are an option for disseminating results more quickly via preliminary, non–peer-reviewed reports. Postings on medRxiv expanded greatly during the pandemic.

Josie Briggs asked about the adjudication of quality and the need to have several settings in which research is reviewed critically. Harlan Krumholz described the usefulness of preprints for sharing results quickly and the opportunity for journal editors to leverage commentary on preprints as part of the peer review process. Authors can also learn from the comments and incorporate what they learn during revision.

Emily O'Brien asked when preliminary data should be used to guide clinical practice. Harlan Krumholz discussed the caveat that preprints have not been vetted through the peer review, though this caveat will not always dissuade experts from making determinations about implications for clinical practice. Josie Briggs noted that the COVID-19 pandemic has required some rapid clinical decision making that is not representative of the whole evidence-building apparatus. Peer review is one element; there is also regulatory decision making, development of guidelines, etc. There is general recognition that this process of careful readjudication gradually moves us in the right direction. However, the urgency of the pandemic has not allowed for that more deliberative process. Harlan Krumholz noted that, in situations of dire need and few options, changing practice based on early information means also relying on rapid evaluation with fellow experts along with using real-world evidence to confirm whether the results are as expected.

Attendees also discussed the importance of changing the incentive structure to better support team science over the independent investigator model, and making preprints the expectation for junior investigators as a way to start changing the culture of research.

SESSION III: RAPID DISSEMINATION OF RESULTS

Moderator Esther Krofah (FasterCures) started the session by polling the attendees about preprint services. Seventy percent of attendees had not submitted their research to a preprint service. When asked whether they would use data published in preprints to change their clinical practice, 33% said they would wait for a peer-reviewed publication, and 28% said yes, but only if the findings were compelling.

Panelist Ivan Oransky (Retraction Watch) observed that the number of retracted papers about COVID-19 was not higher than would be expected. Retraction is not a new phenomenon; however, there is a lot of attention being paid now because of the speed and quantity of publishing during the pandemic. Ivan Oransky also discussed the importance of being transparent and honest about what peer review can and cannot do. Scientific knowledge is provisional and always changing; framing scientific knowledge as categorically correct feeds public mistrust of science when that knowledge evolves.

Panelist John Whyte (WebMD) echoed concerns about erosion of public trust in science. Early in the COVID-19 pandemic, there was a surge in public trust in health care providers and researchers. In March 2020, 80% of the public had a favorable opinion of CDC. Today, less than one-third of respondents in a survey said they trust the CDC. A main criticism is that guidance and information seems to change. A fundamental problem is that public information campaigns rarely acknowledge that scientific information is incomplete and that there is uncertainty in the data.

Sharon Terry (Genetic Alliance) discussed the importance of moving away from top-down communication with patients and research participants. Collaboration with communities is key, and researchers should focus on building trust with people "where they live, eat, work, play,

and pray." There are also lessons to be learned from the marketing and communication industry about how to target and disseminate information. It is important to be honest and transparent with patients and communities to know that research studies can have negative results and that those results are also important for science and learning.

Jean Sposaro (Bristol-Myers Squibb) discussed the importance of returning study results to participants. Technology has increased the feasibility of data sharing, use of portals, and patient-facing apps. Patients and research participants increasingly expect to have access to health data and to be active partners. Industry is recognizing the value of patient contributions to research and is engaging in data sharing pilots. Regulators are focused on increasing the patient voice in drug development. Returning study results to patients should be user-friendly and in plain language, be integrated into existing care networks, and focus on the information most important to patients.

Esther Krofah asked the panelists to reflect on what trends will be or should be sustained coming out of the COVID-19 pandemic. Ivan Oransky highlighted the importance of not saying we have the right answer all the time, but that scientific knowledge is supposed to evolve and adapt. John Whyte agreed with the importance of making information available while acknowledging that it is imperfect and requires interpretation. Sharon Terry identified the level of clinical research literacy as the most durable change. Jean Sposaro observed that researchers are doing better at bringing people into early planning stages of drug development and engaging more diverse communities.

TAKEAWAYS

- The past year has brought a shift in mindset from linear or stepwise thinking about clinical trials to ecosystem thinking.
- Platform trials have come of age over past year, especially outside the United States. Moving away from the status quo will require commitment from a broad group of stakeholders.
- The promise of decentralized trials and thinking of home as the new site—leveraging things like telemedicine, e-consent, ePROs—is that it can bring research to people rather than the other way around. Regulatory barriers are the key challenge.
- We have an obligation to disseminate research findings. We should work toward a research culture that rewards team science rather than independent investigators.
- Rebuilding public trust in science will require resetting people's expectations and being honest about the fact that scientific knowledge is provisional and always changing.
- The burden of building trust with research participants is with us, not with those whose trust we want. Trust is to be found in involving patients early in the research process, understanding their needs, and sharing what we learn as a result of their participation.