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*Nothing to Disclose*
For more than two years, the COVID-19 pandemic has affected every sector of the global economy, including the clinical and translational research enterprise.\(^1\) Academic medical centers (AMCs) have faced the challenges of an apprehensive health system concerned with maintaining patient and healthcare worker safety with an emergent call to advance COVID-19 knowledge through research.\(^2\) Even as AMCs implemented investigational approaches and treatments, the pandemic exposed the need for new and broader strategies in order to successfully operationalize and manage research as both an urgent and now clearly a long-term response.\(^{1,3}\) However, a review of the pandemic’s impacts on the larger clinical research landscape is needed to fully understand the environment in which newer research processes have been and continue to be implemented.

Importantly, this article illustrates the wide-ranging impact of COVID-19 on research processes and associated best practices that have emerged to manage these impacts on the research environment at The Ohio State University Medical Center. Four overarching key strategies are highlighted: 1) leveraging existing research management infrastructure; 2) establishing a COVID-19 research policy; 3) developing multidisciplinary research working groups; and 4) strengthening connections among institutional research stakeholders. These strategies demonstrated success in the initial response to the pandemic and have remained critical for research management throughout the ongoing pandemic.
Leverage Research Management Infrastructure

The pandemic has permeated academic and administrative operations. Figure 1 illustrates the impact of COVID-19 on research processes at the institutional level as unprecedented shifts in routine clinical practices continue to be reflected in updated and ever-changing federal, state, and local university guidelines for research.

Figure 1: COVID-19’s Impact on the Research Landscape

The literature to date has discussed how some AMCs mobilized their research response through the creation of a COVID-19 oversight group located within their College of Medicine, Office of Research, Clinical Translational Science Award Center, or some combination of these institutional entities.{4} Our AMC leveraged a centralized administrative infrastructure for managing non-cancer human subjects research, the Center for Clinical Research Management (CCRM), to rapidly oversee and implement COVID-19 research. The CCRM, supported through
The Ohio State University’s College of Medicine, strategically aligns resources and research personnel with the needs of investigators and disease-specific research teams.

The connectivity of the research infrastructure with the larger landscape and multiple stakeholders is demonstrated in Figure 1. The red circles highlight the pandemic-related impacts and/or adjustments that have been necessary to successfully implement and maintain overall research activity. As such, the infrastructure of the CCRM has rapidly addressed the continuously evolving direction of COVID-19 research, offering an organized pathway for conducting research while also managing these efforts with ongoing regulatory, fiscal, operational, and personnel oversight.

The size of the CCRM (1,600 studies with 250 principal investigators and 219 research staff across 22 departments, centers, and institutes) has provided the ability to disseminate information quickly and broadly. At the pandemic’s onset, COVID-19 research was prioritized while other ongoing and new non-COVID-19 studies were temporarily halted. Importantly, the CCRM’s infrastructure fostered movement out of individual research silos into collaborative research groups, as well as connected multiple stakeholders who brought several types of expertise together to address the research questions generated by the pandemic.

The utilization of existing centralized research infrastructure has offset challenges that would have been inherent to decentralization of activities, including effort redundancy, miscommunication, and lack of cohesive research strategy. The centralized oversight has also allowed for ease in administration as over time non-COVID-19 research, placed on hold at many AMCs, has largely restarted and continues amid the ongoing pandemic.

**Establish COVID-19 Research Policy**

The pandemic response has been unprecedented with investigators from all areas of medicine, not simply virology and infectious disease, designing projects to understand, treat, and prevent COVID-19.[5] Many investigators initially lacked experience in conducting research in an environment where the patients, staff, and scientists are at risk through even the simplest of in-person interactions, where biospecimens present significant and often unknown risks, and where personal protective equipment (PPE) has been in short supply and, at times, appropriated by the clinical mission.
In response to managing these risks, a comprehensive research policy was implemented through the College of Medicine, with oversight by the CCRM, to identify and guide investigators seeking to engage in COVID-19 research. This policy has required investigators to complete an impact and planning assessment for any COVID-19 research (e.g., laboratory-based, biorepository, observational, interventional, and therapeutic). The assessment includes those factors identified as most important by research and medical leaders as to whether to engage in a proposed research study: impact on healthcare and research team safety, PPE resources needed, ability to implement regulatory and biosafety safeguards, scientific merit, and funding status.

In practice, assessment approval has been required prior to seeking institutional review board (IRB) approval for COVID-19 studies or modification of existing studies adding COVID-19-related aims. Figure 2 (next page) illustrates the strategy for managing COVID-19 research. The policy with its associated review process has been successful in the identification, tracking, and management of our AMC’s COVID-19 research response (215 assessments received; 145 approved to move forward, e.g., IRB submission as applicable).

Create Multidisciplinary Research Working Groups

In response to the pandemic and the call for clinical research, four multidisciplinary coronavirus-centric working groups (e.g., inpatient/intensive care, outpatient, biorepository, and healthcare workers) were created and have served as another means of organizing the research response. These working groups consisting of investigators and clinical research personnel from differing disciplines, have been responsible for driving study feasibility (reviewing 90 proposals and opening 43 studies to date), making final recommendations for study selection and prioritization, and reporting progress and associated obstacles to the centralized research leadership (CCRM).

Study selection and prioritization was based on those studies deemed as contributing data to the larger understanding and treatment of the COVID-19 virus and were consistent with investigator interest/knowledge, patient availability for enrollment, and resources (e.g., personnel, equipment). The working groups have also helped with early identification of ineffective investigational therapies enabling prompt operational pivots to subsequent studies in the queue.
Additionally, studies are grouped and prioritized by intervention type to limit those with overlapping mechanisms of action. Study categorization has improved selection efficiency and allowed for the development of a diverse portfolio of COVID-19 studies that improve patient care by providing treatment options. Whenever possible, research protocol requirements have been aligned to standard of care/daily care practices to manage added work for practitioners.
The working group model, further illustrated in Figure 2, has provided a structure that fosters consensus building across disciplines in the selection and implementation of studies that show the most promise for treating patients, as well as contributing to scientific knowledge (the two highest priorities for study selection). Currently, these working groups have remained in place to continue guiding study selection and prioritization regarding treatments and the long-term impacts of the SARS-CoV-2 virus.

**Connect Institutional Research Stakeholders**

Increased institutional connectivity and regular review and interpretation of COVID-19 guidelines have been conducted communally amongst Ohio State research stakeholders (e.g., CCRM, Center for Clinical and Translational Science (CCTS), disease-based research units, IRBs, sponsored programs, compliance offices) to ensure clarity and ease of implementation. Throughout the pandemic, guidelines reviewed have included definitions of essential versus non-essential research, cessation of in-person research visits, increased use of telemedicine, transition to telework, and utilization of touchless consenting practices.

For those investigators and research staff involved in consenting COVID-19 patients into studies, a weekly call was initially established to review updates to guidelines and research processes specifically related to e-consenting, documentation, and screening. This has helped to establish common practices and maintain regulatory compliance standards (see Table 1 on next page for a summary of workflow adjustments and policy changes that have been related to COVID-19). These research-related adjustments remain pertinent to ongoing research operations as the pandemic continues and COVID-19 studies have largely transitioned from emergency use studies to randomized clinical trials and, more recently, into long-term outcome studies.

Additionally, communication between the centralized research infrastructure (CCRM) and the CCTS has contributed to the alignment of institutional COVID-19 research priorities with national initiatives to combat the pandemic. The Network Capacity Program of the CCTS has identified opportunities to participate in COVID-19 clinical and translational research studies supported through national and regional collaborative networks. This communication has allowed the CCRM to engage in prompt dissemination of interest to the appropriate
investigator(s) and their respective disease teams as they are readily identifiable. This, in turn, has allowed for timely responses to research inquiries and site questionnaires, and for timely initiation of study startup activities.

Table 1: Clinical Research Workflow Adjustments and Policy Changes Related to COVID-19

<table>
<thead>
<tr>
<th>PERSONNEL</th>
<th>CONSENT PROCESS</th>
<th>RESEARCH CONDUCT</th>
<th>RESEARCH DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of PPE (limit use to essential and/or COVID-19 research)</td>
<td>Submission of remote/distance consent discussion processes with initial IRB applications</td>
<td>Utilization of telemedicine for study visits</td>
<td>Alignment of study procedures with standard of care to limit staff exposure</td>
</tr>
<tr>
<td>Transition to telework (ensure staff had compliant and adequate technology)</td>
<td>Application of eSignature platforms for obtaining subject/Legally Authorized Representative signatures</td>
<td>Utilization of home healthcare to obtain key safety data (labs, ECG, etc.)</td>
<td>Execution of adaptive protocol design</td>
</tr>
<tr>
<td>Formation of interdisciplinary teams of coordinators</td>
<td>Utilization of electronic communication platform for facilitating consent process (discussion and signatures)</td>
<td>Increased use of remote monitoring of data</td>
<td>Engagement with IRB to include vulnerable populations (prisoners, pregnant women)</td>
</tr>
<tr>
<td>Implementation of weekly virtual meetings with COVID-19 research staff to improve efficiency and recruitment</td>
<td></td>
<td>Application of eSignature platforms for obtaining regulatory document signatures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhancement of remote investigational product distribution</td>
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The overall benefit of connectivity to stakeholders has been even more clearly manifested throughout the pandemic, as our evolving understanding of the nature of the virus and the associated guidances have significant consequences for all members of the clinical and scientific community. Swift implementation of large-scale COVID-19 practices has required numerous successive and parallel operations on every level of the AMC, thereby showcasing collaboration and institutional connectivity.
Conclusions

Along with illustrating the pandemic’s initial and ongoing impacts on the AMC research landscape at The Ohio State University Medical Center, this article has highlighted best practices for navigating these impacts. The key strategies of utilizing and extending existing research infrastructure, establishing common policies, implementing identifiable leadership through multidisciplinary working groups, and driving increased connectivity and consensus building among stakeholders has placed this AMC in the best position possible to handle the challenges as the pandemic initially developed, worsened, and now continues to evolve into waxing and waning episodes.

These best practices, born out of necessity, highlight how quickly effective research management changes can be created and implemented and serve as a guidance for other AMCs as well as other groups engaged in clinical research. Importantly, the processes successfully mobilized to ensure adaptability and consistency in clinical research operations have remained in place throughout the ongoing pandemic in order to continue effective and responsive clinical research management.

The lasting impact of COVID-19 on research-specific processes (e.g., use of eConsent, offsite monitoring) will also continue to evolve along with the pandemic, as the need for advancements in research will coexist with the need for effective clinical management of the COVID-19 illness.

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Opinion: More Sites, Sponsors, and CROs Should Leverage eSource as a Study Manager in Remote Monitoring Situations

Takoda H. Roland, CCRA, CCRP, CNA

I have long been a proponent of the potential of electronic source documentation (eSource) and its advantages in clinical trials. From my experience as a clinical research associate (CRA), I wrote about eSource several times\(^1,2\) in a period when I had come to see that clinical research was only just scratching the surface on leveraging the technology to fundamentally change the way we monitor clinical trials.

At the time, I did not expect to find myself in a position to make a meaningful shift toward remote monitoring. Several years later, while working as a clinical team manager on a global pivotal Phase III study for an Investigational New Drug application, COVID-19 forced contract research organizations (CROs) to rethink their monitoring paradigm. Drawing from both my own and my team’s experience with a leading provider of eSource services, our study was able to successfully implement a remote monitoring process to mitigate the issues of running the trial during the pandemic. Even as someone who had long advocated for remote monitoring using eSource, I found myself astounded at the success our team achieved.

*Despite the myriad additional issues caused by COVID-19, our study team’s efficiency dramatically increased with remote monitoring.*

As a CRA in 2018, I was fortunate to come across several research sites that were early adopters of eSource and to see how its benefits were immediately evident. Switching to eSource dramatically reduced the workload for sites by streamlining their entire documentation process.
The improved efficiencies in data entry vs. handwritten notes, along with a clear step-by-step process for each specific visit, reduced patient visit times.

Leveraging eSource also delivered a significant reduction in errors and missed procedures at sites thanks to real-time data validation. When I did find errors, the audit logs and queries directly on the eSource page were considerably easier to close than the traditional pile of sticky notes monitors are accustomed to utilizing.

One of the inefficiencies I previously noted in earlier publications is the lack of standardization in site sources. Too much time is spent as a CRA familiarizing yourself with each site’s specific source. Due to every site creating a unique source, it is not uncommon for critical datapoints to go uncaptured in the beginning of a study. Standardization of the initial source would reduce the workload of both sites and CRAs, while ensuring critical datapoints are not missed and increasing the chances of noticing trends across sites. With robust eSource tools in play, standardization makes study management and version control in protocol amendment situations much easier, as well. eSource also allows the CRA to spot check the site’s source remotely to ensure it captures all required visits prior to the first patient’s visit.

I have seen firsthand how sites can leverage eSource in several surprising ways. Some sites indicate that using eSource allows them to work with more doctors and in different therapeutic areas that they had previously been unable to find help with. With the ability for principal investigators (PIs) and sub-investigators to review patients charts as eSource from their private practices or homes, the burden on doctors is greatly reduced. For example, investigators’ review times for adverse events are reduced since they no longer need to physically travel to the research office to access charts. One site I encountered even outsourced electronic data capture entry of its source to an offsite facility in a different state.

*While eSource offers many advantages to research sites, I believe it benefits sponsors and CROs even more.*

To unlock the full potential of eSource by enabling remote monitoring, a study needs the buy-in of both the CRO and sponsor. I had been pushing several years at my CRO to try to implement remote monitoring leveraging eSource to no avail. Then, everything changed when COVID-19
shut down onsite monitoring. Remote monitoring was no longer just an idea or small add-on, it was something we needed immediately and should have started implementing years ago. Flights were getting cancelled, CROs grounded CRAs, and sites decided the last people they wanted to see during a pandemic were CRAs who had travelled through multiple major airports that week.

As soon as the impact of COVID became evident, I started working with our study team and sponsor toward potential solutions. Reaching out to our study sites, we identified several sites that were already using eSource for tasks tied to such areas as their clinical trial management systems (CTMSs), payments, patient recruiting efforts, electronic regulatory needs, and more. Sites that had standardized their eSource practices were able to continue recruiting patients and running trials with minimal to no interruptions. This was not the case for sites that had not made the switch to eSource.

*Our team pulled in resources from data management, the sponsor, sites, and our clinical team to amend our study monitoring plan to allow for remote monitoring visits, resulting in improved monitoring metrics across the board.*

While other study teams were stuck at the mercy of COVID-19 restrictions, our team achieved some of our highest metrics. Our company’s expectation is around the industry average for days on site (DOS), requiring CRAs to perform in-person onsite monitoring at a research site eight to 10 days per month. However, virtually every study struggled to have CRAs meet their DOS metrics as sites were closed. Even once sites reopened to allow CRAs, the backlog from other studies caused a ton of intra-study competition for space on site for monitors.

Many research sites had additional staffing issues related to cutbacks from COVID-19 that further exacerbated the issue of getting monitoring time onsite. With the implementation of remote monitoring, our CRAs exceeded their traditional DOS metrics, resulting in more pages monitored, improved patient safety due to the reduction of monitoring lag times, and improved CRA efficiency from no longer losing valuable time to travel.

After a few successful trial remote monitoring visits using our favored eSource tool, the study team started to reach out to more sites to see if there were any others using potential eSource solutions. We identified two sites that were using a particular CTMS in this manner. While it did
seem to have the potential to be used as an eSource that was compliant with the expectations of the Code of Federal Regulations (CFR) Part 11, we met with mixed results using it. One site was successfully using it in a way that met industry standards for source data capture, however our CRA’s page monitoring rates there were a bit lower than at sites using the eSource our company favored. The other site was using that same CTMS in a way that was not CFR Part 11–compliant, and this continued to be an issue throughout the study.

We had several sites implement eSource mid-study as a COVID-19 mitigation with mixed results. While implementing eSource mid-study did allow us to complete remote monitoring for new study information, it remained a challenge to verify source data for earlier visits. Some coordinators reported that learning a new system mid-study was an additional burden under already-stressful conditions.

Ideally, an eSource solution is implemented prior to study start. While eSource has great potential, it is critical that due diligence is being done when selecting a vendor and that there is a defined plan to ensure successful implementation.

On our study, we also utilized a hybrid model for monitoring support. Our monitors would attempt to achieve their full DOS expectations at their dedicate sites, however logistics challenges related to COVID-19 made this impossible. Last-minute cancellations due to new policies, COVID-19 outbreaks at sites, flight cancellations, and site closures often left our monitors without scheduled DOS.

Sites with eSource can accommodate many monitors with much shorter notice since they do not need to plan for physical space for the monitors. Monitors onsite are more disruptive to a study coordinator who likely has patients to see. With eSource queries, study coordinators were willing and able to accommodate last-minute visits and address study findings without the visit disrupting their schedules.

*Beyond the obvious increase in DOS that we were able to achieve with our monitors not losing time to travel, our study team also saw an increase in the number of pages monitored per day with the remote model.*
Our monitors gained access to study data more quickly without the restriction of planning onsite visits. Early access to data meant errors were captured more quickly and corrective actions implemented faster. With corrective actions in place, our sites participating in the remote monitoring saw fewer errors overall.

Further, study timelines were much more easily managed for our sites participating in remote monitoring. Last-minute visits were no trouble to schedule for our sites enrolling their first patient, allowing our study team to meet our monitoring plan requirement of monitoring the first patient within two weeks of enrollment. Meeting schedules for data management batch-cleaning and achieving goals for database locks were also easy for our team with remote monitoring, due to reduced friction in timelines. Medical review timelines were met with remote monitoring access to data, cutting out the traditional middleman between the PI and medical monitor.

Our study team members were more efficient when monitoring with multiple screens from the comfort of their home offices as opposed to being crammed in a makeshift monitoring room. This change in the monitoring workflow resulted in improved CRA retention, as many studies had CRAs leaving the clinical trials industry completely. Even from our less tech-savvy monitors, the feedback was unanimous:

*Remote monitoring was preferred due to lifestyle comfort, efficiency in monitoring, and ease of scheduling.*

Our CRAs were happy to increase their monthly DOS from the expected eight to 10 to as high as 12 to 16 when it meant not having to endure long hours at airports away from their families. Our study was so successful due to our implementation of remote monitoring, that our study alone accounted for more than 25% of the company’s third-quarter revenue.

*The study greatly exceeded revenue expectations despite the pandemic, all thanks to our implementation of remote monitoring.*

Our study implemented remote monitoring as a COVID-19 mitigation. While I was excited to finally leverage eSource to enable remote monitoring, it is disappointing that it took a global pandemic for the clinical research enterprise to finally wake up to the 21st century. Remote
monitoring should be the integral component of every clinical trial. With remote access to source study data, the model of dedicating an entire DOS to one specific site will change.

Specific visits like those for first enrollment and pages like those for adverse events can be prioritized study-wide for monitors to add the most value toward the study and improve patient safety.

Continuous monitoring breaks the traditional monitoring cycle. Trip reports are based on the frequency at which monitors can get onsite and are not always an accurate representation of the amount of work being performed at a given site. Continuous monitoring allows for regular reports for individual sites to be run and written at scheduled intervals to improve their value. Regular reporting across all sites also allows for easy site-to-site comparisons. Performing such comparisons makes it easy for study teams to identify high-risk sites and allows for true risk-based monitoring, which calls for clear action when risks are identified.

When remote monitoring is the standard, onsite monitoring serves as an excellent tool to mitigate risks identified in site risk reviews.

While our study team was able to prove many of the benefits of eSource not just for sites, but also for the CRO and sponsor, I’ll wrap up with the same message I started with:

We have still only scratched the surface of how eSource will change monitoring in clinical trials.

References


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Digital therapeutics (DTx), the use of software-based interventions to prevent and treat disease, is one of the biggest areas of growth in life sciences. CB Insights reported that 2021 funding in the digital health industry grew 79% over 2020,¹ and the global DTx market is projected to hit $13.1 billion by 2026,² up from $3.4 billion in 2021.³ Many say digital therapeutics will re-write the future of healthcare.³

The DTx industry isn’t just aspirational. Studies show improved outcomes from DTx, either alone or in conjunction with conventional therapeutics, in a broad range of indications, including cancer, ADHD, asthma, schizophrenia, and insomnia. Some examples of products include video games to treat mental and behavioral health issues; a platform that incorporates neurological music therapy, sensors, and artificial intelligence to help patients who have suffered a stroke or other neurological disorder to rebuild motor skills; and a smartphone app that can conduct electrocardiograms anytime, anywhere.

**Background**

While exciting, this is still unchartered territory. Regulatory lines are often blurry between prescription DTx, non-prescription DTx, and combination digital therapeutics/traditional medication. It’s worth noting, however, that the U.S. Food and Drug Administration (FDA) has demonstrated its commitment to supporting digital health technologies through the publication of multiple guidance documents and the launch of the Digital Health Center of Excellence, which
aims to connect and build partnerships to accelerate digital health advancements, in September 2020. In April 2021, too, the FDA loosened regulations surrounding approval of digital mental health tools to hasten their time to market.\(^{4}\)

Even so, not all DTx manufacturers choose to seek FDA approval, but they all need to prove efficacy through clinical studies for payers to consider coverage and consumers to consider purchase. Regulatory approval is not always the end goal—or at least, not initially.

AstraZeneca, for instance, has designed a rigorous and low-patient-burden digital therapeutic to monitor metastatic breast cancer patients. The prescription DTx, which is currently being tested in clinical trials in 23 countries, was developed using insight from a review of medical literature, pulmonary and breast cancer experts, technology review, and real-world evidence gathered through conducting a deep cohort analysis of approximately 500 patients in U.S. health systems.\(^{5}\) The therapeutic’s aim is to monitor patients’ symptoms and vital signs and, based on algorithms and expert rules, alert a physician as to how well the patient is doing on the treatment to maximize both safety and outcomes.

“Regulation will differentiate between a fitness app a consumer can simply download, with no regulation required, versus something that is scientifically proven to have a direct impact on someone’s health condition or outcome, which a doctor may prescribe,” said Cristina Duran, chief digital health officer for AstraZeneca, in a statement. “In a few years, I think we will see that shift to it being commonplace for your doctor to prescribe a digital therapeutic, a medication, or both.”

Indeed, it’s a complicated and quickly evolving arena in healthcare.

On top of the current regulatory limbo, DTx manufacturers face many of the same clinical trial challenges as traditional drug makers, including those tied to patient recruitment and retention, quality of data, and costs. They also must carefully consider the unique technical security concerns of an all-digital therapeutic and face strategic decisions around either provisioning smart devices or leveraging a “bring your own device” (BYOD) policy. At the same time, clinical trial models are rapidly evolving, adding further complexity for companies working to develop innovative digital therapeutics in a post-pandemic environment. Decentralized clinical
trials (DCTs) are becoming a preferred model for research in biopharma and offer even greater benefits to companies conducting studies on digital therapeutics.

Wave Neuroscience, a medical device manufacturing company that specializes in designing software and physics-based personalized brain-based interventions, is moving toward more decentralized clinical trial designs. “DCTs can improve patient recruitment and retention by reducing burden and eliminating geographic barriers,” explained Dr. Erik Won, president and chief medical officer of Wave. “This also results in a more representative sampling of the population, such as patients from rural areas who often don’t have access to major institutions.”

Dr. Won continued, “DCTs can also increase the quality of data by minimizing the Hawthorne Effect—where individuals modify an aspect of their behavior in response to their awareness of being observed, also known as ‘white coat syndrome’—because patients are in their home environment.” Finally, DCTs can be more cost-effective, he added.

**When Stars Align: DCTs and DTx**

Fundamentally, a DTx is software rather than a pill or injectable, so there is no distribution or administration of medicines. There are no physical logistics—no shipping, storing, chain of control, cold storage, or biohazards—plus endpoints can be captured within the DTx application itself, making DCTs ideally suited for DTx studies whether the goal is regulatory approval or consumer and payer confidence.

In all cases, though, the unique advantage is that the DTx being studied in a trial is also the data collection device, so manufacturers often don’t need extra technologies like an electronic patient-reported outcome (ePRO) system to capture data in a clinical trial. It’s all in one, and this can result in big cost savings.

For example, Texas A&M and Wave Neurosciences are conducting a hybrid clinical trial on the safety and efficacy of magnetic EEG-guided resonance therapy to treat post-traumatic stress disorder (PTSD). This therapy uses transcranial magnetic stimulation, which has been cleared by the FDA for treatment-resistant major depressive disorder, obsessive compulsive disorder, and nicotine cessation. With this algorithm-driven therapeutic, a personalized treatment is delivered
via conventional (in-person) appointments. Screening and follow-up visits, in which participant-reported data are collected, take place virtually to the extent possible.

“America is experiencing a crisis in mental health,” said Dr. Won. “Software- and physics-based personalized therapeutics are a modern, non-pharmaceutical, non-invasive option to help in this area. We are testing our therapeutic with an eye to pursuing an FDA marketing approval for the PTSD indication. We are exploring the decentralized trial model to introduce greater flexibility and speed into our research efforts.”

**Best Practices for Designing DTx Trials**

With the quickly growing and evolving DTx market, and the complexities associated with clinical research, here are five considerations for decentralized trial design:

1. **Know your regulatory roadmap before embarking on a trial.**

   Because the regulatory pathway for digital therapeutics is not as clear-cut as it is for traditional investigational drugs, it is critical to outline your regulatory roadmap before recruiting the first patient. Feasibility studies can be a good place to start, especially to help map out an expansion plan down the line. Some important considerations also include how future versions of your DTx product will be tested, benchmarked, and evolve over time.

   “It is always best to seek meetings with the FDA’s device division [the Center for Devices and Radiological Health] early, and often,” said Dr. Daniel Karlin, chief medical officer at MindMed, a clinical stage biopharmaceutical company developing novel products to treat brain health disorders. Dr. Karlin is also the lead medical advisor to the makers of the first and only FDA-cleared, prescription DTx that improves sleep in adults 22 and older with nightmare disorder or nightmares related to PTSD.

   Dr. Karlin continued, “It is easier for DTx providers to secure meetings with the FDA because digital therapeutics are typically less biologically complex and therefore pose less risk. Request a meeting at the start of your development efforts to agree on the claims you plan to make based on the indication for use, and to establish what related evidence will satisfy the FDA. This is
fundamental. Also, seek institutional review board [IRB] clearance on anything that could conceivably be research-related before you bring an experimental device to humans for studies.”

Of course, regulatory approval—while often considered the ultimate validation for the safety and efficacy of a drug or device—isn’t the only reason for conducting clinical research, especially with DTx. Health economic outcomes and human factor research are often equally important for product adoption. Even in the digital realm, real-world function and outcomes are important to create products that lead to meaningful outcomes for patients. “All manufacturers want payers and patients to be confident in our product’s efficacy, safety, and economics,” added Dr. Won.

For instance, some DTx products that have minimal risk may not require regulatory approval but are just as valuable as those that do. Decide if regulatory approval is on your short-term or long-term roadmap and design the trial accordingly. If it is not, then there is greater flexibility in study design.

2. **Map out an immediate and long-term commercial strategy.**

Given how quickly the DTx marketplace is evolving, the best that can be done may be to sketch out a preliminary commercialization strategy that has plenty of leeway to deviate from that path, if necessary. For instance, if your therapeutic will not be intended for regulatory approval, you may need to focus on a consumer strategy that focuses on everyday wellness. If you know this up front, you can design your clinical trial around endpoints that mirror your target consumer’s biggest pain points. However, if your end-goal is to develop a DTx that will be used in combination with an FDA-approved drug, then you will need to design your trial based on endpoints relevant to that drug maker’s target patient population.

3. **Carefully consider and incorporate protections against technical security breaches.**

Data security and privacy are crucial for all clinical trials, but especially when studying DTx that are 100% tech-driven and, therefore, potentially vulnerable to more issues. One of the most important decisions that needs to be made up front is whether the protocol will strictly enforce a BYOD strategy (which could prevent some patients from participating) or require the sponsor to
provision devices to all participants (which could be cost-prohibitive)—or some combination thereof. Each option comes with different security considerations, so decide this up front.

Regardless of device strategy, all data collected on the smartphone will need to be encrypted and then sent to a secure central platform in the cloud that follows all regulatory compliance parameters. Additionally, invest in a platform provider or tech-enabled CRO that maintains a strict security perimeter, including a “zero-trust” architecture with individual logins and audit trails for everyone who has access to the data every time they log in or out—this, on top of the digital therapeutic app’s security standards.

4. Develop digital endpoints that are fully validated and meaningful to patients.

Traditional medicine trials measure against accepted endpoints that are validated in accordance with standards set forth by the IRB and regulatory organizations. However, DTx studies are typically measuring novel digital endpoints that are different for each DTx app and do not have a history of vetted benchmarks against which to be validated. Even so, reviewers will need to ensure that the novel endpoints aren’t bogus, and this can require some extra steps and creativity.

In many cases, endpoint validation in DTx studies requires a comparison to something similar that has been already validated or the use of previously vetted ratings scales. For example, when conducting a depression study, the DTx sponsor may first administer the Columbia-Suicide Severity Rating Scale—a suicidal ideation and behavior rating scale created by researchers at Columbia University, University of Pennsylvania, University of Pittsburgh, and New York University—to potential participants at screening. The patient’s score can be the baseline for the study, so if the DTx is efficacious, that score should drop and serve as a validated digital endpoint for symptoms of depression.

Similarly, DTx studies may leverage ePROs to administer quality-of-life questionnaires compared against prior research already accepted and validated by the IRB and FDA. Another way to validate endpoints in a decentralized DTx trial is to incorporate an initial site visit with a clinician who can compare the measurement of, say, a wearable device against an equivalent onsite, hospital-grade machine. Doing so can prove the wearable is as valid a measuring tool as another.
Finally, as important as endpoint validation is patient validation—in other words, identify the measurements or endpoints that are meaningful to patients. For example, with Fern Health’s digital musculoskeletal platform, the company shifted the focus of pain management from pain relief to functional restoration. Early on, the company found that functional pain endpoints are more important to patients in the long term than pain relief alone and made that critical adjustment.

5. Assess the use of DTx placebos or sham apps early and often.

In a DTx clinical trial, dummy or “sham” apps are often used as a control in comparison to the actual treatment or intervention app—like a placebo pill used in a randomized control trial. There are unique considerations in using sham apps, however, including the potential for an unintentional placebo effect.

Here is the challenge: It is very difficult to make a sham app similar enough to the real one, which means patients often suspect that they were not assigned to the treatment arm. In addition, patients who do interact with the sham app can experience a placebo effect that negatively skews study results. For instance, patients in the treatment arm of a study would typically show significant symptom improvement compared to the non-treatment arm, but when using a sham app, that disparity is not as dramatic.

The FDA has not yet ruled on whether placebos or “sham” apps must be used in DTx trials, but the agency often prefers a sham control. DTx companies that opt not to use a sham control will need to work very hard to find creative ways to design an FDA-acceptable trial that won’t be criticized—even then, there is no guarantee that the FDA will accept the results.

“It is highly unusual to view sham controls as unnecessary in clinical trials,” said Dr. Karlin. “Not only do regulatory bodies prefer sham-controlled evidence in digital therapeutics studies, but also clinicians. Reluctance to use sham apps will cause companies to struggle to get both FDA clearance and physician buy-in, which is critical for commercial success with patients.”

Dr. Karlin’s team for the PTSD DTx leveraged a sham control on a wearable device that, rather than buzz when detecting a nightmare, simply recorded it. “When we assessed the reliability of
our blind through a survey of our trial participants, we found that most did not know whether 
they were using the real therapeutic or the sham,” he noted. “This helped validate the research 
because it meant that we could reliably compare the active intervention with the placebo for 
more meaningful results. Randomization and sham control are not magic bullets, but they’re the 
best options we have right now.”

As the Digital World Turns…

There’s still a lot to be learned in the DTx market, but they are here to stay with growing 
reliance, trust, and adoption of digital health products. COVID-19 pushed researchers to lean into 
the decentralized model for research, and the pandemic has simultaneously fueled a growing 
need for DTx products—an ideal marriage of process and product. Remaining flexible and open- 
minded will be critical to succeed in this evolving and exciting area—as the digital world turns.

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ACRP HOME STUDY
CLINICAL RESEARCHER—JUNE 2022 (VOLUME 36, ISSUE 3)
Mapping the Way to Modern Trial Design, Management, and Analysis

Article #1: Finding Perspective and Identifying Research Best Practices Amid the Ongoing COVID-19 Pandemic

LEARNING OBJECTIVES
After reading this article, the participant should be able to list multiple challenges to clinical trial conduct posed by COVID-19 in academic medical centers and best practices that have emerged to manage their impacts, summarize the COVID-19 research policy enacted through The Ohio State University College of Medicine, and describe the institutional stakeholders involved.

DISCLOSURES
Deanna M. Golden-Kreutz, PhD; Angela O. Sow, MACPR; Michelle R. Bright, MA; Brad H. Rovin, MD: Nothing to disclose

1. This article highlights which of the following key strategies for managing the impacts of COVID-19 on research at The Ohio State University Medical Center?
   a. Leveraging existing research management infrastructure
   b. Establishing a COVID-19-focused institutional review board
   c. Developing multidisciplinary research working groups
   d. Strengthening connections among institutional research stakeholders
   a. 1, 2, and 3 only
   b. 1, 2, and 4 only
   c. 1, 3, and 4 only
   d. 2, 3, and 4 only

2. The academic medical center leveraged which of the following for overseeing and implementing COVID-19 research?
   a. Sponsored Programs Office
   b. Center for Clinical and Translational Science
   c. Office of Responsible Research Practices
   d. Center for Clinical Research Management

3. What happened to ongoing and new non-COVID-19 studies at the medical center with the pandemic’s arrival?
   a. Nearly half were shut down to allow for COVID-19 studies to start.
   b. They were temporarily halted as COVID-19 studies were prioritized.
   c. Most were terminated abruptly as staff were laid off or furloughed.
   d. They were outsourced to smaller academic medical centers in the state.
4. Which of the following is a requirement of the comprehensive research policy implemented through the College of Medicine for COVID-19 research?
   a. All research staff must complete updated Good Clinical Practice training.
   b. Study team members working from home must provide their own computers.
   c. Investigators must complete impact and planning assessments for studies.
   d. Department heads must update COI statements on relationships with vaccine manufacturers.

5. Which of the following are among the multidisciplinary coronavirus-centric working groups created at the medical center?
   1. Healthcare workers
   2. Biorepository
   3. Data analysis
   4. Ethics/compliance
   a. 1 and 2 only
   b. 1 and 4 only
   c. 2 and 3 only
   d. 3 and 4 only

6. Which of the following tactics limits the number of COVID-19 studies with overlapping mechanisms of action at the medical center?
   a. Conducting only one study at a time for a given sponsor.
   b. Grouping and prioritizing studies by intervention type.
   c. Blinding investigators to the studies’ primary endpoints.
   d. Declining studies involving repurposed treatments.

7. The topics of COVID-19 guidelines undergoing regular review and interpretation at the medical center include which of the following?
   1. Relocation of study sites to off-campus facilities
   2. Definitions of essential versus non-essential research
   3. Increased use of telemedicine
   4. Utilization of touchless consenting practices
   a. 1, 2, and 3 only
   b. 1, 2, and 4 only
   c. 1, 3, and 4 only
   d. 2, 3, and 4 only

8. Which of the following entities has identified opportunities for the medical center’s investigators and their teams to participate in COVID-19 studies with backing from national and regional networks?
   a. Network Capacity Program
   b. Office of Research
   c. Grants Management Office
   d. Department of Biomedical Informatics
9. Table 1 includes which of the following examples of clinical research workflow adjustments and policy changes related to COVID-19 at the medical center?

   1. Transition to telework
   2. Utilization of electronic communication platform for facilitating consent process
   3. Prohibition of home healthcare to obtain key safety data
   4. Engagement with IRB to include vulnerable populations

a. 1, 2, and 3 only  
b. 1, 2, and 4 only  
c. 1, 3, and 4 only  
d. 2, 3, and 4 only

10. What has become of the processes mobilized to ensure adaptability and consistency in clinical research operations at the medical center?

   a. They have been significantly loosened as the pandemic continues.  
b. They were removed after a time, only to be quickly reinstated.  
c. They have remained in place throughout the ongoing pandemic.  
d. They have been challenged repeatedly on legal grounds.

**Article #2: Opinion: More Sites, Sponsors, and CROs Should Leverage eSource as a Study Manager in Remote Monitoring Situations**

**LEARNING OBJECTIVES**

After reading this article, the participant should be able to summarize the main reasons behind recent trends in increased use of remote monitoring for trials, list several advantages to using eSource as a study manager in such situations, and outline the different roles of sites, sponsors, and CROs in bringing the tactic to bear in more studies.

**DISCLOSURE**

Takoda H. Roland, CCRA, CCRP, CNA: *Nothing to disclose*

11. The author notes witnessing data entry efficiencies enabled by switching from handwritten notes to eSource lead, in part, to which of the following at sites that were “early adopters”?  

   a. Cutbacks in site staffing levels.  
b. Reduced patient visit times.  
c. Increased investigator compensation.  
d. Fewer Form FDA 483 observations.

12. Which of the following is noted as resulting from every site creating a unique source?  

   a. Study coordinators from different departments duplicating work.  
b. Data managers stepping in to handle source entry themselves.  
c. Critical datapoints going uncaptured in the beginning of a study.  
d. Institutional review boards insisting on standardized initial source.
13. The author cites which of the following as spurring the adoption of eSource by sponsors and contract research organizations (CROs)?
   a. The necessity of remote monitoring in pandemic conditions.
   b. Severe budget cuts at most clinical trial sites in 2020-2021.
   c. Mandates from the U.S. Food and Drug Administration.
   d. Walkouts by study monitors who demanded the change.

14. The implementation of remote monitoring led to which of the following for the author’s company?
   a. Cost savings sufficient to open up a second location.
   b. A “fully compliant” audit by regulatory authorities.
   c. CRAs exceeding their traditional days on site metrics.
   d. Several sponsors terminating studies due to failed technology.

15. What was the difference between two sites the author’s company found using a clinical trial management system for eSource?
   a. One conducted only U.S. studies and the other multinational ones.
   b. One was following Good Clinical Practice and the other was not.
   c. One was devoted to drug studies and the other to device studies.
   d. One was compliant with CFR Part 11 and the other was not.

16. Implementing eSource mid-study as a COVID-19 mitigation was found to result in which of the following?
   a. Challenges in verifying source data for earlier visits.
   b. Confusion in budgeting and sponsor payments.
   c. Study-wide resignations by CRCs and sub-investigators.
   d. Necessity of repeating many study procedures.

17. What advantage does the use of eSource offer sites in terms of monitors?
   a. Sufficiently well-trained visiting monitors can enter eSource data themselves.
   b. More monitors can be accommodated since office space is unnecessary.
   c. eSource prevents monitors visiting for different sponsors from spilling trade secrets.
   d. Site leaders can now decline in-person monitoring visits as often as they wish.

18. The author cites which of the following as an advantage when planning for onsite monitor visits was no longer necessary?
   a. Fewer coordinators were required.
   b. Investigators took on more studies.
   c. Early access to data was enabled.
   d. Adverse events were minimized.

19. How have monitors from the author’s company reacted to remote monitoring?
   a. They prefer it for reasons tied to lifestyle, efficiency, and scheduling.
   b. Most have rejected the practice and left clinical research altogether.
   c. Many new hires now refuse to travel to study sites for any reason.
   d. Current monitors are split about 50/50 in preferring or rejecting it.
20. Which of the following is noted as being allowed by “continuous monitoring” or “regular reporting” across study sites?
   a. Greater investigator delegation of authority.
   b. Fewer line items in study budgets.
   c. Rapid swapping of monitor assignments.
   d. Easy site-to-site comparisons.

Article #3: Unique Considerations in Designing Decentralized Trials for Digital Therapeutics

LEARNING OBJECTIVES
After reading this article, the participant should be able to define the nature of digital therapeutics, summarize the U.S. Food and Drug Administration’s approach to them, and list multiple best practices for designing trials for such products.

DISCLOSURE
Pam Diamond, MD: Nothing to disclose

21. Which of the following is an example of a goal cited in the article for a digital therapeutics (DTx) product?
   a. Teaching conversational skills in foreign languages for healthcare emergency situations.
   b. Addressing panic attacks arising from phobias and social anxieties on demand.
   c. Rebuilding motor skills through music therapy in patients who have suffered strokes.
   d. Organizing online events for patients in trials who have rare disorders in common.

22. The FDA launched which of the following as part of its commitment to supporting DTx?
   a. The Center for Devices and Radiological Health
   b. The Office of Combination Products
   c. The Digital Health Center of Excellence
   d. The Office of Strategic Partnerships and Technology Innovation

23. Are all DTx products on the market approved by the FDA?
   a. Yes, and the agency has mandated all such therapeutics pass rigorous trials.
   b. Some are and some aren’t, even when clinical studies have been conducted.
   c. DTx products are not currently suitable for review by FDA, nor ever expected to be.
   d. No, but the agency has a long-term goal of regulating nearly all such products.

24. Technical security concerns may prompt DTx manufacturers to consider which of the following options?
   a. Working with new technology partners on product upgrades or going it alone.
   b. Designing products with English-only interfaces or offering a range of languages.
   c. Seeking full FDA approval for a DTx with health benefits or only proving efficacy.
   d. Provisioning smart devices or leveraging a “bring your own device” policy.
25. Decentralized clinical trials can increase the quality of data by minimizing effects from which of the following?
   a. White coat syndrome
   b. Low patient diversity
   c. Conflicts of interest
   d. Placebo effect

26. What is the relationship between a DTx and a data collection device?
   a. A top goal of DTx development is to eventually turn them into data collectors.
   b. A DTx is also a data collection device, so extra data technologies are not needed.
   c. The use of DTx in clinical trials requires supplemental data collection technologies.
   d. DTx cannot be used in conjunction with data collection devices for FDA approvals.

27. The author cites which of the following as a good starting point on the regulatory roadmap for DTx approval?
   a. Investigator meetings
   b. FDA Warning Letter reviews
   c. Feasibility studies
   d. Protocol amendments

28. What does “zero trust” architecture for data security involve?
   a. Individual logins and audit trails for everyone who has access to the data in question.
   b. Only assigned clinical research coordinators have access to raw trial data.
   c. Clinical research associates may only review blinded data during study site visits.
   d. Principal investigators must undergo security clearances for every study they lead.

29. What is a challenge regarding the validation of digital endpoints in DTx studies?
   a. Only the study sponsor knows what the digital endpoints are supposed to be.
   b. The FDA has declared digital endpoints to be invalid data for product approvals.
   c. Patients who are aware of the endpoints can alter related data collected by DTx.
   d. The endpoints are typically different for each DTx app and lack vetted benchmarks.

30. What is a challenge regarding the use of a sham app in a DTx clinical trial?
   a. Sham apps have been found to lead to high levels of adverse events in trials.
   b. Most regulatory authorities prohibit the use of sham apps in Phase III studies.
   c. Sham apps are typically too expensive to create for use in small sponsors’ trials.
   d. Patients receiving sham apps often suspect they are not in the treatment arm.