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IMPLEMENTING SOLUTIONS TO VIRTUALIZE AND DECENTRALIZE CLINICAL TRIALS

Traditional clinical trials are multi-site human studies that integrate numerous in-person study visits and endpoints. However, as clinical studies become more complex, it is more important than ever to develop new trial models that can accommodate novel endpoints and provide greater flexibility to study participants[1].

The increasing complexity and number of on-site visits and procedures also has a direct effect on patient recruitment, retention, study timelines and costs.[2,3] One solution to address some of these limitations of traditional clinical trials has been the emergence of decentralized clinical trials (DCTs).

DCTs are trials in which some or all study-related procedures and data collection take place at locations remote from the investigator. This is contrasted with traditional trials that are 100% site dependent. The development of DCTs has been accelerated by the adoption of digital technologies in healthcare clinical practice. DCTs allow study sponsors to focus clinical trials around the patient rather than a centralized trial site. One of the benefits of decentralized trials are the options that they provide to patients. DCTs take advantage of recent advances in electronic communication and digital technologies to create new methods of sharing and collecting information from remote locations and conduct virtual study specific visits.

Another major benefit of DCTs is that they capitalize on a patient's existing access to videoconferences, mobile technology tools, and biosensors for patient reporting. This can be integrated into participants' existing healthcare system, maximizing convenience for study participants. There are also hybrid trials that combine elements of traditional and decentralized approaches. DCTs are increasing in their wide-scale adoption, so much so that the FDA-sponsored Clinical Trial Transformation Initiative has published recommendations for conducting decentralized clinical trials through telemedicine and mobile healthcare providers[4].

DCTs have the potential to significantly improve how study sponsors conduct clinical trials by accelerating recruitment and improving patient retention. By working to virtualize

critical steps in clinical trials, study participant data can be collected at any time and from any location. Incorporating some of the new tools to virtualize and decentralize clinical trials can allow sponsors to collect more longitudinal, real-world data than a single visit can provide, while sparing study participants the inconvenience of making regular visits to a physical study site.

The Impact of the COVID-19 Pandemic on Clinical Trials

The ongoing COVID-19 pandemic has further shifted how sponsors are able to execute clinical trials. It has focused much clinical work and hospital effort on the response to the pandemic. This shift in priorities has also come with increasing restrictions on elective procedures and a complete moratorium on many clinical studies. This has had the combined effect of halting or severely disrupting open trials and delaying new study approvals. Study sites have struggled to find ways to keep trials on schedule in this new paradigm. Interestingly, of the sites surveyed in a recent report, just over a third have quickly switched all their trials to virtual visits[5]. With the end to the ongoing pandemic unclear, long delays and protocol deviations are likely inevitable.

Approximately 35% of sites are still awaiting trial re-activation due to sponsor postponement of recruiting and enrollment[6]. Among sites that are currently enrolling patients, 48% cite issues with patient recruitment and retention. These and other on-site restrictions have contributed to a third of all presently active sites reporting protocol deviations[7].

While these new restrictions have severely restricted hospital access, their aim is to protect both physicians and patients by adhering to social and physical distancing guidelines. Currently, some Institutional Review Boards (IRBs) restrict research-specific visits, while others are requiring that all trials move to virtual platforms as soon as possible. Many IRBs have closed down all non-COVID research studies in heavily impacted therapeutic areas.

In many free-standing clinical sites, which are typically heavily invested in clinical trial work, there has been a faster adoption of virtual visits. Eighty percent of these facilities are now conducting virtual visits. The impact of this pandemic on how we conduct clinicals could be long lasting. Some form of decentralized or virtual trials might become routine, as existing studies show that about 75% of study participants prefer a mobile trial over a traditional trial, with 80% of patients reporting that they are more likely to take part in a trial that uses mobile technology[8].

I. Decentralizing Patient Recruitment, Retention, and Engagement

DCTs have revolutionized patient recruitment, retention, and engagement by increasing the use of digital tools to virtualize study startup activities. These tools utilize data analytics and digital marketing to connect with patient advocacy groups and other potential study participants from all over the world—working to directly link them to a study for enrollment in virtual clinical trials. Key to virtual recruitment is ensuring that the patients are also properly consented to participate in the clinical studies.

There are now various eConsent tools which allow study sites to gather informed consent for new patients remotely, while also providing auditing tools that rapidly track digital informed consent in compliance with clinical trial regulation (CTR) and GDPR regulations. For these virtual consent tools, it is important to build trust digitally in order to overcome the typical challenges of recruiting patients. This includes educating them about the study and addressing any other concerns about safety.

Here are some examples of virtual tools that are being used to decentralize ongoing patient recruitment and engagement efforts:

A. Online Patient Recruitment: global data and analytics to

identify the right patients and facilitate web-based eligibility screening

i. Virtual patient finders: using data analytics to identify possible patients and link to study information

ii. Mobile patient recruitment: study coordinator informational calls that update possible patients about available studies

iii. eConsent: remote consent and patient education based on released FDA standards for eConsent, using telehealth that incorporates both video and quiz based informed consent

B. Patient Engagement / Communication

i. Online correspondence and communication: with access to 24/7 patient support

ii. Online webinars: provide informational content to study participants and investigators

iii. Virtual patient focus groups: create communities among study participants and track patient satisfaction and engagement levels

iv. Electronic medication reminders and calendars

C. Study Investigator Engagement

i. Investigator site portals: foster site-engagement by creating a virtual community with news, announcements, frequently asked questions, and other study documents

II. Virtualizing Patient Study Visits and Protocols

DCTs allow sponsors to recreate how study visits and protocols are executed and creates opportunities to gather novel endpoints. Importantly, these virtual visits must be fit for purpose, allow sponsors to execute all aspects of approved study protocols, and track protocol deviations. DCTs also have the potential to improve patient adherence and retention as they are more flexible and amenable to patient schedules. One example of this was a key feasibility study of remote research visits in Parkinson's disease patients. Patients reported high satisfaction with participation and felt more willing and able to participate in trials with remote data collection[9].

Clinical study sponsors can leverage the widescale adoption of telehealth visits to interact with patients through their various devices. During this end-to-end circle of care with digital devices, patients can remotely access caregivers, clinical research coordinators (CRC)/sites, sponsors, contract research organizations (CRO), mobile health care providers (HCPs) for screening and follow up visits, as well as study PIs for telemedicine visits, adverse event management and assessment, and clinical oversight.

Additionally, because some study designs also require clinicians to complete questionnaires, these clinician-reported outcomes (ClinROs) can be recorded remotely and integrated into the other study data collected. Similarly, virtual trials provide an opportunity to integrate more patient-reported outcomes (PROs) collected at home. The type and variety of assessments that can be recorded remotely is increasing, along with the quantity and quality of the data received. By combining these technologies, sponsors can provide an easy-to-use tool for clinicians to remotely grade and assess their study patients. For the execution of study protocols and visits, the following are some examples of solutions that support virtualization:

A. Virtual Visits / Telehealth

i. Electronic Clinical Outcome Assessment (eCOA): technology solutions with integrated telehealth capabilities allow clinicians to perform assessments remotely

ii. Virtual ClinRO: using telehealth, data is accessed in real time, allowing clinicians and sponsors to monitor and support participants

iii. ePROs: integrate available ePRO and eDiary technology solutions into the new virtual trial workflows, these can also

include data from sensors and IoT devices

iv. Virtual physician consultation via text, audio, and/or video

v. Virtual/in-home nurse assistance

B. Remote/Outpatient Lab Work and Imaging:

i. Remote drugs and devices: are shipped to study participants' homes

ii. Remote laboratory tests: conducted virtually, at community laboratories or mobile nurse-aided facilities or securely track lab kits shipped directly to patients

iii. Virtual medical records and visit documents: upload medical records and visit documents

III. Digitizing study documentation and workflows

Traditional clinical trials require various in-person trainings and site initiation procedures. They also require both sponsor personnel and research coordinators to spend time dedicated to in-person study management and documentation. By virtualizing most of the study documentation processes and training requirements, the overall study becomes more flexible and productive by giving study sites and sponsors more options for completing training and compliance requirements. Virtualizing study documentation and workflows also allows protocol and Good Clinical Practice (GCP) trainings to be assigned automatically and updated with real-time audit trails. Virtual trials can allow for greater collaboration and communication across study sites, as study sites work to share study design, protocols and clinical trial management information online. The following solutions are further examples that can allow study sponsors to efficiently digitize study documentation and workflows:

A. Site Training and Initiation

i. Virtual Site Initiation visits: using a mix of online meetings and webinars

ii. Digital site contracts and disclosure agreement — with eSignature process and document security

iii. Virtual institutional review boards

B. Study Documentation: create standardized template for recording items, such as missed assessments, with procedure for documentation

i. Virtual document center that expedites document collaboration and tracking (with electronic trial master file (eTMF) integration)

ii. Electronic safety letter: to allow electronic distribution and automated compliance tracking

iii. Online compliance dashboards: to track patient activity and site documentation

iv. Digital laboratory management platforms: to provide near-real-time visibility into lab results and reports

IV. Behavioral Science in Decentralized Clinical Trials

While DCTs offer operational efficiencies to study teams and greater convenience to patients, incorporating behavioral science strategies can help maximize their utility. By allowing study teams to leverage human decision making, behavioral science can further improve patient engagement, compliance, and retention. These strategies should be interwoven into each touchpoint and process, helping maintain patient centricity in study design.

The following are examples of behavioral science concepts that can be incorporated into decentralized clinical trial technologies:

A. Building Participant Identity: strategies that help

patients develop a positive identity associated with their participation and scientific contribution as key members of the study team, who are actively helping to find a treatment or cure.

a. Avatars: Digital avatars built into eCOA or other patient facing interfaces allows patients to associate themselves with trial participation and completion

b. Communications: Leveraging digital communication mediums to send purposeful messaging, using collaborative verbiage that treats patients as partners instead of subjects

B. Creating Motivational Intervals: reinforcing instrument completion and marking milestones help break long studies into more manageable intervals.

a. Digital rewards: Can be used to unlock new customizations and digital content, building short-term **positive reinforcement.**

b. Study journeys: enable patients to visually progress as they complete study activities, and can include encouraging messages when they complete activities or reach study milestones, instilling a sense of accomplishment and progress.

C. Reducing Friction: by avoiding negative surprises, prioritizing user experience in design of patient interfaces, and eliminating patient pain points, while identifying opportunities for passive data collection.

a. Virtual visits: Discussed previously, these virtual visits eliminate transportation time and costs for patients.

b. Passive data: Capturing events through passive methods, including sensors, wearables, or smartphones reduce the amount of time patients spend entering data.

Summary and Considerations

Virtual trials are not a one-size-fits all approach. Every trial setting and patient population has unique needs, and these can be customized using virtual solutions to ensure success. It is critical to ensure that all the technology solutions comply with GCP, CTR e-Signature processes, and security standards. Also, to comply with 21CFR Part 11 and HIPAA guidelines, it is important that all technology solutions utilized for virtual trial process have an audit trail, as well as robust and reliable data. For instance, the sensors and wearable devices used in the trial must be customized, verified and validated – in addition to the verification and validation studies conducted by their manufacturers. Also, when it comes to telehealth laws, which are continuously evolving and vary across the United States for example, it is important to be cognizant of these differences when implementing clinical research protocols that utilize telemedicine components. Ultimately, these virtual solutions and applications need to be relatively easy to use and intuitive in order to foster wide-scale adoption, and to continue enhancing or replacing in-person protocols and processes.

Undoubtedly, some version of virtual clinical trials is here to stay. For study sponsors and sites, virtual trial solutions can increase flexibility for study sites and patients, lower the clinical trial administration burden, and streamline clinical trial protocols by minimizing data entry and essentially eliminating the need for data reconciliation. All these advantages, in addition to the changing trial environment, indicate that the adoption of virtual trial solutions into most clinical trial programs will continue to accelerate.

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