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WHITE PAPER: DIRECT-TO-PATIENT REMOTE RESEARCH

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The challenges associated with conducting and managing today's larger, multinational Phase III clinical trials have never been greater. There has been a dramatic increase in costs and trial complexity over the last several years. Managing a single study site averages between $1,500 and $2,500 per month[i] and the total number of procedures performed for a Phase III trial increased by 70% from 2001-2005 to 2011-2015. This had a corresponding increase to the cost per visit by 34% and to the site work effort to administer procedures by 61%[ii] which adds to trial costs, duration and a design that is not favorable to patients and caregivers.

Every day we hear about biopharmaceutical companies exploring novel and innovative approaches to conduct studies that will have a significant impact on cost savings, timelines, improve overall patent recruitment and retention, and also create a more meaningful patient experience. While many companies have considered implementing a direct-to-patient clinical trial design (virtual trial), most have a watch-and-wait mentality, citing concerns over data quality, technological feasibility, drug safety and regulatory hurdles.

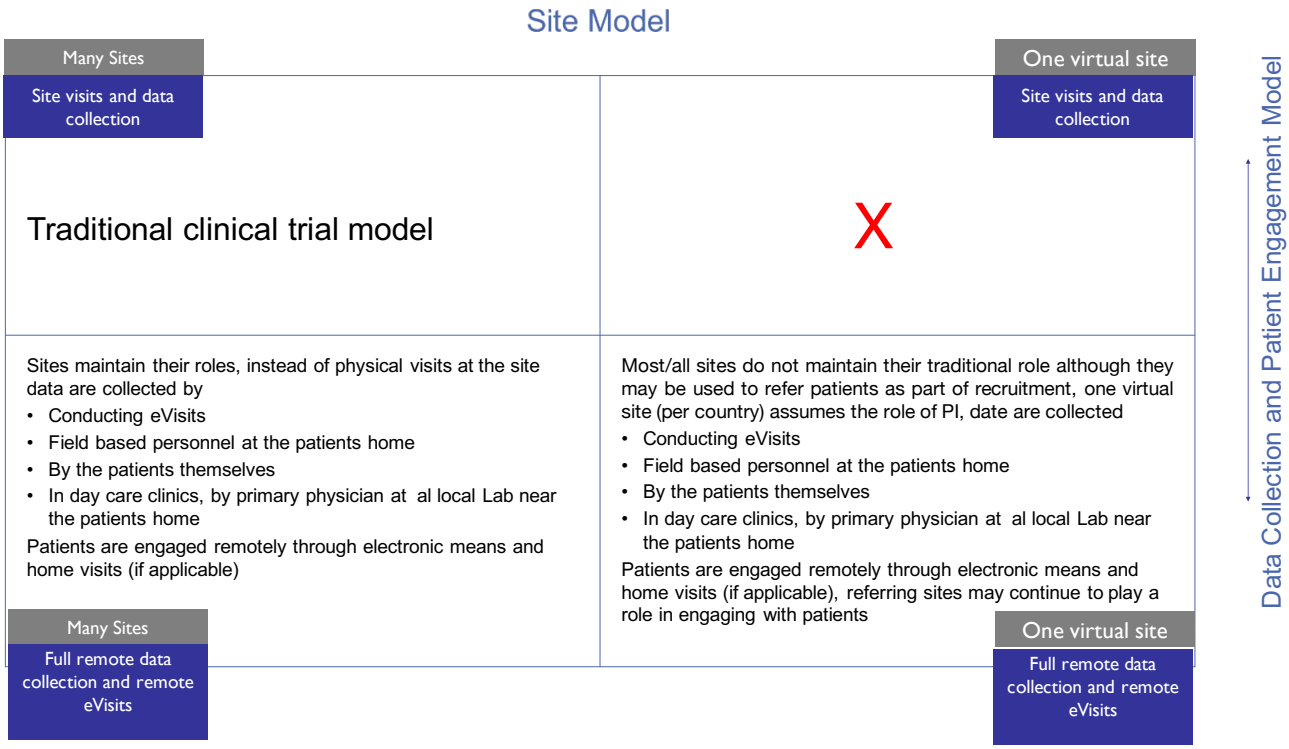
While no single study design and conduct strategy should be taken as the solution to the financial and operational burdens of clinical development, the clinical research industry is poised to begin introducing a more patient-centered clinical trial research model. As with any novel approach, there are many factors that

must be evaluated, pertinent to scientific, operational, technological, regulatory, and other considerations. This whitepaper provides a basic overview of what is involved in designing and implementing a virtual clinical trial and includes a discussion of important considerations and solutions.

What Is Direct-to-Patient Remote Research?

The term direct-to-patient remote research is often used loosely. We attempted to assess the design options for a study that would qualify for it being classified as direct-to-patient remote research. In essence, the direct-to-patient Remote approach revolves around two main design dimensions for a study:

1. The use of remote data collection and patient engagement methods
2. The role of the sites



According to our definition, both lower quadrants do qualify as direct-to-patient remote trials.

There are also other important concepts and attributes when designing clinical trials that need to be positioned:

- **Patient-Centricity**: The research is independent of site, data collection and engagement model but becomes a key element of any remote approach and must be supported by such an approach.
- **Telemedicine**: "*Closely associated with telemedicine is the term "telehealth," which is often used to encompass a broader definition of remote healthcare that does not always involve clinical services. Videoconferencing, transmission of still images, e-health including patient portals, remote monitoring of vital signs, continuing medical education and nursing call centers are all considered part of telemedicine and telehealth"* (http://thesource.americantelemed.org/resources/telemedicine-glossary)
- **Remote Patient Monitoring**: "*Remote patient monitoring (RPM) uses digital technologies to collect medical and other forms of health data from individuals in one location and electronically transmit that information securely to health care providers in a different location for assessment and recommendations"* (http://www.cchpca.org/remote-patient-monitoring)

We will introduce the concept of eVisits which do encompass all of the above, but can be tailored to the specific need of a trial.

- **eSource data** (FDA, "Guidance for Industry: Electronic Source Data in Clinical Investigations", 2013): data initially recorded in electronic format. They can include information of clinical findings, observations or other activities captured prior to or during a clinical investigation used for reconstructing and evaluating the investigation. Like Source data, eSource data should also be attributable, legible, contemporaneous, original, and accurate (ALCOA). Reconstruction of the course of modification (such as additions, deletions or alteration) relating to this data is facilitated by the use of an audit trail.

In essence, using the definitions and classifications introduced above, clinical trials may be categorized along the following dimensions into 'Traditional', 'Hybrid' and fully 'Virtual' trials.

	Traditional	Hybrid	Virtual
Study Visits	Occurs primarily at a Principal Investigator's site	Visits can occur at a site, patient's home , care clinic, or remotely as eVisits	Visits occur in a patient's home, care clinic, or remotely as eVisits
Data Collection	Data is mainly captured via sites medical records and transcribes to EDC (electronic data capture) at study site	Data is captured by study sites as part of traditional or eVisits , by field-based staff from patients, caregivers etc.	Data is captured by study sites as part of eVisits, by field-based staff from patients, caregivers, etc.
Monitoring	Monitoring by field-based staff at study sites, remote monitoring can be used as appropriate	Monitoring by field-based staff at study sites (reduced as fewer visits and more eSouce), remote monitoring may be used as appropriate	Field-based staff to monitor only one central study site onsite or remotely
Drug Shipments	Completed in bulk to study sites	Distributed at study site or sent to patient's home (direct ship or by field-based nurses)	Delivered to patient's home (direct ship or by field-based nurses)
Site Mgmt	Sites maintained individually by CRAs (clinical research associates)	Fewer sites can be used along with remote elements and home health nurses (due to less travel/onsite visits for patients)	One centralized site is used with remote elements along with home health nurses
Regulatory Documents	Informed consent conducted through site or eConsent system	Informed consent conducted through site or eConsent system	Informed consent conducted through eConsent / patient platform
Site costs	High due to sites performing "high-touch" study administration	Lowered due to fewer sites being activated and fewer site visits	Minimal due to central site being activated

Fully virtual trials are not limited by the need to have an established network of qualified sites that can be physically accessible by the patient. Instead, a central site may be used for patient enrollment and management, acting as a virtual site. In this scenario, the role and the burden of the site is greatly reduced, leading to significantly better quality, more cost-effective and patient-centric trials, and a vastly improved bottom line for sponsors. Better quality and improved service to patients is achieved by having one site handling higher volumes allowing for more flexible and efficient resourcing of professional staffing and better training and also introducing the use of eSources and electronic tools that may become more affordable in this scenario, minimising human error either during data collection (directly via devices) or during data entry (e.g., validation of data during data entry).

Forces Driving Towards Direct-to-Patient Remote Research

Focus on more patient-centered trial designs: Remote clinical trials offer a patient-focused approach to pharmaceutical research. Many of the barriers to participation in site-centered studies are no longer an issue in a remote trial. The study is conducted in the patient's home, so travel is no longer a consideration, allowing those who have mobility issues, or who live in rural areas, the opportunity to participate.

In site-centered studies, lack of convenient access to study sites, combined with the number of study visits required, often leads to lower recruitment and higher dropout rates among participants. In a 2015 survey of clinical trial participants polled about their study experience[iii], nearly a third of all respondents said the visit schedule was not at all, slightly, or only moderately flexible. Only 27% said getting to the study site was not at all, slightly, or moderately easy. Twenty-six percent found parking at the study site was not at all, slightly, or only moderately convenient. All of these considerations are potential hurdles to retention that do not exist in a remote study, where data collection and monitoring is done in the patient's home.

Empowered Patients: People living with chronic, acute, or terminal illnesses are turning to the Internet for information in ever-increasing numbers, and empowering themselves to make better healthcare decisions. According to a 2015 survey, 62% of smartphone owners used their phone to seek out information regarding a health condition, with that number expected to grow as the global mobile healthcare market continues to grow[iv].

As patients take charge of their health and grow more tech-savvy, they are engaging in more patient-driven research initiatives. With organizations such as patient-centered Outcomes Research Institute (PCORI) educating patients and providing a vehicle to learn about research specific to their condition, these patients are leveraging technology to stay informed and engaged.

Finding and Retaining Patients: Recruiting and enrolling participants is often the most difficult aspect of a clinical trial, with nearly 80% of studies failing to meet initial targets[v]. Enrollment for traditional site-centric studies is limited to patients who live within a reasonable radius of the study site. Recruitment relies mainly on physician referrals of, and advertising to, local patients. As the distance from the site grows, so do the hurdles to participation.

In a remote study, participants are not limited by their proximity to the study site. Advocacy groups, trial finder websites, and social media campaigns can all be harnessed to find patients within any geographical region — or across the country or the entire world.

As many as 40% of participants in traditional Phase III trials lose interest and drop out of the study[vi], so keeping patients engaged is critical. Remote studies can leverage patient portals, data collection devices, and interactive smartphone apps to promote engagement and enhance the patient experience. Participants transmit data via wireless devices, complete questionnaires in the privacy of their home, and meet virtually with study staff.

The direct-to-patient clinical trial reduces site visits and lessens the overall burden on patients and their families. A clinical trial that minimizes the impact on a patient's lifestyle has the potential to increase recruitment by 60% or more, while over 95% of participants typically complete the study.[vii]

Real World Evidence studies: As companies are looking to demonstrate value for their products "beyond the pill," there is a push and interest in designing and running more post-approval studies that provide real world evidence (RWE), with patients in a more naturalistic setting. RWE studies often use many stakeholders contributing to data collection and patient engagement tactics (e.g., caregivers, personal trainers, GPs, nutritionists). Such studies often target broad populations of patients and have a long duration, posing cost, retention and data quality challenges, lending themselves to use many of the concepts of direct-to-patient remote research.

Increased Costs and Complexity of Traditional Research: Clinical trials have more eligibility criteria, protocol amendments, patient-recorded-outcomes (PRO) assessments, procedures, and endpoints today than they did just a decade ago. All of these factors combine to increase both the cost and complexity of the study. Add in the costs associated with supporting a network of study sites to provide monitoring, guidance and insuring the quality of data collection and the economic burden of traditional studies becomes orders of magnitude greater.

Direct-to-patient remote studies add new costs and supporting services. While the number of study sites is greatly reduced, sponsors must invest in technology, platforms, and equipment they otherwise would not have to purchase.

Technological Advances: Internet and mobile network access around the world has grown exponentially in the past five years. By the end of 2015 over 80% of households in developing countries had internet access and 78% of inhabitants in Europe and the Americas had mobile broadband access[viii]. This connectivity has created a cultural shift in the mind-set of consumers and raised levels of expectation regarding how they prefer to engage in everything from online shopping to interacting with their healthcare providers.

This Internet and mobile network access has created a level playing field for patients living in remote locations, and those with mobility issues, allowing them to participant in remote research with the same convenience and accessibility as patients who live near study sites.

Considerations

Not all studies lend themselves easily to the direct-to-patient remote study model, however. There are many factors to consider designing a successful virtual study.

Scientific

The Patient Population – Careful consideration to the patient population may provide insight as to whether or not remote research would be a successful alternative to a traditional study. In aging populations, for example, proficiency with technology may prove too great a hurdle to participation or may compromise the integrity of the data being collected.

Technology Adoption & Training – Adopting new technology comes with a learning curve. Device training for field nurses, site staff and participants is critical to proper data collection and device management.

The Study Design – Does the protocol lend itself to remote research? Will the study rely on patient-reported data or is there a greater need for investigator assessments? Review the protocol to determine if remote technologies can be used in place of certain study visits. Are there ways to leverage technology to increase patient engagement and adherence?

Integrity of the Data – Selecting the best technology to support a remote study is imperative. Without checkpoints to insure clean and quality data at the source, data verification becomes a significant burden on site staff.

Remote Monitoring – When selecting technology to support the study, the ability to monitor data remotely offers additional optimal efficiency and cost savings.

Adverse Events – Even in traditional studies, adverse event reporting begins with the patient sharing information. Reports are often made by phone, email, or in person at study visits. With remote studies, the technology must be able to capture adverse event reports and relay them in a timely manner for follow up by site staff.

Device Delivery or BYOD (bring your own device) – Careful consideration must be given to disbursement of devices or using the patient's own devices. For maximum utilization and reach, the best model is using a platform that can work on multiple devices (smartphone, laptop, tablet, etc.).

Global Studies – When conducting global studies, all relevant languages and local cultures must be supported. Country-specific privacy regulations must be observed.

Operational

Online systems can be utilized to support clinical operations. In a remote study, participants share their data via the Internet from their home using a study portal or website on their computer or mobile device. Multiple stakeholders, including sponsors, sites, and healthcare professionals can provide real-time support through solutions such as online chats, call-centers, or email. Important operational considerations include:

- Is special equipment (i.e., MRI, CT scan, etc.) needed?
- What are the drug distribution regulations (at the state level in the US or at country level)?
- Are there special physician/rater assessments that only a trained clinician can perform?
- Is the physician the best method of recruitment (i.e., newly diagnosed patients)?

- Can physical exams or lab work be performed by a nurse or is a physician required?

Patient Care and Data Collection – If the protocol requires special oversite or equipment for testing patients, a remote study may not be the best choice for study design. Careful consideration should be given to the logistics involved in managing participant needs and study requirements. Not all data collection can be passively transmitted back to the study site. However, one solution to this dilemma might be to utilize the services of home health nurses. Often they can be the conduit between study site and the patient's home, performing some of the activities traditionally conducted at sites such as specimen collection, physical exams, and administration of study drug. This patient-centric approach can decrease the need for site visits and monitoring while increasing patient retention.

Patient Recruitment – Similar to a traditional clinical trial, virtual trials must have a proactive, well planned patient recruitment strategy. There are a variety of cost-effective techniques that can be employed, including physician referrals, community efforts, patient advocacy groups, as well as online tactics, such as social media and various internet sites. Online outreach is an ideal way to reach patients, as they will likely be seeking medical information online, related to their condition or a set of symptoms. Additionally, online tactics are very easy to turn on and off, so it is easy to closely monitor sources of referrals and maximize funds spent without wasting budget. No matter which tactic is employed, it is essential to source the efforts by creating unique links, eliminating the need for a separate pre-screening website or asking the patients how they heard about the program. The goal is to eliminate/reduce as many clicks as possible for the patient.

Technological

Software systems supporting direct- to- patient remote trials must be easy to use and cost effective, while providing a high level of security during processing of health data. They should act as a single source of information for all participants, giving them easy access to the information they need in a compliant way based on the need to know/use/see this information.

Essential Requirements

Patient Accessing the System

- The system must provide an easy mechanism to onboard patients.
- The system should be able to inform patients about their progress in the study and patients should be guided by the system on which task to perform next.
- The system should act as a conduit to keep patients engaged and informed, e.g., by providing them additional information such as study news, overall progress of the study, and educational videos.
- Ideally, electronic informed consent should be supported by the same system, giving the patients a reduced number of systems to use and login to. (If this is not feasible, a single sign-on solution should be deployed.)
- The system must support the patient's preferences on how to access it and should be be intuitive, to accommodate varying demographics.

Data Integrity and Support of eSource

- The system must allow for patients and other contributors to enter data.
- Checkpoints and confirmations must be built into the technology to enable clinicians to reduce overhead attributed to data verification.
- The system must be able to ensure clean and quality data at the source of input with user-friendly verification.
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Multiple Roles, Entering Data, Co-operating and Reviewing Data

- The system must support multiple roles being able to enter data, view, and communicate via the system, e.g., site staff reviewing data entered by patients, as well as alerts for adverse events.
- The software system should be adaptive and support multiple device types and/or allow for a deployment model using mobile apps.

Desired / Required Depending on Trial Design:

High-Touch eVisit, Interactive Model

- The system should support eVisits which can be conducted by telephone or videoconferencing. Data entry forms should allow capturing eSource information during the eVisit, both from the sites as well as directly from the patients (questionnaires, eDiary entries, medication compliance, etc).
- Ideally, the videoconferencing tool is an integrated part of the system. More loosely coupled systems may provide an alternative (e.g., via Quicklinks) and in some settings using tools like Skype (or similar).
- A call/communications log for all communications with the patient should be captured automatically by the system or support a manual input according to operating procedures.
- The system should provide sites, a call center and/or supporting team members with the ability to communicate with patients securely via a regulatory-compliant messaging platform.
- During in-home visits by a visting nurse (or any other role), data should be captured within the system as well along with visit reports. All appointments and visits should be easily scheduled through the system and reminders should be sent out to ensure adherence to protocol requirements.
- Building on the patient communication capabilities, the interactive model should be extensible, allowing the monitors and sites easy access to a videoconferencing service.

Reminder Systems (Medication, Visit Scheduling) for Study Participants

- The system should have a task management and scheduling system which uses reminders that use different channels to alert participants (in application messaging, push messages, e-mail, SMS).

Reward System

- Ideally, a reward mechanism is provided as part of the system. This is especially beneficial for long-term studies to help keep the patients engaged. Specific rewards should be granted based on action carried out,

for example, the completion of an electronic patient-reported outcomes (ePRO) questionnaire, compliance with medication intake, or completion of study eVisits.

Capability to Collect Data from Smart Devices (Blood Glucose Meter, Spirometer, Scales, Wearables)

- The system should provide a way to collect data from a range of different bluetooth or cloud-connected devices.

Drug Supply Management

- The system should support the drug dispensing, tracking and management process and comply with local and country-level regulations.

Remote Monitoring

- Monitoring data remotely, visit reports, summary, and progress reports should be supported by the same system allowing for efficient management and near-real time progress overview.

Whatever system is selected for direct-to-patient remote trials, it should be easy to integrate with other systems selected and become an integrated tool for day-to-day operations. The number of systems should be minimized to eliminate complexity and the integration and interfacing hassle that in many cases make such deployments impossible within the tight timeframes. From an end-user perspective, the reduction of the amount of systems they use will increase engagement significantly. A flexible, adaptable management of roles that contribute to the trial's success is best orchestrated within one 'master' system that manages their tasks and provides real-time overview of progress and bottlenecks reducing reporting and monitoring burden significantly.

Finally, reducing the number of systems and having a 'single' scaleable system providing many of the features described above makes the direct-to-patient remote trial model economically affordable, even with very large, multi-national studies.

Regulatory: The regulatory hurdles to conducting a global, remote study often center around the informed consent process, drug shipment rules and regulations, and protection of personal data. It is important to engage regulators early and often throughout the protocol development process. Some European Ethics Committees, for example, require the patient and Investigator to meet face to face to complete the informed consent form (ICF), and to retain an original, paper copy signed by both parties on file. It may be difficult to obtain approval for an electronic version of the ICF. Also, in many countries shipment of the study drug directly to patients' homes would not be approved. These factors must be considered and often "negotiated" at the onset to ensure the design is accepted and approved.

Commercialization of Approved Drug: Often, physicians who are included in a Phase III or Phase IV clinical study become early prescribers/adopters of the drug upon approval. If a patient-centric study is employed where physicians are not used, the sponsor may not have those early-adopting physicians to count on for initial sales. Physician experience and support is an important part of any launch strategy. It is important to consider whether the drug being studied is a novel, first generation therapeutic and possible product launch model. Creating a role for sites, even if not full investigators, which provide exposure to the new compound, may be beneficial as a company prepares for drug approval and launch. (For example, referring sites (if used) may have access to study progress and view the progress of patients they referred).

Clinical (exams, labs, drug shipment/administration): From a clinical standpoint, direct-to-patient research can represent new challenges. Superficial physical examinations can be performed using video conferencing tools like Skype, but unless other vital signs are recorded via the technology used as part of the study (smartphone app, electronic device) site visits or home health nurses may need to be employed.

For specimen collection, working with national laboratories such as Quest Diagnostics or LabCorp may be a viable solution, allowing participants to visit a lab near them with an order they can download from the study portal.

The Patient Perspective (mindfulness in design): We have spoken to hundreds of patients and caregivers from more than 25 countries over the past two years, including trial-naïve patients and patients who have participated in clinical studies, to gain insights into what patients care about. What we have heard is that regardless of whether the patient has a rare disease, is an oncology patient, or has a more common condition such as asthma, a common theme emerges across the board – that patients trust and rely heavily on their physicians and value the care and support they get from them. When we talk to patients, they use words like "appreciation", "communications", "responsive", "support", "education", "care", "compassion", and "trust" as the most important aspects of deciding to participate and as part of their active participation in a study. But in the same breath, patients say transportation is a major issue, as well as time away from school and work, and that convenience is a critical factor influencing patient participation, retention, and overall satisfaction.

There are numerous advancements of new, high-touch technologies that can help create a personalized environment for the patient, allowing for a high-touch experience with all the benefits of a more convenient design. And, because individuals across the globe have improved bandwidth, are using smartphones and wearables more and more, and are comfortable with telemedicine and video-conferencing systems like Skype, the virtual study offers a unique opportunity. Studies can be designed to meet the "sweet spot," where the technologies now available to support virtual clinical trials is, in equal measure, balanced with the patient's need for human interaction and a model that works for – and within – patients' lives, to improve the patient experience and ultimately remove the burdens of traditional participation. Designing these studies so they can be patient-centric and create a meaningful experience for patients is critical to their success.

As we begin exploring these types of trials, with patient support and care always central to design, remote studies have the potential to improve the patient experience significantly if executed properly. Taking the patient perspective into consideration when designing the study is crucial to success. Recruitment and retention often hinge on how much of an impact the study will have on the patient's daily life. The number of study visits required, logistics regarding transportation, taking time off from work, and access to child care can all influence the decision to join a study or to continue participating.

Creating a personal – even intimate – connection between the trial team and the patient is imperative. While technologies can have great, robust features, they still must be suited for the patient. Often, combining technology with high-touch efforts such as home health nurses, regular phone or video calls, more two-way interaction and communication will enrich the technology-based model.

The Caregiver Role: In traditional, site-based studies, if a patient relied on a caregiver to drive him or her to a research site, the caregiver may no longer have a primary role in a remote trial and may not feel as needed. Consider other ways to support and involve caregivers. Teaching them about the technology being used in the study so they can support the patient, or incorporating caregiver reminder notifications if a patient hasn't taken their medication are examples of useful ways to include caregivers, and ultimately increase compliance.

Caregivers can be instrumental in recruitment and retention. Appealing to those who have to commit, outside of just the patient, and also addressing their needs is critical. Excluding caregivers because they are not needed to drive the patient to visits, for example, may feel like alienation and not reduction of burden. Caregivers should be given a role in a virtual trial and should be able to access the system and contribute in defined ways to keep them engaged.

Conclusion and Recommendations

Virtual clinical trials, can potentially solve a real problem we have with access, especially among hard to reach populations, people who live in rural locations, and very sick individuals. Patient-centric trials can truly ease the burden on the patient and allow patients, especially in remote locations, to have access to clinical research. And while there are important operational, scientific, and technological considerations, if designed and executed successfully, virtual trials can be significantly more cost-effective, efficient, and a patient-friendly model for clinical research programs globally.

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