# Hybrid and Virtual Trials: Understanding the New Clinical Development Paradigm

Faced with low recruitment rates, perennial site underperformance, protracted timelines and the high cost of drug development, sponsors are exploiting technology, recent advancements in artificial intelligence (AI), machine learning (ML), wearables and proprietary data assets to conduct virtual trials (also known as decentralized trials) with the goal of improving patient engagement, accelerating recruitment and increasing patient retention.

However, disruption of the deeply entrenched site-based clinical trials approach with more innovative, nimble and patient-centric trial designs has been a slow process. The sheer complexity of the clinical development process continues to be an obstacle to fundamentally changing the paradigm and achieving a more streamlined, technology-enabled and cost-effective delivery modality.

This white paper discusses current challenges of traditional clinical trials, the emergence of eClinical applications and microservices that can enable virtual trials, barriers to adoption of innovative study delivery models and the role of contract research organizations (CROs) in partnering with biopharma to unlock the benefits of virtual trials and maximize trial efficiency.

## Recognizing the current challenges in the traditional clinical trial landscape

Patient participation in clinical trials continues to be challenging with less than 5% of eligible patients opting in. While this percentage can vary from country to country, this statistic highlights that patient participation in clinical trials is a persisting problem that requires an innovative solution. While study design and awareness play a role in limiting patient participation, there is ample evidence indicating that increased burden and inconvenience of clinical trials are the main barriers.

To better understand the issues, Covance developed a proprietary Patient Intelligence Database of over 435,000 LabCorp customers and garnered insights about patients' attitudes and preferences towards clinical studies. This database was used to poll 70,000 potential clinical trial participants. One-third of the survey responders indicated that inconvenience was the primary reason that prevents participation. Accordingly, the biggest driver of inconvenience is the need to travel to a clinical trial site. Further, a Covance survey of over 600 trial participants showed that in the U.S., the average one-way distance to their investigator site is more than 25 miles, representing a total travel distance of 50 miles to a clinical trial investigator site. Travel distances are greater in Europe, supporting the narrative that clinical trials are burdensome to patients.

For studies requiring lengthy travel, the lack of sufficient site and patient support or travel reimbursement can be a barrier to enrollment. Finally, depending on the number of clinic visits required, many patients struggle to find the time to keep up with the study requirements, as each visit may pose a financial burden and disruption to personal lives.

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## Finding opportunities to enhance clinical trials

Given continued challenges to patient recruitment, biopharma companies are focusing on increasing patient centricity by increasingly designing trials around patients. This shift to reducing patient burden involves early identification of patient and caregiver needs and perspectives.

Incorporating "the voice of the patient" and thereby increasing enrollment rates can be strengthened by deploying a variety of new technologies, healthcare information, processes and advanced analytics, which include:

**Digital health and mobile technologies.** These technologies can enable the remote capture of drug efficacy and safety data beyond the investigator site. This approach can enable decentralized trials, improve data quality and reduce the cost of onsite monitoring due to automated and direct digital data capture of source data. In addition, wearables and mobile technologies can streamline collection of patient-reported outcomes (PRO), which are expected to provide richer insights about the patient experience, drug efficacy and safety in a real-world setting.

**New data sources and analytic tools.** Curated real-world data (RWD) sources can be used to geo-locate patient populations, evaluate their laboratory values and design stronger inclusion/exclusion parameters for protocols. These data can also help optimize trial design and accelerate timelines through expedited selection of investigators. New data sources can also enable innovative trial designs, for example, by acting as virtual/synthetic control arms and supporting pragmatic, adaptive and real-world evidence (RWE) registry trial designs.

**Predictive analytics and artificial intelligence (AI).** In addition to RWD and big data, predictive analytics and AI are expected to optimize study delivery, identify new clinical hypotheses to test, minimize trial design risks and rapidly identify patients who may be eligible for recruitment for a particular protocol.

**Targeted therapeutics and precision medicine.** These more personalized treatments have fundamentally shifted the types of drugs being tested to disease modifying drugs, targeted therapies and next-generation biotherapeutics. They may improve efficacy and success rates and accelerate development timelines, but will require longer-term patient follow-up.

**An increased availability and ease of biomarker testing.** Biomarker testing has allowed for novel trial designs like basket trials, and has helped to narrow patient populations to expected responders to treatment, resulting in improvements in efficacy, safety and success.

**Access to pools of pre-screened patients and direct-to-patient recruitment.** With efforts that include social media and well-entrenched patient advocacy groups, other "non-traditional" channels are expected to facilitate trial recruitment. The LabCorp Patient Direct group of consented and interested patients is one example.

The confluence of these macro-level factors is disrupting clinical development and concurrently allowing sponsors to address existing trial challenges with an entirely new approach that is more patient-centric while also potentially delivering greater value across all clinical stakeholders including physicians, biopharma and caregivers.

## Improving the patient experience with hybrid and virtual trials

Virtual trials, also referred to as "site-less" trials or decentralized trials, essentially bring the clinical trial experience to the patient's home via a central, virtual coordinating site. The term hybrid trial is also common, representing a trial that incorporates some virtual elements into a site-based study. Virtual trials enabled through new technical capabilities can help improve efficiency to identify, recruit and monitor patients while also improving patient experience, compliance and retention, as shown in Figure 1 below. While not entirely "site-less," as there must always be an investigator, the site can be "centralized" and, depending on the study design, patients may not have to physically visit a site.

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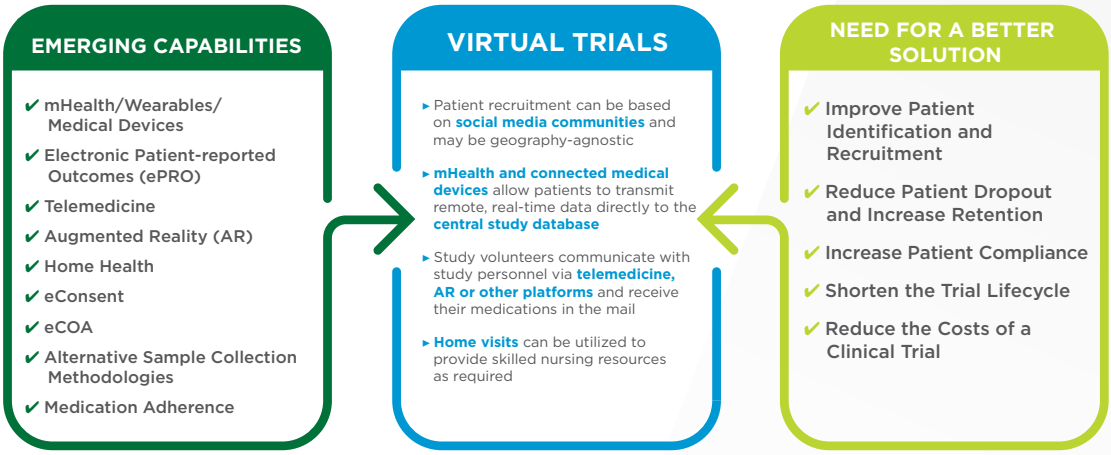
A virtual investigator model can work particularly well for rare diseases and other serious illnesses where patients may be restricted to stay close to home. Some materials needed for a patient visit such as the investigational product, wearables and equipment, are sent to the patient's home, or a local convenient "depot," and study physicians and pharmacists provide support via videoconferencing. Remote data collection can also be instituted for collection of primary and secondary endpoints. However, these instruments will have to be validated to demonstrate data consistency as compared to on-site assessments. Mobile health applications and telehealth technologies are used to capture medical information from patients and, in clinical trials, to transmit remote real-time data directly to the central study site.

Mobile phlebotomists, nurses, nurse practitioners and physicians can also be deployed to the patient's home for sample collection and to perform study procedures such as physical examinations, clinician assessments and vital signs measurement. Patients are able to set their own schedules for procedures, which typically mimics a real-world setting, thus reducing the burden of traveling to a site and spending hours at the clinic.

Virtual trials can also expand the geographic patient catchment areas resulting in a more diverse patient population, as patients who live far away from the site in less population-dense regions now have an opportunity to participate in clinical trials. Access to this wider population available for recruitment expands the currently limited and saturated pool of patients who are interested in participating in clinical trials.

### Figure 1: The intersection of emerging capability with need for a better drug




## Balancing risks and benefits

Sponsors have been keen to explore the concept of virtual trials given that site location is a key driver of patient participation. The benefits of virtual trials extend beyond reducing patient and site burden by accelerating start-up and enrollment timelines and increasing patient diversity. With an optimal study design, virtual trials may also reduce the cost of clinical trials.

Other potential benefits of virtual trials include increased data quality because study data can be automatically transferred from smartphones or other wearable devices instead of depending on site staff to transfer from source documents to the clinical database. This automatic transfer enables faster, higher-quality data collection.

Without the need for multiple physical sites to conduct study procedures, site staffing or storage facilities, sponsors may witness a dramatic reduction in investigator grant payments. Even when some investigator sites are retained, in a hybrid model, the scope of their involvement is reduced, which may reduce direct costs.

Despite these benefits, transitioning to a fully virtual trial, as with any new disruptive model, can present practical challenges. Virtual trials are often positioned to make trials more convenient for patients; however, they can also be perceived as increasing the responsibilities of a patient.

Increased responsibility can be overwhelming to patients, particularly those who are not technologically savvy. To ensure success, it is essential to develop and implement the appropriate patient support ecosystem that includes virtual study coordinators and study concierges who can provide logistical and technological support ensuring that patient burden and responsibilities are minimal.

It is also vital to train patients on how to use the technology that can include devices for ePRO assessments and wearables, data provisioning and management and administration of the investigational product.

Technical support for the wearables and any applications will also need to be made available 24/7 to troubleshoot issues, and for any questions patients may have regarding the study assessments. Local patient service centers could serve as a support site, for example, if a patient needs to pick up a wearable device or needs in-person help setting up or calibrating their device. Sponsors must also overcome challenges associated with data security, implementation of complex trial designs and seamless interconnectivity of all data streams to ensure that all platforms, processes and study stakeholder are in sync.

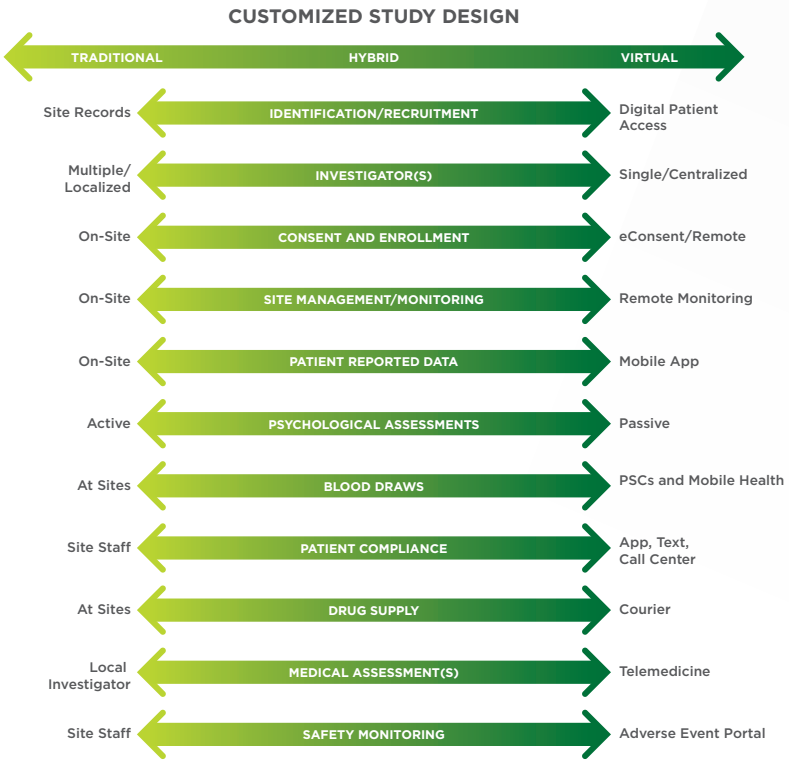
## Evaluating "virtual friendly" elements of a trial

Even with a robust network of support, not all trials are suitable for a virtual delivery modality. Trials with complex imaging needs, radiographic and surgical procedures such as biopsies, or complex investigational product administration require on-site visits. Hybrid trials may be a good alternative for these trials.

Often referred to as "convenient trials," as they offer certain virtual elements depending on patient and/or study need, hybrid trials also retain traditional elements, such as physical sites for more complex patient procedures. These trials also present an opportunity for sponsors to gain experience, generate proof points and gain the needed expertise for virtual trials.

Evaluating the study design to balance between activities that can be conducted remotely or at the investigator site is key to optimizing any protocol for virtual trials. Depending on the trial's needs, each category of service can be offered in the traditional or virtual modality to optimally meet the trial's goals as shown in Figure 2.

### Figure 2: Finding balance in the decentralized clinical trial continuum

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## The role of the CRO in hybrid/virtual trials

CROs are recognizing their role in supporting sponsors beyond traditional trials. Armed with a number of both traditional and digital assets, as shown in Table 1, CROs can offer a number of tools, processes and systems that enable hybrid/virtual trials.

### Table 1: CRO Tools to Partner with Sponsors in Hybrid/Virtual Trials

| | |
|---|---|
| Central laboratory services | Global logistics |
| Patient service centers | Specialty testing labs |
| Mobile health experience | Call centers |
| Direct patient communications | Proprietary real-world data |
| Clinical trial applications | Home health networks with nurses |
| Technology platforms | Phase IV expertise |
| Pharmacy partnerships | Data insights |
| Voice of the patient | Regulatory engagement |
| Remote sample collection | |

This array of technologies, platforms, physical locations, data and advanced analytics can add value to a hybrid/virtual trial model. The operational and therapeutic expertise derived from conducting thousands of studies over the past few decades is also invaluable knowledge that CROs can use to optimize design and execution of virtual trials and support implementation of the technology, data and infrastructure ecosystem that is requisite for delivery.

CROs are also well positioned to be technology aggregators and data integrators. The proliferation of virtual trial technologies must be interoperable with the existing delivery ecosystem, such as the clinical trial management system (CTMS), interactive response technology (IRT), connected devices, investigator site files (ISFs), electronic data capture (EDC) systems and many more. CROs will play a critical role in ensuring the interoperability of all platforms to seamlessly execute and maximize the benefits of virtual trials.

Adopting a digital mindset is a critical first step as it will help shift the focus from plug and play technologies to the more important question on how these technologies collectively help accomplish patient centricity, improve data quality and transparency and maximize clinical outcomes.

There is no question that hybrid/virtual trials have gained momentum since the first hybrid trials were launched in 2001. The industry is working aggressively to identify tools, partners, data and infrastructure required to enable site-less trials. The best partners will be CROs that have diverse capabilities in drug development and beyond, have access to data that can generate insights, enabling them to lead the way in the development of patient and sponsor support ecosystems that deliver better, more efficient trials.

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