Boldly Going Where Few Have Gone Before: Key Considerations for 'Siteless' Clinical Trials

Advancements in technology are impacting many aspects of clinical research, opening doors to innovative study designs and clinical operations that may not have been possible even five years ago. This is especially true when evaluating the potential of emerging technology for home-based assessments as a component of observational or interventional research. In this article, we'll explore the implications of 'siteless' clinical trials for patients and researchers, the range of potential clinical assessments within these studies, and key considerations for exploiting this emerging opportunity.

Siteless Clinical Trials

A siteless clinical trial (also referred to as a remote trial or a virtual trial) is the concept of designing a clinical trial that uses site visits in combination with mHealth or digital technological capabilities to enable patients to complete assessments that would traditionally occur within a clinic[1]. This convenience is particularly relevant for patients with conditions characterised by significant morbidity in which access to centres of excellence is impaired and it brings benefits for sponsors, including enhanced patient interest, reduced dropout rates, environmentally relevant outcomes and reduced study visit costs.

Clinical Assessments in Siteless Studies

There is a rich mosaic of potential clinical assessments contingent upon indication, phase of research, and the intended study objective. Devices such as smartphones and wearable technologies particularly have piqued the industry's interest in a siteless approach to research due to their capability to offer continuous monitoring for physiological parameters such as activity, electrocardiography, electroencephalography, blood pressure, glucose, sleep quality, diurnal variation in fatigue, and other modalities. Additionally, the accelerated use of electronic medical records has created the potential for linkages between diverse sources of information that could help populate a clinical trials database.

For example, the High-STEACS trial has no trial-specific data collection visits and illustrates the potential of this approach[2]. The MI-FREE study in contrast employs a healthcare database to follow participants longitudinally with outcomes that are determined through an algorithm[3]. However, the shift towards home-based trials is about more than just putting a device into the hands of patients and linking data across platforms. Today, typical studies have 5 to 15 safety and efficacy assessments within a given protocol. While home-based studies may refine and reduce some of these assessments, ultimately, there will still be a number of safety and efficacy assessments required from multiple perspectives in the vast majority of trials. A hybrid approach incorporating site- and home-based assessments seems more likely.

The impetus for home-based measures is particularly acute with patient-reported outcomes (PRO) which have been the most compatible for developing protocols for home-based assessments. As noted by Gnanasakthy *et al.* in 2012[4], the FDA is now accepting PRO data for secondary claims associated with safety, but also as primary efficacy points associated with a PRO. Currently pain assessments are the most common, closely followed by assessments of mood, behaviour, and function particularly within neurological/psychiatric indications, although virtually every therapeutic area is amenable to this consideration.

While growth in PRO assessments will be the easiest to incorporate in home-based protocols, biomarker or surrogate endpoints derived from some of these devices may also be considered. Limitations would need to acknowledge the sentiments of both regulatory authorities as well as clinicians who require companion endpoints related to functional, behavioural or symptomatic effects. Put simply, not all endpoints are amenable to capture through a wearable, digital device or electronic diary. Correspondingly, trials will still need to heavily rely on an element of clinic-based, clinical reported outcomes (ClinRO) as well.

PRO Considerations for Siteless Trials

There are multiple versions of PROs available, each with differing endpoints and specifications for use. The selected PRO has to be fit for use for the specific underlying disease or indication. In addition to including appropriate clinical constructs, linguistically and culturally validated translations for every geography in which it will be used are required. Statistical considerations become prominent due to the multiplicity of assessments, as continuous monitoring may change some of the statistical aspects of the sampling process. Study teams also have to be mindful of the quality of PROs, ensuring that there is an appropriate recall period, with provisions available to address missing assessments. Self-reported data by definition are subject to delays in availability and incompleteness as well as possible distortions due to the influence of social media exchanges.

The use of paper-based assessments versus ePRO provides another dimension for consideration. While it is easy to assume that electronic methods would be the obvious choice, moderating variables include the nature of the indication, demographics, geographies in which ePROs are introduced, and the extent of training required to assure adherence to guidelines for specific assessments. While there is some conflict in opinion, it can be said that the frequency of assessments as well as

length and complexity are a significant factor dictating ePRO selection, along with the hierarchy of these measures as primary or secondary endpoints within a proposed study.

ClinRO Considerations for Siteless Trials

ClinRO, where an investigator or specialised clinician undertakes an assessment of patients involved in a clinical trial, is often thought of as being too difficult for home-based assessments. However, remote administrations of very complex assessments are already included in many studies and, increasingly, are considered as standard for many subjective endpoints, especially in neurological and psychiatric indications, as well as indications in which assessments such as global measures of improvement and symptom severity are included. In these settings, the method of acquisition becomes a moderating influence, i.e., phone- or web-based assessment, or a trained nurse or expert physician that can conduct assessments either through web-enabled technology or through a home-based visit.

Best Practices for Operationalising Late Phase Research

Worldwide is currently using a direct-to-patient Research Contact Center to collect data from 5000 patients taking part in a large cardiovascular outcomes study across multiple geographies. The design of the protocol has facilitated ethics committee approval of direct patient contact by telephone to collect PROs as well as other healthcare utilisation data without the mediation of study sites. Data is collected at six-monthly intervals from both patients and caregivers with a response rate of approximately 90 %, which, after three years of research, is high. Part of this success is attributable to flexibility in the timing of patient contact, as well as automated local language SMS and email to maintain study visibility and ensure assessments are conducted within a defined visit window structure. Using methods and tools that suit the target population with professional staff familiar with culture, language, and standards of clinical care is essential to the success of this approach. Early engagement of regulatory authorities is required.

As an industry steeped in precedent within a matrix of regulation, hesitancy in incorporation of electronic data platforms for patient assessments during prototypical registration programmes is anticipated, and perhaps prudent. The move towards home-based studies, or hybrid investigations that include a mix of clinic versus home assessments, means that we are now detecting site-based operational issues within the home setting, such as incomplete or out-of-window assessments, patient non-compliance, issues with gathering and verifying source documents, as well as challenges in scheduling travelling nurses to undertake assessments or problems with visits cancellation. In addition, the necessary shift in training patients and caregivers rather than staff at sites creates an impetus for creativity both in terms of appropriate content, and study logistics. Nevertheless, an ability to utilise technology early in research facilitates innovation in study design as well as trial conduct. This brings us to the question of how we embrace new technology in this area and what will it mean for patients, healthcare providers, sponsors, and other stakeholders.

Where Do We Go From Here?

Bringing new patient-centric technologies into clinical trials requires understanding of the patient experience and journey, particularly for those illnesses characterised by chronicity and multiple comorbidities. For example, Generation X (birthday: 1965-1980) and Millennials (birthday: 1981-1996) have a relationship with technology that is largely incorporated into their everyday lives and it reasonable to conclude that integration of advanced technology into the process of healthcare for these individuals can be used to benefit long-term health promotion and treatment outcomes. Pragmatic trials informing healthcare policy decisions, for example, likely can exploit this penchant and familiarity with an electronic media interface for both data acquisition and patient management to support adoption for novel interventions into clinical practice[5].

The use of data mining and analytics also is allowing us to use these technologies to extract scientifically sound data characterising longer-term patient outcomes for regulatory agencies and healthcare providers who particularly wish to define the value of an intervention, given the therapeutic novelty. Risk stratification algorithms based upon these data, for example, could help prioritise the range of treatments likely to have the most significant clinical impact for given patient characteristics[6], specifically, the therapy most likely to produce a substantive impact *and* be adopted by a patient. That being said, there are many areas where the industry now needs to work together to ensure the best standards and practices are adopted. Collaboration is essential across consenting processes, data cleaning activity, analytics, and data accessibility to enable this area to mature and evolve into new ways of operationalising home-based assessments.

Implications for "Best" Practices

Technology has a considerable impact on most areas of our lives. How many of us would choose to live without our smartphones or our tablets for just a day? The same phenomenon increasingly is relevant for the design and operation of clinical trials. The IT team now plays a major role in the cross-functional study team, sitting alongside site management, project management and regulatory operations, and is increasingly involved in every aspect of study operational planning – providing the "enabling infrastructure" which is necessary for successful study operations. As an industry, therapeutically focused, smaller, more informed teams with a creative problem-solving mindset appear ideal and critical for successful CRO-sponsor collaboration. This will be foundational in conducting siteless clinical trials, given the interplay of clinical, technological, and regulatory constraints.

As new practices and standards are developed, the

evolution of roles within the industry will also need to be considered. In the future, for example, the CRO may play a larger role in training and site management and surveillance for medical convergence of diverse assessments, in addition to ensuring the accuracy of data through traditional site-based monitoring. Some of data monitoring responsibility is already subsumed under the umbrella of various technologies employing error-detecting algorithms, allowing site management to assume an increasingly strategic role. This will especially be the case in late phase research, where the continuum of clinical research shifts toward a pragmatic rather than explanatory trial focus. In this environment, data warehousing and analytics will take centre-stage.

A Harbinger for Changes in Clinical Research

Having the ability to place assessments at home, whether they are physiological assessments, measures of functional status, or assessments of quality of life, can exist in service to a number of objectives. Use of home-based assessments facilitates study participation by patients with significant morbidity located remotely from centres of excellence, and it enables acquisition of a range of measures sampling different dimensions of patient health in a continuous rather than episodic fashion. In earlier phase explanatory research, the use of home-based measures permits access to additional dimensions of data that hitherto had not been considered based upon exclusive reliance on within-clinic assessments.

In the post-approval environment, reliance upon home-based assessments permits continued evaluation of "under-investigated" treatment modalities in more heterogeneous patient populations, which potentially is more representative of patients likely to receive therapy than those that may have been evaluated during the pre-registration process. This last activity generates ecologically relevant data that better maps into the practice of medicine, providing a more nuanced and expanded operational definition for translational research, i.e., research that transitions from clinical development into commercialisation.

*This article is informed by discussions shared during a Worldwide Clinical Trials webinar – 'Are we moving towards 'siteless' clinical trials?' To listen to the webinar, please visit www.Worldwide.com.

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