Pursuing Protocol Designs That Maximize The Value of Hybrid Clinical Trials

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In the pharmaceutical industry, clinical trials are designed to address a hierarchy of drivers – from efficacy to safety, comparability to compliance, there are a slew of considerations that are vital to conducting a successful study. There are also factors that, while not necessary for regulatory approval, are nevertheless important to ensuring a trial itself is efficient, fast, and tailored to its patient population.

Hybrid and decentralized clinical trials(DCT), which have existed in some form for decades, have seen renewed interest in recent years, owing to increasing trial complexity, the need for greater accessibility across patient populations, and the need for more flexibility to respond to emergent situations like the COVID-19 pandemic. While the pandemic served to spur unprecedented investment in hybrid and decentralized models in order to facilitate and accelerate vaccine trials, geopolitical and macroeconomic factors post-pandemic, coupled with a widespread slump affecting emergent DCT tech companies following a peak in innovation, have slowed the rapid adoption of these technologies. Today, industry players have entered a "normalization" phase, a slow and sustained recovery marked by another increase in adoption and greater technology integration across the space.

The future of hybrid and decentralized trials hinges on facilitating speed, cost-effectiveness, and data accuracy while ensuring regulatory compliance. Enabling both the necessary elements (safety, compliance, etc.) and those desirable to improving the outcomes for a trial (speed, cost effectiveness, etc.) come down to protocol design. The best protocol designs, in turn, are patient centric – by prioritizing patient experience during trial design, sponsors can maximize the value of other solutions, balancing technology elements with in-home care, site visits, logistics, and other key variables to arrive at the right trial design.

Designing a Trial With Centricity in Mind: High-Touch vs. Low-Touch

The proliferation of DCT solutions in fully virtual and hybrid trials – those that combine remote and traditional site elements – has created a need for more individualized, accessible, straightforward processes for both trial participants and healthcare personnel. When it comes to arriving at a trial design, determining which activities can be undertaken by a patient at home and which require the presence of medical professionals is a crucial distinction. For hybrid trials, this determination can be made by establishing the "degree of touch" required.

Ultra-low-touch trials are, naturally, those that are lower risk; protocols with a low likelihood of adverse events involving a well-understood investigative medicinal product (IMP) that is administered easily, with low sample demand, and more simplistic clinical data needs may be considered ultra-low touch. Conversely, trials where the risk of adverse events is unknown, the IMP is administered parenterally, physical examinations are necessary, and sampling demand is high are classed as high-touch trials. For these studies, Home Trial Support (HTS) and home nursing, coupled with site visits, will dominate the design, whereas technology is the primary support for low-touch designs. The primary impetus for incorporating and integrating solutions in a trial is streamlining; however, sponsors may experience additional benefits, such as greater patient diversity, in the course of pursuing a hybrid trial design.

There are a few scenarios that are particularly well-suited to a hybrid approach – rare disease trials, for example, are often conducted largely in centers far removed from many patients' homes, making hybrid trials a useful way to reduce the burden for patients participating in these studies. This is likewise true for therapeutic areas that require a significant number of hospital visits, and for which home nursing may supplant some of those visits.
At the other end of the spectrum are technology-only DCTs, often referred to as virtual trials. Because these trials are usually low-risk and low-touch, the

advantages conferred by most DCT technologies when compared to analog, paper-based approaches – recording time-series data, flagging missing data, and simplifying eConsent and user interfaces – make them valuable technologies for conducting these trials.

Likewise, real-world evidence (RWE) trials can benefit hugely from a DCT and hybrid approach. Direct intervention on the part of medical personnel is de-emphasized as part of these studies, which are often conducted with broad patient populations being treated with a range of comparative products. Some RWE trials still require significant patient-physician interaction, so converting some of this interaction to digital avenues such as telehealth can result in faster, more accurate data.

Clinical trials of every type are likely to require more work going forward, as therapeutics in the pipeline become more complex. While DCT technologies and hybrid design may represent a heavy lift during adoption, they possess huge potential for streamlining the patient experience, which can be instrumental in promoting greater adherence to a protocol or improving retention for a study.

Balancing 'Needs' With 'Wants' For Better Trial Outcomes

Promoting patient centricity requires a unique approach that balances the technology solutions involved with the nursing tools utilized, and which arrives at just the right amount of data, as collecting more data than is necessary to demonstrate safety and efficacy can inflate costs and undermine speed-to-market. Designing a hybrid protocol often means starting with the "obvious" – in a traditional trial design, for example, since patient visits are all at the site, complex testing can occur at any visit to spread the workload. Finding ways to combine activities into single visits, therefore, is one of the first steps trial teams can take in hybrid design, aggregating tasks that can be safely performed off-site to specific home nursing visits, and those that must be done at the hospital to traditional site visits. This simplification, always ensuring patient safety, can go a long way toward improving recruitment and retention.

On the technology side, achieving patient centricity means taking a consumer-driven approach to platform development. Ideally, these technologies should be as robust and useable as a mainstream smartphone or tablet application, with a simple user interface and responsive support infrastructure. Additionally, accessibility considerations, including making technologies available to users in their local language, can help sponsors recruit faster and more widely. DCT technologies are not guaranteed to be patient centric; unoptimized for the user, they can create work for patients in terms of device management, data entry, and data cleaning. Even medical device design can be served by a patient-centered approach, as more ergonomic, easy-to-use devices, such as those used to administer self-injections, can enable even greater degrees of decentralization.

Prioritizing patient safety is critical for every type of clinical trial but can be especially complex for high-touch hybrid trials. Having the appropriate monitoring in place from the start is key to ensuring that clinical staff are performing up to standards both on- and off-site. Likewise, adequate monitoring applies to data collected both on- and off-site and from providers and patients alike – clinical research associates should be constantly checking that protocols are being performed correctly and data is complete, accurate, and being reviewed by the trial team appropriately. The near real-time access to data that technologies can enable is valuable only if that insight is leveraged in a timely and appropriate manner. As clinical trials become more complex, hybrid trial strategies are likely to evolve to meet new demands, such as managing patient-derived endpoints, just as the FDA currently requires for medical devices.

Trial Design With The Patient In Mind

Any organization working to design a trial protocol that prioritizes patient centricity must first look at a study's participants and IMP to determine what level of on-site care is necessary for safety, as well as what elements of a protocol can be digitized, sourced to home health, or scheduled concurrently to maximize the patient experience. Identifying the personnel needed and the training required to facilitate a hybrid approach is next, followed by ensuring that both participants and medical personnel can be easily familiarized with the technology interfaces supporting the trial. Ultimately, for trials that require a significant degree of "touch," in-home care can hugely influence accessibility for certain patient groups (based on therapeutic area or demographics) and positively impact their clinical trial experience. Balancing patient needs with safety and clinical endpoints can help sponsors arrive at a trial design that encourages retention and improves the life of a participant, all while helping to reach study milestones faster.

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