Top ten rules for success in decentralized trials

Guido Epple, Innovation Ambassador and Head of Clinical Trial, Supplies & Logistics Product Management
Alexandra Holzum, Associate Director, Integrated Solutions, Clinical Trial, Supplies & Logistics
Julia Lakeland, Solutions Architect and Program Director
Sarah Pilkington, Associate Director, Patient Innovation Center
Ada Wowk, Director, Patient Innovation Center
Parexel®

The global coronavirus pandemic catapulted the emerging field of decentralized clinical trials (DCTs) to the forefront of clinical research in a matter of months. With approaches like home nursing, telehealth, direct-to-patient (DTP) drug shipments, and mobile sensors, DCTs are making it easier for patients to participate in trials, especially for those who live far away, are too sick to travel, or are too busy.

Parexel's DCT experience spans more than 100 fully decentralized or hybrid trials, and more than 250 trials with DTP drug shipments. Patients' needs and insights are central to how we design and conduct trials, so we talked with Parexel DCT experts to find out what they have learned. Here are their top ten rules for a successful DCT:

1. Anticipate and mitigate DCT-specific risks.
Traditional trials carry plenty of risks: Missing or erroneous data, improper drug handling, and accidental unblinding, to name a few. With DCTs, these risks may be more obvious—and that enables study designers to mitigate them through careful planning.

For example, a patient in a clinical trial always has the right to withdraw from the study for any reason. But some therapies can't be stopped immediately: patients need to take increasingly lower (titrated) doses and taper off the treatment gradually for safety reasons. In a traditional site-based trial, the titration process is explained and handled by site staff. In a DCT, we prepare a study-specific titration kit that is distributed to patients at the start of the

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study. If they withdraw at any time, the instructions and medication doses are pre-packaged and ready to go.

"Smarter" processes can also help deliver investigative medicinal products (IMPs). In a DCT, if we know that we must control the temperature of an IMP from site to storage in a patient's home, we build layered systems, including specially trained couriers to transport it in a temperature-controlled environment with a monitor that provides continuous readouts. If an IMP drops below or goes above the specified range, the courier does not deliver it.

2. Think through every aspect of DTP logistics.

Sponsors tend to focus on IMP delivery when they think about DTP logistics, but there is a lot more to it. Effective DTP operations also involve study support materials (such as patient instructions), devices, consumables, sample collection, the return and reconciliation of unused IMP, and packaging materials, among other things. Successful DTP logistics require attention to detail and an overall view of the IMP supply and storage chain.

Parexel recently conducted a trial where we planned to provide each patient with a 'smart' refrigerator that registered activity. In many patients' homes, the whole family uses the kitchen refrigerator, and it's unlikely to maintain a stable temperature. Also, there may not be enough space to store medication for several weeks. So, we supplied patients with study-specific refrigerators. Since some patients could not easily accommodate an extra refrigerator in their home or apartment, we checked each participant's size and space requirements. This is the level of detail that is necessary, yet easy to overlook, when devising a DTP delivery system.

3. Embrace the expertise and motivation of patients and their caregivers.

Conventional wisdom in the pharmaceutical industry was: "We need to restrict information about the inner workings of clinical trials, or it will confuse and discourage patients." At Parexel, we've found just the opposite. Patients and caregivers—especially those with chronic and rare diseases—are often experts in their condition. And they eagerly assume responsibilities in DCTs.

For example, diabetes patients know how to inject themselves, and kids who have grown up with diabetes are adept with electronics and devices. Patients with rare and orphan diseases, particularly those who live far from academic research centers, are deeply knowledgeable and motivated.

Since COVID-19 hit in late 2019, patients in clinical trials have adapted to new devices and telehealth visits in what *The Lancet* recently called a "fast, effective readjustment." The results demonstrate that giving patients and caregivers more responsibility provides enormous benefits, while the risks to patient safety and trial integrity were not as high as sites and sponsors feared.

DCT trial designers can learn a lot by asking patients, caregivers, and advocacy groups the right questions. Does the treatment being tested address a relevant patient need? Can it be administered in a non-site setting? For this patient population, is a DCT the

right approach? Why or why not? For example, some chronic disease patients have trusted relationships with investigational site staff and may prefer in-person visits. If caregivers will perform some or most of the trial assessments (or even procedures), do they agree that a DCT is preferable to a traditional trial?

4. Plan ahead for complications in eConsent and telehealth.

Remote tools such as eConsent and telehealth can be great enablers of DCTs. But they can bring complexities that need to be anticipated.

For example, Parexel recently conducted a study in adolescents that required numerous layers of consent, including opt-ins and opt-outs, and the signatures of parents and guardians. For patients with divorced or estranged parents, the consent form had to collect multiple signatures. We solved the problem by utilizing two remote technologies; e-Consent and telemedicine. We sent an e-Consent form to patients and their parents or guardians in advance of a telemedicine video conference call. By engaging participants with a chance to review the trial documents in advance, we increased their comfort and familiarity with the study. During the subsequent online meeting, patients, parents, and site staff reviewed the eConsent form together. The remote format allowed people in different locations to participate in the conversation, asking questions and learning details about the study's schedule and procedures. At the end of the meeting, parents signed the eConsent form and adolescents signed an electronic assent form.

The process went smoothly because we planned ahead to get the most out of the digital health technologies we used—and made sure both had the functionality we needed. While telemedicine can transform clinical trial visits, it requires more than a reliable internet connection (though it also requires that). Parexel recently helped a client incorporate a skin assessment for eczema into a telehealth visit for a DCT. Questions we had to think through before proceeding included whether we would need a home nurse or caregiver to help an investigator observe the patient's skin, whether remote assessments would be comparable to in-person assessments, and how we could achieve adequate camera quality and lighting.

5. Validate the processes in which new technologies will be used.

Recently, a Parexel client designing a DCT asked us to incorporate video recordings of patient-site interactions as part of the data capture. And how would one analyze this type of data? After studying the issue and discussing it with our preferred vendor, we determined we could capture video data, but we had to validate the processes first.

Alluring new mobile devices and technologies are flooding the market. But each must be used in a validated process. The technology landscape is evolving rapidly, and how a platform works today can be vastly different from how it worked six months ago. When incorporating technology into a trial, questions to answer include:

- Does the technology work as intended? This question is distinct from user acceptance testing

at the study level—it's about rigorous qualification and validation at an overall level.

- How does the patient consent to the technology? If a patient wants to opt-out of a specific form of data capture, such as a video recording, can they?
- How is access to the data granted, and how are access rules defined?

6. Adjust protocols for better compliance at home.

If your goal is 100% patient compliance for a DCT, and you have restricted time windows for the activities in your protocol, you are not likely to succeed.

For example, we recently worked with a sponsor to tweak the protocol design of a DCT because it was unrealistic. The study specified that patients record their blood pressure twice per day within two 90-minute windows over six months. However, patients with young children to care for, mobility problems, or chronic pain would have difficulty doing that. So instead of keeping a rigid timeframe and seeing, say, 50% compliance, we broadened the time windows and achieved 80%. Having patients use medical devices, wearables, and sensors at home (or as they go about their day) introduces the "real-world" into clinical trials.

Balance what is reasonable and feasible with what is allowed from a regulatory standpoint. 80% compliance with a suitable device (or wearable) and good engagement and monitoring is achievable and acceptable.

7. Don't collect more data than you need.

Sensors and wearables offer the ability to capture more data than ever before. Frequent or continuous in-home data collection could provide more study endpoints and less artificial ones than those in traditional site-based trials. That's enticing, but unlimited data has limits.

Recently, a Parexel client asked us to help them make sense of results from a clinical trial they had recently completed. The problem was they were drowning in data. They had collected data about patients' movement and sleep activity via a wristwatch in the hope it would yield insights. But they had not thought through which endpoints would be informative and why: How many steps per day? How much REM sleep? There wasn't a plan to find meaning in the sea of 24/7 data. That's a common, understandable mistake. It's critical to define study objectives, a data management plan, and the workflow upfront in the study's design.

Sometimes, a simple data capture at a discrete point in time gives more insight than continuous data. Rather than scrambling to make sense of data at the end of a study, sponsors can ask better questions at the start and plan more carefully:

- What is a meaningful and interpretable unit for measuring the outcome of interest?
- Is continuous capture of the data informative? What does it tell us?
- Does the data need context? For example, if a patient is exercising, their heart rate will be higher.

8. Make sure that remote sensors are fit-for-purpose.

Sensors can be a substantial investment: medical-grade devices can cost up to $1,500 a patient. Usability is critical. Can patients use the sensor/wearable/device? How is the data transmitted from home? What is the burden of data collection?

Be aware, a license from the FDA (510(k) equivalence) or EMA (CE mark) is not a guarantee of accuracy. An approval of a new technology based on a brief clinical trial in a small number of subjects does not imply that it can be scaled up overnight for use in a global study. One recent Parexel study found that several mobile technologies cleared for use by regulatory agencies did not work in practice. Anticipate the need to validate devices ahead of time.

It may also be important to give patients support for their devices. Who do patients call when they have a problem? Sites may not understand the technology involved. Can home nurses solve the problem? You may need a dedicated patient call center with extended coverage for troubleshooting.

9. Consider all the benefits of home nursing.

Sponsors are often shocked at the price tag of home nursing. Once seen as a minor tool for recruitment support, home nursing in a DCT can be the primary staffing structure for a trial.

Home nursing visits increase upfront costs, but can decrease patient burden and drop-out rates, speed recruitment, and improve compliance. In a DCT, home nursing can be combined with other elements, such as interactive devices and telemedicine visits, to create a comprehensive patient support system. Patients and caregivers receive more frequent and better trial communications and are therefore more engaged than in a traditional trial. In turn, studies can enroll and complete on time.

10. Ask your patients to define patient-friendly.

Often trial planners theorize in meetings about what would work best for patients, but only patients know. To bring that knowledge to planning, talk with patients, caregivers, and sites, and solicit practical feedback about what they need.

For example, some patients do not find home nursing visits convenient or desirable. In certain cultures, chronic or serious illness or disability is taboo, a sign of weakness, or even a trigger for harsh judgment and shunning by the community, so having nurses visit the patient at home risks their privacy. Others may feel embarrassed by constrained economic circumstances such as several generations or many individuals living in one home. Or by a psychological disorder such as hoarding.

It's important to be flexible. If research shows that your target patient population doesn't want home nursing, consider local community centers or even hotels for nursing visits. That still reduces travel time for trial participants, a prime benefit of DCTs.

With Heart

Parexel International Corporation
275 Grove Street, Suite 101C, Newton, MA 02466, USA
+1 617 454 9300
info@parexel.com

Offices across Europe, Asia, and the Americas

www.parexel.com

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