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The Virtual Opportunity in Rare Disease Trials

Karen Kaucic, MD, Horacio Plotkin, MD, Christopher Komelasky

Challenges in rare disease research can be solved with virtual trials and their supporting technologies

Special challenges in rare disease research—small, geographically dispersed patient populations, the predominance of pediatric patients and the great economic demands of traditional site-based trials—make virtual trials ideal for rare disease drug development. Virtual trials reduce or even eliminate travel to study sites, making it possible to conduct rare disease studies that cannot otherwise be undertaken due to logistical and economic barriers.

Digital health technologies, including Internet-based communications, smart devices, and mobile health (mHealth) technologies, are transforming trial operations to enable remote patient enrollment and data collection—solutions that offer unprecedented opportunities to advance both rare disease research and virtual trial models. Early applications of remote technologies, together with a positive regulatory climate, promise rapid adoption in rare disease research—an advance that could make dramatic progress to address more than 7,000 identified diseases, 90% of which currently lack specific treatments.[1]

Brick and mortar vs. virtual operations

In traditional site-based trials, time to site activation averages one year at costs ranging from $20,000 to 30,000;[2] during a trial, site maintenance averages $1,500 per month.[3] Patient recruitment—typically a major bottleneck—accounts for the lion's share of study delays. An estimated 11% of sites fail to enroll a single patient;[2] less than 10% of trials are completed on time.[4] Efficient time and cost management depends upon enrolling the largest number of patients at the fewest number of sites. In the rare disease setting, site-based subject enrollment and data collection pose the opposite efficiency scenario—fewer patients enrolled by more sites. By definition, rare diseases affect fewer than 200,000 people in the U.S.;[5] the EU considers a disease rare if it affects five or less in 10,000.[6] In one example, a trial of a treatment for ANCA vasculitis expects to involve 200 centers in order to enroll the 300 patients required.[7] In a 2014 survey of 2,759 rare disease trials registered on ClinicalTrials.gov, actual enrollment in the majority of trials (955) was fewer than 50 patients.[1]

In concept, the virtual trial brings research to the patient—a perspective of great value in rare disease research.[8] Remote data collection would eliminate geographic barriers and reduce the costs of traditional site management. In a rare disease study, a virtual trial could include:

- One clinical site and virtual study coordinating center to manage medical issues and all study operations, including clinical trial materials management and multiple stakeholder engagement: trial management supported by a real-time data management platform for monitoring, tracking, reporting, and analytics.
- Online patient recruitment, screening, and enrollment via disease-specific online registries or social media sites: health data access via physician and electronic medical records (EMRs).
- Electronic informed consent supported by telemedicine meetings with patients and families.

- Remote, at-home data collection via electronic patient reported outcomes (ePRO), research-grade sensors, and smartphones to take measurements and transmit data directly to investigators.
- Virtual patient visits: initial and interim visits conducted via telemedicine for training, to oversee use of sensors and devices, adverse event reporting from patients to sites, and manage protocol compliance. In fact, replacing some in-person visits with virtual visits may be a next transitional step for much of the industry as it heads toward the complete virtual trial.
- Remote patient prompts and information via smartphones and other devices to support engagement and retention and facilitate follow-up activities.

Patient access is the greatest advantage of virtual models in rare disease research. Widely dispersed patients can participate in trials regardless of their location and their physical ability to travel. In addition to the obvious benefit of reduced site costs, virtual trials collect real-world data during the patient's everyday activities. This increases the likelihood that study findings will more closely reflect therapeutic effects in real-world use. With traditional dropout rates as high as 30%,[9] virtual studies can improve retention by offering greater convenience and continuous patient-centric communications and support.

Coming of age

Virtual trial initiatives began with Pfizer's 2011 pilot study, "REMOTE." Conducted under an investigational new drug application, the randomized REMOTE trial used online informed consent and remote data collection to evaluate an overactive bladder therapy. The goal was to determine whether the virtual model could replicate findings of a previously conducted Phase IV site-based trial. As a first attempt to change years of traditional clinical trial conduct, REMOTE failed, due to insufficient enrollment, but demonstrated that electronic informed consent, distribution of blinded investigational drug to patients, and remote data capture is feasible, both from operations and regulatory points of view.[10]

Following REMOTE, a host of studies piloted trial operations using virtual technologies, building necessary experience to validate the feasibility, accuracy, and security of remotely conducted trials. In 2015, the virtual trial came of age with "VERKKO," conducted by eClinical Health and Sanofi.

The European-based VERKKO trial enrolled 60 patients recruited on Facebook to study the use of a patient-centric, online clinical trial platform that integrated a 3G-enabled wireless glucose meter. Study materials were mailed to patients, who took measurements using the smart glucose meter. The smart device transmitted data to the trial platform, which made findings available for real-time review by the coordinating site and patients. VERKKO was managed at a single site by one investigator and one study nurse.

Results of the successful trial reported in 2016 provided evidence for the presumed advantages of remote designs. In post-study surveys, patient satisfaction earned a positive score of 4.5 out of 5. Compared to a site-based comparator study, the virtual trial improved protocol compliance by 18%; increased patients' glucose profiling time by 22%; and reduced study site's time for study coordination activities by 66%.[11]

Virtual technologies

Virtual research capabilities have matured with the increasing availability of and patient familiarity with a broad array of digital health technologies—telemedicine, intelligent devices, and mobile health technologies, including smartphone-based software applications (apps) and wearable sensors.[12] Forty-three percent of these health-related apps are designed for healthcare professionals to conduct remote health monitoring and disease management.[13] And the number of telemedicine visits continues to climb. For example, Teladoc, just one of the many providers of telehealth services, recorded almost one million visits in 2016, which is 65% more than a year earlier.[14]

The integration of health monitoring devices with smartphones has generated medical-grade mobile technologies to measure heart rate, blood pressure, respiration, ECG, core temperature, and galvanic skin response. "Intelligent" devices transmit data directly to the caregiver or research site. Among the most widely used are a mobile telemedicine system that interfaces with a computer server to record and report video consultations; a fetal heart rate monitor used with a smartphone for data transmission, and a smartphone image transmission system used for diagnosis.[15]

Virtual solutions

Rare disease patients are well attuned to Internet-based support communities and rely heavily on social media for disease-specific information and research opportunities. Rare disease research has been a major catalyst in patient-centric trial design. In-home clinical trial support programs, which field good clinical practices (GCP)-trained nurses to collect trial measurements during home visits, are already a feature of rare disease studies. The rare disease community is well positioned to be a rapid adopter of virtual trials.

Recruitment. RareConnect, Inspire, PatientsLikeMe, RareMark, and OneVoice are just a few of the online communities now being leveraged to identify and recruit rare disease patients. Disease-specific social media sites, registries, advocacy and support groups, and research consortia have demonstrated power to identify and maximize enrollment of scarce, geographically dispersed patients. Enrollment speed is another important benefit. In a single week, the rare disease social networking site Inspire identified 18 potential subjects for a Mayo Clinic rare disease study that hoped to enroll 12 participants.[16]

Reduce patient and caregiver burden. Remotely conducted trial operations eliminate the stress, time loss, and costs of traveling to a site for multiple visits. This is especially important for rare disease patients. Children comprise roughly half of the rare disease population, and care depends on complex treatment and support networks. In addition to family members, stakeholders often include primary care physicians, multiple medical specialists, physical therapists, and home care providers. Difficulties posed by travel, disruption of care routines, and lost days of school and work are major barriers to trial participation.

Protocol compliance and retention. Virtual models provide ongoing support and information for compliance-related matters and engage patients throughout the trial. Online communications, smartphones and mobile health technologies deliver prompts that direct patients to adhere to protocol. Smart devices signal times to take measurements, and telemedicine visits are used to observe health status, elicit questions and provide support to engage patients. The convenience of in-home research is a compelling advantage, encouraging both participation and retention.

Next steps: progress and challenges

Rare disease studies are among the first generation of virtual designs, some of which include several onsite clinic visits in addition to virtual visits. The Lunasin Virtual Trial, launched recently by online patient community PatientsLikeMe and the Duke ALS Clinic, enrolled 50 ALS patients in only five months. Participants will make three clinic visits and monthly virtual visits via PatientsLikeMe to collect measurements for weight, evaluate the Lunasin regimen, and complete a PatientsLikeMe-developed PRO rating scale during the 12-month trial.[17] Science 37, a developer of site-less trial models, used its "metasite" virtual platform to speed enrollment of a Phase III trial for the rare disease pemphigus vulgaris—an autoimmune disorder of the skin. The virtual site enrolled 30% of the trial's subjects 20 times faster than the rate expected for the 60 traditional sites conducting the study.[18] More recently, Transparency Life Sciences partnered with researchers at Mount Sinai to test the feasibility of replacing in-person study visits with virtual visits using a telemedicine platform. The research concluded that telemedicine-enabled studies are feasible and can overcome the enrollment challenges of geographically dispersed populations.[19]

Regulation is advancing as mHealth technologies offer benefits of patient access and lower research costs, although it will take time and experience to address all the issues posed by the emerging digital health environment. Issues range from cyber security to the acceptability of a given mHealth device for use in a clinical trial setting. In the U.S., the FDA's 2015 Mobile Medical Applications guidance is being further assessed in light of the 21st Century Cures Act of 2016, which clarified regulation of medical software and amended the definition of "device." The FDA is in the process of gathering information on the use of mobile technologies in research and is developing draft guidance on oversight for medical device software.[12]

Sponsors will be challenged to manage changing—and varying—global regulation as rare disease studies adopt virtual designs to access patients worldwide. Virtual study coordination centers will be aided by increasingly sophisticated IT platforms with capabilities to integrate telemedicine, smart devices, and mHealth data and to efficiently manage remote recruitment, screening, consent, and patient prompts across global sites. Experience using such real-time, integrated platforms is still relatively limited but will increase as virtual practice expands.

Buoyed by expanding scientific knowledge, accelerated regulatory pathways, and monetary incentives, rare disease research delivered 30 new therapies and accounted for more than 40% of new drug approvals in 2015 and 2016.[20,21] With an estimated 560 agents in the development pipeline, virtual trial models hold the promise to significantly expand delivery of novel therapies to waiting rare disease patients.[22] Virtual trials will advance the operational efficiencies and, more importantly, increase the feasibility of drug development for rare diseases.

References

[1]S.A. Bell and C. Tudar Smith, "A Comparison of Interventional Clinical Trials in Rare Versus Non-rare Diseases: An Analysis of ClinicalTrials.gov," *Orphanet J Rare Dis*, 2014; 9:170, available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4255432/ (Accessed June 2017).

[2]M.J. Lamberti, R. Chakravarthy, K.A. Getz, "New Benchmarks for Trial Initiation Activities," *Applied Clinical Trials*, December 2016, available at: http://www.appliedclinicaltrialsonline.com/new-benchmarks-trial-initiation-activities?pageID=3 (Accessed June 2017).

[3]M.J. Lamberti, C. Brothers, D. Manak, K. Getz, "Benchmarking the Study Initiation Process," *Therapeutic Innovation & Regulatory Science*, 2013; 47(1): 101-109.

[4]Society for Clinical Research Sites (SCRS), "An Industry in Crisis: The Escalating Cost to Society of Our Inability to Sustain the Performance of Clinical Research Sites Today and Into the Future," March 2014, available at: http://myscrs.org/wp-content/uploads/2014/06/Industry_in_Crisis_Gates_Position_Paper_14.pdf (Accessed June 2017).

[5]National Organization for Rare Disorders (NORD), available at: https://rarediseases.org/for-patients-and-families/information-resources/resources-faqs/ (Accessed June 2017).

[6]European Commission. "Rare Diseases," available at: https://ec.europa.eu/health/rare_diseases/policy_en (Accessed June 2017).

[7]K. Ribbink, "Rare Recruitment," *PharmaVOICE*, May 2017, available at: http://www.pharmavoice.com/article/2017-5-rare-disease/ (Accessed June 2017).

[8]D. Covington and K. Veley, "The Remote Patient-Centered Study Approach in Clinical Research," *Applied Clinical Trials*, February 2015,

available at: http://www.appliedclinicaltrialsonline.com/deborah-covington (Accessed June 2017).

[9]National Academy of Sciences, "The Prevention and Treatment of Missing Data in Clinical Trials," Washington, D.C. National Academies Press, 2010. http://www.nap.edu/openbook.php?record_id=12955&page=14 (accessed November 25, 2015).

[10]Pfizer, "Pfizer Conducts First 'Virtual' Clinical Trial Allowing Patients to Participate Regardless of Geography," Press Release June 7, 2011, available at: http://press.pfizer.com/press-release/pfizer-conducts-first-virtual-clinical-trial-allowing-patients-participate-regardless- (Accessed June 2017).

[11]BusinessWire, "eClinicalHealth Announces Successful Results for an Entirely Remote Online Clinical Trial," June 21, 2016, available at: http://www.businesswire.com/news/home/20160621005604/en/eClinicalHealth-Announces-Successful-Results-Remote-Online-Clinical (Accessed June 2017). [12]U.S. Food and Drug Administration, "Digital Health," available at: https://www.fda.gov/medicaldevices/digitalhealth/ (Accessed June 2017).

[13]Global Mobile Health Trends and Figures Market Report 2013-2017, "500m People Will Be Using Healthcare Mobile Applications in 2015," Research2Guidance, available at: https://research2guidance.com/500m-people-will-be-using-healthcare-mobile-applications-in-2015-2/ (Accessed June 2017).

[14]Teladoc, "Teladoc Announces Full-Year and Fourth Quarter 2016 Results," available at: http://communications.teladoc.com/downloads/TDOC_Q4_2016_Earnings_Release.pdf (Accessed July 2017).

[15]B.M. Silva, J.J. Rodrigues, I. Torre Diez, et al, "Mobile-health: A Review of Current State in 2015," J *Biomedical Informatics*, 2015; 57: 265-272, available at: http://www.sciencedirect.com/science/article/pii/S1532046415001136#b0215 (Accessed June 2017).

[16]N. Taylor, "Social Network Used to Enroll Rare Disease Patients Quickly," *Outsourcing-Pharma*, September 2011, available at: http://www.outsourcing-pharma.com/Clinical-Development/Social-network-used-to-enrol-rare-disease-patients-quickly (Accessed June 2017)

[17]Business Wire, "PatientsLikeMe Launches Virtual Trial for ALS Patients," October 25, 2016, available at: https://finance.yahoo.com/news/patientslikeme-launches-virtual-trial-als-120000106.html (Accessed June 2017).

[18]A. Neuer, "Technology for Patient-Centric Clinical Trials Wins for Science 37," *ClinicalInformaticsNews*, March 25, 2016, available at: http://www.clinicalinformaticsnews.com/2016/3/25/technology-for-patient-centric-clinical-trials-wins-Science-37.aspx (Accessed June 2017).

[19]M. Galsky, M. Shahin, R. Jia, et. al., "Telemedicine-Enabled Clinical Trial of Metformin in Patients With Prostate Cancer," JCO Clinical Cancer Informatics, August 10, 2017, available at: http://ascopubs.org/doi/abs/10.1200/CCI.17.00044 (Accessed August 2017).

[20]U.S. Food and Drug Administration, "Novel Drugs summary 2015," available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm474696.htm (Accessed June 2017).

[21]U.S. Food and Drug Administration, "Novel Drugs Summary 2016," available at: https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm534863.htm (Accessed June 2017).

[22]Pharmaceutical Research and Manufacturers of America, "Medicines in Development for Rare Diseases, 2016 Report," available at: http://phrma-docs.phrma.org/sites/default/files/pdf/medicines-in-development-report-rare-diseases.pdf (Accessed June 2017).

Karen Kaucic, MD, Senior Vice President, Global Head of Early Development, and Rare Disease and Pediatric Center of Excellence; Horacio Plotkin, MD, is Vice President and Medical Lead, Rare Disease and Pediatric Center of Excellence; Christopher Komelasky is Senior Director, Strategic Feasibility, Site and Patient Access, PPD