*Commentary*

# Incorporating Site-less Clinical Trials Into Drug Development: A Framework for Action

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## ABSTRACT

**Purpose:** Options for leveraging available telemedicine technologies, ranging from simple webcams and telephones to smartphone apps and medical-grade wearable sensors, are evolving faster than the culture of clinical research. Until recently, most clinical trials relied on paper-based processes and technology. This cost- and labor-intensive system, while slowly changing, remains an obstacle to new drug development. Alternatives that use existing tools and processes for collecting real-world data in home settings warrant closer examination.

**Methods:** The site-less clinical research organization (CRO) model, whereby pharmacists or other health care professionals provide useful and timely counseling for protocol compliance by regular phone and videoconferencing sessions, is a flexible approach to managing clinical trial participants directly from their homes. An expert panel, including clinical specialists in metabolic or neurodegenerative diseases, health information technology and CRO innovators, and the pharmaceutical industry, met in Dallas, Texas, December 2016, to discuss advancing avenues for site-less CRO and other remote clinical trial practices, taking into account investigator, sponsor, and regulatory perspectives.

**Findings:** Real-time "site-less" management of clinical trials can augment traditional research and development methods by providing data from a broader, more diverse group of patients in real-world practice settings. This methodology also helps to proactively identify safety profile and operational issues. Current use of site-less CRO practices constitutes an important bridge to alternative trial models, including "large simple trials" that strive to answer one or two questions using data derived from representative patient populations treated in typical clinical settings.

**Implications:** Site-less CROs offer a working example of how remote technologies and in-home monitoring methods can address shortcomings of conventional drug development. This model maximizes time and cost, as well as potentially earlier identification of adverse events. Coordinated communication among investigators, sponsors, regulators, and patients will be needed to develop standardized strategies for incorporating site-less CROs into current and future study design. (*Clin Ther*. 2017;39:1064–1076) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

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## BACKGROUND

In 2011, Pfizer conducted the first clinical trial of a US Food and Drug Administration (FDA)-approved pharmaceutical, using Web- and smartphone-based technologies to recruit and manage participants entirely

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from their homes. Called REMOTE (Research On Electronic Monitoring of Overactive Bladder Treatment Experience), this feasibility study was initiated in response to an increasingly challenging drug development environment marked by rising costs, lengthening cycle times, escalating levels of protocol complexity, and a dynamic regulatory environment.[1] Despite early termination of the REMOTE trial (described below), lessons learned about the strengths and weaknesses of its specific Web-based components have stimulated interest in the potential of technology-driven clinical trial methodologies to complement conventional methods of drug development.

The need for such innovation is well documented. According to the Tufts Center for the Study of Drug Development, bringing a new therapeutic entity through research and development (R&D) takes at least 10 years, and the average capitalized cost, factoring in the shared cost of compounds that fail, exceeds US$2.6 billion.[2,3] The period of clinical testing is particularly time- and cost-intensive, with site monitoring alone comprising between 9% and 14% of overall expenditures.[4] Uncertainties of recruitment and retention pose additional, ever-present risk. An estimated 11% of sites in any multicenter global clinical trial fail to enroll a patient, almost 40% fail to meet initial recruitment targets, and 49% of all enrolled participants drop out before study completion.[2,5]

Perennial barriers to recruitment and retention are lack of proximity to academic medical centers, where trials are usually conducted, and the inability (or unwillingness) of participants to commit to multiple follow-up visits.[6] Inefficient trial management and the demand for larger and more diverse sample sizes over wider geographic areas, to determine whether a drug is well tolerated and efficacious across all age groups and ethnicities, are additional hurdles.[7]

## THE EVOLUTION OF SITE-LESS CLINICAL TRIALS

The aforementioned Phase IV REMOTE trial was considered groundbreaking in its objective to validate the use of Web-based methodologies in clinical research. The efficacy and tolerability of the active treatment (tolterodine tartrate extended release) had been previously found in site-based trials, thus allowing comparison with results derived from Web-based methodologies. The protocol received endorsement from two institutional review boards and the US FDA.[1,8] After viewing the introductory webpage, candidates could opt to create an account, which began the screening process. Of 20,901 individuals who viewed the study's introductory webpage, 17,950 watched an online informational video, more than 7000 people completed the account registration page, and more than 5000 re-confirmed their e-mail address. However, each step was associated with a loss of potential participants.

Ultimately, 118 participants proved eligible for the study under informed consent, but only 18 were randomly assigned to treatment. Sharp dropouts occurred at two points: the multiple-stepped online identity verification procedure and the placebo run-in period when participants were asked to enter bladder e-diary data on a sponsor-supplied mobile phone. Investigators observed that processes and equipment could have been simpler and more user-friendly at both junctures. Aspects that worked well were the interactive online consent and the shipment of the study drug directly to patients.[1]

In 2015, the "virtual" trial concept was reinforced when the US FDA solicited feedback on the use of telehealth technologies to improve efficiency of clinical trial conduct.[9] Major drug companies in Europe and the United States launched feasibility trials using Web-based methods. The European trial, sponsored by Sanofi, assessed the utility of a 3G-enabled wireless blood glucose meter for glucose profiling from remote sites.[10] Participants registered themselves by a clinical research cloud platform, reviewed patient information electronically, signed informed consent electronically, and received other study materials directly at home. Coordination of the study required 66% less time compared with a conventional site-based study using a similar protocol, and compliance improved 18%.[11] In the United States, Genentech incorporated a videoconferencing and messaging platform into a trial of treatment for a rare autoimmune skin condition occurring in less than 1/100 of 1% of the global population.[12] Candidates from seven US states were recruited through the "virtual" site, and enrollment was more than 20 times faster than that projected for non-remote sites.

In keeping with this movement, the first "site-less" clinical research organization (CRO) was set up by the organization of one of the current authors.[13,14] Described in more detail below, it uses certified