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Novel Methods and Technologies for 21st-Century Clinical Trials:

A Review

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Abstract

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IMPORTANCE—New technologies are rapidly reshaping health care. However, their effect on drug development to date generally has been limited.

OBJECTIVES—To evaluate disease modeling and simulation, alternative study design, novel objective measures, virtual research visits, and enhanced participant engagement and to examine their potential effects as methods and tools on clinical trials.

EVIDENCE REVIEW—We conducted a systematic search of relevant terms on PubMed (*disease modeling and clinical trials; adaptive design, clinical trials, and neurology; Internet, clinical trials, and neurology; and telemedicine, clinical trials, and neurology*), references of previous publications, and our files. The search encompassed articles published from January 1, 2000, through November 30, 2014, and produced 7976 articles, of which 22 were determined to be relevant and are included in this review.

FINDINGS—Few of these new methods and technologies have been applied to neurology clinical trials. Clinical outcomes, including cognitive and stroke outcomes, increasingly are captured remotely. Other therapeutic areas have successfully implemented many of these tools and technologies, including web-enabled clinical trials.

CONCLUSIONS AND RELEVANCE—Increased use of new tools and approaches in future clinical trials can enhance the design, improve the assessment, and engage participants in the evaluation of novel therapies for neurologic disorders.

The cost of successful development of a new compound is rising, with recent estimates exceeding \$1 billion.^{1,2} The primary driver of the rising costs is clinical costs, especially clinical trials, which increased 10-fold from 1991 through 2003 (**Figure 1**).³ Cash outlays are important, but the primary driver for the rising economic costs of drug development is time.³

The rising costs have not led to the availability of more drugs.⁴ The resulting decline in productivity in drug development began in the 1950s and continues.⁵ Although much of the world follows the Moore law on the doubling of output (eg, computing power) per unit cost every 2 years,⁶ drug development and clinical trials are moving in the opposite direction. While the productivity of drug development is decreasing, the understanding of the etiopathogenesis of disease and the number of therapeutic targets is rapidly increasing. To capitalize on these opportunities, clinical trials must change.

Fortunately, new methods, tools, and approaches—often enabled by technological advances—are increasingly available to bring clinical trials into the 21st century (**Table 1**). This review focuses on the following 5 such advances: disease modeling and simulation, alternative trial designs, novel objective outcome measures, virtual research visits, and engagement of research participants. Although not exhaustive, these 5 advances have the potential to decrease the cost and time required to determine whether novel interventions are safe and efficacious.

We conducted a systematic search of relevant terms on PubMed (*disease modeling and clinical trials; adaptive design, clinical trials, and neurology; Internet, clinical trials, and neurology; and telemedicine, clinical trials, and neurology*), references of previous

publications, and our files. The search encompassed articles published from January 1, 2000, through November 30, 2014, and produced 7976 articles, of which 22 were determined to be relevant and are included in this review.

Disease Modeling and Simulation to Facilitate Design of Clinical Trials

Clinical trials are complex and dynamic systems that depend on biological, pharmacologic, and trial-related components. Unlike other industries (eg, aerospace) that have costly and rigorous manufacturing practices, clinical trials historically have not used analytic model-based approaches. However, modeling and simulation have increased in the past several years as a means to increase the efficiency of drug development.^{7,8}

Clinical trial simulations test various clinical trial scenarios before commencing a trial and calculate the probability of a specific outcome. These simulations are based on models of disease and drug trials. Disease progression models quantify the natural history of disease (**Figure 2**). Pharmacokinetic and pharmacodynamic models describe the temporal relationship between dose concentration and effect. Trial design models include specific study design features (eg, entry criteria) and assumptions (eg, adherence to a drug regimen).

By evaluating the shape and variance of disease progression, models can better estimate the trajectory of disease and identify factors that contribute to variance.⁹ For example, a nonlinear model describing the progression of amyotrophic lateral sclerosis predicted individuals as having slow or rapid progression based on 4 weeks of initial evaluation. These estimated trajectories can then be used for stratification and enrichment strategies based on progression rate status (ie, fast vs slow) in future trials.¹⁰ Quantitative models for Alzheimer disease, bipolar disorder, and Parkinson disease are now available for clinical trial planning purposes from the US Food and Drug Administration (FDA).¹¹

Regulators and industry are now embracing modeling and simulation. For the first time, the FDA has deemed a clinical trial simulation model for Alzheimer disease “fit for purpose” as a quantitative tool for planning future clinical trials related to study design selection and inclusion criteria.¹¹ For example, a disease model describing longitudinal changes in the Cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-cog) is available to simulate the natural progression of disease as well as progression of the placebo and active treatment arms. This information can be used in simulations to test variables of the study design, such as sample size estimations, power, and bias between competing study designs (eg, crossover vs parallel studies) based on assumptions of a drug having symptomatic or disease-modifying effects.¹¹ Future models are likely to build on and refine the models for Alzheimer disease, Parkinson disease, and other disorders.

Alternative Designs to Speed the Development of Drugs and to Lower Costs

Traditional clinical drug development progresses from “learning” to “confirming”^{12(p275)} and is reflected in successive phases 1, 2, and 3 trials. Although this generalization is overly simplistic, the process highlights some problems. By performing initial safety and

pharmacokinetic (phase 1) testing in healthy populations vs those with the disease, investigators may miss important interactions until phase 2. Next, the effort to identify and recruit research participants for phase 2 studies is often duplicated in phase 3. Finally, phase 3 confirmatory trials are often launched without an adequate understanding of responsive subpopulations because phase 2 studies are generally underpowered to identify treatment-response interactions.

More contemporary trial methods exist to address these issues and have been evaluated¹³ and implemented¹⁴ in neurologic conditions. Phase 1 testing, for example, to identify the maximal tolerated dosage, can be performed in individuals with the disease. Specific trial methods, such as the continual reassessment method,¹⁵ can include features to control risk, to identify the maximal tolerated dosage more efficiently, and to study dosages closer to that dosage than typical algorithmic 3 + 3 designs.¹⁶

Phase 2 studies have also seen the rise of novel trial methods, including nonsuperiority designs, adaptive randomization designs, and integrated phases 2 and 3 studies. An example of a responsive-adaptive trial design is the Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis (I-SPY 2) trial in breast cancer.¹⁷ Efficiencies are obtained from simultaneous assessment of multiple neoadjuvant therapies and identification of responsive subpopulations based on clinical, biomarker, or genetic characteristics. As the trial progresses, positive responses are identified, the randomization process directs individuals toward potentially effective therapies, and noneffective therapies are stopped.

Nonsuperiority designs are another approach to eliminating ineffective therapies efficiently. In nonsuperiority studies, the natural history of the disease is known, and interventions that cannot improve on that expectation by a fixed amount (eg, 20%) are considered not worthy of future investigation (ie, nonsuperior).¹⁴ Failure to find nonsuperiority does not guarantee future success, but nonsuperiority provides a strong signal to abandon development.

Recruitment is a great time burden and is often duplicated in separate phases 2 and 3 trials. Novel ways to include participants already enrolled in a single trial for phases 2 and 3 purposes would be efficient. Embedding a series of phase 2–like analyses in a large phase 3 confirmatory trial is an example. Assessment of safety could occur after relatively few participants are recruited, and an analysis for nonsuperiority could be conducted later. Both analyses could stop a trial that is unsafe or likely to fail. Neither analysis would be used to stop the trial for efficacy, so the penalty to preserve statistical power is minor.

Novel Objective and Sensitive Clinical Measures to Detect Efficacy Signals More Rapidly

Many measures in neurology clinical trials have significant limitations (Table 1). Consequently, trials, especially for neurodegenerative conditions, require large sample sizes and long durations that have a high risk for failure of efficacy.¹⁸ For example, two of the largest clinical trials ever in Huntington disease^{19,20} and the largest trial in Parkinson disease²¹ were all recently stopped early for futility.

Although biomarkers, especially imaging, have made considerable progress in the evaluation of outcomes (eg, for multiple sclerosis), they are also critical for confirming engagement of the relevant biological target in phase 2 studies. When applied in phase 2 studies, such measures can determine whether the short-term effects of target engagement reflect predictions from preclinical studies. Absent such assessments, an interventional drug may fail in phase 3 owing to lack of efficacy simply because the target is not engaged as expected.

In addition to assessing biological activity, objective and sensitive outcome measures can augment currently used measures to determine whether an intervention is efficacious.²² Although rating scales (eg, the Unified Parkinson's Disease Rating Scale²³) have been used to gain FDA approval of many drugs, their results are observer dependent and thus subjective.²⁴ Objective measures are in various stages of development to address these shortcomings.^{25,26} Cross-sectional²⁷ and longitudinal analyses²⁸ of such assessments have demonstrated their ability to objectively quantify functional decline. For example, in Parkinson disease, sophisticated mathematical analysis of voice recordings can track disease progression.²⁹

In addition to their subjectivity, many current outcome measures for amyotrophic lateral sclerosis,²⁶ epilepsy,³⁰ multiple sclerosis, and prodromal periods of disease (eg, Alzheimer disease) are insensitive. For example, approximately 50% of seizures recorded during video electroencephalographic monitoring are unknown to patients and thus cannot be documented in seizure diaries.³⁰ More recent studies have shown that the seizures reported by patients and those that are detected by implantable devices do not match.^{31,32} Use of sensors, including accelerometers to assess seizures in epilepsy³⁰ and gait in multiple sclerosis,³³ is increasing; these sensors may be more sensitive to change than conventional clinical ratings.²⁵

These measures have the additional benefit that they can be assessed frequently and outside the clinic. At present, most clinical trial assessments are performed in the clinic under artificial (although often standardized) conditions at certain study intervals. Such episodic assessments are commonly used even when fluctuations (eg, in Parkinson disease) are key disease features.

Passive remote monitoring will allow increasing detection of events that are currently undetectable. Wearable sensors can now monitor tremor for as long as 10 hours daily.³⁴ Remote measurement of daily computer use can detect mild cognitive impairment,³⁵ and smartphones can map out the geographic area where individuals with Parkinson disease live.³⁶ Potentially more powerful applications are on the horizon.³⁷ For example, implantable devices in individuals with drug-resistant epilepsy increasingly can predict seizures and alert patients.³¹

Beyond neurology, passive continuous monitoring has progressed to routine use in trials and care in cardiology. Remote monitoring of implantable cardiac devices, such as defibrillators and pacemakers, has led to more rapid detection of potential adverse events,³⁸ greater retention of patients,³⁹ and improved care.⁴⁰ A new cardiology study⁴¹ will use an inserted

cardiac monitor to detect potentially occult atrial fibrillation, and the primary outcome measure in an antiarrhythmic trial is the frequency of atrial fibrillation as detected by pacemakers.⁴² Evaluating new objective measures in neurology alongside traditional clinical measures in observational studies, and, importantly, in early-state clinical (eg, phase 2) trials will be critical to determining their sensitivity and value.

Virtual Research Visits to Increase Reach and to Lower Cost

Owing to increasingly ubiquitous and inexpensive telecommunications technology, telemedicine allows patients to connect to physicians almost anywhere. In research, virtual visits, which can occur by telephone, video, or asynchronous communication platforms, such as texting, can facilitate greater participation, decrease burden on the participants, and reduce variability in assessments. More generally, assessments of clinical outcomes, including for stroke, are increasingly captured by remote means.⁴³ In addition, for research purposes, virtual research visits (eg, web-based surveys, telephone calls, and field research) that do not provide health care are generally not subject to state medical licensing laws that typically define telemedicine as the “delivery of clinical health care services.”⁴⁴

One major reason for the low rate of participation in clinical trials is the need for frequent in-person visits and the resulting time and travel costs,⁴⁵ which can be reduced with virtual visits. In a study of Parkinson disease, a single site conducted clinical assessments of 50 individuals in 23 states remotely through web-based video conferencing to verify self-reported diagnoses and conduct standardized assessments of cognition and motor function. Such a study would typically require multiple sites, institutional review board approval, contracts, and considerable time. Instead, this single-site study completed the assessments in less than 3 months. In stroke, where telemedicine has dramatically changed care, similar technology is being used to enroll research participants in stroke trials.^{46,47}

These approaches could be especially powerful for rare conditions for which typical studies involve air travel to research centers. In addition, virtual visits could facilitate participation in clinical trials for populations who, because of disability, cannot participate otherwise. A study of Alzheimer disease found that home visits were the factor most likely to enable greater participation in clinical trials.⁴⁸ Although virtual visits are unlikely to supplant in-person visits altogether, they could assess the natural history of rare conditions and carriers of specific genetic mutations. Video visits could also augment existing audio calls as interim safety assessments or decrease the number of in-person interim assessments in clinical trials. An upcoming clinical trial of lisinopril in multiple sclerosis will have 10 visits, of which only 2 will be in person (John Holland, BA, AMC Health and Transparency Life Sciences, written communication, August 19, 2014). Virtual visits can also be applied to extend the observation of individuals who have completed a clinical trial, and such an approach has already been applied using the telephone.⁴⁹

Finally, virtual visits can enable centralized rating of disease states and reduce variability. The feasibility and reliability of remote video assessments has been demonstrated for a wide range of conditions, including stroke, Parkinson disease,⁵⁰ and Batten disease.⁵¹ Centralized rating for many psychiatric assessments can reduce measurement error in clinical trials.⁵²

Greater Participant Engagement to Generate Multiple Secondary Benefits

Perhaps the greatest change in the conduct of future clinical trials will be the role of the research participant. Traditionally, research participants have been viewed and treated as passive subjects on whom procedures were conducted and from whom data were obtained. As such, participants had no role in a study's design or conduct, and, despite exposing themselves to health risks, they were not informed of study results, including those outcomes with adverse health consequences.⁵³⁻⁵⁵ The passive role of study participants is changing to an increasingly active one that includes expanded roles as participant, designer, sponsor, organizer, and investigator.

Clinical trials increasingly are including participant-reported outcomes in addition to those rated by investigators. The National Institutes of Health funded the development and validation of the Patient Reported Outcome Measurement Information System (PROMIS) for general use,⁵⁶ and the National Institute of Neurological and Communicative Diseases and Stroke funded a neurologic quality-of-life measure (Neuro-QOL), a neurology-specific off-shoot of PROMIS.⁵⁷ These patient-reported outcomes are increasingly desired by the FDA,⁵⁸ and their development often reflects considerable input from patients.⁵⁹

While the role of participants is expanding within trials, greater changes are occurring outside trials. Individuals or families affected by the disease increasingly take roles traditionally left to government, foundations, industry, and researchers. Unwilling to be neglected and frustrated by the slow pace of innovation, patients and their communities are funding, organizing, and even conducting their own clinical trials.^{60,61} Parents of children with Duchenne muscular dystrophy recently drafted an FDA guidance on clinical trials for children with the disorder.⁶² Even publicly funded research organizations are providing patients with an unprecedented voice in research. The newly created Patient-Centered Outcomes Research Institute⁶³ explicitly requires that all studies engage participants in the study's design and conduct. In some cases, the lead investigator is not a traditional researcher but a patient. Such models of citizen-researchers are proliferating globally.⁶⁴

The expanded role and engagement of research participants is not a threat but an opportunity. Some of medicine's greatest advances in the 20th century, including a vaccine for poliovirus and effective treatments for human immunodeficiency virus infection, have arisen from the demands and engagement of the public (eg, March of Dimes⁶⁵) and patients (eg, activists for AIDS⁶⁶). Greater access to knowledge and people (from investigators to similar patients) is fueling this change. Although unrealistic expectations and lack of familiarity with the research process are potential challenges, the public overwhelmingly supports clinical research⁶⁷ and is the ultimate beneficiary of its advances. Research participants are a powerful force for change; while these expanded roles are increasing in rare disorders, they have the opportunity to expand to more common disorders (eg, autism) in which patient communities are exceptionally well organized.

Glimpses of the Future

A few innovative studies have implemented virtual clinical trials that encompass several of the methods and technologies described herein (**Table 2**).⁶⁸⁻⁷² More than a decade ago, the

BMJ published the results of a feasibility study of an online randomized clinical trial of glucosamine.⁷³ The investigators conducted a 14-week, Internet-based, placebo-controlled study in 205 individuals with osteoarthritis of the knee. Individuals were recruited online and received a mailed copy of a consent form and medical records release to confirm the diagnosis. Participants also completed online pain assessments and received the study drug by mail. No difference was found between patients in the online study and those in previous investigations.⁷³ The estimated cost of this pioneering study was half that of a traditional study owing to savings of space, labor, and travel. The study limitations included the time required to obtain consent and medical records, the components of the study that were not Internet based.

Another more recent 21st-century clinical trial was conducted by members of an online patient community called PatientsLikeMe (<http://www.patientslikeme.com/>). PatientsLikeMe provides a forum for individuals, predominantly those with chronic disorders, to discuss their conditions, report on their treatments, and measure their own symptoms. The community of individuals with amyotrophic lateral sclerosis recently organized itself to conduct a controlled study of lithium.⁷¹ The self-reported data on the ALS Functional Rating Scale (<http://www.outcomes-umassmed.org/als/alsscale.aspx>) of 149 participants who took lithium for 12 months were compared with data from a matched control population of 447 individuals. After 12 months of treatment, no effect of lithium on disease progression was observed.⁷¹ The study design, while clearly limited, offered the advantage of speed (the time from initiation of the study to preliminary results was 9 months), access to widely dispersed patients, and a large pool of control participants. Its limitations, including missing data, losses to inadequate follow-up, and lack of an independent rater, highlight the substantial work that remains.⁷¹ Moreover, the value of such approaches should be assessed in interventions that are known to be beneficial.

A third proof-of-concept study was a postmarketing trial. Pfizer Inc sought to evaluate whether it could replicate findings on the efficacy of the extended-release formulation of tolterodine tartrate for the treatment of overactive bladder in an entirely web-based approach to a randomized clinical trial.⁷² The investigators found that most elements of the virtual study (eTable in the Supplement), including online consent, online identity verification, dispensing of study medication, remote collection of specimens, reporting of efficacy assessments via mobile phones, and offering participants access to their electronic clinical data, worked well. However, the study was concluded prematurely because of low participant enrollment,⁷² which may have been driven by the absence of trusted clinicians or investigators involved in the recruitment process. Although most of these trials are outside the field of neurology, they provide a guide as to what is possible and what is likely to come.

Future Directions

The methods, tools, and approaches to 21st-century clinical trials are largely disruptive. In *The Innovator's Dilemma*, Christensen⁷⁴ points out that disruptive technologies are generally viewed as inferior and cheap and are treated with skepticism by the establishment. Similarly, these novel approaches to clinical trials will be met with skepticism and will not readily integrate into the currently established processes and values of drug development.⁷⁴

Many of these approaches (eg, virtual visits) will be perceived as inferior to current criterion standards. Indeed, disruptive approaches and technologies (eg, digital cameras) initially enter the lower end of the market.⁷⁴ In clinical trials, disease modeling, alternative trial designs, remote assessments, and web-based clinical trials generally have evaluated safe interventions (eg, glucosamine). In addition, like many disruptive approaches, these trials have generated their results at much lower costs than those of conventional trials.^{70,71,73} Finally, many new entrants, such as PatientsLikeMe and Transparency Life Sciences, a drug development company based on open innovation that uses crowdsourcing and mobile health technology, are leading this disruption.

However, interest in disrupting the current model is not limited to new entrants. Large pharmaceutical firms, notably Eli Lilly and Company⁶⁹ and Pfizer Inc,⁷² have invested in developing web-based approaches that include greater participant engagement and remote assessments. The FDA is also willing to support such novel approaches.⁷² In the end, the status quo of declining productivity of drug development is in no one's interest. New approaches to drug development and clinical trials are needed. The approaches described herein can enhance the design, improve the assessment, and engage the participants in the development of novel therapies at a time when the potential for therapeutic advances is greater than ever.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. DiMasi JA, Grabowski HG. The cost of biopharmaceutical R&D: is biotech different? *Manage Decis Econ*. 2007; 28(4-5):469–479.
2. Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov*. 2010; 9(3):203–214. [PubMed: 20168317]
3. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003; 22(2):151–185. [PubMed: 12606142]
4. US Food and Drug Administration. 2013 Novel New Drugs Summary. US Food and Drug Administration; Silver Spring, MD: 2014.
5. Booth B, Zimmel R. Prospects for productivity. *Nat Rev Drug Discov*. 2004; 3(5):451–456. [PubMed: 15136792]
6. Moore GE. Cramming more components onto integrated circuits. *Electronics*. 1965; 38(8):114–117.
7. Milligan PA, Brown MJ, Marchant B, et al. Model-based drug development: a rational approach to efficiently accelerate drug development. *Clin Pharmacol Ther*. 2013; 93(6):502–514. [PubMed: 23588322]
8. Holford NH, Nutt JG. Interpreting the results of Parkinson's disease clinical trials: time for a change. *Mov Disord*. 2011; 26(4):569–577. [PubMed: 21370266]
9. Mould DR. Models for disease progression: new approaches and uses. *Clin Pharmacol Ther*. 2012; 92(1):125–131. [PubMed: 22617225]
10. Gomeni R, Fava M. Pooled Resource Open-Access ALS Clinical Trials Consortium. Amyotrophic lateral sclerosis disease progression model. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014; 15(1-2):119–129. [PubMed: 24070404]
11. US Food and Drug Administration. Disease Specific Model Library. <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180485.htm>. Accessed June 24, 2014
12. Sheiner LB. Learning versus confirming in clinical drug development. *Clin Pharmacol Ther*. 1997; 61(3):275–291. [PubMed: 9084453]
13. Chataway J, Nicholas R, Todd S, et al. A novel adaptive design strategy increases the efficiency of clinical trials in secondary progressive multiple sclerosis. *Mult Scler*. 2011; 17(1):81–88. [PubMed: 20798135]
14. Kaufmann P, Thompson JL, Levy G, et al. QALS Study Group. Phase II trial of CoQ10 for ALS finds insufficient evidence to justify phase III. *Ann Neurol*. 2009; 66(2):235–244. [PubMed: 19743457]
15. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics*. 1990; 46(1):33–48. [PubMed: 2350571]
16. Iasonos A, Wilton AS, Reidel ER, Seshan VE, Spriggs DR. A comprehensive comparison of the continual reassessment method to the standard 3 + 3 dose escalation scheme in Phase I dose-finding studies. *Clin Trials*. 2008; 5(5):465–477. [PubMed: 18827039]
17. I-SPY 2 Trial. <http://ispy2.org/>. Accessed June 10, 2014
18. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really 802 million dollars? *Health Aff (Millwood)*. 2006; 25(2):420–428. [PubMed: 16522582]
19. Huntington Study Group. Announcement of 2CARE early study closure [press release]. 2014. <http://www.huntington-study-group.org/LinkClick.aspx?fileticket=LurnLVT3rw%3d&tabid=95>. Accessed August 22, 2014
20. Huntington Study Group. Announcement of CREST-E early study closure [press release]. 2014. <http://www.huntington-study-group.org/CurrentClinicalTrials/CRESTE/CRESTEOctober2014PressRelease/tabid/316/Default.aspx>. Accessed November 19, 2014
21. Statement on the termination of NET-PD LS-1 study. 2013. <http://parkinsontrial.ninds.nih.gov/netpd-LS1-study-termination.htm>. Accessed June 25, 2014
22. Elias T, Gordian M, Singh N, Zimmel R. Why products fail in phase III. *In Vivo*. 2006; 24:49–54.
23. Fahn, S.; Elton, R. Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn, S.; Marsden, C.; Caine, D.; Goldstein, M., editors. *Recent Developments in*

- Parkinson's Disease. Vol. 2. Macmillan Health Care Information; Florham Park, NJ: 1987. p. 153-163.
24. Reilmann R, Bohlen S, Kirsten F, Ringelstein EB, Lange HW. Assessment of involuntary choreatic movements in Huntington's disease: toward objective and quantitative measures. *Mov Disord*. 2011; 26(12):2267–2273. [PubMed: 21661053]
 25. Heldman DA, Espay AJ, LeWitt PA, Giuffrida JP. Clinician versus machine: reliability and responsiveness of motor endpoints in Parkinson's disease. *Parkinsonism Relat Disord*. 2014; 20(6):590–595. [PubMed: 24661464]
 26. Andres PL, English R, Mendoza M, et al. Developing normalized strength scores for neuromuscular research. *Muscle Nerve*. 2013; 47(2):177–182. [PubMed: 23168880]
 27. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. TRACK-HD investigators. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol*. 2009; 8(9):791–801. [PubMed: 19646924]
 28. Tabrizi SJ, Scahill RI, Owen G, et al. TRACK-HD Investigators. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol*. 2013; 12(7):637–649. [PubMed: 23664844]
 29. Tsanas A, Little MA, McSharry PE, Ramig LO. Accurate telemonitoring of Parkinson's disease progression by noninvasive speech tests. *IEEE Trans Biomed Eng*. 2010; 57(4):884–893. [PubMed: 19932995]
 30. Fisher RS, Blum DE, DiVentura B, et al. Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav*. 2012; 24(3):304–310. [PubMed: 22652423]
 31. Cook MJ, O'Brien TJ, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol*. 2013; 12(6):563–571. [PubMed: 23642342]
 32. Holmes D. Can technology reveal the natural history of epilepsy? *Lancet Neurol*. 2014; 13(4):347–348. [PubMed: 24646869]
 33. Weikert M, Suh Y, Lane A, et al. Accelerometry is associated with walking mobility, not physical activity, in persons with multiple sclerosis. *Med Eng Phys*. 2012; 34(5):590–597. [PubMed: 21968005]
 34. Pulliam CL, Eichenseer SR, Goetz CG, et al. Continuous in-home monitoring of essential tremor. *Parkinsonism Relat Disord*. 2014; 20(1):37–40. [PubMed: 24126021]
 35. Kaye J, Mattek N, Dodge HH, et al. Unobtrusive measurement of daily computer use to detect mild cognitive impairment. *Alzheimers Dement*. 2014; 10(1):10–17. [PubMed: 23688576]
 36. Grajales FJ III, Sheps S, Ho K, Novak-Lauscher H, Eysenbach G. Social media: a review and tutorial of applications in medicine and health care. *J Med Internet Res*. 2014; 16(2):e13. doi: 10.2196/jmir.2912. [PubMed: 24518354]
 37. The Michael J. Fox Foundation and Intel join forces to improve Parkinson's disease monitoring and treatment through advanced technologies [press release]. <https://www.michaeljfox.org/foundation/publication-detail.html?id=555&category=7>. Accessed August 13, 2014
 38. Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH, CONNECT Investigators. The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) trial: the value of wireless remote monitoring with automatic clinician alerts. *J Am Coll Cardiol*. 2011; 57(10):1181–1189. [PubMed: 21255955]
 39. Varma N, Michalski J, Stambler B, Pavri BB, TRUST Investigators. Superiority of automatic remote monitoring compared with in-person evaluation for scheduled ICD follow-up in the TRUST trial: testing execution of the recommendations. *Eur Heart J*. 2014; 35(20):1345–1352. [PubMed: 24595864]
 40. Mabo P, Victor F, Bazin P, et al. COMPAS Trial Investigators. A randomized trial of long-term remote monitoring of pacemaker recipients (the COMPAS trial). *Eur Heart J*. 2012; 33(9):1105–1111. [PubMed: 22127418]
 41. Reiffel J, Verma A, Halperin JL, et al. Rationale and design of REVEAL AF: a prospective study of previously undiagnosed atrial fibrillation as documented by an insertable cardiac monitor in high-risk patients. *Am Heart J*. 2014; 167(1):22–27. [PubMed: 24332138]

42. Ezekowitz MD, Nagarakanti R, Lubinski A, et al. PASCAL Investigators. A randomized trial of bupropion in paroxysmal atrial fibrillation. *J Interv Card Electrophysiol*. 2012; 34(1):1–9. [PubMed: 22205496]
43. Saposnik G, Reeves MJ, Johnston SC, Bath PM, Ovbiagele B, VISTA Collaboration. Predicting clinical outcomes after thrombolysis using the iScore: results from the Virtual International Stroke Trials Archive. *Stroke*. 2013; 44(10):2755–2759. [PubMed: 23887844]
44. Center for Connected Health Care Policy. Telehealth policy. 2014. <http://cchpca.org/jurisdiction/12>. Accessed November 19, 2014
45. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol*. 1999; 52(12):1143–1156. [PubMed: 10580777]
46. Alfredo Caceres J, Greer DM, Goldstein JN, et al. Enrollment of research subjects through telemedicine networks in a multicenter acute intracerebral hemorrhage clinical trial: design and methods. *J Vasc Interv Neurol*. 2014; 7(3):34–40. [PubMed: 25298858]
47. Silva GS, Schwamm LH. Use of telemedicine and other strategies to increase the number of patients that may be treated with intravenous thrombolysis. *Curr Neurol Neurosci Rep*. 2012; 12(1):10–16. [PubMed: 21997715]
48. Karlawish J, Cary MS, Rubright J, Tenhave T. How redesigning AD clinical trials might increase study partners' willingness to participate. *Neurology*. 2008; 71(23):1883–1888. [PubMed: 19047560]
49. Tanner CM, Meng CC, Ravina B, et al. A practical approach to remote longitudinal follow-up of Parkinson's disease: the FOUND study. *Mov Disord*. 2014; 29(6):743–749. [PubMed: 24515275]
50. Achey M, Aldred JL, Aljehani N, et al. International Parkinson and Movement Disorder Society Telemedicine Task Force. The past, present, and future of telemedicine for Parkinson's disease. *Mov Disord*. 2014; 29(7):871–883. [PubMed: 24838316]
51. Cialone J, Augustine EF, Newhouse N, Vierhile A, Marshall FJ, Mink JW. Quantitative telemedicine ratings in Batten disease: implications for rare disease research. *Neurology*. 2011; 77(20):1808–1811. [PubMed: 22013181]
52. Kobak KA, Leuchter A, DeBrot D, et al. Site versus centralized raters in a clinical depression trial: impact on patient selection and placebo response. *J Clin Psychopharmacol*. 2010; 30(2):193–197. [PubMed: 20520295]
53. Partridge AH, Winer EP. Informing clinical trial participants about study results. *JAMA*. 2002; 288(3):363–365. [PubMed: 12117402]
54. Dorsey ER, Beck CA, Adams M, et al. Huntington Study Group TREND-HD Investigators. Communicating clinical trial results to research participants. *Arch Neurol*. 2008; 65(12):1590–1595. [PubMed: 19064746]
55. Berenson, A. After a trial, silence. *New York Times*. Nov 21, 2007 <http://query.nytimes.com/gst/fullpage.html?res=950CE6DC1330F932A15752C1A9619C8B63&smid=pl-share>. Accessed June 25, 2014
56. PROMIS. Dynamic Tools to Measure Health Outcomes From the Patient Perspective. Home page. <http://www.nihpromis.org/?AspxAutoDetectCookieSupport=1#4>. Published 2014. Accessed August 7, 2014
57. Neuro-QoL. Quality of Life in Neurological Disorders. 2014. <http://www.neuroqol.org/Pages/default.aspx>. Accessed August 7, 2014
58. US Department of Health and Human Services Food and Drug Administration. Guidance for Industry-Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>. Published December 2009. Accessed June 3, 2014
59. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. *Value Health*. 2007; 10(suppl 2):S125–S137. [PubMed: 17995471]
60. Landro, L. Services match patients with clinical trials. *Wall Street Journal*. Apr 23, 2012 <http://online.wsj.com/news/articles/SB10001424052702303459004577361972881249382>. Accessed June 3, 2014

61. Marcus, AD. Frustrated ALS patients concoct their own drug. Wall Street Journal. Apr 15. 2012 <http://www.wsj.com/news/articles/SB10001424052702304818404577345953943484054?mg=reno64-ws>. Accessed June 25, 2014
62. Parent Project Muscular Dystrophy. The Duchenne community imperatives for the guidance for industry on Duchenne muscular dystrophy: developing drugs for treatment over the spectrum of disease. http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_fdaguidance. Published June 25, 2014. Accessed August 22, 2014
63. Selby JV, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. JAMA. 2012; 307(15):1583–1584. [PubMed: 22511682]
64. Riggare, S. Sara: Not Patient but Im-Patient [blog]. <http://www.riggare.se/>. Accessed June 3, 2014
65. Helfand WH, Lazarus J, Theerman P. “...So that others may walk”: the March of Dimes. Am J Public Health. 2001; 91(8):1190. [PubMed: 11499100]
66. De Cock KM, Jaffe HW, Curran JW. Reflections on 30 years of AIDS. Emerg Infect Dis. 2011; 17(6):1044–1048. [PubMed: 21749766]
67. Research America. An Alliance for Discoveries in Health; America Speaks. 2014. p. 14 <http://www.researchamerica.org/uploads/AmericaSpeaksV14.pdf>. Accessed June 25, 2014
68. McAlindon T. Why are clinical trials of glucosamine no longer uniformly positive? Rheum Dis Clin North Am. 2003; 29(4):789–801. [PubMed: 14603583]
69. Eilenberg KL, Hoover AM, Rutherford ML, Melfi CA, Segal S. From informed consent through database lock: an interactive clinical trial conducted using the Internet. Drug Inf J. 2004; 38(3): 239–251.
70. Jacobs BP, Bent S, Tice JA, Blackwell T, Cummings SR. An internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. Medicine (Baltimore). 2005; 84(4): 197–207. [PubMed: 16010204]
71. Wicks P, Vaughan TE, Massagli MP, Heywood J. Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm. Nat Biotechnol. 2011; 29(5):411–414. [PubMed: 21516084]
72. Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. Contemp Clin Trials. 2014; 38(2):190–197. [PubMed: 24792229]
73. McAlindon T, Formica M, Kabbara K, LaValley M, Lehmer M. Conducting clinical trials over the internet: feasibility study. BMJ. 2003; 327(7413):484–487. [PubMed: 12946971]
74. Christensen, CM. The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail. Harvard Business School Press; Boston, MA: 1997.

Figure 1. Preclinical and Clinical Drug Development Costs

The total cost of research and development cost (in 2000 US dollars) per approved new drug has increased dramatically during the past 3 decades, with the most notable cost increases occurring in the clinical phases. Data are obtained from DiMasi et al.³

Figure 2. Disease-Drug Trial Models

Clinical trial modeling and simulation help to optimize trial designs by investigating assumptions and variability of different factors that affect trial performance. Disease progression models quantify changes in disease status over time, typically in the untreated state. Pharmacokinetic models represent the time course of drug disposition in the body. Pharmacodynamic models characterize the exposure-response relationship of the drug. Together, these models are integrated and applied to simulate different trial scenarios (eg, power calculations, dosing strategies, and trial execution) for predictive purposes. Curves represent interaction between both variables.

Table 1

Characteristics of 20th- vs 21st-Century Clinical Trials

Characteristic	20th Century	21st Century
Study design	Randomized, double-blind, parallel-group, placebo-controlled trial	Randomized, double-blind, parallel-group, placebo-controlled trial using adaptive designs
Study population	All comers with a given disease	Individuals selected based on phenotypic and genetic results
Study recruitment	Clinical practices	Global clinical trial registries and social networks organized by individuals affected by the disease
Trial visits	In person and audio calls	In person and audio and video calls
Data management	Paper and electronic forms	Electronic forms
Participant feedback	Limited, delayed	Almost universal, approximately real time
Outcome measures	Insensitive	Sensitive
	Episodic	Frequent or continuous
	Subjective	Objective
	Provider centered	Patient centered
	In clinic	Remote
	Unidimensional	Multidimensional

Table 2

Characteristics of Select Web-Based Clinical Trials

Source	Design	Intervention	No. of Participants	In-Person Visits	Web-Based Recruitment	Web-Based Enrollment	Web-Based Consent	Web-Based Outcome Measures	Results Consistent With Traditional Trials
McAlindon, ⁶⁸ 2003	Randomized, double-blind, placebo-controlled trial	Glucosamine for osteoarthritis of the knee	205	No	Partial, plus magazine advertisements	Partial, plus review of medical records and radiograms	No	Yes	Yes
Eilenberg et al, ⁶⁹ 2004	Randomized, double-blind, placebo-controlled trial	Tadalafil for erectile dysfunction	83	Yes	No	No	Yes	Yes	Yes
Jacobs et al, ⁷⁰ 2005	Randomized, double-blind, placebo-controlled trial	Kava for anxiety and valerian for insomnia	391	No	Yes	Yes	Yes	Yes	Partial; previous results were mixed
Wicks et al, ⁷¹ 2011	Open-label, matched-control, observational study	Lithium for amyotrophic lateral sclerosis	149 Plus 447 matched controls	No	Yes	Yes	NA	Yes	Yes
Orri et al, ⁷² 2014	Randomized, single-blind, placebo-controlled trial	Tolterodine tartrate extended release formulation for overactive bladder	18	No	Yes	Yes	Yes	Yes	Yes

Abbreviation: NA, not applicable.