Virtual Clinical Trials

CHALLENGES AND OPPORTUNITIES

PROCEEDINGS OF A WORKSHOP

Joe Alper, Eeshan Khandekar, and Carolyn Shore, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

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Acronyms and Abbreviations

ALS	amyotrophic lateral sclerosis
CCPA	California's Consumer Privacy Act
CTTI	Clinical Trials Transformation Initiative
CYP2C19	Cytochrome P450 2C19 Enzyme
D2P	direct-to-participant
EHR	electronic health record
FDA	U.S. Food and Drug Administration
GDPR	Global Data Protection Regulation
GWAS	genome-wide association study
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HiMSS	Healthcare Information and Management Systems Society
HIPAA	Health Insurance Portability and Accountability Act
ICD	*International Statistical Classification of Diseases and Related Health Problems*
IRB	Institutional Review Board
LRRK2	leucine-rich repeat kinase gene

MCT	Mobile Clinical Trials
NIH	National Institutes of Health
ONC	The Office of the National Coordinator for Health Information Technology
PCSK9	Proprotein Convertase Substillsin/KexIn Type 9
UNC13A	Unc-13 Homolog A gene
VA	U.S. Department of Veterans Affairs

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Introduction[1]

Clinical trials are a cornerstone of drug development, providing scientific evidence on the safety and efficacy of novel pharmaceutical compounds and informing clinical care. At the same time, traditional clinical trials are slow, expensive, and inefficient (Fogel, 2018). Additionally, given the requirement to travel to trial sites, clinical trials can place time and financial burden on research participants, depending on the number of clinical visits required by the study protocol (Fogel, 2018). Narrow eligibility criteria for participation in clinical trials also creates an issue in that studies may not fully reflect the patient population for which a new therapeutic is intended to treat (i.e., patients in the real world who may receive a specific therapeutic intervention are generally more diverse than study participant cohorts when it comes to age, gender, race, ethnicity, disease severity, or comorbidities) (Blumenthal et al., 2017; Heneghan et al., 2017; Hill et al., 2008). As a result, the link between clinical research and clinical practice is also frequently misunderstood by patients and providers. There is growing recognition by stakeholders from across the clinical trials enterprise that transformational change in the way traditional clinical trials are conducted is needed to address these challenges and meet the needs of patients.

[1] The planning committee's role was limited to planning the workshop, and the Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

An emerging trend in the clinical trial landscape has been the incorporation of digital health technologies—such as mobile devices, mobile apps, remote monitoring devices, and online social engagement platforms—into study design (see Appendixes D and E for examples). Such virtual clinical trials can leverage digital health technologies for collecting information at each stage of the clinical trial, improving trial participant recruitment and retention, enabling online-based informed consent, measuring real-time clinical endpoints, and continuous tracking of adverse events. Digital health technologies may give trial participants a choice of participating from the convenience of the home rather than traveling to a trial site, which can increase participant engagement and retention (Sharma, 2015). This may be particularly important for engaging patients with mobility issues or those who live in rural areas, which can be far from the research centers at which studies are conducted. Additionally, data collected through digital health technologies may enable continuous real-time data collection of endpoints during the course of a trial participant's daily life (Gold et al., 2018) rather than periodic data collection during site visits, which may only offer a snapshot of relevant health information. Researchers and providers can use information collected through digital health technologies to enhance monitoring and improve understanding of treatment effects and disease progression.

Despite the benefits, virtual clinical trials also come with risks, as described by workshop participants:

- Patient privacy concerns, such as the risk of sharing sensitive health information over the Internet, said Deven McGraw from Ciitizen Corporation;
- Operational challenges, such as the lack of community and provider engagement, said Craig Lipset from Pfizer Inc. and Silas Buchanan from the Institute for eHealth Equity;
- Technical barriers, such as the digital health technology user interface, said Donna Cryer from the Global Liver Institute; and
- Cultural barriers, such as concerns over data integrity and fear of technology failing, said Leonard Sacks from the U.S. Food and Drug Administration.

It is important to note that virtual clinical trials are not a "one-size-fits-all" model and only a fraction of clinical trials are fully virtual. In the near term, digital health technologies may only be accepted in a few settings, such as disease areas in which telemedicine is already an accepted practice or for evaluating medical products with a known safety profile and endpoints that can be measured remotely, noted Kimberly Hawkins from Sanofi Genzyme. However, in the longer term, virtual clinical trials have the

potential to streamline the process of drug development and may offer new opportunities for a modern, more patient-centric clinical trial enterprise, noted Lipset and Ray Dorsey from the University of Rochester.

To explore the current clinical trials infrastructure and highlight potential opportunities for supporting the practical implementation of virtual clinical trials, the National Academies of Sciences, Engineering, and Medicine's Forum on Drug Discovery, Development, and Translation (the forum) hosted a 2-day workshop on November 28 and 29, 2018, titled Virtual Clinical Trials: Challenges and Opportunities. Linda Brady of the National Institute of Mental Health, National Institutes of Health, and Clay Johnston of the Dell Medical School, The University of Texas at Austin, opened the workshop by reflecting on the barriers and inefficiencies that currently exist in the clinical trial enterprise and how digital health technologies could be leveraged to address some of these challenges. The following workshop sessions aimed to advance discussions and common knowledge among key stakeholders about opportunities for a modern, patient-centric clinical trials enterprise in light of digital health technologies that could enable virtual clinical trials for new medical product approval (see Box 1-1 for the workshop Statement of Task).

This proceedings builds on a body of related forum work. Proceedings based on previous workshops hosted by the forum include *Examining the Impact of Real-World Evidence on Medical Product Development* (NASEM, 2019), *Advancing the Science of Patient Input in Medical Product R&D: Towards a Research Agenda* (NASEM, 2018a), and *Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020* (IOM, 2012).

DEFINING VIRTUAL CLINICAL TRIALS

For this proceedings, different terms were used by workshop participants to refer to clinical trials in which all or part of the study incorporates digital health technologies and enables remote participation outside of the traditional brick-and-mortar clinical trial site. Johnston observed that although the term "virtual clinical trials" is included in the workshop title, an adequate umbrella term for the variety of clinical trials under discussion is not easy to define. He noted that terms such as "decentralized," "remote," or "site agnostic" may describe some types of trials that incorporate digital health technologies, but many study activities still require a centralized location—a comment that Dorsey made in his presentation (see Chapter 2). Additional terms referred to by workshop participants include "direct-to-participant" (see Chapter 3), "location variable" (see Chapter 2), and "mobile" (see Chapter 5) clinical trials. Each of these terms highlights different aspects of how digital health technologies may be incor-

BOX 1-1
Workshop Statement of Task

Clinical trials are a cornerstone of medical product development—supporting the evaluation of efficacy and identification of safety issues of new drugs—and a necessary regulatory requirement for bringing novel therapies to market. This workshop will examine opportunities for a modern, patient-centric clinical trials enterprise in light of digital health tools that could allow virtual clinical trials (e.g., studies that deploy various digital health tools or virtual site visits) for new medical product approval.

Participants will discuss the current state of the clinical trials enterprise; highlight opportunities for systemic improvements; and discuss mechanisms to facilitate participation in clinical trials, including enhanced collaboration among sponsors, researchers, regulators, patients, providers, and health systems.

Subject-matter experts will be invited to participate in the workshop through presentations and discussions that will:

- Highlight opportunities for systemic improvement to support virtual clinical trials, including
  - Potential implications of virtual trials for cost, speed, regulation, and knowledge generation and dissemination of clinical trials; and
  - Elements of an information technology infrastructure, including integrating data from electronic health records, mobile health applications, remote monitoring, virtual visits, and other relevant technologies with the capability to enhance the interface between clinicians and clinical trial participants.
- Explore potential opportunities to use digital health tools to engage with patients and potential research participants, facilitate recruitment of participants to join a clinical trial, and maintain participation of diverse populations in the trial:
  - Collaborative approaches and incentives involving sponsors, researchers, patient advocacy groups, patients living with the particular condition being studied, and health systems—including regulations, quality measures and outcomes, or reimbursement strategies—to support the implementation of virtual clinical trials; and
  - Opportunities and challenges to enhancing equity in access and participation through virtual clinical trials.

porated into study design. Nomenclature was a topic of discussion during the final session of the workshop (see Chapter 6). While identifying one umbrella term to describe all of the trials discussed at the workshop would be difficult, as noted by Steven Cummings, director of the San Francisco Coordinating Center, individual workshop speakers and participants suggested a few terms, including “flexible,” “modern,” and “21st century” clinical trials.

ORGANIZATION OF THE PROCEEDINGS OF A WORKSHOP

This proceedings is intended to provide a factual summary of the presentations and discussions that took place during the workshop. In accordance with the policies of the National Academies, the workshop did not attempt to establish any conclusions or recommendations and instead focused on the information presented, questions raised, and improvements recommended by individual workshop participants. Chapter 2 summarizes workshop presentations and discussions regarding the inefficiencies of the current clinical trial enterprise, the boundaries of what might be considered a virtual clinical trial for medical product development, the opportunities to expand access for patients, and regulatory questions regarding the remote collection of endpoints. Chapter 3 explores perspectives and experiences with digital health technologies in interventional and observational studies, as well as in clinical care—highlighting the impact on participant recruitment, engagement, and input on research and study design. Chapter 4 discusses how the use of digital health technologies may alleviate or exacerbate access and equity in the context of clinical trials. Chapter 5 reviews the current and future policy landscape governing clinical trials and their relevance for virtual trial methodologies. Chapter 6 presents reflections by the panel moderators on their key takeaways from the workshop and a summary of discussions on possible opportunities for future action.

2

Opportunities to Improve Clinical Trials

Key Messages Identified by Individual Speakers

- A quality clinical trial is one that generates the minimal amount of credible, replicable, and evaluable data needed to answer meaningful questions with the least time and cost burdens on participants. (Cryer)
- Virtual clinical trials can be used to improve the comfort, convenience, and confidentiality for research participants compared with what they might receive in a more traditional site-based clinical trial. (Dorsey)
- Additionally, they offer an opportunity to foster ongoing relationships between researchers and research participants to better understand conditions longitudinally, and generate new and relevant questions. (Cryer)
- Mining data in new ways to better understand which patient populations can and should be enrolled in trials would lead to more realistic inclusion/exclusion criteria and improve patient recruitment and retention. (Cryer)
- Traditional clinical trials rarely answer questions that are of greatest concern to patients, such as whether the treatment will lead to a better life. The development and availability of better endpoints and outcome measures could help meet this need. (Cryer)

- Giving participants the ability to decide on site-based or remote engagement during a clinical trial will require the development of endpoints that are resilient and agnostic to location. (Lipset)
- A virtual trial should engage providers who treat patients in the health care setting in a way that complements the treating physician's practice rather than adding unnecessary burden and responsibility. (Cryer, Lipset)
- Moving toward virtual trials may be a matter of will, and may not merely require a new regulatory or technical framework. (Dorsey, Lipset)

During the first workshop session, a diverse panel of speakers considered the inefficiencies of the current clinical trial enterprise; the boundaries of what might be considered a virtual clinical trial for medical product development; the opportunity of virtual clinical trials to expand access for participants; and regulatory questions regarding the remote collection of endpoints. Donna Cryer, president and chief executive officer (CEO) of the Global Liver Institute, offered a patient perspective on considerations necessary for designing clinical trials to meet the needs of trial participants. Craig Lipset, head of clinical innovation within global product development at Pfizer Inc., provided an industry perspective on the potential for virtual clinical trials to improve the efficiency of Phase 3 clinical research. Ray Dorsey, professor of neurology and director of the Center for Health and Technology at the University of Rochester, provided an academic perspective on the clinical trials landscape and how virtual clinical trials could increase participant access. The session was moderated by Linda Brady and Clay Johnston.

A PATIENT PERSPECTIVE

Donna Cryer, President and CEO, Global Liver Institute

Cryer explained that a quality clinical trial is one that generates the minimal amount of credible, replicable, and evaluable data needed to answer meaningful questions with the least time and cost burdens on participants. At the core of her definition is the hope that trials can generate and use data collected in the day-to-day course of a participant living his or her life or receiving care. In addition, Cryer emphasized the importance of being mindful of the divergence between research-setting and real-world effects. The lack of applicability or generalizability of clinical trial results can be disheartening to patients who did not meet trial inclusion criteria. This can be particularly problematic for patients who rely on treatments

developed from a study from which they would have been excluded, as inclusion criteria are listed on a drug label and can inform reimbursement decisions.

According to Cryer, virtual clinical trials should not be thought of as a separate type of trial, but as a way of thinking about trial design that meets her definition of a "quality clinical trial." Merely addressing the challenges that new technologies can pose, such as computer literacy, would reduce a virtual trial to its underlying technology platform. A more important issue, Cryer proposed, is whether a virtual trial allows the study to operate well from the patients' perspective. For example, scientific questions, as currently framed, may seek to understand if a treatment works. However, they may not address questions about whether the treatment will lead to a better lived experience with a disease. Cryer expressed hope that as more virtual trials are conducted and patient communities are engaged, the quality of endpoints and outcome measurements will be improved in a way that allows questions about a patient's quality of life to be better addressed.

Cryer drew attention to the limited protocol flexibility of clinical trials, which often excludes large groups of patients from trials. Novel data mining techniques can shed light on which patient populations should be included in clinical trials, lead to more realistic inclusion/exclusion criteria, and result in better participant recruitment and retention. The consent process is also an issue, which can often be an "all-or-nothing" form filled with complex jargon. However, as Cryer noted of an Apple Research Kit demonstration, the consent process can be broken into easy to understand, digestible chunks of information, in which consent is serially provided as needed.

Cryer discussed issues related to the number, length, timing, and location of site visits. She agreed with Dorsey that technology can help lessen the burden on participants who have to travel to clinical trial sites, especially because 70 percent of potential trial participants live more than 2 hours away from a study center (Anderson, 2018). Given the availability of wearable technology and other home-based digital health technology, Cryer questioned the need for site-based visits to measure vitals given that these measurements could be collected passively using digital health technology.

The default model for clinical research, Cryer emphasized, should be a virtual trial because it offers an opportunity to foster ongoing relationships with participants, better understand clinical conditions longitudinally, and generate new and relevant research questions.

AN INDUSTRY PERSPECTIVE

Craig Lipset, Head of Clinical Innovation, Global Product Development, Pfizer Inc.

Advances in computing and technology that have expanded health care access for the community can also be applied to the conduct of clinical trials. When doing so, it will be important for industry to consider what aspects of a trial should be centralized (e.g., the investigator, coordinator, labs, or Institutional Review Boards [IRBs]) to achieve the benefits of trial decentralization, such as increased access, improved representation, and decreased burden of participation.

Lipset introduced a 2011 study conducted by Pfizer, REMOTE,[1] which was designed to validate available virtual technologies by repeating a standard brick-and-mortar clinical trial that Pfizer had conducted for Detrol, a drug used to treat overactive bladder. The trial's components (e.g., recruiting patients online and capturing patient-reported outcomes electronically) were not novel at the time. However, the linkage between different components of the study and the introduction of unique components, such as delivering the investigational drug directly to the participant, were new approaches. REMOTE was eventually discontinued because it failed to recruit enough women with a disease severity matching those who participated in the original trial (additional details on challenges leading to early termination can be found on p. 27). However, it did successfully demonstrate the ability to screen and acquire consent from participants, monitor safety, and capture required data to indicate both safety and efficacy.

According to Lipset, the REMOTE trial did not operate at the available limit of technology when it was conducted in 2010, nor did it require any new legislation, safe harbor, or guidance from regulators. As a result, new regulatory or technical frameworks may not be necessary to successfully launch virtual trials. However, Lipset mentioned that even though virtual trials are not limited by U.S. regulatory policies, there is state-by-state variability in regulations regarding telemedicine and Internet prescribing for domestic trials, as well as regulatory variability by country.

Lipset noted that since REMOTE, and mostly over the past 2 to 3 years, the industry has evolved, with well-capitalized companies and contract research organizations entering the virtual space. What seems to be missing, he noted, is movement beyond pilot programs and so-called hybrid protocols that dictate specific "visits" be done remotely to let the participant choose how, when, and where they want to participate. Lipset asserted that the ultimate goal should be protocols that allow participants

[1] Additional information can be found in Appendix D.

to decide whether they want to participate at a site or remotely—what he calls a "location variable" trial.

Accommodating patient desires would require flexible processes based on different patient needs and preferences, but doing so is not impossible. Most patients already have a diagnosis, course of treatment, and a treating physician overseeing their care. Virtual trials could take advantage of this paradigm and complement the clinical position and practice of the treating physician without requiring them to become a clinical investigator. However, more effective engagement between the research and clinical practice communities would depend on the development of endpoints that are more resilient and agnostic to location than those relied on today. A major rate limiter for virtual trials to be conducted and for these benefits to be realized will be a lack of will and culture. Additionally, it is likely, Lipset noted, that cost savings from virtual trials would occur in the long term.

AN ACADEMIC PERSPECTIVE

Ray Dorsey, Director, Center for Health and Technology, University of Rochester

Current Model for Clinical Trials

Clinical trials as currently conducted are expensive, inefficient, and inaccessible. Citing a study conducted by DiMasi and colleagues (2016), Dorsey stated that the cost of drug development has doubled every 12 years, from $200 million in 1979 to $2.6 billion in 2016. At the same time, pharmaceutical industry productivity, in terms of new molecular entities developed, has declined for the past 50 years (Scannell et al., 2012).

Furthermore, Dorsey noted that clinical trials fail to adequately represent the patient population (with trial participation as low as 5 percent for patients with certain conditions[2]) and fail to be participant centered.[3] Participants, who are often sick, have financial and time burdens placed on them to travel to research sites where they volunteer to be exposed to known and unknown risks. This all occurs, Dorsey continued, on the investigator's terms, not the participants' terms.

Dorsey described drug development as "long, inefficient, and likely to fail" (see Figure 2-1). For example, drug development for neurological

[2] Trial participation for patients with cancer typically does not exceed 5 percent (Sacristan et al., 2016).

[3] Participant centered: If a clinical study is participant centered, the burden of participation, such as time spent in travel and in clinics, financial costs associated with travel and missed work, and complications to a person's routine due to additional examinations and procedures, is minimized (Holloway, 2018).

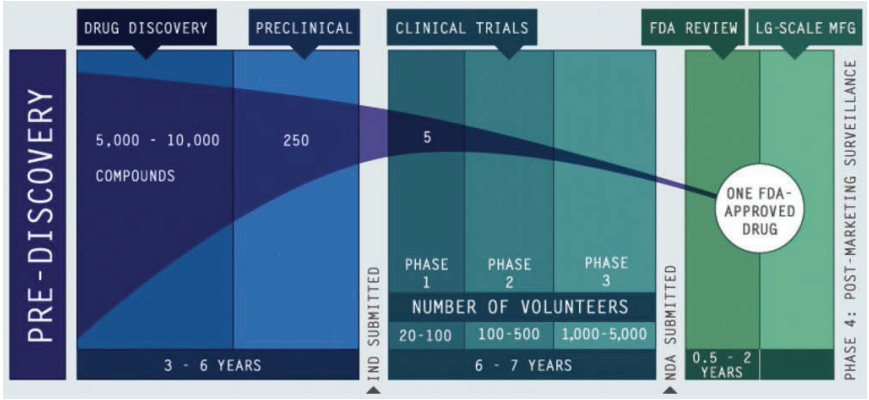

FIGURE 2-1 Drug discovery, development, and approval process.
NOTE: FDA = U.S. Food and Drug Administration; IND = Investigational New Drug; NDA = New Drug Application.
SOURCES: As presented by Ray Dorsey, November 28, 2018; PhRMA, 2012. An updated figure is available at https://www.phrma.org/graphic/the-biopharmaceutical-research-and-development-process (accessed June 25, 2019).

disorders, which are the leading cause of disability in the world (Collins, 2017), is marked by failure,[4] emphasized Dorsey. The mismatch between the burden of neurological disorders and the success rates of drug development indicates there is a need for new tools to be used by industry, noted Dorsey.

New Models for Clinical Trials

The pharmaceutical industry has already begun to leverage emerging digital health technologies to make clinical research accessible, convenient, and less costly. For example, Pfizer's REMOTE study conducted all aspects of the clinical trial remotely via Web-based approaches (ClinicalTrials.gov, 2013; Orri et al., 2014). This trial, Dorsey added, laid the groundwork for how virtual clinical trials may be conducted going forward. As depicted in Table 2-1, most aspects of a clinical trial take place at individual trial sites. However, Dorsey envisions that in the near term, clinical trials could be conducted using a mix of venues, including centrally (at one trial site), at multiple individual trial sites, and/or remotely (via digital health technolo-

[4] From 2002 to 2012, the failure rate of drug development for Alzheimer's disease was more than 99 percent (Cummings et al., 2014). Drug development for Parkinson's disease has also been unsuccessful. The most effective drug to provide symptomatic relief for Parkinson's, Levadopa, was discovered as a therapeutic agent in 1967 (Hornykiewicz, 2010).

TABLE 2-1 Current and Future Models for Clinical Trials, Categorized by Stages in Clinical Trials

	Recruitment	Pre-Screening	Enrollment	Interim Assessments	Final Assessments	Longitudinal Follow-Up
Current	Site					
Future	Centrally and remotely		Site(s)	Remotely	Site(s)	Centrally and remotely

SOURCE: As presented by Ray Dorsey, November 28, 2018.

gies), depending on the type of data needed. For example, pre-screening could occur centrally at one trial site, biopsies and medical imaging could be conducted at multiple trial sites, and interim assessments could be conducted remotely through digital health technologies, noted Dorsey.

Dorsey presented a diagram (see Figure 2-2) created by Andrea Coravos, CEO of Elektra Labs, that categorizes clinical trials based on where and how the data are captured (Coravos, 2018). According to Figure 2-2, decentralized trials have deceased reliance on an intermediary (e.g., a member of the study team) and physical trial site location. The REMOTE trial mentioned earlier, said Dorsey, was unique in that remote and fully virtual methods were used to capture data. However, Dorsey continued, there are likely to be more clinical trials that incorporate both traditional and decentralized models.

Examples of Virtual Clinical Trials

Dorsey provided three examples that illustrate how virtual trials can increase participant access and geographic representation, improve the participant experience, and enhance recruitment for patient subpopulations: (1) a Michael J. Fox Foundation virtual study, (2) AT-HOME PD,[5] and (3) a 23andMe LRRK2 (leucine-rich repeat kinase gene) study.

The Michael J. Fox Foundation Virtual Study

Individuals with and without Parkinson's disease were enrolled using The Michael J. Fox Foundation's tool, Fox Trial Finder,[6] a clinical trial

[5] Available at https://clinicaltrials.gov/ct2/show/record/NCT03538262?term=AT+HOME+PD&rank=1 (accessed April 29, 2019).

[6] Fox Trial Finder was created to help increase the flow of willing participants into clinical trials, thereby accelerating the development of drugs for Parkinson's disease. Fox Trial Finder lists ongoing Parkinson's disease clinical trials and matches participants to trials for which they are best suited (The Michael J. Fox Foundation, 2019a).

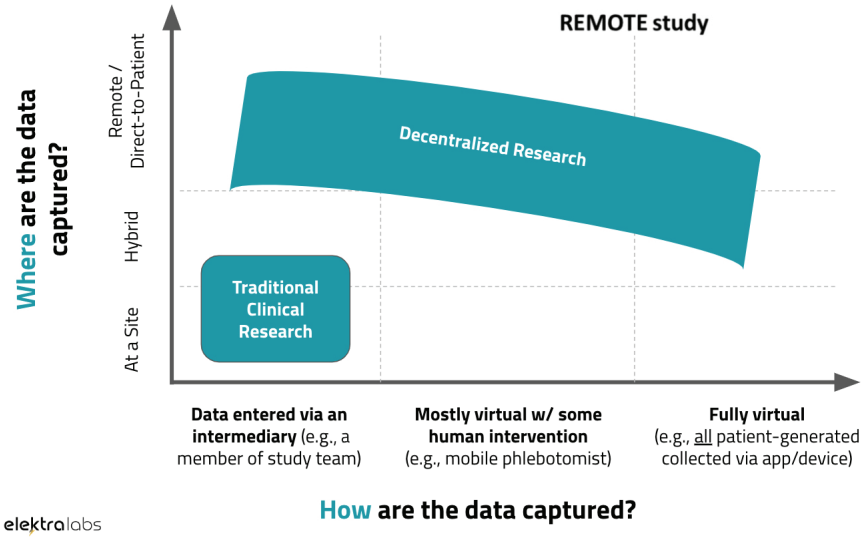

FIGURE 2-2 Typology of clinical research based on location and methods of data captured.
SOURCES: As presented by Ray Dorsey, November 28, 2018; Coravos, 2018. Published on https://blog.andreacoravos.com/decentralized-clinical-trials-e9dbde90ea95 (accessed March 20, 2019).

matching tool (Dorsey et al., 2015). More than 160 participants from 39 sites spread across the country were enrolled in the study. Parkinson's disease is typically visually diagnosed. The virtual platform used in the study allowed investigators to visually examine Parkinson's disease status remotely via videoconferencing, without requiring participants to leave their homes. Furthermore, it allowed for wide geographic representation and enabled participation for those who previously had no means of doing so. In a follow-up evaluation of participants' experience, 90 percent of participants reported satisfaction with the trial, 80 percent reported they were more willing to participate in a similarly designed trial, and 85 percent reported they would be more able to participate if they could do so remotely (Dorsey et al., 2015). Similar research, said Dorsey, has shown this to be the case for Alzheimer's disease.

AT-HOME PD

This study will follow-up with participants from two large, multicentered Phase 3 Parkinson's disease studies (Steady PD III[7] and Sure PD3[8]) remotely via an annual virtual visit using Web-based video conferencing. AT-HOME PD participants will also provide self-reported outcomes quarterly through Fox Insight[9] (an online clinical study) in addition to providing monthly assessment data on tremor, gait, voice, and balance collected via a smartphone.

23andMe LRRK2 Study

This study will investigate the linkage between the leucine-rich repeated kinase (LRRK2) genetic mutation[10] and Parkinson's disease by recruiting a national cohort of carriers. Given LRRK2's rarity in the general population, a traditional study would require establishing multiple sites around the world. However, by leveraging Fox Insight's online platform, this study was able to recruit a cohort of 300 participants—50 of whom have Parkinson's disease. This study will follow participants remotely, with annual virtual Parkinson's disease examinations (University of Rochester–Udall Center, n.d.).

In Dorsey's opinion, virtual trials offer numerous advantages compared with traditional studies (see Table 2-2); perhaps most importantly, they enable studies to be more participant centered. The geographic reach of a virtual trial, Dorsey noted, will not be determined by where someone lives, but by whether they have Internet access. Additionally, virtual trials can offer benefits such as comfort, convenience, and confidentiality for participants. Virtual trials can also reduce the time to initiate study,[11] allow

[7] Available at https://clinicaltrials.gov/ct2/show/NCT02168842?term=Steady+PD+III&rank=1 (accessed April 29, 2019).

[8] Available at https://clinicaltrials.gov/ct2/show/NCT02642393 (accessed April 29, 2019).

[9] Fox Insight is an online study that seeks to build a large, diverse cohort of participants that is representative of Parkinson's patients. Once enrolled and every 90 days thereafter, participants are asked to enter health and disease information. Fox Insight is meant to complement in-person research and curated data are made available to researchers worldwide in real time. Launched as a beta in March 2015, more than 5,000 participants (80 percent of whom have a Parkinson's disease diagnosis) contributed data before the study's formal launch in April 2017 (The Michael J. Fox Foundation, 2019b).

[10] The majority of Parkinson's disease cases are idiopathic (meaning there is not a known cause). However, for approximately 10 percent of cases there is a genetic linkage. Of this subset of Parkinson's disease cases, a mutation in the LRRK2 gene is the most common cause and represents up to 2 percent of all Parkinson's disease cases (The Michael J. Fox Foundation, n.d.).

[11] The AT-HOME PD trial, which used a virtual platform, was able to enroll its first participants in less than 6 months after receiving funding.

TABLE 2-2 The Many Advantages of Virtual Clinical Trials

Characteristic	Traditional Study	Virtual Study
Focus	Participants, investigator, sites	Participants
Geographic reach	Sites	Internet access
Sites	Many	One
Institutional Review Boards	Many	One
Time to initiate study	Long	Medium
Investigators	Many	Handful
Assessments	Episodic	Frequent
Variance	High	Low
Comfort	Low	High
Convenience	Low	High
Confidentiality	Low	High
Cost	High	Moderate

SOURCE: As presented by Ray Dorsey, November 28, 2018.

for more frequent participant assessments, and simplify the complexity of dealing with multiple IRBs.

Dorsey envisions that virtual trials could reduce costs in the long term. While the tools to conduct virtual trials already exist, the main barriers preventing industry from applying these tools may be creativity and will, which Dorsey hopes can be increased and galvanized.

DISCUSSION

Johnston opened the discussion by noting that like the U.S. health care system, clinical trials are not designed based on the needs of the patient (participant), but rather the needs of the investigator. Cryer acknowledged this deficiency and reiterated the importance of the clinical trial infrastructure to be a complement for treating physicians' clinical practices to enable seamless access to and participation in clinical trials—especially for minority populations for whom treating physicians may not have an adequate set-up for traditional clinical trials. Technologies used to drive health care transformation could be leveraged to better access those physicians and patients, Cryer emphasized. Dorsey echoed this sentiment, stating that the availability of digital health technology has extended health care beyond institutions and into the community and patients' homes.

Steven Cummings, director of the San Francisco Coordinating Center, provided a different perspective that resulted from analyzing 12 clinical

trials at Genentech-Roche for efficiency opportunities, including transformation to siteless trials. Given the necessity of intensive examinations and monitoring of participants, in Cummings's opinion, none of these trials could be converted to completely siteless studies. However, through the course of the reviews, it was discovered that the number of assessments could have been reduced by 20 to 80 percent, with potential reductions in the number of visits to clinical sites. Simplifying protocols, Cummings emphasized, would make trials more participant centered.

Adrian Hernandez from Duke University posed the question of what incentives participants might need to remain engaged in a virtual trial over the long term. Dorsey responded by suggesting that many individuals with Parkinson's disease, for example, want to participate in research and contribute to the development of knowledge. However, for continued engagement, the study design and virtual interface of a study platform is important, such as providing participants with real-time data on their health, or use of data analytics to project long-term health outcomes. Regardless of the purpose, the basic aim should be to provide value to the participants, Dorsey emphasized.

Lipset and Cryer both made distinctions on the appropriateness of providing feedback depending on study type and patient population. Lipset agreed that providing real-time feedback to participants is a good idea in observational trials. However, it would involve significant planning to determine what data could be returned and when in blinded, randomized clinical trials. Cryer, on the other hand, distinguished between the trial design considerations for participants who need to consciously manage conditions with high-burden symptoms versus those with low-burden symptoms. Cryer proposed that the former could be provided feedback with health management strategies, while the latter may need a creative approach to inspire engagement with their health data. Human-centered design,[12] Cryer emphasized, should be leveraged to make retention more fulfilling for participants.

Nitin Desai, chief medical officer at Health Wizz, asked the speakers to comment on any legal or ethical barriers that may prevent engagement with potential trial participants. Lipset acknowledged this issue, but noted that a more significant upstream challenge is the lack of awareness by treating physicians about trials in which their patients could be enrolled. Virtual trials can make trials more accessible, but should be accompanied by other channels to improve awareness of trial participation, such as social media,

[12] Human-centered design is a design and management framework that seeks to develop solutions made for the people at the core of the problem. By building deep empathy for whom the trial is being designed, innovative solutions will be more likely to fit seamlessly into people's lives and address their needs (Design Kit, n.d.).

said Lipset. Cryer and Johnston also commented on repurposing ClinicalTrials.gov to allow people to more optimally identify, learn, and engage with trials in a user-friendly way.

Sally Okun, vice president of policy and ethics at PatientsLikeMe, noted the regulatory challenges associated with using real-world data (e.g., claims data, electronic health record [EHR] data, and data emerging from digital health technologies). According to Okun, the use of such technology is not prohibited by regulation, but the use of data generated from these technologies does face regulatory hurdles. Related to Okun's comment, Lipset emphasized that there is an opportunity for using real-world data in prospective virtual trials, in which participants provide their own EHR data—a process that does not require special regulatory approval. The proliferation of tools such as AppleHealth provides potential for patients to bring their own data into studies. Dorsey suggested that EHR data may not necessarily be real-world data because they are sporadically collected. For example, he might see a patient with Parkinson's disease four times per year, which means that he has a limited idea of how that patient is dealing with his or her disease day to day. The use of digital health technologies can help illuminate the patient's daily experience. For example, based on data collected from these technologies, Dorsey and his colleagues observed that Huntington's disease patients were lying down for about half the day (Adams et al., 2017). In Dorsey's opinion, regulators might like to see more digital health technologies being leveraged to capture new and useful data.

Lipset emphasized a core problem regarding the lack of reliable and stable digital biomarkers, regardless of whether they are sourced from medical grade devices or consumer grade devices. He emphasized the importance of investing in validation of new biomarkers in early research phases so they are ready for use during Phase 3 of clinical trials, while at the same time being mindful of substitution of prior measures.

Emily Butler, a statistician from GlaxoSmithKline, commented that a not-insignificant proportion of data collected during a clinical trial is not examined, and asked the speakers if there should be a balance between optimal data collection upfront and collecting data that are valuable. According to Dorsey, overemphasizing data collection is not necessarily a bad thing, citing examples of medical discoveries such as nocturnal hyperglycemia and sleep disorders, which resulted from more intensive measurements. On the other hand, Cryer emphasized the importance of including the patient in developing the data collection plan. Citing her own experiences as a patient with multiple conditions, she highlighted how a large number of measurements could be consolidated by involving the patient. According to Lipset, the burden and complexity of collected data may be used to justify the necessity of an in-person visit. However, the fear of missing something is more likely to explain this trend, Lipset added.

3

Exploring Virtual Clinical Trials

Key Messages Identified by Individual Speakers

- Virtual clinical trial methodologies may allow for direct recruitment of large, diverse cohorts of participants as well as faster assessments and recruitment of select patient groups for targeted clinical trials. (Denny)
- Virtual clinical trials embedded in a health care system work well when the trial outcome is captured in the electronic health record (EHR), the health care system partner is interested in the study outcome, the intervention is familiar but being tested for a new indication, and few competing interventions or trials are ongoing in the health care system. (Weber)
- Trial design simplicity is essential to engage and retain participants. Community- and provider-based recruitment may be more successful than strictly Web-based recruitment. (Cummings)
- While it may be possible for researchers to access EHR data directly, working in close collaboration with trial participants and having them bring their data to the study themselves could result in a deeper, richer, and more rewarding relationship with study participants. (White)
- Successful direct-to-participant (D2P) trials are designed for specific outcomes that include patient preferences in terms of the kind of research they would like to be part of, when they want to be part of it, and how they will be part of it. There is

a need to advance the science of patient engagement in clinical trials. (Craft, Hernandez)
- Change management within the pharmaceutical industry is important to gain more widespread acceptance of D2P trials. (Hawkins, Rose)
- The goal of providing feedback to clinical trial participants during the course of a trial should not be to replace the provider, but to provide patients with information that empowers them to talk to their providers. (Bollyky)

The workshop's second session explored a variety of perspectives and experiences with virtual and digital health technologies in interventional and observational studies as well as in clinical care. It also highlighted potential opportunities to use digital health technologies to improve clinical trials of investigational products, the challenges of doing so, and best practices for designing and implementing a virtual clinical trial. Jenna Bollyky, vice president for clinical research and analytics at Livongo Health, and Joshua Denny, professor of biomedical informatics and medicine at the Vanderbilt University Medical Center, provided lessons learned from clinical care and observational studies, respectively. Insights on lessons learned from interventional virtual clinical trials were presented by Steven Cummings, director of the San Francisco Coordinating Center; Wendy Weber, acting deputy director at the National Institutes of Health's (NIH's) National Center for Complementary and Integrative Health; and Kimberly Hawkins, clinical sciences and operations project leader head at Sanofi Genzyme. The session ended with a panel discussion composed of Noah Craft, chief executive officer (CEO) of Science 37; Adrian Hernandez, vice dean for clinical research at the Duke University School of Medicine and faculty associate director of the Duke Clinical Research Institute; Jon White, deputy national coordinator for health information technology at The Office of the National Coordinator for Health Information Technology in the U.S. Department of Health and Human Services; and Josh Rose, vice president and global head of strategy for IQVIA. An open discussion, moderated by Kelly Simcox, head of the Americas, clinical study units, and clinical operations at Sanofi, followed the discussion.

LESSONS LEARNED FROM CLINICAL CARE

Jenna Bollyky, Vice President for Clinical Research and Analytics, Livongo Health

Bringing Together Technology and Health Care Expertise

Launched in 2015, Livongo is a participant-centered digital health business that seeks to address the confusion, complexity, and cost of interacting with the health care system for those living with chronic diseases. Livongo initially focused on diabetes monitoring and prevention, but is now expanding its programs to address cardiovascular disease. Livongo has developed a platform, Applied Health Signals,[1] which aggregates real-world patient health data from multiple sources, interprets these data using medical literature and clinical insights, applies data to solutions, and iterates until desired patient outcomes are achieved.

In addition to the data collected from digital health technologies, Livongo aggregates data on people's health behavior, physical activity, and medical and pharmacy claims, with the aim of helping people lead healthy lives and spend less time worrying about their conditions. Livongo leverages a diverse team of data scientists, behavioral health specialists, certified diabetes educators, and physicians to interpret and apply these data in a way that is clinically meaningful to the patient and their treating physician.

Challenges of Managing Chronic Conditions Remotely

Bollyky described three challenges associated with remote management of chronic conditions: attribution of data, creation of meaningful data, and coordination of care. The first challenge involves ensuring that aggregate measurements are coming from the person being observed. As an example, Bollyky illustrated how a digital weight scale used by multiple people can create noisy data and make it difficult to determine which measurements should be attributed to the participant. This can be rectified by various approaches, such as by introducing capabilities in the digital weight scale that allow the participant to indicate when he or she is using it, or by collecting self-reported weight at registration from the participant and leveraging data science techniques to filter out obvious outlier data.

The second challenge Bollyky emphasized is the creation and provision of meaningful health signals to the participant in the context of the disease being monitored. Using Livongo's glucose meter as an example, Bollyky discussed how this digital health technology can provide participants value in

[1] Available at https://www.livongo.com/applied-health-signals (accessed April 11, 2019).

terms of instant feedback on their blood glucose levels, measurement trends, and tailored recommendations based on those trends. For people living with diabetes, a very meaningful measurement is their glycated hemoglobin A1c (HbA1c) level.[2] However, Livongo currently does not have the capability to take this measurement. As a result, it uses data science techniques to derive HbA1c values from collected blood glucose data and validates the reliability of estimated HbA1c values based on the medical literature (Ford et al., 2018). However, reliable estimates require that observed data have a high enough frequency to confer statistical power.

The third challenge Bollyky discussed is in regard to coordinating care for people with chronic conditions. While Livongo does not currently serve as a health care provider or write prescriptions for its members, it does have algorithms to identify when someone may not be on the right medication or the right dose of medication. Bollyky noted that Livongo's goal is not to replace providers, but rather to support them. By giving its members health information, Livongo empowers them to talk to their providers. In addition to engaging providers, Livongo has ongoing relationships with pharmacy benefit managers and health plan managers, which enable more streamlined care coordination for participants.

Leveraging real-world evidence can offer health benefits in part, Bollyky observed, due to the Hawthorne Effect—the alteration of behavior by the subjects of a study due to their awareness of being observed (McCambridge et al., 2014)—which can pose complications in the research setting. Though using digital tools to support clinical trials may provide convenience, allow for more frequent assessments, and offer cost savings, it will be important to take into account how monitoring may impact the outcomes being measured.

LESSONS LEARNED FROM OBSERVATIONAL STUDIES

Joshua Denny, Professor of Biomedical Informatics and Medicine, Vanderbilt University Medical Center

All of Us

Joshua Denny centered his presentation on cohort research and how it can facilitate clinical trials, using *All of Us*,[3] U.K. Biobank,[4] and Project

[2] Glycated hemoglobin A1c (HbA1c) is a gold standard measurement of long-term glycemic control. Similar to a blood glucose test, an HbA1c test measures how much glucose is bound to hemoglobin. This test can provide information on a person's average level of blood sugar over the past 3 months (CDC, 2018; Leow, 2016).

[3] Available at https://www.joinallofus.org/en/about (accessed April 16, 2019).

[4] Available at https://www.ukbiobank.ac.uk (accessed April 16, 2019).

Baseline[5] as examples. The *All of Us* Research Program was launched by NIH nationally in May 2018 with the goal of enrolling at least 1 million diverse participants.[6] Enrollment, he explained, occurs through two routes: (1) health care provider organizations, and (2) direct enrollment of volunteers. Currently, more than 200 sites enroll participants through health care providers or directly at numerous consumer health sites, such as Walgreens clinics, blood banks, Quest, EMSI,[7] and QTC/Leidos.[8] To ensure that similar information is collected for all individuals, *All of Us* uses a common interface for recruitment, a common process for consent (which includes sharing EHR data), and common modules for health surveys. A key part of *All of Us*, said Denny, is that participants will have access to their data and may be recontacted over time.

All of Us will aggregate data from a variety of sources, including EHRs, collected specimens, claims data, and data provided directly by participants. *All of Us* is piloting the Sync for Science mechanism,[9] a national collaboration among EHR vendors, to receive medical records data directly from participants. To harmonize these disparate types of data, *All of Us* uses the observational medical outcomes partnership common data model (OHDSI, 2019).

Denny noted that *All of Us* will begin collecting genome-wide association study (GWAS) data on participants and eventually plans to add whole-genome sequencing data. The program also plans to pilot Fitbits, Apple Watches, and other wearables in addition to working to link participants' geographical locations with data.

U.K. Biobank

U.K. Biobank, an open-access, prospective study, recruited more than 500,000 men and women ages 40 to 69 from 2006 to 2010. Participants consent for a wide range of research and for long-term follow-up. U.K. Biobank takes extensive baseline assessments of its participants and links to them longitudinally through their health record.

U.K. Biobank currently has GWAS data on all participants and the results from a standard panel of biochemical assays, such as lipids and metabolites. Whole-exome sequencing for every participant is under way, as well as whole-genome sequencing and metabolomics assays. There are plans

[5] Available at https://www.projectbaseline.com (accessed April 16, 2019).

[6] At the time of the workshop, approximately 83,000 have completed all enrollment elements. Of those enrolled, more than 45 percent are non-white and more than 75 percent are considered to be from an underrepresented population in medical research.

[7] Available at https://www.emsinet.com/About-EMSI (accessed April 28, 2019).

[8] Available at https://www.qtcm.com (accessed April 28, 2019).

[9] Available at http://syncfor.science (accessed April 20, 2019).

for proteomic analyses, too. For a subset of participants, U.K. Biobank is collecting whole-body imaging data.

Project Baseline

Project Baseline is a large-scale project being conducted by Verily, Duke University, Stanford University, and Google that will collect real-world and clinical data, as well as biospecimens and survey results from some 10,000 individuals. Project Baseline will also heavily leverage digital tools by providing participants with home sensors and wearables, Denny emphasized.

The Role of Cohorts in Supporting Clinical Research

The combination of data that emerges from cohorts, such as EHRs, survey data, and wearable data, can be leveraged to conduct a wide range of clinical research activities, including

- Phenotyping and genotyping research to identify new disease targets or enable pharmacogenomics discovery;
- Phenome-wide investigations to test for indications and adverse drug events; and
- Artificial intelligence research and clustering approaches to identify disease subtypes.

To illustrate the potential of cohorts in informing drug discovery, Denny provided examples of studies that used EHR and genomic data to identify new classes of drugs to treat patients with rheumatoid arthritis, validate adverse effects for an enzyme-metabolized drug, and identify a novel class of cholesterol-lowering drugs (see Box 3-1).

Large, diverse observational study cohorts, Denny continued, stand to accelerate clinical trials by generating basic discoveries, enabling direct and targeted recruitment of diverse populations and facilitating their assessment through existing cohort technology platforms, and enabling more intelligent trial design. The cohort landscape, Denny noted, is expanding and includes groups such as the China Kadoorie Biobank,[10] the Electronic Medical Records and Genomics (eMERGE) Network,[11] Estonian Genome Center,[12] Kaiser Permanente's Division of Research,[13] Million Veterans Program,[14]

[10] Available at http://www.ckbiobank.org/site (accessed April 16, 2019).
[11] Available at https://www.genome.gov/27540473/electronic-medical-records-and-genomics-emerge-network (accessed April 16, 2019).
[12] Available at https://www.geenivaramu.ee/en (accessed April 16, 2019).
[13] Available at https://divisionofresearch.kaiserpermanente.org (accessed April 16, 2019).
[14] Available at https://www.research.va.gov/mvp (accessed April 16, 2019).

BOX 3-1
Investigation of Genetics Data to Identify Drug Targets and Drug Response

Identifying Drug Targets for Rheumatoid Arthritis

In a study in which Joshua Denny was involved, the research team looked at genome-wide association study data from more than 100,000 individuals—approximately 27,000 with rheumatoid arthritis and more than 70,000 controls. The researchers identified 101 genetic loci for rheumatoid arthritis, about half of which were new and many of which pointed to active treatments for this disease. This study provided large-scale validation, suggesting that genetics can be used to recapitulate drug targets and identify potential other targets that could treat rheumatoid arthritis.

Variation in Clopidogrel Adverse Effects

Data from clinical trials of the prodrug* clopidogrel, which is activated by the enzyme Cytochrome P450 2C19 (CYP2C19), found that patients with genetic variants that lead to a loss of function of this enzyme were more likely to experience an adverse effect. A retrospective mining of clinical trial data indicated that those with a loss of CYP2C19 function were 50 percent more likely to experience a stroke, heart attack, or other cause of death compared with patients with functional enzyme. This effect size was confirmed in an analysis of electronic health records combined with DNA analysis that showed the same response.

Novel Drug Class Developed Based on Proprotein Convertase Substilisin/Kexin Type 9 (PCSK9) Enzyme Variation

Studies on a diverse population indicated that people of African ancestry who had very low cholesterol and loss of function variants in the enzyme PCSK9 had lower levels of low-density lipoprotein and decreased risk of heart disease. This finding, which could only have come from studying a diverse population, led to the development of a new class of drugs (e.g., alirocumab and evolocumab) inhibiting this enzyme that dramatically reduce cholesterol when taken with statins and reduce risk of heart disease.

* Prodrug: A medication or a compound that is metabolized in the body to produce the active form of the drug.

SOURCES: Cohen et al., 2006; Delaney et al., 2012; Mega et al., 2009; Okada et al., 2014; Sabatine et al., 2017. As presented by Joshua Denny, November 29, 2018.

PCORnet,[15] and 23andMe.[16] These emerging platforms and their capabilities for continuing contact will provide opportunities for investigators to discover novel therapeutic compounds.

[15] Available at https://pcornet.org (accessed April 16, 2019).

[16] Available at https://www.23andme.com (accessed April 16, 2019).

LESSONS LEARNED FROM INTERVENTIONAL STUDIES

Direct-to-Participant Trials

Steven Cummings, Director, San Francisco Coordinating Center

Cummings discussed what he termed D2P trials, which he defined as having no physical clinical sites, and thus no geographic limits on recruitment. Unlike the term "virtual" clinical trial, Cummings expressed that the term D2P trial more aptly captures the importance of building relationships with participants. Using examples of three D2P trials, Cummings provided lessons learned about the importance of incorporating the participant perspective and simplicity in trial design.

KALM[17]

KALM, Cummings explained, was an Internet-based, randomized, placebo-controlled trial that examined whether two herbal products, kava and valerian root, were effective in helping individuals self-manage anxiety and insomnia, respectively (Jacobs et al., 2005). Launched by 1747, Inc., with venture capital investment from Lilly Ventures (then called e.Lilly Venture Fund) (Lilly, 2001), the paper-free trial was based out of one center in San Francisco. It used a participant-facing electronic data capture system, eConsent (use of multimedia on a digital platform to develop an interactive consent process), and a quiz to confirm that the participant understood the study (Grady et al., 2017). Kava and valerian root were sent via FedEx to participants with proof of identification confirmation. The trial design, Cummings continued, was simple, with fewer than 10 steps to enroll in the trial and be randomized.

Over 8 weeks, Cummings and his team screened 1,500 potential participants and randomized 391 participants from 45 states. While participant adherence was 83 percent, there were no differences in anxiety and sleep scores between those receiving the treatment or placebo. Because the trial was entirely electronic, Cummings's team was able to analyze all of the data within 1 hour of the trial's ending and return results of the trial to the participants within 1 day.

e.Lilly Venture's upfront investment cost approximately $3,224 per participant. Due to the simplicity of conducting the trial (and relative cost-effectiveness), the parent company Eli Lilly adopted 1747's technology for a trial of Cialis. However, it became increasingly complex and involved enrollment and consent at sites, resulting in the most expensive trial per

[17] Additional information can be found in Appendix D.

participant it had ever run to date, prompting Eli Lilly to abandon the trial model.

REMOTE

REMOTE was an Internet-based trial, launched by Pfizer Inc., designed to mimic a site-based trial for overactive bladder to test the efficacy of Detrol. REMOTE used similar identification verification and consent as in the KALM trial, was run from a single center, and used Web-based recruitment.

However, replicating a site-based trial was complex, largely attributed to protocol requirements and regulations that increased the burden of enrollment. For example, the protocol involved more than 90 interactions with participants to enroll and be randomized. Additionally, after signing eConsent, study staff were required to call the participant and read the full consent over the phone. Although REMOTE had received U.S. Food and Drug Administration (FDA) approval to ship the investigational product directly to participants' homes, prescribing laws limited recruitment to nine states, some of which required physical examinations by a physician prior to dispensation. Furthermore, during the run-in period, participants were asked to carry a plastic container to measure urine volumes and enter this information into a digital health technology. If the participant made an entry error, there was no opportunity to correct it and that participant could be excluded from the trial.

Recruitment was also challenging, noted Cummings. While nearly 21,000 women viewed the online introduction to the trial, only 1,159 were deemed eligible to participate. Of those eligible, only 1.6 percent of those women, or 19 women, made it through enrollment and randomization (see Figure 3-1). Although the perception is that REMOTE failed because of recruitment issues, Cummings noted that if the protocol were simplified so that 25 percent of the interested and eligible women could have easily enrolled, the trial would have achieved its goal of having 283 women participate.

TOPAZ[18]

TOPAZ, funded by the National Institute on Aging in partnership with the Parkinson's Foundation, is a planned trial that will start recruitment in 2019 and will test the efficacy of zoledronate[19] to prevent fractures in Parkinson's disease patients over age 65. TOPAZ aims to recruit 3,500

[18] Additional information can be found in Appendix D.

[19] Zoledronate is an FDA-approved generic drug that increases bone density. Administered by intravenous infusion, one dose lasts for more than 2 years.

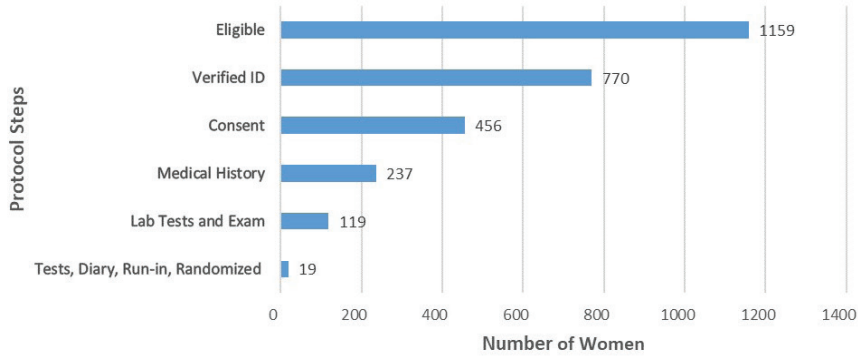

FIGURE 3-1 Attrition of interested and eligible participants at each step of the REMOTE trial protocol.
NOTE: ID = identification
SOURCE: As presented by Steven Cummings, November 29, 2018.

participants and, given this ambitious goal, will need to depend on nationwide recruitment unencumbered by sites. Therefore, the entire trial will be conducted from participants' homes, making it easier for disabled or cognitively impaired individuals who may benefit most from participation.

There will be only three interactions for participants to enroll in the study. First, initial eConsent and eligibility screens will be collected online. Second, a teleneurology examination will be conducted to confirm the diagnosis of Parkinson's disease in the participant. Third, a nurse will administer a finger stick at the participant's home to assess kidney function, then provide either zoledronate or a placebo. Endpoints for the study are assessed by either surveying the participants' EHRs, or following up by mail, email, or phone every 6 months to identify those who have had fractures.

Cummings said the methods for D2P trials are well established. Simplicity for the participant is essential, and recruitment from trusted communities and known providers may be more successful than solely Web-based recruitment. Such studies could reach participants in more states if prescribing laws were changed to allow for the shipment of study drugs without requiring physical examinations, said Cummings.

NIH's Health Care Systems Research Collaboratory

Wendy Weber, Acting Deputy Director,
National Center for Complementary and Integrative Health

The NIH Health Care Systems Research Collaboratory[20] (The Collaboratory), explained Weber, aims "to strengthen the national capacity to implement cost-effective, large-scale research studies that engage health care delivery organizations as research partners." In leveraging data already passively collected as part of the EHR, it will be important, Weber noted, to determine when it is possible to partner with health care systems to answer the questions on improving health. The Collaboratory refers to its approach as *embedded pragmatic trials* because they are set in the health care system based on how patients see their health care providers and receive care in the health care systems. The Collaboratory has completed nine trials involving sites across the country, initiated six trials in the spring and summer of 2018, and will fund an additional set of trials in September 2019.

The Collaboratory Coordinating Center assists the trials via working groups[21] and releases lessons learned into The Collaboratory's knowledge repository.[22] Materials posted include how to design and conduct trials embedded in health systems and disseminate their results for diffusion into learning health systems, noted Weber. Using these lessons learned, The Collaboratory is able to help projects troubleshoot real issues as they arise, such as transitioning from *International Statistical Classification of Diseases and Related Health Problems* (ICD)-9 codes to ICD-10 codes in the middle of trials.

Leveraging the EHR

While the EHR provides a cost-effective resource of information collected during routine care, it will be important for investigators to consider what data are routinely captured to assess if those outcomes are useful for a study, noted Weber. Data collected consistently in the EHR include billed services, such as codes for procedures, hospital stays, medical visits, laboratory measures, and in some cases, medication fills. However, using EHRs poses its own challenges, such as blank data fields, a lack of information on services received at different clinics, and the inability to consistently capture patient-reported outcomes and adverse events. The biggest challenge, noted

[20] Available at https://rethinkingclinicaltrials.org (accessed April 20, 2019).

[21] The Collaboratory has five active working groups that focus on biostatistics and study design, electronic health records, health care systems interactions, patient-reported outcomes, and ethics and regulatory issues.

[22] Available at www.rethinkingclinicaltrials.org/welcome (accessed January 14, 2019).

Weber, is that patient follow-up in a health care setting may not have the desired schedule of a clinical trial.

The principal investigators of the various Collaboratory trials have developed some solutions to these challenges. To fill in missing data in a pain study, for example, the project team augments data capture of the Brief Pain Inventory[23] by emailing participants a link so they can complete the instrument themselves online. Those participants who did not respond to the email then received an automated call that enables them to enter in their pain scores using their touchtone phones. Failure to respond to the automated call triggers an in-person call to capture the data. The project team also bypassed the issue of missing data by conducting trend analysis rather than attempting to consistently collect data from all participants at the same time point.

Weber noted that every project associated with The Collaboratory first has to complete a year-long planning activity before starting the trial to demonstrate the ability to capture the needed data from the EHR, identify how much data will be missing, and assess the overall feasibility of conducting a trial using EHRs.

Lessons Learned

One lesson learned from The Collaboratory has been to expect the unexpected, said Weber. For example, while staff turnover is to be expected, the frequency of staff turnover can be a surprise. In some cases, systems launched new EHRs in the middle of a trial. Given that these are pragmatic trials, there is likely to be lower adherence to the interventions, so it is important to power a study for a smaller effect size. Systemic changes in health care systems can also create challenges, as can changes in treatment guidelines. The biggest lesson learned, though, was how much time it takes to get data out of the EHR and clean them so that they can be analyzed, said Weber. She emphasized the importance of periodic data checks to make sure the data needed to answer the study question are still being collected in the EHR.

The majority of data collected in EHRs, Weber noted, will be for billing, so research may not be high on a health system's agenda. As a result, it is important for investigators to keep embedded trials simple, such that the endpoints under investigation do not add undue burden to patients and clinicians during routine health care visits. Given these constraints, embedded pragmatic clinical trials will work well when the outcome of interest is

[23] The Brief Pain Inventory is a medical questionnaire used to assess the severity of pain and its impact on functioning among patients with pain from acute conditions, cancer, chronic disease, lower back pain, and osteoarthritis (MD Anderson Cancer Center, 2019).

captured in the EHR; when the health care system partner is interested in the study outcome; when the intervention is familiar, but being tested for a new indication; and when there are few ongoing, competing interventions or trials. If done correctly, embedded trials, Weber noted, can be less costly than a conventional trial. In fact, Weber noted that over a 5-year period, The Collaboratory spent approximately $4.5 million on clinical trials, with sample sizes ranging from 200 to nearly 200,000 participants. This is in contrast to conventional trials, which have recently been estimated to have a median cost of $19 million (Moore et al., 2018).

Decentralized Clinical Trials

Kimberly Hawkins,
Clinical Sciences and Operations Project Leader Head, Sanofi Genzyme

While the public has expressed an interest in participating in clinical trials, recruitment and participation rates are low due to a lack of awareness of trials, the necessity to travel long distances to study sites, and the duration and number of clinical visits required. Emerging digital health technologies provide an opportunity to design decentralized clinical trials, which she called a disruptive approach to organizing the trial around the patient. In particular, Hawkins noted five opportunities that decentralized trials provide:

1. Increased flexibility such that the burden of participation is reduced for both the patient and clinical trial sites;
2. Increased participation of diverse patient populations by expanding access to those who may not reside near traditional academic centers, particularly for patients with rare diseases;
3. Increased frequency of data collection and use of continuous data flows to more accurately and rapidly detect signals;
4. Improved patient recruitment and retention; and
5. Improved long-term follow-up to increase understanding of drug safety profiles and home-based dispensing.

Through work on decentralized clinical trials, Hawkins and her colleagues have identified a number of operational, ethical, regulatory, and management challenges.

Operational Challenges

Hawkins and her colleagues faced issues integrating the new types of data from digital health technologies into the standard datasets the

company was accustomed to handling. Mapping out the data flow, Weber continued, will be important for sponsors to do before implementing such technologies into clinical trials. While D2P shipments can be challenging in terms of maintaining the temperature across the supply chain or delays in delivery, it can offer a lot of value for patient populations that are highly mobile. Patient management must be well defined and documented, but must also be mindful of not adding unnecessary safeguards in a decentralized trial. Given these operational challenges, conducting a decentralized trial will likely require additional resources and skillsets to work appropriately with tech vendors.

Hawkins also noted that the increased use of eConsent and eSource (data that are initially recorded in electronic format or data that are collected digitally without the need to record data on a piece of paper first) (FDA, 2013) has worked well when working with larger institutions and central Institutional Review Boards (IRBs), but can be challenging when working with smaller institutions and local IRBs.

Regulatory Challenges

Regarding regulatory challenges, Hawkins said she has found regulatory agencies to be quite interested in working collaboratively to implement and pilot these new digital technologies in the context of clinical trials. An important concern, however, is endpoint validation using a specific digital health technology, which requires implementing a time to validate the technology into a clinical development plan.

Change Management

Hawkins indicated that change management is likely the biggest challenge of adopting decentralized clinical trials. Decentralized clinical trials are disruptive to the status quo, noted Hawkins, and there are risks to integrating them into the development plan for a medical product. At Sanofi Genzyme, this requires educating teams about the decentralized approach, allowing them to experiment with new ideas, and having good backup plans knowing that some approaches will fail.

The best fits for decentralized clinical trials are likely products for which safety is well characterized or that can be ingested easily by patients in the home, suggested Hawkins. Another consideration, she noted, is to use decentralized clinical trials for therapeutic areas in which telemedicine is already well established.

PANEL REACTIONS

Noah Craft, CEO, Science 37

Achieving the shift from organizing activities around the doctor to the patient will likely be a difficult undertaking, noted Craft. In his opinion, the impact of doing so will be profound and the resulting scientific discoveries will be more potent.

The technical challenges, however, will not be small, he added. Craft shared that when he was working with the innovation group at a large pharmaceutical company to help address the problem of slow, expensive, and burdensome clinical trials, he observed that neither academic medical centers, contract research organizations, nor technology companies were equipped to truly create a D2P clinical trials paradigm. The company he started, Science 37, created an end-to-end system that brings together doctors, technology, telemedicine, and most importantly, a direct-to-patient approach to clinical trials.

Craft relayed the primary lesson from the projects Science 37 has completed thus far—trial design should fit participant needs. Trial complexity and merely trying to retrofit a standard trial into an at-home trial are the two main challenges he has faced. An additional challenge is to better understand the science of how to engage patients. Based on his experiences so far, Craft suggested that there is not a universally effective approach to recruitment, so he cautioned against extrapolating lessons learned from recruitment in any single trial.

Adrian Hernandez, Vice Dean for Clinical Research, Duke University School of Medicine

Adrian Hernandez noted there is no one-size-fits-all approach to D2P trials. He agreed with Cummings and others who believe the word "virtual" is not appropriate given that these trials aim to get closer to people and form real relationships with them.

A theme in the presentations that struck Hernandez is that successful D2P trials focus on specific outcomes informed by patient preferences in terms of the kind of research people want to be part of, when they want to be part of it, and how they will be part of it. Having motivated participants is also important, said Hernandez, but the field also needs to develop the science of what makes participating in a trial valuable enough to keep participants engaged through the course of the study and beyond. Hernandez noted the need for a decision tree in terms of fit-for-purpose versus retrofitting an existing trial design to ensure achieving complete outcomes and deciding what to include in a D2P trial versus what to let go. A decision tree

could also help high-level leaders and regulators better understand various risks and trade-offs involved with D2P trials.

Jon White, Deputy National Coordinator, The Office of the National Coordinator for Health Information Technology, U.S. Department of Health and Human Services

Jon White pointed out that 96 percent of hospitals and 80 percent of physicians that participate in Medicare or Medicaid have certified health information technology systems (i.e., EHRs) in place that they use daily. The Office of the National Coordinator for Health Information Technology (ONC) received the statutory imperative in the 21st Century Cures Act to make EHR data available to patients without special effort, said White. Proposed rules have been issued from ONC and the Centers for Medicare & Medicaid Services that will lay out the federal government's policy for how it will regulate those health information systems to make the data available through application program interfaces without special effort. White reported that his office is going to work on freeing health data and challenged workshop participants to more actively partner with clinical trial participants—not least of all because in the future participants will have their data and researchers will need to work directly with participants to study the data. Although it will be possible to get these data in other ways as well, his counsel was that "the right way, the virtuous way, to get these data is to embrace people and have them bring their data to you on their terms."

Josh Rose, Vice President and Global Head of Strategy, IQVIA

Josh Rose noted that flexibility is key when interacting with participants. Some clinical trial participants want more in-person interaction while others prefer to use just the technology. He commented that his impression from working with FDA is that the agency is open to these types of virtual, D2P trials. Rose noted that he would like to see FDA develop positions to help guide the field through issues such as shipping medications directly to participants' homes or determining whether a digital health technology can make a desired measurement as opposed to requiring an office visit. Regulators outside the United States look to FDA for guidance, he said, so FDA can play an important role in shaping the global regulatory environment regarding D2P trials.

Turning to the subject of investigators, Rose said it is important to recognize that there are investigators who are quite happy with the current system, and others, especially younger investigators, who are not interested in running a clinical site and might be quite amenable to adopting these

newer approaches. In fact, he believes this new paradigm can serve as a way to bring more young researchers into clinical studies.

Rose echoed Hawkins's remarks about change management in that he has seen a great deal of interest and excitement among pharmaceutical company clinical teams only to see their enthusiasm stall because they do not want to be the first to go ahead with a large virtual trial. The solution, he offered, is to receive assurance from senior executives that failure will be acceptable because failure will still move knowledge forward.

Rose suggested that virtual trials are not solely about the technology, but rather about leveraging technology to be able to bring together the complex pieces of process and science in the context of virtual trials.

DISCUSSION

Cummings asked if there was a mechanism or organization to aggregate the experiences of researchers running D2P trials with regard to endpoints, recruitment, retention, and shipping study drugs, for example. Hernandez replied that one of the purposes of The Collaboratory is to serve as a knowledge repository; it is starting to put together this type of information in a manner that could establish more universal approaches to these trials.

Simcox asked Denny if *All of Us* will provide participant feedback in real time. According to Denny, *All of Us* is still in its building stages. While it can return survey data in near-real time to participants, it cannot do so with EHR data. Because *All of Us* is not the health care provider, it must first wait to receive EHR data and clean them before they are ready for research use. *All of Us* is working on building mechanisms so that EHR and other data, such as genomics data, can be returned to the participants.

One challenge of new technologies, said Cummings, is that they can collect large amounts of data relatively cheaply, but that leaves the challenge and expense of analyzing those data and dealing with the consequences of unexpected findings. He suggested that enthusiasm for collecting remote measurements of clinical trial participants should be tempered by the realization that analyzing the data in a meaningful way is not cost free.

John Gardinier, retired from the National Center for Health Statistics, noted his concern regarding data reliability arising from the inevitable errors in EHRs and the fact that wearable sensors can be unreliable. Denny replied that the key is to understand that although some of the data are unreliable, much of the data *are* reliable. By understanding that the data are imperfect, there are ways to get enough signal from bigger datasets to overwhelm the noise from imperfect data. He added that existing benchmarks are enabling better analysis of activity monitors and EHR data. Bollyky remarked that her company uses two-way digital health technologies to reach out to people and confirm reading accuracy.

Craft commented on the idea that technology will make every study better, faster, and cheaper all at once. He suggested that the benefits of technology will include reducing participant burden, speeding up medical product discovery and development, and significant cost savings. But these benefits will be realized over the course of decades. Currently, costs are shifting from participants (in terms of the burdens of participating) to the sponsor or to the owner of the intellectual property, and that is how it should be, he added. Instead of the participant having to spend time and money to get to a clinical site, trial sponsors will increasingly bear the cost of sending a nurse to the participant's home, for example.

Turkan Gardenier, a statistician, remarked on the parallels between developing D2P approaches and personalized medicine. Rose replied that D2P approaches can help the field of precision medicine by increasing participation among populations traditionally underrepresented in clinical trials.

Lipset noted that the metric of success for his group at Pfizer Inc. is not how many pilots his team can run, but when those approaches are ready for scaling across the organization. From the workshop discussions, his impression is that scale is not going to occur until there are simplified protocols and better endpoints. Hernandez agreed and said it will take time to reach that state. Craft, however, remarked that learnings are accumulating quickly and that Science 37's clients are shifting rapidly to design trials to fit patient needs. In his opinion, momentum in the field argues that these approaches are ready for scale.

Simcox asked if any of the panelists would comment on eConsent and the need to ensure the identity of a participant receiving a medication. Craft said his experience has shown that investigator–participant relationships are enhanced in D2P trials. Additionally, due to the use of digital health technologies by research staff and participants, it is harder to commit fraud in a virtual clinical trial than in a regular trial. Craft also noted that participants are not required to provide photo identification in a traditional clinical trial, and it is wrong to set the bar higher for D2P trials. Disenfranchised and underserved populations often do not have photo identification cards and cannot get them easily, said Craft. Hernandez agreed with Craft, but noted that some state regulations require authentication of those participating in these studies. Another issue is that people share phones and technology, which can make it difficult to understand who a digital health technology is taking measurements from over the course of a study. Rose also agreed with Craft, but added that there are certain areas where verification is important, such as ensuring that a medication does not go to a neighbor. The process does not need to be complicated, and there are ways of using telemedicine to ask a patient if they are the one receiving a medication. Rose also noted that technology can improve compliance with medication regimens by checking in with patients on a daily basis.

4

Access and Equity

Key Messages Identified by Individual Speakers

- Including participants in the design of trials, engaging them in dialogue throughout a study, and returning their data to them can lead to new insights on diseases and therapies and help build trust among participants. (Buchanan, El-Toukhy, McIntyre, Okun)
- Expanding inclusion criteria so that individuals with advanced forms of a disease can participate in clinical trials would allow a larger and more representative patient population to be recruited. (Cummings, Okun)
- Digital health technologies have been presented as a solution to address health inequities or disparities, but these technologies may also risk exacerbating existing and/or create new disparities. (El-Toukhy)
- A key to success in engaging with underrepresented populations in clinical trials is to have a strong ethos for community engagement, acknowledge histories of discrimination and marginalization, and have transparent discussions about power and responsibilities. Building a network of partnerships with community trust brokers can help facilitate engagement with the community. (Buchanan)
- By increasing engagement with minority communities, from outreach and consultation to collaboration and shared leader-

> ship, researchers can help build trust and overcome barriers to participation. (El-Toukhy)

The workshop's third session considered the issues of access and equity in the context of clinical trials and how a virtual model could alleviate or exacerbate current inequities. The discussions focused on the importance of creating partnerships with participants and underrepresented communities, as well as the potential benefits and risks of using digital health technologies to support clinical trials for populations that are traditionally underrepresented in research and whether this type of trial design could potentially exacerbate current inequities or create barriers to access for other communities. Will McIntyre, a patient advocate for The Michael J. Fox Foundation, provided a patient's perspective on access and equity. Sally Okun, vice president of policy and ethics at PatientsLikeMe, described innovative opportunities to increase participant engagement for people living with amyotrophic lateral sclerosis (ALS). Silas Buchanan, chief executive officer (CEO) of the Institute for eHealth Equity, described an approach to conducting meaningful outreach and engagement for underserved communities, and Sherine El-Toukhy, the Earl Stadtman Investigator at the National Institute on Minority Health and Health Disparities, offered lessons learned from behavioral interventions on equitable participation of minorities in research. An open discussion, moderated by Kathy Hudson, executive director of the People-Centered Research Foundation, and Rebecca Pentz, professor of hematology and medical oncology in research ethics at the Emory University School of Medicine, followed the four presentations.

Hudson noted that despite the 1993 National Institutes of Health Revitalization Act requiring National Institutes of Health (NIH) investigators to include women and ethnic minorities in clinical research (IOM, 1994), this goal has not been achieved. In 2004, 67 percent of papers presenting results from clinical trials did not include sex in the analysis, whereas in 2015, 72 percent of NIH-funded clinical trials did not include sex in the analysis (Geller et al., 2018). Similarly, in 2004, 83 percent of NIH-funded studies did not include race or ethnicity in the analysis while in 2015, 85 percent of papers did not include race and ethnicity in the statistical analysis (Fornai et al., 2008). Keeping this lack of progress in mind will be important, Hudson emphasized, as new approaches, opportunities, and methods are considered.

A PATIENT PERSPECTIVE

Will McIntyre, Patient Advocate, The Michael J. Fox Foundation

Will McIntyre, a Parkinson's disease patient, advocate, and volunteer with The Michael J. Fox Foundation, emphasized the need to engage with patients in the design of trials. Making it easy for patients to contribute their feedback on the trial participation experience can result in a plethora of information that researchers can use to improve clinical trials and trial outcomes. High-speed cellular networks should be leveraged to make the clinical trial experience as easy as possible for participants, said McIntyre. Not only could they enable patients to participate remotely, they could also address geographic inequities that result from participants living away from trial sites. As an example, McIntyre described an initiative at Fox Insight,[1] in which a team is initiating dialogue with patients enrolled in Fox Insight studies to collect and aggregate information on the daily lived experience of people with Parkinson's disease. This information is collected remotely, but as McIntyre noted, representation reflects the rural–urban divide in Internet connectivity, highlighting the concentration of participation across coastal urban centers with little geographic representation in the Midwest. To address this unmet need, the research and technology sectors could work together to equip participants with technologies that will better enable them to connect with research studies.

RECRUITMENT FOR CLINICAL TRIALS

Sally Okun, Vice President of Policy and Ethics, PatientsLikeMe

Sally Okun, using ALS as a use-case, focused her presentation on how unique trial designs, such as virtual trials and patient-initiated trials, can not only create new insights, but also increase participation rates of those who are typically excluded from clinical trials. Though PatientsLikeMe now focuses on a variety of disease areas, its story began with the desire to increase access to real-world data for people living with ALS.

One of the first studies conducted by PatientsLikeMe was in response to a request from ALS patients to investigate the efficacy of lithium-carbonate—

[1] Fox Insight is an online study that seeks to build a large, diverse cohort of participants that is representative of Parkinson's patients. Once enrolled and every 90 days thereafter, participants are asked to enter health and disease information. Fox Insight is meant to complement in-person research, and curated data are made available to researchers worldwide in real time. Launched as a beta study in March 2015, more than 5,000 participants (80 percent with a Parkinson's disease diagnosis) contributed data before the study's formal launch in April 2017 (The Michael J. Fox Foundation, 2019b).

a compound found to be effective in slowing ALS progression in a prior study (Fornai et al., 2008). Given ALS's fatality, it was understandable that patients were both seeking to get access to lithium-carbonate and validate its efficacy, said Okun.

PatientsLikeMe recruited 160 patients to participate in the study and used a similar method of self-monitoring used in Fornai and colleagues' (2008) study. While PatientsLikeMe and subsequent NIH studies (Wicks et al., 2011) refuted the results found in Fornai et al. (2008), a recent meta-analysis of all ALS studies using genomic data identified that those with the Unc-13 Homolog A (UNC13A) genetic variant[2] may have a response to lithium-carbonate (van Eijk et al., 2017). This finding in a subgroup of patients with ALS is being explored further by researchers in the United Kingdom and the Netherlands, noted Okun.

Identifying Off-Label Treatments for Possible Clinical Trials

PatientsLikeMe is also a member of ALSUntangled, a consortium of patients, clinicians, and researchers that seeks to understand the efficacy of alternative and off-label treatments to which people living with ALS turn. ALSUntangled engages in patient-driven inquiry by basing research initiation decisions on patient input regarding which alternative treatments to test further. As of 2015, ALSUntangled has reviewed more than 40 therapies and graded them based on validity and potential benefit, using the following metrics: mechanistic plausibility, strength of relevant pre-clinical data, case reports, existence of trials, and identified risks (ALSUntangled Group, 2015). One such product is Lunasin, a soy peptide for which there is some theoretical basis to believe it could be relevant for ALS, some potentially supporting case study data, and a peer-reviewed trial. As a result, PatientsLikeMe and the Duke ALS Clinic decided to explore this product more.

The resulting study, ALSUntangled No. 26: Lunasin study (ALSUntangled Group, 2014),[3] a hybrid virtual trial, required the 50 participants who enrolled to have a clinic visit on day 1, day 30, and day 365. At all other times, participants entered information into their PatientsLikeMe online profile, and they were also contacted by the clinic nurse and community moderator. Lunasin therapy did not produce improvements in progression scores, but the study did show that participants liked engaging in research that did not require frequent trips to the clinic (Bedlack et al., 2019). Furthermore, by

[2] UNC13A is a gene that encodes the Unc-13 homolog A protein, which is involved in neurotransmitter release (Bohme et al., 2016).

[3] Available at https://clinicaltrials.gov/ct2/show/NCT02709330 (accessed April 22, 2019). Additional information can be found in Appendix D.

eliminating the typical requirements[4] for inclusion, the study was able to get a more representative subset of ALS patients (ALSUntangled Group, 2014). Retention in the study was nearly 89 percent, indicating that participants were satisfied with the trial design and were committed to participating in the trial. Regarding access, inclusion, and engagement, Okun and her colleagues concluded that this approach could serve as a model for other diseases in which PatientsLikeMe could become involved.

Based on their experience with the Lunasin trial, PatientsLikeMe and the Duke ALS Clinic are designing two virtual trials: ALS Reversals (Harrison et al., 2018) and ALSUntangled No. 44: Curcumin (Bedlack, 2018). The studies will investigate "differences in demographics, disease characteristics, treatments, and co-morbidities" between patients who have experienced ALS reversals and those who have not, in addition to the efficacy of curcumin in treating ALS, respectively (Okun, 2018). Both studies will include a range of phenotypic data entered online by patients as well as multi-omics data from in-home biospecimen collection.

UNDERSERVED COMMUNITY OUTREACH AND ENGAGEMENT

Silas Buchanan, CEO, Institute for eHealth Equity

Silas Buchanan emphasized the importance of engaging directly with community members when deploying digital interventions. Building a network of partnerships and leveraging trust brokers within the community can be instrumental in the success of public health campaigns. Using his social impact firm, Institute for eHealth Equity, as an example, Buchanan provided key lessons learned for how virtual trials can be designed and positioned to increase inclusion of underrepresented populations, and if there are specific trial design considerations needed to address the unique socioeconomic factors those populations face.

Will Technology Improve or Exacerbate Problems with Access and Equity?

The Institute for eHealth Equity was formed to address the concern that the adoption of technology in health care might exacerbate health disparities given that developers rarely seek input from underserved populations. For example, Buchanan remarked how academic medical centers in the Cleveland area often receive grants from developers to study African American infant mortality rates, but none have invited community organizations or members to offer input when grants are being written. To address this problem, the

[4] Inclusion requirements for ALS clinical studies include high scores for respiratory and swallowing functions and having ALS for less than 36 months.

Institute for eHealth Equity has built social networks, systems, and platforms for faith- and community-based organizations that have relationships with the individuals in their communities. The Institute for eHealth Equity's approach to community health is based on Buchanan's prior experience with a project called Text for Wellness[5] in which he and his colleagues asked pastors in five faith-based organizations—in Atlanta, Georgia; Columbus, Ohio; and Dallas, Texas—to talk about health from the pulpit. Churchgoers were also asked to interact with a mobile health service, in which they received evidence-based healthy eating and activity text messages and queries. The five churches generated 2,500 participants, 43 percent of whom responded to the questions. According to Buchanan, the program had a 100 percent retention rate, indicating the success of a public health campaign that leverages faith- and community-based organizations as an entry point.

An Online Portal for Community Engagement and Collaboration in Clinical Trials

The Institute for eHealth Equity has recently developed a platform called Our Healthy Community[6] in collaboration with faith- and community-based organizations, including the African Methodist Episcopal Church.[7] Our Healthy Community enables underserved faith- and community-based organizations to coordinate community health improvement campaigns sponsored by health care payers, providers, and government and academic stakeholders. Recently, Our Healthy Community signed a memorandum of understanding with the City of Cleveland Office of Minority Health to provide 30 community-facing organizations with access to this platform in order to cover approximately 30,000 community members in targeted public health campaigns. Our Healthy Community is designed with six broad features to achieve desired, trackable outcomes around sponsored public health campaigns (see Figure 4-1):

1. Standardized and public health campaign–specific training for faith- and community-based organizations.
2. Coordination of partners to shape campaign scope and strategy (see Box 4-1 for an example of early communication to develop tools for infant mortality).

[5] Available at http://text4wellness.com (accessed April 22, 2019).

[6] Available at http://www.ourhealthycommunity.com/Public/About-OurHealthyCommunity (accessed April 22, 2019).

[7] The African Methodist Episcopal Church is the largest historically black denomination worldwide, with more than 2,000 congregations and more than 2 million members. Approximately 30 percent of these congregations have a dedicated health minister embedded in the church to foster relationships with health care systems in their communities.

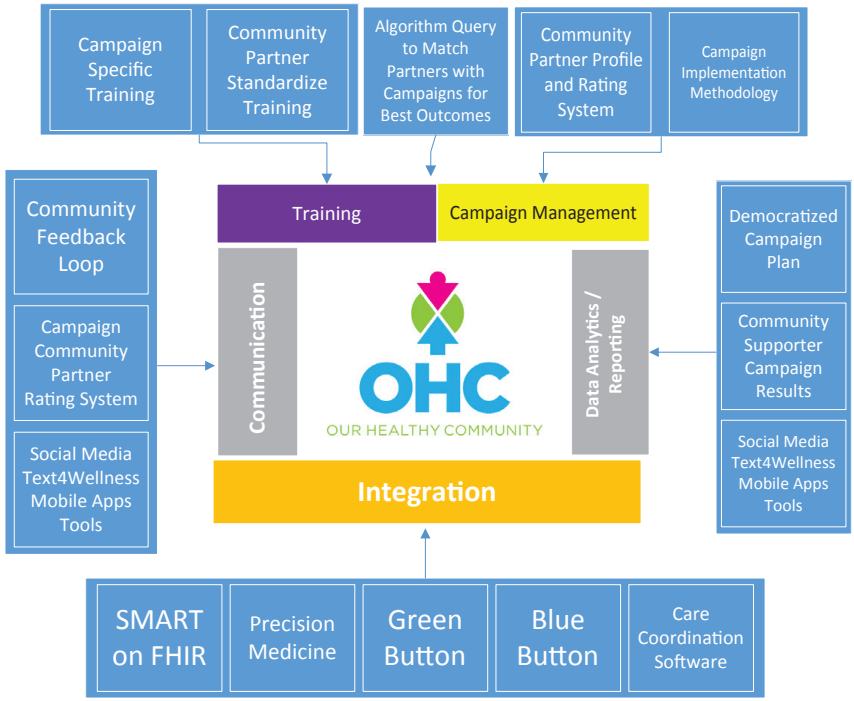

FIGURE 4-1 Our Healthy Community model for community engagement.
NOTE: FHIR = Fast Healthcare Interoperability Resources; SMART = Substitutable Medical Applications, Reusable Technologies.
SOURCE: As presented by Silas Buchanan, November 29, 2018.

3. A queriable database to match community partners with the right public health campaign.
4. Consistent communication with community members to push the message of the public health campaign.
5. Integration with an open-source system, such as SMART on FHIR[8] and Blue Button,[9] and other care coordination systems to allow community members to own and control health data.

[8] SMART on FHIR "is a set of open specifications to integrate apps with electronic health records, portals, health information exchanges, and other health information technology systems" (SMART, 2017).

[9] Blue Button is a system for patients to view their personal health records online and download them into a text file or a PDF (VA, 2018).

BOX 4-1
Facilitating Early Communication Between Community Organizations and Technology Developers: The Battle for Our Babies Campaign

In Cleveland, Ohio, the African American infant mortality rate is higher than the statewide average. In partnership with the Healthcare Information and Management Systems Society (HiMSS) Innovation Center, Our Healthy Community, a social impact firm that engages underserved communities through the innovative use of technology, created the Battle for Our Babies Infant Mortality awareness campaign. Approximately 85 community leaders participated in a discussion at the HiMSS Innovation Center to provide technology developers with insight about what was important to various groups in the Cleveland community. Developers entering the contest were given access to Our Healthy Community's online platform to continuously communicate with community organizations for 5 weeks. This allowed developers to inquire about community needs while creating their technology solutions. After receiving 45 submissions, HiMMS and Our Healthy Community facilitated funding from the Cleveland Clinic for three finalists: the "SMILE Team" (Nationwide Children's Hospital and The Ohio State University), the "Tackle Fatherhood Team" (University of Rochester), and the "Gabby System Team" (Boston Medical Center and Northeastern University). Our Healthy Community and HiMSS are now partnering on a venture with Children's Hospital Los Angeles to introduce a technological solution for adolescent homelessness and mental health issues.

SOURCES: As presented by Silas Buchanan, November 29, 2018; from HiMSS, 2018.

6. Sharing of data along the value chain, including community members, community organizations, and public health campaign funders, to issue campaign updates and create a feedback loop between community members and funders.

A key to the successful introduction of digital tools in health care is to have a mechanism to hear what the community wants rather than designing them in a vacuum, said Buchanan. This will require a strong ethos for community engagement, including the acknowledgment of histories of discrimination, transparent discussions about power and responsibilities, documentation of community strengths, collection of local knowledge to understand a community's culture intimately, and building capacity within the community to identify opportunities for co-learning and sustainable, equitable partnerships. Primary outcomes of successfully launching a digital tool ultimately will be the establishment of democratized feedback loops with community members. By being part of Our Healthy Community,

community partners will gain access to tools that will enhance their ability to reach community members. They will also receive accurate and timely feedback reports using community member input that will contribute to a public health campaign's success.

According to Buchanan, virtual or direct-to-participant (D2P) trials can be positioned and designed to increase inclusion of underrepresented populations, though they will need to address unique considerations to sustainably build relationships with the community. He also believes that data-driven insights and emerging tools can be leveraged to both generate data on access and equity, in addition to improving inclusion of underrepresented populations. Furthermore, Buchanan noted that there are specific disease areas, such as sickle cell anemia, in which access and equity can be improved immediately.

LESSONS LEARNED FROM BEHAVIORAL INTERVENTIONS

Sherine El-Toukhy, Earl Stadtman Investigator,
National Institute on Minority Health and Health Disparities

Sherine El-Toukhy highlighted lessons she has learned from research on the participation of underserved populations in digital behavioral interventions. She suggested that while health information technology may reduce health inequities, it can unintentionally exacerbate existing disparities or create new ones.

Data show that the digital divide is shrinking in the United States. Cell phone ownership[10] of any kind in the United States is now at nearly 95 percent, with smartphone ownership reaching 77 percent (Pew Research Center, 2017). Mobile phone ownership is seen across nearly all socioeconomic groups, though disparities still exist based on age, education, and income level (see Figure 4-2).

Data from the Health Information National Trends Survey, sponsored by the National Cancer Institute, also show that 80 percent of Americans report having Internet access, either through a broadband connection, cellular plan, or Wi-Fi (El-Toukhy et al., In Review). However, older individuals, those of low socioeconomic status, people who are separated or widowed, and those with limited English proficiency are less likely to report using the Internet, noted El-Toukhy. El-Toukhy identified similar trends with respect to patient portal access. Lower educational attainment, she noted, was a main characteristic associated with less access to and use of electronic health records (EHRs) (El-Toukhy et al., In Review).

[10] Cell phone ownership indicates the percentage of U.S. adults, age 18 and above, who own a cell phone (Pew Research Center, 2017).

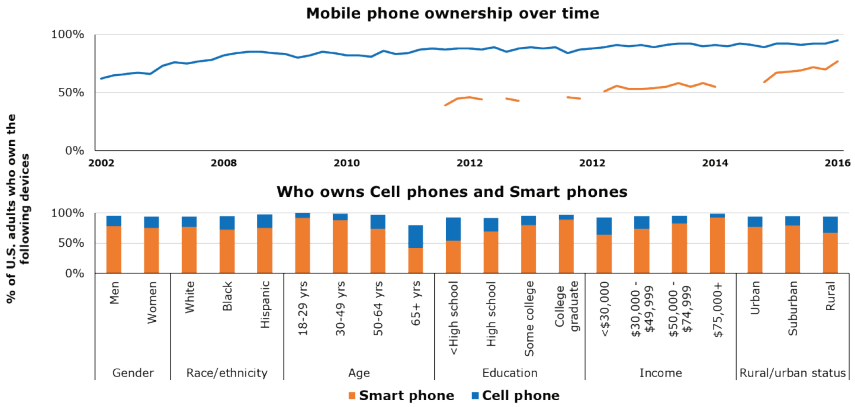

FIGURE 4-2 Mobile phone and smartphone ownership trends across socioeconomic demographic groups.
NOTE: Breaks in the line graph for smartphone ownership indicate where there is a gap in data.
SOURCES: As presented by Sherine El-Toukhy, November 29, 2018; data from Pew Research Center, 2017.

Community Member Engagement

El-Toukhy noted that evidence-based behavioral interventions have shown promise for addressing social and behavioral factors that underlie morbidity and mortality. For example, a National Cancer Institute text messaging program, SmokeFreeMOM, can increase smoking cessation rates among pregnant women who want to quit smoking (Kamke et al., In Review). Cessation rates were found to be comparable among Hispanics, African Americans, and whites at interventional milestones (e.g., quit day, intervention end, and 1-month follow-up). However, only 9 percent of study participants were Latina and 16 percent were African American, which is well below the national representation for these groups.

Understanding the target population's needs, values, and preferences, as well as their barriers to participation, is key to designing culturally and linguistically appropriate clinical trial recruitment material, said El-Toukhy. She noted there are websites[11] that can create customized recruitment materials to meet the needs of target populations based on age, race, ethnicity, and other factors. Furthermore, investigators should consider modes and outlets of recruitment to ensure efforts are targeting desired populations.

[11] See Make It Your Own for an example of a platform to facilitate creation of customized health information for targeted populations (MIYO, n.d.).

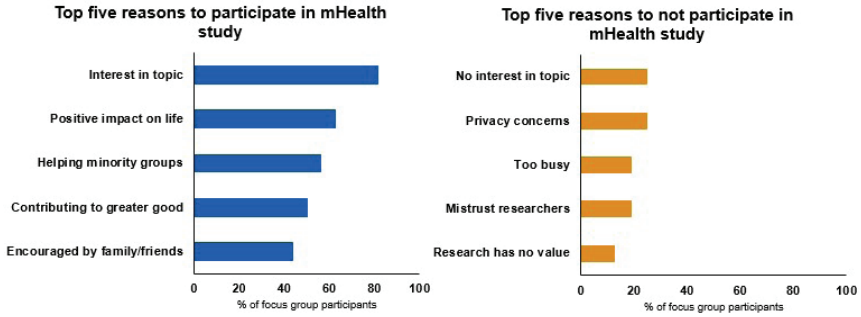

FIGURE 4-3 Reasons for minority participation and non-participation in mHealth research.
NOTE: mHealth = mobile Health
SOURCE: As presented by Sherine El-Toukhy, November 29, 2018.

Sustained engagement of research participants is important in the context of digital interventions. Unfortunately, high dropout rates can be common. For example, in the text messaging-based smoking cessation intervention mentioned earlier, dropout rates were highest during the first week of the intervention, with continued dropouts over time. To improve engagement, it is important to involve the end users in the creation and design process and to prioritize the needs and wants of marginalized populations, said El-Toukhy. Furthermore, the use of passive or automated data collection or simplified assessment instruments[12] can reduce the time and resource intensiveness of assessment. Providing an example of an algorithm used to improve outcomes in Drug Court (Marlowe et al., 2012), El-Toukhy emphasized the potential of adaptive designs to monitor and adapt a trial in case of missing responses based on predetermined rules. In the context of a virtual clinical trial, for example, a reminder schedule can be designed to prompt the participant to enter the missing data only if someone fails to log a piece of information.

While there is a myth that minorities and underserved populations do not want to participate in studies, El-Toukhy presented unpublished data from two focus groups with 16 African American women that found the opposite. In fact, these women are willing to participate in research to generate knowledge that will help their communities and contribute to the greater good (see Figure 4-3). Barriers to participation, El-Toukhy noted, are not as prominent as expected, with the main barriers being lack of interest and skepticism about the researchers or value of a study.

[12] El-Toukhy provided examples of instruments, including PROMIS, Neuro-QoL, ASCQ-Me, and NIH Toolbox (Health Measures, 2019).

El-Toukhy emphasized the need to leverage the willingness of minorities and underserved populations to participate in clinical trials. By increasing engagement with minority communities, from outreach and consultation to collaboration and shared leadership (NIH, 2011), trust will be fostered and barriers to participation can be alleviated.

DISCUSSION

Hudson noted that a common theme raised by panelists was the importance of inviting patients to inform study design early in the process, and asked the panelists to provide examples of how to do this effectively. A specific approach on how to do this was proposed by McIntyre, who reflected on a practice at The Michael J. Fox Foundation that involved adjusting language in the recruitment and engagement processes to make participants feel like contribution was more meaningful than just inputting data into their phones or computers. Similarly, Okun shared that PatientsLikeMe has been developing two tools:

- Patient Trial Experience Survey: Queries those who join PatientsLikeMe about their prior participation in a clinical trial and their experiences with previous clinical trials.
- Trial Mark: Targets those who run clinical trials to gauge what they perceive the participant experience to be. Trial Mark will be released in 2019 and will benchmark trials against others in terms of participant centeredness and give participants a voice in being able to measure what is important.

El-Toukhy echoed these comments, indicating that an iterative approach that includes usability testing and focus groups to perfect the design of an application or an intervention would be useful. Another approach could involve crowdsourcing, but would likely prove more useful for diseases that affect large numbers of people.

In addition to involving patients early in the study design phase, patient engagement can be strengthened by returning data. Cynthia Geoghegan from the Clinical Trials Transformation Initiative (CTTI) noted that a survey CTTI conducted on 400 potential research participants revealed that 98 percent of respondents wanted their data retuned in real time. In fact, the National Academies report *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm* (NASEM, 2018b) called for a return of individual results to participants. According to Hudson, this is a reflection of a broader cultural shift from paternalism to partnership in medicine and research. However, strengthening participant engagement through return of data, according to Geoghegan, may need to

be balanced with impacts on randomization. Both Okun and El-Toukhy acknowledged this risk, emphasizing that participants should be educated about randomization upon recruitment and that data returned should not expose inappropriate information that can damage the integrity of the trial. Creating a mechanism for return of data that people trust will be important, noted Buchanan. Furthermore, establishing a plan on returning data in the research design itself will make it more likely that it occurs, noted Okun, in reference to a data giveback plan that PatientsLikeMe uses.

Valerie Barton from FasterCures asked Buchanan how Our Healthy Community notifies community members once a public health campaign has been completed. She also asked about how data collected by Our Healthy Community are used, aggregated, and analyzed and whether that plays into outreach efforts. According to Buchanan, Our Healthy Community is able to share aggregated data from its campaigns with community organizations for their own uses. Buchanan noted that a long-term goal of Our Healthy Community includes analyzing trends and capturing data on social determinants of health and integrating this information with EHRs.

Cummings commented on the unique needs of patient and community engagement to ensure that clinical trial research can account for differences in outcomes that may be attributable to demographic and/or disease severity differences. NIH requirements to recruit a population that represents the underlying U.S. demographics may not be sufficient to account for the power needs to investigate if, for example, there is a biological reason for why Hispanics and whites respond to an intervention differently, said Cummings. He then remarked that for some studies, such as one he is doing on Parkinson's disease and aging, people with more severe forms of the disease need to be better represented, which is hard to achieve. More unique and creative forms of engagement would be required to include underrepresented populations for these purposes, Buchanan suggested.

Emily Butler from GlaxoSmithKline asked the panelists if they had ideas on how to incentivize industry sponsors to more actively involve patients in trial planning and design. Hudson replied that her organization, the People-Centered Research Foundation, involves patients as partners from the start of a project and compensates them for their efforts. Then, when the foundation starts working with prospective sponsors of a study, it clearly states that it has requirements for meaningful participation, something that potential sponsors have embraced uniformly. However, for the widespread culture of the pharmaceutical industry to change, said Hudson, there needs to be evidence showing that involving patients to this extent improves outcomes and a continued expectation from the U.S. Food and Drug Administration that clinical trials focus on patient partnership.

5

Policy Considerations

Key Messages Identified by Individual Speakers

- Regulatory considerations for applying remote technologies in decentralized trials are not unique, but there is a need to apply existing regulations to a new environment. Those considerations will vary based on the disease area, the type of investigational drug, and the types of trial activities that are decentralized. (Sacks)
- An important consideration when it comes to new technological tools is ensuring the integrity and security of electronic records and the accuracy and precision of remote sensor measurements. (Sacks)
- In the context of a virtual or decentralized clinical trial, the Health Insurance Portability and Accountability Act covers the data collected during the trial, even if those data are submitted from a patient's mobile phone. (McGraw)
- Recent developments in privacy laws, such as California's Consumer Privacy Act and the European Union's Global Data Protection Regulation, require more explicit consent and set a higher bar for data to be considered "de-identified." This is not as large of a concern for primary data collection in a clinical trial setting as it is for onward secondary uses, such as replication of results or additional studies. (McGraw)

- Investigators should clearly articulate procedures and train staff on processes unique to decentralized clinical trials. In addition, trial participants must know what to do in the case of experiencing an adverse event. (Madre)
- Patient-facing entities, such as a consumer-directed data exchange, may provide an opportunity to more easily reach people who are eager to participate in clinical trials and have data they want to contribute. The challenge is to ensure that people are truly informed about how they will be sharing their data and not place all of the responsibility on consumers. (McGraw)
- Taking full advantage of the opportunity for incorporating passive data into clinical trials may require new policies for mixed uses and sources of data, dynamic ways to inform participants about data collection, and innovative approaches to seek consent for research uses of data. (McIntyre)

In the workshop's fourth session, the panelists discussed current and future policies that govern clinical trials and their relevance to virtual trials. They examined the challenges and potential solutions to issues involving the collection of remote data from participants (e.g., how to ensure collected data comes from the actual participant and if participants are using a digital health technology properly) as well as privacy considerations. Leonard Sacks, associate director for clinical methodology in the Office of Medical Policy at the U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research, discussed his views on policy considerations for decentralized trials. Leanne Madre, director of strategy at the Clinical Trials Transformation Initiative (CTTI), discussed her organization's decentralized clinical trials project. Deven McGraw, general counsel and chief regulatory officer at Ciitizen Corporation, spoke about privacy protections for virtual trials, and Matthew McIntyre, senior scientist for data collection at 23andMe, discussed considerations for informed consent in relation to passive data collection and its associated paradata. An open discussion moderated by John Wilbanks, chief commons officer at Sage Bionetworks, and David McCallie, senior vice president for medical informatics at Cerner, followed the four presentations.

A REGULATORY PERSPECTIVE

Leonard Sacks, Associate Director for Clinical Methodology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Sacks highlighted the opportunities to use mobile technologies and engage local providers to promote inclusivity and convenience for trial participants, and for gathering information on real-world patient experience. These opportunities will require policies and regulations to address patient safety, privacy, the integrity of the data that remote technologies produce, and the responsibilities of the investigators involved in technology-enabled decentralized trials.

Decentralized clinical trials are not new, said Sacks, but recent advances in communication, data capture, and transmission technologies have created opportunities to conduct decentralized trials better—as has the recognition of local health care providers' value in performing trial-related functions. While the considerations for using new technologies in decentralized trials are not unique, there is the need to apply existing regulations to a new environment. Those regulatory considerations may vary, he added, depending on the disease area, the type of investigational drug, and the types of trial activities that are decentralized.

According to Sacks, there are four areas of interest for regulators when thinking about policy considerations for technology-enabled decentralized clinical trials: (1) the personnel involved in the trial, (2) the trial site, (3) the tools being used, (4) and participant safety.

Clinical Trial Personnel

Current FDA regulations say little about encounters with study participants, said Sacks, but they do address personnel oversight responsibilities. The Code of Federal Regulations defines an investigator as an individual who actually conducts a clinical investigation, that is, the person under whose immediate direction the drug is administered or dispensed to a subject.[1] He pointed out that this definition does not require a face-to-face encounter. In the event that a team is conducting the study, the investigator is the responsible leader of the team. A sub-investigator includes any other individual member of that team. The investigator and any sub-investigators need to have a good understanding of the protocol and investigational product and they need to have direct and substantial involvement in the trial, regardless of whether it is a site-based or decentralized trial. The

[1] 21 CFR § 312.3.

investigator and sub-investigator are listed on the Form FDA 1572, a legal agreement signed by the investigator that he or she will comply with FDA regulations[2] related to the conduct of a clinical trial. Local providers, such as phlebotomists or those who prepare pathology reports, do not have to meet those criteria.

Clinical Trial Site

A clinical trial site traditionally has been a physical location. However, FDA regulations do not have a clear definition for this term. Typically, a site is where the intervention is provided and where assessments for the trial are conducted. Given this lack of clarity, a key issue to consider is whether there are practical limits to the decentralization of trial activities under a single investigator's supervision. Another issue regulators may need to address is how supervision, monitoring, and inspection will be conducted at decentralized sites, said Sacks. For some trials, investigator supervision of participants may not be much of a concern, but for others, such as a trial for a new antidepressant during which participants' behaviors may not be predictable, closer supervision might be necessary.

Clinical Trial Tools

Regardless of the type of communication tool used in a clinical trial, an important consideration will be to ensure the integrity and security of electronic records, said Sacks. Additional concerns include the attribution of data and appropriate use of audit trails to reconstruct how data are generated. Lastly, Sacks emphasized that the accuracy and precision of remote biosensors are critical to prevent false-positive readings.

Participant Safety

Ensuring participant safety in a decentralized trial is no different than in a traditional clinical trial, said Sacks. Participants would require access to qualified professionals to address adverse events, for example, and investigators would need to make provisions for prompt capture of safety data from participants and their providers during the course of a trial. However, Sacks noted that remote sensing technologies are creating opportunities

[2] Responsibilities include follow the protocol, personally conduct or supervise the study (delegation is permitted), receive informed consent covered by an Institutional Review Board (IRB), report adverse events, understand potential risks and side effects, ensure that all associates assisting in the conduct of the study are informed about their obligations, adequate and accurate recordkeeping and retention, and reports to the IRB.

for greater oversight of safety by replacing episodic monitoring with continuous monitoring of variables such as blood glucose levels or heart rate and rhythm. At the same time, he cautioned, it is important to ensure that technology failure does not jeopardize participant safety or the integrity of the data and that technical support is available for when a digital health technology malfunctions.

Sacks envisions decentralized trials to operate like a hub-and-spoke model, with the investigator and sub-investigator at the center and participants at the periphery, and connected by local providers and mobile technologies. If the technologies used in decentralized trials can collect robust data with high signal-to-noise ratios,[3] it may be possible to shorten trials and possibly increase participant retention. Remote tools may also reduce the number of participants required to power a study if the signal-to-noise ratio is high enough. However, for mobile technologies to reach their potential of bringing a clinical trial to the participant, policies and regulations to address participant safety, privacy, data integrity, and the responsibilities of investigators in a decentralized trial environment need to be in place.

CLINICAL TRIALS TRANSFORMATION INITIATIVE: DECENTRALIZED CLINICAL TRIALS PROJECT

Leanne Madre, Director of Strategy, Clinical Trials Transformation Initiative

CTTI, explained Leanne Madre, is a public–private partnership cofounded by Duke University and FDA. Currently, more than 80 members, representing stakeholders from academia, biotech companies, pharmaceutical companies, patient groups, regulators, and others, are working to "develop and drive adoption of practices that will increase the quality and efficiency of clinical trials" (Madre, 2018). CTTI started its Mobile Clinical Trials (MCT) program[4] (see Figure 5-1) at FDA's suggestion, with the purpose of influencing the widespread adoption and use of mobile technology in clinical trials.

The MCT program consists of four projects: novel endpoints, mobile technologies, decentralized clinical trials, and engaging patients and sites. The first project focused on how to collect existing endpoints differently using technology and how to validate endpoints that are now available due to emerging technologies (CTTI, 2019d). The second project focused on

[3] Signal-to-noise ratio compares the level of a desired signal to the level of background noise. It is a measure of how much useful information a technology can produce.

[4] Available at https://www.ctti-clinicaltrials.org/programs/mobile-clinical-trials (accessed April 20, 2019).

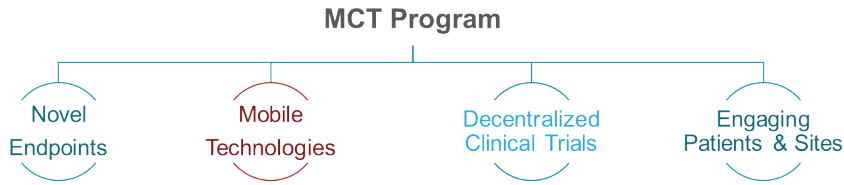

FIGURE 5-1 CTTI's Mobile Clinical Trials (MCT).
SOURCE: As presented by Leanne Madre, November 29, 2018.

the mobile technologies themselves: how to select one while keeping data quality and implications for regulatory submission in mind (CTTI, 2019c). The third project investigated the benefits of conducting clinical trials outside of traditional brick-and-mortar sites (CTTI, 2019a). The fourth project focused on understanding how patients and investigators viewed the opportunities and challenges of applying digital technology in clinical trials (CTTI, 2019b).

Decentralized Clinical Trials Project

Madre focused her discussion on the third project under CTTI's MCT program. Key benefits of a decentralized clinical trial that CTTI was able to identify included those that previous speakers discussed: faster trial participant recruitment; improved retention; greater control, convenience, and comfort for participants; and increased participant diversity. To achieve these benefits, CTTI issued recommendations that fell into six categories: protocol design, telemedicine state licensing laws, mobile health care providers, drug supply chain, investigator delegation and oversight, and safety monitoring.

Protocol Design

Protocol design for a decentralized trial, said Madre, does not require an all-or-nothing approach. In fact, elements of decentralization, such as telephone or video conferencing, can be incorporated in a protocol that uses a traditional site. However, engaging with FDA early in the design process and highlighting the unique attributes of a decentralized trial when developing the trial protocol and standard operating procedures will be important for trial success. FDA has a number of established pathways through which investigators can meet with regulators early in the process of designing a study, said Madre. CTTI also encourages investigators to talk to those who have already conducted a decentralized trial, including other sponsors and even technology vendors, to avoid having to relearn lessons and instead build on what others have already accomplished.

Telemedicine State Licensing Laws

When the project started, there was a perception that there were notable legal barriers to conducting decentralized trials, noted Madre. However, there were only a few legal issues to deal with—particularly state licensing. Physicians or health care providers require a professional license from the state in which they practice as well as the state where they see patients. Given that laws can vary by state, conducting a decentralized trial can require different strategies to meet licensure requirements (i.e., maintaining licensed investigators in each active trial state, using investigators licensed in multiple states, or contracting with vendors that have a network of licensed investigators in place). Madre noted that the Center for Connected Health Policy maintains a website[5] that compiles information on telemedicine laws across the United States.

Mobile Health Care Providers

As a decentralized clinical trial can cover a wide geographic area, it might be necessary to use mobile health care providers—or health care providers who can travel to participants for protocol contributions. Activities can include blood draws, administration of the investigational products, clinical assessments, and in-home compliance checks. Thus, it will be important for such providers to be properly credentialed and trained.

Drug Supply Chain

Similar to licensure, direct-to-participant shipment of drugs can also vary by state. State laws governing shipment of the investigational product should be reviewed, noted Madre, prior to conducting a decentralized clinical trial. Furthermore, it is also important that the supply chain is well documented so that everyone involved in a study understands their role in the supply chain. Engaging with vendors who have prior experience shipping investigation medical products to participants would be useful to sponsors, noted Madre.

Investigator Delegation and Oversight

Developing procedures for investigator delegation and oversight is highly protocol specific, said Madre. The standards employed in a decentralized trial do not need to be higher than for a standard trial, but the differences between

[5] Available at https://www.cchpca.org/telehealth-policy/legislation-and-regulation-tracking (accessed January 30, 2019).

a standard and a decentralized trial must be accounted for when thinking about delegating responsibilities to investigators, sub-investigators, and local providers. This is another area, she added, where talking to regulators early can pay dividends.

Safety Monitoring

Given the different array of providers involved in a decentralized clinical trial, it will be important for investigators to ensure that trial participants and trial staff are aware of procedures related to adverse events and that the response plans are pre-coordinated. Furthermore, sponsors should consider how communication escalation plans may differ based on the elements of decentralization being used.

PRIVACY PROTECTIONS FOR VIRTUAL CLINICAL TRIALS

Deven McGraw, General Counsel and Chief Regulatory Officer, Ciitizen Corporation

McGraw discussed the importance of protecting participant privacy and data generated by participants, as well as policy mechanisms used in the United States and in Europe to protect privacy. Privacy protections matter, emphasized McGraw, because they build trust and help ensure that people will seek health care and enroll in clinical trials. McGraw noted that one out of six people withhold information about their health because of confidentiality concerns, and as many as two-thirds of adults suffering from a diagnosable mental health disorder do not seek treatment, in part because of fear of disclosure of sensitive health information. Additionally, racial and ethnic minorities express stronger concerns about health privacy, noted McGraw.

Privacy, said McGraw, is about enabling appropriate data use with good data stewardship that engenders trust among trial participants by getting them comfortable with how data will be used and disclosed as a part of the study. Engendering trust also requires investigators to make and keep commitments to trial participants concerning how their data will be used and disclosed. Informed consent plays an important role here, as does honoring the autonomy of the individual participant by being transparent about how data will be used, minimizing the amount of data collected, minimizing who has access to the data, and having some accountability and adherence to policies.

The Role of the Health Insurance Portability and Accountability Act

McGraw noted that the terms "clinical trial" and "virtual clinical trial" are not defined terms in the Health Insurance Portability and Accountability Act[6] (HIPAA) regulations, though HIPAA does define research as a systematic investigation that has as its primary purpose the development of, or contribution to, generalizable knowledge. In the context of a virtual or decentralized clinical trial, HIPAA covers the identifiable data collected by the investigator if the investigator is a HIPAA-covered entity. Furthermore, HIPAA will apply to the data collected by the investigator even if they originated from a participant's mobile phone. Whether HIPAA covers data that reside in consumers' mobile devices, such as a Fitbit or an Apple Watch, is less clear, McGraw said. If the mobile device is given to the participant by the study, for example, the data are likely to be covered by HIPAA, but if the participant is using a commercial mobile device that is not under the control of the investigator, the data in the device may not be covered by HIPAA. However, the Federal Trade Commission does have the authority to ensure that vendors of mobile devices are held liable for data breaches.

In terms of data reuse, new laws in place shift the emphasis to consent, as de-identification is potentially more difficult, noted McGraw. Both HIPAA and the Common Rule[7] allow for more generalized consents for future research purposes, but in the context of a specific trial for medical product development, consent likely needs to meet both FDA regulations and Common Rule requirements.

Recent developments in privacy laws, such as California's Consumer Privacy Act (CCPA)[8] and the European Union's Global Data Protection Regulation (GDPR),[9] are now requiring more explicit consent and set a higher bar for data to be considered "de-identified." This is not as large of a concern for primary data collection in a clinical trial setting as it is for onward secondary uses, such as replication of results or additional studies, noted McGraw, because CCPA contains exceptions for regulated clinical trials. McGraw explained that GDPR applies to all personal data collected from individuals within the European Union. Although it does allow for scientific research, data use is subject to various safeguards. CCPA, which goes into effect on January 1, 2020, pertains to data collected from any-

[6] The Health Insurance Portability and Accountability Act of 1996 addresses security provisions and data privacy to keep patients' medical information safe (45 CFR § 164.512(j)).

[7] Common Rule: The "Common Rule," or the Federal Policy for the Protection of Human Subjects, governs biomedical or behavioral research involving human subjects. Codified into separate regulations by 15 federal departments, the "Common Rule" provides a legal baseline on the standard of ethics by which human subjects research is conducted (45 CFR § 46).

[8] Available at https://oag.ca.gov/privacy/ccpa (accessed April 10, 2019).

[9] Available at https://eugdpr.org (accessed April 10, 2019).

one living in California. It has some retroactive provisions that sponsors will need to address in 2019 in order to be in compliance by the effective date, McGraw cautioned. As noted above, one exception in the law is for information collected as part of a clinical trial that will be subjected to the Common Rule or FDA regulations, a space that California legislators considered well regulated already. However, she added, subsequent uses of data may or may not be covered by that exception. McGraw said privacy is a hot topic and Congress could engage in this area more actively in the future.

INFORMED CONSENT FOR PASSIVE DATA COLLECTION

Matthew McIntyre, Senior Scientist, Data Collection, 23andMe

McIntyre discussed the particular policy and regulatory challenges in developing informed consent processes for remote studies in which data will be collected passively. Passive data collection, explained McIntyre, refers to data that are collected from a source that is remote from the researcher and that flows to the researcher continuously or at regular intervals. McIntyre focused on three aspects of passive data collection: when the participant is unaware of passive data collection, use of a third-party vendor, and existence of paradata.[10]

A research participant may not be fully aware of passive data being collected, even if informed consent has been provided, because these data may be collected in the background of some other activity. A concern for investigators is to determine how many details need to be provided to research participants on the type of data being collected. Furthermore, passive data being used for research purposes can come from third party mobile applications, such as Apple HealthKit,[11] which typically does not collect data for research purposes. While privacy considerations for passive data collection draw primarily on HIPAA, as well as more recent regulations on de-identification of data for research purposes, participants may have specific concerns that go beyond de-identification, such as who will have access to their data and how their data will be used. Trial participants, said McIntyre, want to have a more complete understanding of the different ways their data will be used, a desire that has led to many of the new privacy regulations policy makers are promulgating. It will be challenging,

[10] Paradata are "data about the data" (IOM, 2015), such as where data were collected, how long they took to be collected, and at what time they were collected. While a participant has given consent for data collection, flow of paradata from the participant to the research investigator occurs without the participant's effort.

[11] Apple HealthKit "provides a central repository for health and fitness data on iPhone and Apple Watch. With the user's permission, apps communicate with the HealthKit store to access and share these data" (Apple, 2019).

he noted, to develop a way of allowing for mixed uses and sources of data that participants will trust and that will be usable for research.

Handling Paradata

McIntyre addressed the subject of paradata, the additional data collected along with passive data. Paradata can include time stamps, geolocation, digital health technology settings, and other information that could be used in a variety of ways having little to do with a clinical trial. The vast quantity of paradata poses a challenge for researchers to effectively de-identify passively collected data, he explained. His company, 23andMe, faces this challenge with genetic data. There is a vast quantity of genetic data that is nearly impossible to de-identify given that sufficient information about a person's DNA essentially defines that individual. One current solution, he said, is data minimization—a practice in which only the data needed will be collected. However, paradata can be important for quality control, and data minimization may limit audit trail documentation required by regulatory agencies. It might also take away some of the capabilities of study investigators to monitor safety and protocol compliance, noted McIntyre. This can be crucial in a virtual clinical trial, he added, as an investigator may not always be able to document what is happening with a participant.

McIntyre said that for a traditional trial with a narrow focus, passive data probably do not pose challenges that researchers have not already encountered with other types of data. However, taking full advantage of the opportunity for incorporating passive data in virtual and embedded trials and other research studies may require new policies for mixed uses and sources of data, dynamic ways to inform participants about data collection, and new approaches to seeking informed consent for research uses of data.

DISCUSSION

Raj Sharma, chief executive officer of Health Wizz, started the discussion by explaining that his company has developed a user interface for clinical trial participants that resembles a video game, with badges, prizes, leaderboards, and milestones related to a clinical trial—an approach termed "gamification." His question was whether this approach was too extreme to be useful in the clinical trials environment. McGraw replied that in her opinion, an appropriate approach is to first develop a clinical trial with its desired outcomes and endpoints, and only then find the technology tool that will help the trial meet its goals, as opposed to developing a tool and then looking for a clinical trial that would benefit from that tool. She acknowledged that a game-based approach might be an effective way to get people

interested in participating and staying in a trial because the user experience could make data entry more fun rather than tedious. She also noted that if such a tool were used in a clinical trial, it would need an informed consent process built into it, and it might be covered by HIPAA, depending on the circumstances.

Andrea Coravos from Elektra Labs asked the panelists to comment on the participant-centered informed consent developed by organizations that may serially use the data collected, such as the *All of Us* program. McGraw replied that a large effort went into designing the consent process for that program so that it would be understandable and not just a "check the box" encounter. McGraw added that CCPA and GDPR may make mobile consent more challenging because of the amount of information those two sets of regulations will require to be provided to potential participants. Wilbanks noted that several organizations, including RTI International, PatientsLikeMe, and 23andMe, have created effective, mobile, participant-centered consent processes.

John Burch from the Mid-America Angels Investment Group asked Madre if she could talk about the CTTI Registry Trials project.[12] Madre replied that this project issued recommendations that addressed two issues on how to conduct clinical trials embedded in registries. First, if the trial uses an existing registry, it is important to ensure that the data can meet regulatory requirements for a clinical trial. With a new registry, the recommendations call for researchers to think more broadly about how to design the registry so it can be used for research in general, and specifically for clinical trials.

Burch then asked McGraw to comment on any changes to HIPAA that Congress might be considering. The legislation under consideration, McGraw said, is not meant to reform HIPAA, but is rather a response to California's new regulations and GDPR to achieve regulatory convergence with global trends. Those two laws regulate privacy largely by protecting data regardless of its source, rather than the piecemeal approach used in the United States where some data are protected by HIPAA and others by the Common Rule or the Federal Trade Commission. What Congress is considering, she explained, would make the U.S. approach to personal data regulation, including medical data, more like the rest of the world, but there is debate as to whether to regulate globally or allow states to have more stringent laws. The other issue is whether to establish uniform regulations or carve out exemptions for different data sources, such as those already covered by HIPAA. McGraw predicted that this issue will take significant time and effort to solve.

[12] Available at https://www.ctti-clinicaltrials.org/projects/registry-trials (accessed April 10, 2019).

Some individual workshop participants highlighted the significant complexity arising from the variations between state-by-state regulations for distributing pharmaceuticals in the context of a clinical trial. The only solution to this divergence is for Congress to pass legislation preempting state laws, said McGraw.

An unidentified workshop participant asked the panelists for their thoughts on how to enhance public trust in clinical research enterprise if it is going to use data that were not generated in the research setting. McIntyre replied that 23andMe asks people to consent separately to the company's use of passively collected data, such as from the Apple HealthKit; the general consent that covers the company's use of their genetic data and health survey data; and other consents that allow the company to share their data with other parties. Use of aggregated data analyzed for research purposes, added McIntyre, is covered by the general consent because there would be no transfer of any information about a specific person. What is not clear, he said, is whether breaking the consent process into pieces makes it easier for people to understand or if it is overwhelming.

McGraw noted that a scientific hypothesis derived from analyzing aggregated data could count as an inference under CCPA, although if that analysis was conducted in the context of a clinical trial subjected to one of the law's exceptions, the inference would not be subject to the law. McGraw also highlighted the importance of dealing with passively collected data, such as geolocation data, that are collected by digital health technology, but not as part of the trial during the consent process. One issue, she said, concerns the privacy policy associated with the terms of use of the digital health technology being used (e.g., how the data collected will be shared by the technology vendor/manufacturer). Okun suggested not using digital health technologies for which the privacy policies are not acceptable, a position that stands to create a more trusting relationship with trial participants.

McCallie noted the growing movement that takes advantage of the application programming interfaces required of software regulated by HIPAA, such as electronic health records, that make it relatively easy for consumers to download a copy of their medical record onto a digital health technology they control or give proxy rights to a third party to use those data. His question to the panel was whether this approach will change the regulatory landscape in any way. McGraw replied that patient-facing entities, such as a consumer-directed data exchange, would not have the HIPAA compliance hurdles, and they may, in fact, provide the opportunity to more easily reach people who are eager to participate in clinical trials, who are activated, and who have data they want to contribute. The challenge, she said, is to ensure that people are truly informed about how these consumer-facing entities (e.g., apps) will be sharing their data while not placing all of the responsibility for protecting privacy onto consumers. McGraw sug-

gested that investigators using consumer mobile devices could do a better job of choosing the mobile device to be used in research, or at least make recommendations or provide a ratings score that would help people make good decisions about which mobile devices to use.

Wilbanks asked the panelists to address what will happen when technologies designed to monitor safety become inoperable because of an Internet outage, for example. Sacks responded that safety monitoring is not a task appropriately delegated to automation. A clinician's responsibilities, he said, are to react to adverse events and stop a drug when it is causing toxicity. While automation can do that to a point, it is important that human intelligence is involved in the process. Depending on the criticality of the data collected by an automated system, back-up systems should be involved, Sacks added.

Steven Cummings asked if it was possible for mobile applications to notify participants of updates to consent forms, for example. McIntyre thought that was a good idea, but expressed concern that too many notifications might affect study retention. Asking people to do things repeatedly can cause attrition, he said, so it is important to know what the proper cadence is for requesting that the participants complete certain tasks.

6

Reflections on the Workshop and Potential Future Directions

In the final session of the workshop, moderators from the previous four panels shared their takeaways from the day's proceedings, which was followed by an open discussion on potential next steps.

SESSION 1: OPPORTUNITIES TO IMPROVE CLINICAL TRIALS

Clay Johnston reiterated the point that traditional clinical trials are becoming more expensive, inefficient, and inaccessible over time. Given this dysfunction, he highlighted the need for the next generation of clinical trials, which, of course, should incorporate new technologies. Johnston then emphasized comments by workshop participants, such as the importance of using human-centered design and seeking input from patients early in the trial design process. He noted that several speakers stated that the main barriers to progress were a lack of will and creativity. If that is the case, he pointed out that education, reassurance, and demonstrating value would be key to changing the way clinical trials are run.

Linda Brady echoed some of Johnston's comments, adding that while there is reluctance across the different sectors for various reasons (e.g., concerns about the regulatory path forward, lack of experience engaging patients, or fear of the technology), the time to move forward is now. Brady said there seems to be opportunities for the National Institutes of Health (NIH) to do more in this space.

SESSION 2: EXPLORING CLINICAL TRIALS

Recapping the highlights of Session 2, Kelly Simcox said that remote digital tools are clearly having success in clinical care. What still needs to be defined, she said, is how to use these tools in a clinical trial beyond observational studies. Interventional clinical trials have made good use of virtual or direct-to-participant methodologies when digital tools are incorporated into the trial design from the beginning rather than when a traditional clinical trial, with all of its complexity, is later modified to incorporate digital tools. Another point she made regarding interventional trials was the importance of considering what participant access to data looks like in the virtual environment. Although returning data to participants in a virtual environment should be easier, the challenge is how to do this effectively and quickly, she said. Another challenge in this space is in regard to validating a participant's identity in a remote setting.

Simcox noted that there is still work to do regarding the use of electronic health record data given that some of these data may not be reliable or may be missing. She also pointed to the need to have more visibility regarding what clinical trials are occurring in the direct-to-participant space and the need to share the learnings gained from those trials so that direct-to-participant trials can move past doing pilots and become part of the mainstream of clinical trial methodology.

SESSION 3: ACCESS AND EQUITY

Kathy Hudson and Rebecca Pentz recapped some of the key points they heard. They emphasized the importance of relaxing exclusion criteria when they are not needed so that equitable participation in clinical trials can be increased. Another point they raised was the importance of continuous dialogue with patients throughout the entire trial process, from design to completion, to adequately capture their input. Hudson and Pentz also emphasized the importance of community engagement, noting that coordinating with community- and faith-based organizations, such as the African Methodist Episcopal Church in the African American community, can build trust in the trial process. Furthermore, returning data to community members in real time can empower participants and make them feel like partners in the clinical trials team. It will be important, they emphasized, to include partnering community organizations in the trial budget. If the goal of a study is to identify ethnically or disease severity-linked biomarkers, Hudson and Pentz noted that it will be important for investigators to think creatively about ways to engage diverse populations.

SESSION 4: POLICY CONSIDERATIONS

John Wilbanks said his key takeaway from the fourth session related to the disconnect between the technology needed for virtual trials and the policy environment. He also highlighted the importance of paying attention to the impact that policies may have on clinical trials, particularly given that most trials will be hybrids of clinic-based and decentralized trials in a way that does not necessarily align with the current policy infrastructure. He noted that industry's aversion to the risk of running afoul of regulations is something that policy can ameliorate through guidance.

One subject that did not come up, but that concerns Wilbanks, is the need to think seriously about the technical security associated with consumer-grade digital health technologies, which he said are "bleeding data out into the universe." Along those same lines, he noted the importance of consent as an ongoing relationship, not a one-time transactional gate, when digital health technologies are passively collecting data.

Wilbanks suggested that the field look for places where federal and state regulations could be harmonized. He also suggested there could be ways to create "safe harbors" that would enable researchers to experiment and validate new approaches.

David McCallie added that he came to the workshop thinking that observational and interventional trials were two distinct types of trials, but he now sees more of a gray scale of gradation between those two. The regulatory environment changes along that continuum and can sometimes lead to confusing, overlapping, and conflicting policies. To address this problem, he emphasized the value of creating a taxonomy of the spectrum of methodological choices. Doing so, he suggested, could result in clever approaches for attacking the problems that research and clinical trials are trying to address without going through the formal clinical trial channel.

NEXT STEPS

Johnston discussed the value of establishing a regularly updated knowledge repository for sharing information and lessons learned based on ongoing and completed virtual trials (e.g., Health Insurance Portability and Accountability Act [HIPAA] considerations and state-based policies). Leanne Madre noted that as part of its mobile clinical trials programs, the Clinical Trials Transformation Initiative is creating an online resource of feasibility studies using mobile technologies. Initially, this resource will include published examples, but it might be possible to broaden the scope of this resource, said Madre. Brady remarked that the NIH Health Care Systems Research Collaboratory may also be able to host a resource portal. An unidentified workshop participant said some of the elements that

might be included in such a knowledge repository may already be in place (e.g., TransCelerate resources), but it is also important to partner with the U.S. Food and Drug Administration and NIH to ensure that perspectives and contributions include stakeholders in addition to the pharmaceutical industry.

Necessity of an Ontology

Johnston emphasized the power of using meaningful and defining language to describe the types of clinical trials discussed in this workshop. He noted that the planning committee for this workshop struggled with the term "virtual clinical trial," testing out and dismissing other terms (e.g., decentralized, digital health–enabled). Cummings commented that there is not going to be one term that covers all of the important characteristics of the trials discussed at the workshop, but "flexible clinical trials" and "direct-to-participant trials" may serve as useful umbrella terms. He suggested that a "virtual clinical trial" may describe a study in which data are collected passively or actively using digital technologies.

A few workshop participants, including Rodrigo Garcia, EMD Serono, and Ray Dorsey, favored the term "modern clinical trials," which could imply a need for new guidance, rules, legislation, and governance mechanisms. Garcia said it is important to remember that technology should be used to enhance research by transforming the experience of trial participants. A few workshop participants, including Garcia and Ray Sharma, spoke in favor of decentralization to bring the patient into focus and improve access to participation. Sally Okun suggested using the term "21st century trials" based on the 21st Century Cures Act, which could harness the power of a term that is already familiar across federal agencies. Considering the speed at which technology evolves, an unidentified workshop participant suggested leaving some flexibility in the terminology to accommodate future innovation.

Addressing Regulatory Policy

Johnston suggested that the workshop participants have the potential to work with various organizations to advocate for policies that would better support virtual trials. Hudson added that a number of regulatory policy issues stand in the way of modern and traditional clinical trials. She mentioned that these issues could benefit from thoughtful policy analysis and policy recommendations as well as advocacy for implementation. Hudson, Johnston, and Cynthia Geoghegan emphasized that it will be critical to have active patient leadership engaged in policy discussions.

Wilbanks emphasized the need for better harmonization when it comes to the application of HIPAA at the state level. Deven McGraw remarked

that while the U.S. Congress has the ability to pass legislation that preempts state laws, it must articulate a reason for doing so that is constitutionally permitted. Absent that, she said, the federal government could make a powerful and persuasive statement to state boards that regulate drug distribution and telemedicine, for example, by laying out how it interprets this space. This latter approach, which does not overturn state laws, is likely to be the path of least resistance, she added. Craft cited one example of federal regulations that bypasses conflicts with "state's rights that allows any physician who works for the U.S. Department of Veterans Affairs (VA) to treat patients at any VA facility in the country, regardless of state licensure provisions." Craft then suggested one small step that Congress could take, which would be to carve out an exemption to state laws for telemedicine-based clinical research or telemedicine-based clinical research for rare diseases, each of which represents a tiny slice of medical practice.

McCallie commented that an economic analysis comparing traditional trials versus virtual trials could help identify challenge areas and potential advocates. For example, virtual trials may create opportunities for local physicians, who might serve as advocates for changing state regulations.

Governance and Patient Engagement

Johnston noted that virtual trials may require greater inclusion of patients in their design and governance than traditional clinical trials. However, Craig Lipset and Steven Cummings pointed out that more involvement of patients in the governance process is needed for all clinical trials. Furthermore, it would be beneficial if patients were included on drug safety monitoring boards, noted Cummings—a trend he hopes NIH will recommend across its individual institutes.

Hudson remarked that although talking about engaging patients throughout the clinical trials process is easy, doing so in a meaningful way is difficult. What is needed to make patient engagement work, she said, are resources that provide guidance for meaningful engagement and bidirectional training for everyone involved in a project. Geoghegan and Pentz agreed with Hudson and added that there is a need for a workforce and cadre of patient advocates trained in patient-focused drug development and 21st-century clinical trials.

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Appendix A

Workshop Agenda

Virtual Clinical Trials: Challenges and Opportunities

November 28–29, 2018

National Academy of Sciences Building, Lecture Room
2101 Constitution Avenue, NW, Washington, DC 20418

This workshop will examine opportunities for a modern, patient-centric clinical trials enterprise in light of digital health tools that could allow a virtual clinical trial for new medical product approval. Subject-matter experts will engage in presentations and discussions to:

- Highlight opportunities for systemic improvements to support virtual clinical trials, including
  - Potential implications of virtual clinical trials for cost, speed, regulation, and knowledge generation and dissemination; and
  - Elements of an information technology infrastructure, including integrating data from electronic health records, mobile health applications, remote monitoring, virtual visits, and other relevant technologies with the capability to enhance the interface between clinicians and clinical trial participants.
- Explore potential opportunities to use digital health tools to engage with patients and potential research participants, facilitate recruitment of participants to join a clinical trial, and maintain participation of diverse populations in the trial, including

- Collaborative approaches and incentives involving sponsors, researchers, patient advocacy groups, patients living with the particular condition being studied, and health systems—including regulations, quality measures and outcomes, or reimbursement strategies—to support the implementation of virtual clinical trials; and opportunities and challenges to enhancing equity in access and participation through virtual clinical trials.

DAY ONE: NOVEMBER 28

1:00 pm **Welcome and Opening Remarks**

Linda Brady, *Workshop Co-Chair*
National Institute of Mental Health, National Institutes of Health

Clay Johnston, *Workshop Co-Chair*
The University of Texas at Austin

Session I: Opportunities to Improve Clinical Trials

Session Objectives:

- Consider the efficiency and effectiveness of the current clinical trials landscape in the United States—what is working and not working well?
- How could virtual clinical trials improve traditional Phase 3 clinical trials and overall medical product development?

Session Co-Chairs:
Linda Brady, National Institutes of Health
Clay Johnston, The University of Texas at Austin

1:10 pm **Ray Dorsey**
Professor of Neurology and Director, Center for Health and Technology
University of Rochester Medical Center

Donna Cryer
President and Chief Executive Officer
Global Liver Institute

Craig Lipset
Head of Clinical Innovation, R&D
Pfizer Inc.

1:50 pm **Discussion with Workshop Participants**

Session II: Exploring Virtual Clinical Trials

Session Objectives:

- Hear a variety of perspectives and experiences with virtual and digital health technologies in interventional and observational studies, as well as clinical care, and highlight opportunities to use these technologies to improve clinical trials of investigational products.
- Discuss challenges and best practices for designing and implementing a virtual clinical trial.

Session Chair:
Kelly Simcox, Sanofi

2:15 pm **Lessons Learned from Clinical Care**

Jenna Bollyky
Vice President, Clinical Research and Analytics
Livongo Health

2:30 pm **Lessons Learned from Observational Studies**

Joshua Denny
Professor of Biomedical Informatics and Medicine
Vanderbilt University

2:45 pm **Discussion with Workshop Participants**

3:00 pm **BREAK**

3:15 pm **Lessons Learned from Interventional Virtual Clinical Trials**

Steven Cummings
Director, San Francisco Coordinating Center
Professor of Medicine, Epidemiology, and Biostatistics
University of California, San Francisco

Wendy Weber
Acting Deputy Director
National Center for Complementary and Integrative Health
National Institutes of Health

Kimberly Hawkins
Clinical Sciences and Operations Project Leader Head
Sanofi Genzyme

4:00 pm **Panel Discussion and Reactions**

Noah Craft
Chief Executive Officer
Science 37

Adrian Hernandez
Vice Dean for Clinical Research
Duke University School of Medicine
Faculty Associate Director
Duke Clinical Research Institute

Jon White
Deputy National Coordinator for Health Information Technology
The Office of the National Coordinator for Health Information Technology
U.S. Department of Health and Human Services

Josh Rose
Vice President, Global Head of Strategy
IQVIA

4:30 pm **Discussion with Workshop Participants**

5:00 pm **Adjourn Day One**

DAY TWO: NOVEMBER 29

8:30 am **Breakfast**

8:45 am **Welcome and Recap Day One**

LINDA BRADY, *Workshop Co-Chair*
National Institute of Mental Health, National Institutes of Health

CLAY JOHNSTON, *Workshop Co-Chair*
The University of Texas at Austin

Session III: Access and Equity

Session Objectives:

- Consider how to frame issues of access and equity in the context of virtual trials. Could virtual trials potentially exacerbate current inequities or make access to clinical trials worse for some communities?
- Discuss the potential benefits and risks of end-to-end virtual clinical trials for traditionally underrepresented populations in research.

Session Co-Chairs:
Kathy Hudson, People-Centered Research Foundation
Rebecca Pentz, Emory University School of Medicine

9:00 am WILL MCINTYRE
Patient Advocate
The Michael J. Fox Foundation for Parkinson's Research

SALLY OKUN
Vice President, Policy and Ethics
PatientsLikeMe

SILAS BUCHANAN
Chief Executive Officer
Institute for eHealth Equity

SHERINE EL-TOUKHY
Post-Doctoral Research Associate
National Institute on Minority Health and Health Disparities
National Institutes of Health

10:00 am **Discussion with Workshop Participants**

10:30 am **BREAK**

Session IV: Policy Considerations

Session Objectives:

- Discuss existing, and yet to be conceived, policies and standards governing virtual clinical trials for medical product development.
- What are the challenges and potential solutions surrounding the collection of remote data from participants—including how to ensure the data collected are coming from the person you think it is, and how to know they are using the device correctly—all while protecting privacy?
- Consider the landscape of standards and any gaps that may need to be addressed in order to conduct increasingly virtual trials.

Session Co-Chairs:

David McCallie, Cerner Corporation
John Wilbanks, Sage Bionetworks

10:45 am **Leonard Sacks**
Associate Director for Clinical Methodology
Office of Medical Policy, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Leanne Madre
Director of Strategy
Clinical Trials Transformation Initiative

Deven McGraw
General Counsel and Chief Regulatory Officer
Ciitizen Corporation

Matthew McIntyre
Senior Scientist, Data Collection
23andMe

11:45 am **Discussion with Workshop Participants**

12:30 pm **LUNCH**

Session V: Potential Future Directions

Session Objective:

- Discuss key highlights from the workshop presentations and discussions, including identifying potential next steps and promising areas for future action.

Session Co-Chairs:

Linda Brady, National Institutes of Health
Clay Johnston, The University of Texas at Austin

1:15 pm **Observations from the Workshop and Potential Future Directions**

- **Linda Brady and Clay Johnston,** Session I: Opportunities to Improve Clinical Trials
- **Kelly Simcox,** Session II: Exploring Virtual Clinical Trials
- **Kathy Hudson and Rebecca Pentz,** Session III: Access and Equity
- **David McCallie and John Wilbanks,** Session IV: Policy Considerations

2:15 pm **Discussion with Workshop Participants**

3:00 pm **Workshop Adjourn**

Appendix B

Workshop Speaker Biographical Sketches

Linda Brady, Ph.D., serves as the director of the Division of Neuroscience and Basic Behavioral Science at the National Institute of Mental Health (NIMH). In this role, she provides scientific, programmatic, and administrative leadership for an extramural research program portfolio in basic neuroscience to support NIMH's mission of transforming the understanding and treatment of mental illnesses. Dr. Brady has directed programs in neuropharmacology, drug discovery, and clinical therapeutics, as well as organized consortia focused on ways to accelerate the development and clinical application of radiotracers in clinical research. She has provided leadership for many programs, including Development and Application of PET and SPECT Imaging Ligands as Biomarkers for Drug Discovery and for Pathophysiological Studies of CNS Disorders, the National Cooperative Drug/Device Discovery/Development Groups for the Treatment of Mental Disorders, and First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders. Dr. Brady serves as co-chair of the Neuroscience Steering Committee for the Biomarkers Consortium, a public–private research partnership of the Foundation for the National Institutes of Health that focuses on discovery, development, and qualification of biological markers to support drug development, preventive medicine, and medical diagnostics. From 2004–2013, she co-led the Molecular Libraries and Imaging Program, a trans-National Institutes of Health (NIH) Common Fund initiative to provide biomedical researchers access to small organic molecules that can be used as chemical probes to study the functions of genes, cells, and biochemical pathways in health and disease. Dr. Brady was trained in pharmacology and neuroscience. She com-

pleted her Ph.D. at Emory University School of Medicine, followed by post-doctoral work and research positions at the Uniformed Services University of the Health Sciences and the NIMH Intramural Research Program. She is the author of more than 70 peer-reviewed scientific publications and is a member of the Society for Neuroscience and a fellow in the American College of Neuropsychopharmacology. Dr. Brady has received NIH Director's Awards and NIH Merit Awards in recognition of her activities in biomarker development and drug development for mental disorders.

Jenna Bollyky, M.D., M.B.A., is a physician at Stanford who leads Livongo Health's clinical research and analytics team. Dr. Bollyky's research over the years has focused on various aspects of diabetes innovation, including Phase 1/2 clinical investigations of immunotherapies to preserve beta cell function and artificial pancreas technologies for type 1 diabetes (Benaroya Research Institute at Virginia Mason, Seattle) and health outcomes (National Institute of Diabetes and Digestive and Kidney Diseases, RAND). She received her undergraduate degree in economics at Princeton University, her M.D./M.B.A. from the University of California, Los Angeles, clinical training in internal medicine at Brigham and Women's Hospital, and endocrinology and bioinformatics post-doctoral training at Stanford University.

Silas Buchanan is an experienced underserved-community outreach and engagement strategist. As the founding chief executive officer of the Institute for eHealth Equity, he leads partnerships with health care payers, providers, and government and academic stakeholders across the United States. Mr. Buchanan has expertise in crafting Web-based ecosystems that solve for known, underserved-community outreach and engagement failure points. He developed AMECHealth.org as the official health information-sharing channel for the African Methodist Episcopal Church (2,000 congregations/ 2 million members). He is currently developing OurHealthyCommunity.com to more effectively recruit, activate, and connect underserved community members and faith- and community-based organizations with accountable care organizations, accountable communities of health, and other public/ private stakeholders. Mr. Buchanan was selected as a member of the White House Summit to Achieve eHealth Equity. He also served as co-chair of the Awareness Committee for Region V of the U.S. Department of Health and Human Services' (HHS's) National Partnership for Action to End Health Disparities. Mr. Buchanan has testified before HHS, the Health IT Policy Committee, and the HHS Meaningful Use Workgroup, and is an inaugural member of the National eHealth Collaborative Consumer Committee.

Noah Craft, M.D., Ph.D., is the co-founder of Science 37 and a physician, scientist, and entrepreneur. Science 37 transforms the clinical research

process, accelerating biomedical discovery and reducing clinical trial costs by shifting the center for research from traditional institutional investigative sites to the patient's home and local health care system. The organization uses its patient-centered technology platform (NORA®) to create Metasites™, simplify the process of participating in trials, and connect patients safely and securely to the world's best scientists—no matter where they live. For more than years, Dr. Craft has worked on the skin microbiome, parasite immunology, and cancer vaccine development. He also serves as a senior strategic advisor to both VisualDx and Direct Derm. He has published more than 45 peer-reviewed research manuscripts and holds multiple patents. Dr. Craft received a B.S. from Brown University and completed medical school, his residency, and his post-doctoral research at the University of California, Los Angeles.

Donna Cryer, J.D., is a patient, patient advocate, and attorney who founded and leads the Global Liver Institute. She is a frequent speaker on topics of patient engagement in research and health care delivery redesign. She serves on several boards, including the People-Centered Research Foundation and Sibley Memorial Hospital in Washington, DC. Ms. Cryer is a graduate of Harvard/Radcliffe Colleges and Georgetown University Law Center.

Steven Cummings, M.D., is a professor of medicine, epidemiology, and biostatistics emeritus at the University of California, San Francisco (UCSF), and a senior scientist at Sutter Health Research. He is the founding director of the San Francisco Coordinating Center, an academic research organization, and he has designed and/or conducted several multi-center, industry-sponsored pivotal trials of treatments for osteoporosis. He founded 1747, a start-up company that developed and conducted one of the first successful Internet-based clinical trials in 2000. He was also a founder and chief scientific officer of Mytrus, a company that developed technology for direct-to-participant trials and electronic informed consent (e-consent) and that proposed and conducted the Internet-based REMOTE trial funded by Pfizer. Dr. Cummings has also served as innovator-in-residence at Genentech-Roche to streamline their clinical trial protocols. He is the principal investigator of a large National Institutes of Health–funded randomized trial of a drug treatment to prevent fractures in patients with Parkinson's disease that will be conducted entirely from patients' homes. He authored the invited *New England Journal of Medicine* review on *e-Consent and Internet-Based Trials*. Dr. Cummings also co-authored *Designing Clinical Research* (Williams and Wilkins), a textbook on clinical research and clinical trial methods, and teaches about trial methods at UCSF. He has published more than 500 original research papers and was elected to the National Academy of Medicine for his contributions to clinical research.

Joshua Denny, M.D., M.S., FACMI, is a professor of biomedical informatics and medicine. He completed an internal medicine residency as a Tinsley Harrison Scholar at Vanderbilt University. His research interests include natural language processing, accurate phenotype identification from electronic medical record (EMR) data, and using the EMR to discover genome–phenome associations to better understand disease and drug response, including the development of the EMR-based phenome-wide association. At Vanderbilt, Dr. Denny is part of the PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment) program, which prospectively genotypes patients to tailor drug response. He is principal investigator (PI) of the Data and Research Center of the *All of Us* Research Program (previously called the Precision Medicine Initiative Cohort Program), which will eventually enroll at least 1 million Americans in an effort to understand the genetic, environmental, and behavioral factors that influence human health and disease. He is also PI for Vanderbilt sites in the Electronic Medical Records and Genomics (eMERGE) Network, Pharmacogenomics Research Network (PGRN), and the Implementing Genomics Into Practice (IGNITE) Network. Dr. Denny received the Homer Warner award from the American Medical Informatics Association (AMIA) in 2008 and 2009. He received the AMIA New Investigator Award in 2012 and was elected into the American College of Medical Informatics in 2013. He is a member of the National Academy of Medicine, a fellow in the American College of Medical Informatics, and a diplomate of the American Board of Internal Medicine. He serves on several local committees and remains active in teaching medical students and in clinical roles.

Ray Dorsey, M.D., M.B.A., is the David M. Levy Professor of Neurology and director of the Center for Health + Technology at the University of Rochester. Through creative use of technology, he and his colleagues seek to enable anyone anywhere to receive care, participate in research, and benefit from therapeutic advances. Dr. Dorsey previously directed the movement disorders division and neurology telemedicine at Johns Hopkins and worked as a consultant for McKinsey & Company. His research has been published in leading medical, neurology, and economic journals and has been featured on National Public Radio and in *The New York Times* and *The Wall Street Journal*. In 2015, the White House recognized him as a "Champion for Change" for Parkinson's disease.

Sherine El-Toukhy, Ph.D., is an Earl Stadtman tenure-track investigator and a National Institutes of Health (NIH) Distinguished Scholar in the Division of Intramural Research of the National Institute on Minority Health and Health Disparities (NIMHD). Prior to joining NIMHD, she was an intramural training award post-doctoral fellow in the Intramural Research

Programs of the National Heart, Lung, and Blood Institute and NIMHD. She received her doctorate from the University of North Carolina at Chapel Hill in mass communication, where she also earned a graduate certificate in interdisciplinary health communication. She holds a bachelor's degree in broadcast journalism and a master's degree in mass communication from Cairo University, Egypt. At NIH, she gained additional training in epidemiological and clinical research. Dr. El-Toukhy's research is aimed at improving minority health and reducing health disparities through digital public health interventions. She has multi-disciplinary theoretical and methodological training in communication, psychology, and public health. Dr. El-Toukhy has a decade's worth of experience in health communication campaigns and interventions funded by national and international organizations such as the Egyptian Ministry of Health and Population, Ministry of Environment, the United Nations Children's Fund, and the U.S. Agency for International Development. She led projects centered on promoting reproductive health, children's vaccines, HIV prevention, a clean environment, and gender equality, among others. She is a recipient of several research awards, including a visiting scholar award from Cairo University, Egypt; a William R. Kenan Jr. Fellowship from the University of North Carolina at Chapel Hill; the 2013 Health Dissertation of the Year award from the National Communication Association and the International Communication Association; and three top-paper awards. Her work has appeared in journals such as *Pediatrics*, *Tobacco Control*, and *Preventive Medicine*. Her research has been funded by the National Science Foundation and NIMHD.

Kimberly Hawkins, M.P.H., has 25 years of operational experience managing all phases of the drug development process. She started her career at Boston Medical Center as a research assistant working on pediatric AIDS and oncology trials. After working in academia, she moved into industry and held various clinical operations positions at Boston-area biotechnology/pharmaceutical companies, including Genzyme, Antigenics, and Novelos Therapeutics, where she was the vice president of clinical development. Ms. Hawkins joined Sanofi 5 years ago and is the clinical operations lead for the Sanofi Genzyme business unit that includes rare disease, multiple sclerosis/neurology, immunology, and oncology. She is a graduate of Boston University with a bachelor's degree in human physiology and a master's degree in public health.

Adrian Hernandez, M.D., M.H.S., is a cardiologist with extensive experience in clinical research ranging from clinical trials to health services policy research. Since 2017, he has been the vice dean for clinical research at the Duke University School of Medicine. Previously, he was a faculty associate director of Duke Clinical Research and director of health services

and outcomes research at the Duke Clinical Research Institute. He is the coordinating center principal investigator (PI) for multiple networks and clinical trials, such as the National Heart, Lung, and Blood Institute's Heart Failure Research Network, Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network, and the National Institutes of Health's Health Care Systems Research Collaboratory. He has served as the Steering Committee Chair or PI of multiple large studies in the field of cardiovascular medicine and diabetes. Dr. Hernandez has more than 450 published articles in high-tier journals, including the New *England Journal of Medicine*, *Journal of the American Medical Association*, and *The Lancet*. He is an elected member of the American Society of Clinical Investigation and the Association of American Physicians. He received his bachelor's degree from Rice University and his M.D. from the University of Texas–Southwestern School of Medicine. He completed an internship and a residency in the Department of Medicine at the University of California, San Francisco, and a cardiology fellowship at Duke University.

Kathy Hudson, Ph.D., is the former deputy director for science, outreach, and policy at the National Institutes of Health (NIH). Dr. Hudson led the science policy, legislation, communications, and outreach efforts of NIH and served as senior advisor to the NIH director. She directed the agency's efforts to advance biomedical science through policy development and innovative projects and partnerships. Dr. Hudson created major new strategic and scientific initiatives, including the National Center for Advancing Translational Sciences, the BRAIN Initiative, the NIH Precision Medicine Initiative, and the Cancer Moonshot. She led the development of major policies that enable science to advance more rapidly, including enhancing clinical trials, data sharing, and participation of patients as partners in research. She was the key NIH architect responsible for modernizing the regulations governing research with human subjects. Her professional experience includes serving as the acting deputy director of the National Center for Advancing Translational Sciences, NIH; the NIH chief of staff; the assistant director of the National Human Genome Research Institute, NIH; and the founder and director of the Genetics and Public Policy Center at Johns Hopkins University. Also at Johns Hopkins, Dr. Hudson was an associate professor in the Berman Institute of Bioethics, Institute of Genetic Medicine, and Department of Pediatrics. Dr. Hudson holds a Ph.D. in molecular biology from the University of California, Berkeley, an M.S. in microbiology from The University of Chicago, and a B.A. in biology from Carleton College.

Clay Johnston, M.D., Ph.D., has served as the inaugural dean of the Dell Medical School at The University of Texas at Austin since 2014. In this

position, he plans to build a world-class academic medical center focused on providing new models of education and health care delivery. He is also professor of neurology, specializing in stroke care and research. Dr. Johnston arrived in Austin from the University of California, San Francisco (UCSF), where he directed the Clinical and Translational Science Institute, overseeing the planning, development, and implementation of a $112 million, 5-year National Institutes of Health grant award, the second largest among the 60-member national Clinical and Translational Science Awards consortium. Working with a team of more than 300 faculty and staff serving all four schools at UCSF, Dr. Johnston positioned the Institute as a catalyst in efforts to accelerate research to improve health on campus and throughout the University of California system. He founded the Center for Healthcare Value at UCSF in order to engage faculty and trainees in lowering the costs of health care while improving quality. He was also instrumental in cultivating and securing partnerships with leading biotech companies, foundations, and private funders. In his role as associate vice chancellor of research, Dr. Johnston was integrally involved in efforts to realize the University's vision of being the world's preeminent health sciences innovator. After receiving his undergraduate education at Amherst College, he completed medical school at Harvard University. He later received a Ph.D. in epidemiology from the University of California, Berkeley, and was a resident in neurology at UCSF, where he later trained in vascular neurology. During his 20 years at UCSF, he rose through the academic ranks to professor of neurology and epidemiology, and directed the Stroke Service. Dr. Johnston has authored more than 300 publications in scientific journals and has won several national awards for his research and teaching. In particular, he has published extensively in the prevention and treatment of stroke and transient ischemic attack. He is perhaps best known for his studies describing the short-term risk of stroke in patients with transient ischemic attack and identifying patients at greatest risk, and also for his work related to measuring the impact of research. He has led several large cohort studies of cerebrovascular disease and three international multi-center randomized trials, two of which are ongoing.

Craig Lipset is the head of clinical innovation within Global Product Development at Pfizer Inc. Mr. Lipset's team is impacting clinical research through digital tools, innovative research approaches, and game-changing collaborations. He previously served as venture partner in Pfizer Venture Investments (Pfizer's venture capital arm), where he focused on diversifying the company's $50 million annual budget for private investments in the areas of diagnostics and health technology. Mr. Lipset was also senior director in molecular medicine, where he spearheaded initiatives driving innovation in clinical research and personalized medicine by drawing on

tools from health information technology, telemedicine, and eHealth. He brings more than 15 years of leadership and innovation in the field of drug development. He previously served as associate vice president of program management at Adnexus Therapeutics (acquired by Bristol-Myers Squibb), and on the founding management team for Perceptive Informatics (now part of PAREXEL International). Mr. Lipset has been listed among the *PharmaVOICE* most inspiring people in the life sciences, *Pharmaceutical Executive*'s Emerging Leaders, *CenterWatch* Top Innovators, and *AlleyWatch* Who's Who in eHealth. He serves on the Editorial Board for *Therapeutic Innovation & Regulatory Science*. Outside of Pfizer Inc., Mr. Lipset serves on the Board of Directors for the People-Centered Research Foundation, the Foundation for Sarcoidosis Research, and the MedStar Health Research Institute, and is a mentor at health technology accelerator Blueprint Health.

Leanne Madre, J.D., M.H.A., advises and supports the executive director in setting and carrying out organizational strategies in support of the Clinical Trials Transformation Initiative's (CTTI's) mission. She provides senior leadership on communication and membership strategies and programs and is responsible for maintaining awareness and assessing related efforts of government and private-sector organizations, developing and implementing appropriate plans for CTTI in light of those initiatives. Ms. Madre has more than 15 years of experience working on clinical and translational research issues. She previously served as program director of the Centers for Education and Research on Therapeutics (CERT) Coordinating Center, where she played an instrumental role in creating and managing the CERT program organization, including the creation of a model for public–private partnerships. While at Duke University, Ms. Madre also served as manager of strategic relations and client services for the Duke Clinical Research Institute. Prior to joining Duke, she served as an attorney for Sentara Health System. Ms. Madre received her J.D. from the University of Richmond, her M.H.A. from the Medical College of Virginia/Virginia Commonwealth University, and her B.S. (biochemistry) from North Carolina State University.

Deven McGraw, J.D., M.P.H., is the general counsel and chief regulatory officer for Ciitizen, a consumer health technology start-up. Prior to joining Ciitizen, she directed U.S. health privacy and security through her roles as deputy director, health information privacy at the U.S. Department of Health and Human Services' Office for Civil Rights (the office that oversees Health Insurance Portability and Accountability Act [HIPAA] policy development and enforcement) and chief privacy officer (acting) of The Office of the National Coordinator for Health Information Technology. Widely recognized for her expertise in health privacy and security,

she directed the Health Privacy Project at the Center for Democracy & Technology (a nonprofit civil liberties organization) for 6 years and led the privacy and security policy work for the Health Information Technology for Economic and Clinical Health Act of 2009's Health IT Policy Committee. She also served as the chief operating officer of the National Partnership for Women and Families. She has also advised health industry clients on HIPAA compliance and data governance while a partner at Manatt, Phelps & Phillips, LLP. Ms. McGraw graduated magna cum laude from the Georgetown University Law Center and has an M.P.H. from Johns Hopkins University.

Matthew McIntyre, Ph.D., M.S., joined 23andMe in 2013. He is responsible for ensuring that the company maintains high-quality information about its research participants' health and traits in order to conduct innovative genetic research. Previously, he completed a post-doctoral fellowship at Harvard School of Public Health and taught anthropology at the University of Central Florida, where his research focused on hormones and child growth. Dr. McIntyre earned his Ph.D. in anthropology and M.S. in epidemiology, both from Harvard University.

Will McIntyre has been in the technology industry for the better part of two decades. He has worked in all parts of the industry, from selling to customers to distribution support and management. Mr. McIntyre was diagnosed with Parkinson's disease in October 2013. He has been working on a volunteer basis with The Michael J. Fox Foundation in several capacities for the past few years.

Sally Okun, B.S.N., R.N., M.M.H.S., is vice president for policy and ethics at PatientsLikeMe. Since joining the company in 2008, she has overseen numerous aspects of the site's early development related to health data integrity, medical ontology, drug safety platforms, and more, recently leading the development of the company's Ethics and Compliance Advisory Board. Ms. Okun ensures that patient voice and insight are integrated into diverse health policy initiatives at the national and global levels, and is the company's liaison with external organizations, government, and regulatory agencies. She oversees the company's Research Collaboration Agreement with the U.S. Food and Drug Administration and is a member of numerous advisory groups, including the National Academy of Medicine's Leadership Consortium for a Value & Science-Driven Health System; the Commonwealth Fund's National Advisory Group on Health Care Delivery System Reform; the Board of Directors for Public Responsibility in Medicine and Research; and the Advisory Group for the Duke Margolis Center for Health Policy Collaborative on Real-World Evidence. As a registered nurse, she

practiced as a community-based palliative and end-of-life care specialist for many years. Ms. Okun completed her graduate studies at The Heller School for Social Policy & Management at Brandeis University. She was a 2010 fellow in biomedical informatics for the National Library of Medicine and a 2014 Salzburg Global Fellow in New Paradigms for Behavioral and Mental Health.

Josh Rose, M.B.A., is the vice president and global head of strategy for the R&D Solutions business unit at IQVIA. In this role, Mr. Rose is responsible for building the overarching strategy for the clinical development business, establishing and governing strategic initiatives, and leading the identification of acquisition candidates. He focuses specifically on bringing to market new solutions that drive growth and differentiation across the company. He also leads the Virtual Trial service business within the R&D Solutions business unit.

Leonard Sacks, M.D., was born in South Africa, where he received his medical education at the University of the Witwatersrand. In 1988, he moved to the United States and completed a fellowship in immunopathology at Upstate Medical Center in Syracuse, New York, and a fellowship in infectious diseases at the U.S. Department of Veterans Affairs Medical Center in Washington, DC. Since then he has worked as an attending physician in infectious diseases both in Washington, DC, and in South Africa, with particular interests in antimicrobial therapy, tuberculosis, and tropical diseases. In 1998 he joined the staff of the U.S. Food and Drug Administration, where he has served as a medical reviewer and team leader in the Division of Special Pathogens and Immunological Drug Products at the Center for Drug Evaluation and Research (CDER), and is currently the associate director for clinical methodology in the Office of Medical Policy (CDER). He holds an academic position as associate clinical professor of medicine at The George Washington University.

Kelly Simcox, M.S., serves as the head of the Americas, Clinical Study Units, and Clinical Operations at Sanofi (formerly Rhone-Poulenc Rorer, and Aventis and Sanofi-Aventis). She has been a role model regarding staff development and team building, fostering a business mindset as well as a culture of excellence and continuous improvement. After her pre-clinical experience, Ms. Simcox moved to clinical development as a monitor and now manages a group of more than 650 clinical operations in the Americas. A seasoned global pharmaceutical executive, Ms. Simcox has a proven record of accomplishment in clinical development, project management, and global operations. Ms. Simcox has significant leadership experience, having served as one of only 70 leaders in research and development to

be selected to participate in the exclusive Evolve Center for Leadership training. Her contributions have been recognized among the industry—she was honored as a Healthcare Businesswomen's Association Rising Star in 2012. She represents her member company among industry initiatives, such as TransCelerate BioPharma Inc. Ms. Simcox received her undergraduate degree from Muhlenberg College and received a master's degree from Temple University.

Wendy Weber, M.D., Ph.D., M.P.H., is the acting deputy director at the National Center for Complementary and Integrative Health (NCCIH) at the National Institutes of Health (NIH). She also serves as branch chief for clinical research in the Complementary and Integrative Health Branch in the Division of Extramural Research at NCCIH. She joined NCCIH as a program director in 2009. The Clinical Research Branch is responsible for the oversight of all NCCIH-supported clinical trials. Dr. Weber is coordinator of NCCIH's Clinical Trial Specific Funding Opportunity Announcements (FOAs) and point of contact for all natural product-related clinical trial FOAs. She is a member of the NIH Common Fund-supported Health Care Systems Research Collaboratory and the program officer for the Coordinating Center. Dr. Weber is also a member of the planning and oversight team for NIH/U.S. Department of Defense/U.S. Department of Veterans Affairs Nonpharmacologic Approaches to Pain Management Collaboratory and project scientist for its Coordinating Center. At NCCIH, Dr. Weber oversees a portfolio of pragmatic clinical trials, natural product clinical trials, studies of complementary medicine to promote healthy behavior, and complex complementary/integrative medicine intervention research. Dr. Weber's interests include the use of complementary medicine interventions for common pediatric conditions, mental health conditions, promoting healthy behaviors, and health services research. Dr. Weber earned a Ph.D. in epidemiology and an M.P.H. from the University of Washington. She earned a doctorate of naturopathic medicine (N.D.) from Bastyr University. Prior to joining NCCIH, she was a research associate professor at Bastyr University, where her research included the study of herbal treatments for pediatric conditions. Her clinical practice focused on the treatment of children and adolescents with mental health conditions, abdominal pain, headaches, and allergies. She has published on treatment of pain with complementary health approaches, echinacea's effect on colds in children, naturopathic treatment of children, and complementary medicine treatments for attention-deficit hyperactivity disorder.

Jon White, M.D., serves as the deputy national coordinator for health information technology. The family physician has dedicated his career to improving health and health care quality through the use and sharing of

electronic health information. At The Office of the National Coordinator for Health Information Technology (ONC), Dr. White provides high-level executive direction and leadership for all ONC programs and policies, and advances key priorities. He has led mission-critical activities, including the publication of high priority, nationally impactful regulations; the publication of the *Shared Nationwide Interoperability Roadmap*, a widely publicized congressional report on information blocking; and ONC's efforts in the precision medicine initiative.

Appendix C

Examples of Virtual Clinical Trials Included in the Workshop Handout

COMPLETED TRIALS

REMOTE

- Year Posted: 2011
- Sponsor: Pfizer Inc.
- Disease: Overactive Bladder
- Intervention: Tolterodine ER versus Placebo
- Phase: Phase 4
- Digital Health Technology: Web-based trial design

REMOTE was the first randomized clinical trial using Web and mobile phone-based "patient recruitment, enrollment, and collection of study data without requiring patients to visit a physical study site" (Jhadhav, 2016). REMOTE was unable to recruit enough patients as most of the target patient group was older and less literate with the technology being used (Jhadhav, 2016), illustrating the need to appropriately use digital health technology in a trial. For more information on the trial, please view the study record (ClinicalTrials.gov, 2013).

VERKKO

- Year Posted: 2015
- Sponsor: Sanofi
- Disease: Diabetes
- Intervention: Observational
- Phase: Phase 4

- Digital Health Technology: Web-based and 3G-enabled wireless blood glucose meter

This study tested the use of an online platform and a 3G-capable, wireless glucose meter. VERKKO was the first clinical trial using an electronic informed consent approved by European regulatory agencies and indicated that compliance, convenience, and retention can increase by using a virtual platform (Business Wire, 2016; CenterWatch, 2017).

A Computerized Intervention for Depression

- Year Posted: 2016
- Sponsor: William Stone
- Disease: Depression
- Intervention: Behavioral—interactive, media-based problem-solving treatment
- Phase: Not applicable
- Digital Health Technology: Computer-based

This study was entirely automated and did not require involvement of a live clinician, with the goal of providing access to participants who did not have access to traditional therapy due to living conditions or individual preferences. The computer-based treatment offered several advantages, such as the ability to use it anywhere and its standardized and consistent approach. For more information, please view the study record (ClinicalTrials.gov, 2017a).

ONGOING TRIALS

ALS AT HOME

- Year Posted: 2017
- Sponsor: Barrow Neurological Institute
- Disease: Amyotrophic lateral sclerosis (ALS)
- Intervention: Observational study
- Phase: Information not available
- Digital Health Technology: 3G-enabled biological functioning meters

A single-center study of up to 150 participants is being conducted to determine "the extent to which frequent sampling can improve the qualities of outcome measures collected at home by study participants" (ClinicalTrials.gov, 2018c). This study is yet to be completed, but potential benefits include increasing data measurement frequency and increased convenience for ALS patients who may have difficulty visiting a study center to be part of the trial (Barrow Nerulogical Institute, 2017). For more information, please view the study record (ClinicalTrials.gov, 2018c).

Virtual-PND

- Year Posted: 2017
- Sponsor: Women's College Hospital
- Disease: Perinatal depression
- Intervention: Behavioral
- Phase: Not applicable
- Digital Health Technology: Teleclinician visit

This study consists of 12 weeks of supplemental real-time clinician video visits. Though the initial goal is to demonstrate the feasibility of a large-scale randomized controlled trial evaluation of virtual psychiatric care, this study will also inform the effectiveness of providing virtual psychiatric care. For more information, please view the study record (ClinicalTrials.gov, 2017d).

ELECTOR Treat-to-Target via Home-Based Disease Activity Monitoring of Patients with Rheumatoid Arthritis

- Year Posted: 2018
- Sponsor: Frederiksberg University Hospital
- Disease: Rheumatoid arthritis
- Intervention: Observational
- Phase: Not applicable
- Digital Health Technology: Telemonitoring

This study is using telemonitoring tools to manage treatment of rheumatoid arthritis. It will furthermore assess if a virtual approach for home-based monitoring is superior to standard clinical monitoring strategy. For more information, please view the study record (ClinicalTrials.gov, 2018d).

Enhancing Quality of Life Through Exercise: A Telerehabilitation Approach

- Year Posted: 2016
- Sponsor: McGill University
- Disease: Spinal cord injury
- Intervention: Behavioral—physical activity intervention
- Phase: Not applicable
- Digital Health Technology: Video-based telerehabilitation

This study will evaluate video-based telerehabilitation intervention to enhance basic psychological needs, motivation, physical activity, and quality-of-life–related outcomes for adults with spinal cord injuries. This the first video-based physical activity telerehabilitation intervention and it is hypothesized that it will have moderate effects on self-determination theory variables, physical activity, life satisfaction, and depression. For more information, please view the study record (ClinicalTrials.gov, 2016b).

Feasibility and Effect of a Follow-Up Telerehabilitation Program for Chronic Obstructive Lung Disease Versus Standard Follow-Up (2-TELEKOL)

- Year Posted: 2018
- Sponsor: University of Aarhus
- Disease: Chronic obstructive pulmonary disease (COPD)
- Intervention: Behavioral
- Phase: Not applicable
- Digital Health Technology: Telerehabilitation

This study aims to assess and compare the feasibility of a telerehabilitation platform "to standard treatment with respect to exercise capacity, quality of life, and activities of daily living in patients with COPD." For more information, please view the study record (ClinicalTrials.gov, 2018e).

"Recovery 4 US"—A Photovoice-Based Social Media Program (Boston University)

- Year Posted: 2017
- Sponsor: Boston University
- Disease: Mental illness, social isolation, and loneliness
- Intervention: Behavioral
- Phase: Not applicable
- Digital Health Technology: Social media program

This study will evaluate a social media program, "Recovery 4 US," on its ability to enhance community participation and overall recovery of individuals with psychiatric disabilities. The Recovery 4 US platform includes virtually delivered interventions, such as receipt of a hope-inspiring message paired with a corresponding visual image, in addition to community-oriented events initiated by members of the Recovery 4 US community. For more information, please view the study record (ClinicalTrials.gov, 2017c).

Maraviroc to Augment Rehabilitation Outcomes After Stroke

- Year Posted: 2017
- Sponsor: University of California, Los Angeles
- Disease: Stroke
- Intervention: Maravirov versus Placebo
- Phase: Phases 2 and 3
- Digital Health Technology: Telemonitoring via mobile devices

This study will investigate the effectiveness of Maraviroc (in supplement to usual post-stroke care) and will telemonitor all participants via mobile devices (ClinicalTrials.gov, 2017b).

ANNOUNCED PARTNERSHIPS FOR VIRTUAL TRIALS AND PLANNED TRIALS

Sanofi/Science 37 Partnership

Sanofi has partnered with Science 37, a remote research technology company, to allow patients to participate from the comfort of their own homes and report data via an Apple iPhone, which is equipped with Science 37's Networked Oriented Research Assistant (NORA®). Participants will be provided with a phone, other sensors needed for the trial, and medicines being researched. Study mobile devices allow participants to reach study staff at any time. Furthermore, patients' data are sent directly to researchers, who have ready access to the data. This process can eliminate months of searching for participants and travel time to study sites (Adams, 2017; CenterWatch, 2017).

Novartis/Science 37 Partnership

Novartis has partnered with Science 37 to boost its ability to run "remote trials." Its partnership plans to "launch up to 10 trials, with increasing decentralization over 3 years" (Adams, 2018). Set to begin in late 2018 in the United States, trials will focus on dermatology, neuroscience, and cancer. Novartis will leverage Science 37's NORA® technology to facilitate remote collection of data. Novartis is no stranger to this approach and has used a "virtual approach" for cluster headaches, acne, and non-alcoholic steatohepatitis (Adams, 2018; Taylor, 2018).

UCB/Science 37 Partnership

UCB has announced a partnership with Science 37 to bring clinical trials into participants' homes. UCB plans to use Science 37's NORA platform to evaluate its Neupro® patch in pediatric restless leg syndrome (following its approval for adults). The trial plans to enroll 138 participants and will track their sleep, impact of the disease, and quality of life using the app (Hale, 2018).

Appendix D

Virtual Clinical Trials Presented by Speakers at the Workshop

REMOTE – See Appendix C

AT-HOME PD

- Year Posted: 2018
- Sponsor: National Institutes of Health
- Disease: Parkinson's disease
- Intervention: Observational
- Phase: Not applicable (recruited participants from former Phase 3 Parkinson's disease trials)[1]
- Digital Health Technology: Video visits and smartphone

AT-HOME PD conducted longitudinal follow-up for participants in two prior Phase 3 Parkinson's disease trials, using telemedicine and smartphone platforms for monitoring outcomes. This study has the potential to simplify long-term follow-up of large cohorts and will test the feasibility of new technology platforms to fulfill this purpose. For more information, please view the study record (ClinicalTrials.gov, 2019c).

KALM

- Year Posted: N/A
- Sponsor: 1747
- Disease: Anxiety and insomnia

[1] AT-HOME PD recruited from STEADY PD III (ClinicalTrials.gov, 2019a) and SURE PD3 (ClinicalTrials.gov, 2018b), which were launched in 2014 and 2016, respectively.

- Intervention: Kava and Valerian (dietary supplements)
- Phase: Not applicable
- Digital Health Technology: Web-based

This study assessed efficacy of kava and valerian to treat anxiety and insomnia, with recruitment and consent taking place entirely online and study compounds being mailed directly to participants. KALM is likely the first study to test the feasibility of conducting a randomized, blinded trial over the Internet, and it was able to demonstrate the feasibility of such a model (Jacobs et al., 2005).

Omega-3 Fatty Acids for Hyperactivity Treatment in Autism Spectrum Disorder

- Year Posted: 2012
- Sponsor: Hugo Moser Research Institute at Kennedy Krieger, Inc.
- Disease: Autism spectrum disorder (ASD) and hyperactivity
- Intervention: Omega-3 fatty acids
- Phase: Phase 2
- Digital Health Technology: Web-based

This study evaluated the efficacy of an omega-3 fatty acid supplement in reducing hyperactivity in children with autism; it used e-mail invitations and Web-based enrollment and study management. It demonstrated the feasibility of conducting a Web-based clinical trial in children with ASD, with benefits including a fast enrollment rate (Bent et al., 2014). For more information, see the study record (ClinicalTrials.gov, 2018a).

TOPAZ (Trial of Parkinson's Disease and Zoledronic Acid)

- Year Posted: 2019
- Sponsor: National Institute on Aging
- Disease: Osteoporosis and Parkinson's disease
- Intervention: Zoledronic acid
- Phase: Phase 4
- Digital Health Technology: Web- and video-based

This study evaluated the efficacy of Zoledronic acid in reducing bone fracture risk in elderly Parkinson's disease patients. The participants enroll through interactive electronic consent, and if deemed eligible to join the study will be scheduled for a video-based telemedicine assessment to confirm Parkinson's disease diagnosis. A nurse home visit will also be scheduled to confirm final eligibility and administer the investigational drug. For more information, see the study record (ClinicalTrials.gov, 2019d).

Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness (ADAPTABLE)

- Year Posted: 2016
- Sponsor: Duke University
- Disease: Atherosclerotic cardiovascular disease
- Intervention: Aspirin
- Phase: Not applicable
- Digital Health Technology: Combination of electronic health records, a patient portal, and patient-reported outcomes

ADAPTABLE seeks to compare the effectiveness of two doses of aspirin in the secondary prevention of patients with established atherosclerotic cardiovascular disease and is using a combination of electronic health record searches and patient-reported outcomes for follow-up. An important component of ADAPTABLE is its aim to improve engagement with participants, their health care providers, and trial investigators within the trial infrastructure. For more information, see study record (ClinicalTrials.gov, 2019b).

Lithium Carbonate Treatment for Amyotrophic Lateral Sclerosis

- Year Posted: N/A
- Sponsor: PatientsLikeMe
- Disease: Amyotrophic lateral sclerosis (ALS)
- Intervention: Lithium carbonate
- Phase: N/A
- Digital Health Technology: Web-based

PatientsLikeMe tested the efficacy of lithium carbonate by capturing information on the study's participants via an online data collection tool. Though this study did not show a treatment effect, it did note advantages of collecting patient-reported outcome data online, including speed, patient access, and availability of control participants (Wicks et al., 2011).

Lunasin Virtual Study (PatientsLikeMe and Duke ALS Clinic)

- Year Posted: 2016
- Sponsor: Duke University
- Disease: Amyotrophic lateral sclerosis (ALS)
- Intervention: Lunasin
- Phase: Phase 2
- Digital Health Technology: Hybrid (in-person and Internet-based)

This study investigated if Lunasin could slow progression of ALS and used in-person visits, virtual check-ups via the PatientsLikeMe online platform,

and telephone visits, which co-occurred with virtual visits (for trouble-shooting and education on clinical scores). Though the study did not find evidence to support use of Lunasin to slow or reverse progression of ALS, the design of the trial did provide logistical benefits, such as cost efficiency, increased diversity of participants enrolled, and rapid enrollment (Bedlack et al., 2019). For more information, see the study record (ClinicalTrials.gov, 2016a).