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The Role of Digital Health Technologies in Drug Development

PROCEEDINGS OF A WORKSHOP

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Forum on Drug Discovery, Development, and Translation

Roundtable on Genomics and Precision Health

Board on Health Sciences Policy

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Reviewers

This Proceedings of a Workshop was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published proceedings as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

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SUSAN SCHAEFFER, The Patient's Academy for Research Advocacy

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **ERIC B. LARSON,** Kaiser Permanente Washington. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

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The forum and roundtable wish to express gratitude to the members of the planning committee for their work in developing an excellent workshop agenda and to the expert speakers who explored the role of digital health technologies in drug development. The project directors would like to thank the project staff who worked diligently to develop both the workshop and the resulting proceedings.

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Acronyms and Abbreviations

3-MST	3-meter shuttle test
12-MRT	12-minute run test
ADAU	average daily accelerometry units
BYOD	bring your own device
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CPU	clinical pharmacology unit
DDT	Drug Development Tool
DHT	digital health technology
EHR	electronic health record
FDA	U.S. Food and Drug Administration
IND	investigational new drug
IRB	institutional review board
KCCQ	Kansas City Cardiomyopathy Questionnaire

PD	Parkinson's disease
PGHD	person-generated health data
PMC	post-marketing commitment
PMR	post-marketing requirement
R&D	research and development
ReCODE	Research Center for Optimal Digital Ethics
WHO	World Health Organization

1

Introduction[1]

As the pace of technological innovation has accelerated, digital health technologies (DHTs) are becoming increasingly accessible, available, and popular among consumers, clinicians, and researchers. DHTs range from hardware—such as wearable devices and sensors—to software, such as mobile phone apps that enable consumers to monitor their own health and participate in studies; telemedicine platforms to connect patients with clinical providers; and artificial intelligence to support clinical decision making. DHTs offer new modalities for capturing personal and sensitive health data from patients as they carry on with their daily lives (CTTI, 2019). These types of measurements can offer new insights into diseases with characteristics that are not yet well understood, because traditional methods of measurement rely on in-clinic methods that may only represent a patient's data from that day or from a limited timeframe (Coravos et al., 2019a).

[1] This workshop was organized by an independent planning committee whose role was limited to identification of topics and speakers. This Proceedings of a Workshop was prepared by the rapporteurs as a factual summary of the presentations and discussion that took place at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

USE OF DIGITAL HEALTH TECHNOLOGY APPLICATIONS TO ADDRESS PAIN POINTS ACROSS THE DRUG DEVELOPMENT LIFECYCLE

Among the wealth of opportunities afforded by DHTs to advance patient care and shed light on the patient experience outside of the clinic setting is the potential for these technologies to improve the probability of success in drug research and development (R&D) and enable precision medicine. The expanding frontier of biomedical science has led to increasing numbers of new drug candidates in the pipeline (Pharma Intelligence, 2019), but progress from the laboratory bench to the patient's bedside has been hampered at critical points throughout the development lifecycle, such as gaps in data collection, a lack of objective "gold standard" measurements, lack of patient-centricity, study participants not accurately reflecting the broader patient population, and the need to establish comparative effectiveness in post-market surveillance.

Over time, DHTs may help transform current drug development and clinical trial paradigms. For example, DHTs can be used to enable continuous data collection, provide surrogate endpoints for efficacy, support participant engagement to improve adherence and retention, and broaden access to and increase representation of clinical research. Furthermore, DHTs can facilitate decentralized and virtual trials (Coravos, 2019a). DHTs can also provide novel ways to measure phenotypes and outcomes, thereby contributing to the advancement of precision therapeutics (Adamo et al., 2020).

Despite the promise, challenges remain regarding the selection, evaluation, verification and validation, implementation, and standardization of DHTs (Coravos et al., 2020; Goldsack et al., 2020). As DHTs have become more prominent tools in clinical care, challenges have emerged around interoperability and integration of various data types from multiple sources, the establishment of analytical and clinical validity for digital health measures with real-world clinical outcomes, buy-in from clinical providers, and reimbursement issues. Efforts to address these challenges have been hampered by the lack of "gold standard" benchmarks, best practices for data security and governance, and verification and validation among the breadth of stakeholders developing and using DHTs, among a myriad of other issues (Goldsack et al., 2020; Matthews et al., 2019; Vayena et al., 2018). Additionally, DHT applications may give rise to new issues around ethics, as well as data governance, privacy, and security.

Establishing standards and best practices would benefit from the collective work of stakeholders that seek to incorporate DHTs into the drug development lifecycle. The growth in genomics technology in the consumer space and in clinical care may offer useful lessons and caveats for

the incorporation of DHTs into drug R&D (Tung et al., 2018). Optimizing the role of DHTs in drug development may involve collaboration among a broad range of stakeholders from across sectors—including consumers, patients, clinicians, regulators, biopharmaceutical companies, academics, and technology developers—to share insights, experiences, and lessons learned.

ORGANIZATION OF THE WORKSHOP

On March 24, 2020, a 1-day public workshop[2] titled The Role of Digital Health Technologies in Drug Development was convened by the Forum on Drug Discovery, Development, and Translation (the forum) and the Roundtable on Genomics and Precision Health (the roundtable) of the National Academies of Sciences, Engineering, and Medicine. This workshop builds on prior efforts by the forum to explore how virtual clinical trials facilitated by digital health technologies might change the landscape of drug development (NASEM, 2019). The roundtable has previously examined how precision health might be accelerated by applying lessons learned from direct-to-consumer genomics to digital health technologies (Tung et al., 2018). The roundtable has additional convened working groups focusing on digital health and precision therapeutics. Furthermore, both the forum and roundtable have explored how drug discovery value can be derived from large-scale genetic resources (NASEM, 2016). To explore the challenges and opportunities in using DHTs for improving the probability of success in drug R&D, enabling better patient care, and improving precision medicine, the workshop featured presentations and panel discussions on the integration of DHTs across all phases of drug development. The workshop comprised four sessions, which were structured to mirror the drug development lifecycle by examining the role of DHTs in (1) characterizing disease, (2) recruitment and safety trials, (3) pivotal trials, and (4) post-market surveillance. Specific ethical and regulatory considerations were also explored during an ethics briefing and a regulation-focused fireside chat. Throughout the workshop, participants considered how DHTs could be applied to achieve the greatest impact—and perhaps even change the face of how clinical trials are conducted—in ways that are also ethical, equitable, safe, and effective.

In March 2020, when this workshop was convened, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), was spreading around the world. On March 11, 2020, the COVID-19 outbreak was declared a

[2] The workshop Statement of Task, workshop agenda, planning committee biographies, and speaker biographies can be found in Appendixes A, B, C, and D, respectively.

pandemic by the World Health Organization. At the time, evolving guidance from public health and regulatory authorities[3] coupled with widespread measures to mitigate the spread of COVID-19 spurred an abrupt transition to reliance on digital technologies to facilitate many clinical, personal, and professional interactions. The emerging pandemic imbued the workshop with a sense of urgency to develop strategies to rapidly advance DHTs. Throughout the workshop, participants considered specific opportunities for DHTs to support drug development and decentralized clinical trials in the context of the evolving pandemic.

ORGANIZATION OF THE PROCEEDINGS

This Proceedings of a Workshop is structured into seven chapters. Chapter 2 provides an overview of ethical and regulatory considerations that pertain to the use of DHTs in drug development. Chapters 3 focuses on the use of DHTs in pre-clinical research and how they can support characterizing disease. Chapter 4 focused on opportunities and challenges related to incorporating DHTs in early stages of clinical trials, in which they can help inform recruitment and contribute to safety trials. Chapter 5 centers on the use of DHTs in pivotal trials, which provide the evidence on which critical regulatory decisions are based. Chapter 6 describes the role that DHTs can play in supporting post-market surveillance, comparative effectiveness research, and patient centricity. Chapter 7 features reflections on the workshop and key takeaways highlighted by the workshop's co-chairs, Jen Goldsack, executive director of the Digital Medicine Society, and Joseph Menetksi, associate vice president of Research Partnership and director of the Biomarkers Consortium at the Foundation for the National Institutes of Health.

[3] The U.S. Food and Drug Administration released the guidance "Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency." See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency (accessed June 16, 2020).

2

Ethical and Regulatory Considerations for Digital Health Technologies

Key Messages Highlighted by Individual Speakers

- In the context of pre- and post-market evidence generation, digital health technologies (DHTs) have the potential to support data collection, increase patient centricity, and facilitate data curation and trial management. (Abernethy)
- Data generated from DHTs could be used in combination with administrative claims data and electronic health records to build larger and more reliable real-world evidence datasets. Integration of these datasets will require attention to data linkage, longitudinality, and quality. (Abernethy)
- All datasets have limitations—a better understanding of data completeness, reliability, and different types of validity will more optimally enable the use of DHTs in clinical research. (Abernethy)
- Uncertainties related to data management, governance, health care, and informed consent should be addressed before the use of DHTs in clinical care and research can move forward. (Nebeker)
- When developing DHTs in a way that is effective and ethical, it will be valuable for developers to keep in mind access and usability considerations, privacy impacts, data management practices, and risk–benefit assessment. (Nebeker)

- Providing meaningful and pertinent information to trial participants will be important for researchers and DHT developers to consider and should be a key component of a participant engagement strategy. (Nebeker)
- The U.S. Food and Drug Administration (FDA) developed its Technology Modernization Action Plan, released in 2019, to enable FDA to respond in a flexible way to new, continuously updating, structured and unstructured data from DHTs. (Abernethy)
- To mitigate potential challenges with the digital divide, community health workers could be a bridge for helping individuals understand how technologies are used, how data are managed, and who has access, and for building trust within underserved communities. (Nebeker)

The workshop featured a briefing on ethical considerations related to digital health technologies (DHTs) from a behavioral science perspective by Camille Nebeker, director of the Research Center for Optimal Digital Ethics (ReCODE) at the University of California, San Diego. A regulatory perspective was provided by Amy Abernethy, principal deputy Commissioner at the U.S. Food and Drug Administration (FDA), during a fireside chat moderated by Jennifer Goldsack, executive director of the Digital Medicine Society. Nebeker and Abernethy discussed the categories and uses of DHTs, opportunities to leverage them for capturing real-world evidence, and considerations for moving the field forward in an effective, ethical, and safe manner.

CATEGORIES AND USES OF DIGITAL HEALTH TECHNOLOGIES

DHTs have provided new tools for researchers to collect data about people's day-to-day activities and can facilitate the study of trial participant behavior in real time by using wearable and remote sensor technologies, mobile applications, and strategies like ecological momentary assessment.[1] Nebeker provided an overview of DHTs, such as mobile devices, wearables, and other sensors, that can collect data about participants' everyday lives using these new methods (see Box 2-1). Nebeker illustrated how each of these approaches has presented unique challenges due to the large volume, high-dimensional, and diverse data being collected,

[1] Ecological momentary assessment: A clinical psychology method that involves repeatedly sampling data on participant's behavior in real time, with the aim of reducing recall bias and increasing validity (Shiffman et al., 2008).

including geolocation data, physiological measurements, and biometrics. Additionally, Health Insurance Portability and Accountability Act privacy rules may not apply depending on the type of data, given that many of the data captured are not housed within electronic health records (EHRs).

BOX 2-1
Digital Health Technology Methods

Visual: Visual methods can be used to study behavior "in the wild" from a first-person perspective. Nebeker described an early effort to collect data from participants who used an outward-facing camera that captured an image every 7 seconds of the participant's everyday life. At the time, the National Institutes of Health had funded four observational research studies to be conducted using this device, and it encountered a host of challenges relating to ethical concerns, which delayed approval from an institutional review board. These concerns included the rights of bystanders who may be captured by the participants' cameras and subsequently included in the research data, the data privacy of participants, and the management of data (collection, secure storage, and sharing protocols). Data management was especially important given that the data would not be included in the electronic health record and therefore not covered by Health Insurance Portability and Accountability Act requirements.

Sensing: Sensing equipment can be used to observe and monitor physiology in real time. For example, data collected via remote, person-worn sensors can be transmitted wirelessly to the patients or their physician. Nebeker described a remote sensor, developed by Todd Coleman at the University of California, San Diego, which tracked fetal heart rate in pregnant women.[a] The physiological information captured by the sensor was used to help determine when the participant should go to the hospital.

Digital Platforms: Digital platforms—from cloud and communication services to wearable personal activity trackers and other "smart" devices in the home—can be used to collect health data for analysis. A wealth of social media data can now be mined as well. For example, Facebook has an algorithm that has been deployed to flag suicidality, Nebeker said, and publicly available tweets have also been used by scientists to predict infectious disease outbreaks (Alessa and Faezipour, 2018; Muriello et al., 2018). These types of platforms also provide new opportunities for citizen scientists to capture and study their own data. Nebeker emphasized that it will be important to encourage and support this kind of personalized health research in a way that will create meaningful results.

[a] For more information see https://iem.ucsd.edu/centers/cph-perinatal-health.html (accessed June 16, 2020).
SOURCE: As presented by Camille Nebeker, March 24, 2020.

An additional layer of complexity has been introduced by the popularity of commercial technologies and wellness apps designed for consumers to capture their own data. In early studies using DHTs, Nebeker said researchers had full access to and control over the data collected—because, she explained, most technologies used were research-grade tools rather than commercial products. In subsequent years, study researchers began using commercially available health and wellness technologies. The challenge with commercial products, Nebeker said, is the degree to which the products are effective and reliable. Furthermore, the products' terms and conditions and privacy policies often are not, for the most part, written in favor of the consumer or the researcher. Nebeker explained that these terms and conditions directly conflict with federal regulations for human research protections—specifically for release of liability, or a waiver of responsibility for harm a person may be subjected to through use of a product. While the commercial terms of service include a release of liability, federal regulations prohibit this from occurring in human subject research (Nebeker et al., 2017a).

Leveraging Digital Health Technologies for Drug Research and Development

Abernethy identified several opportunities to use DHTs across the drug research and development process. Although DHTs have value in pre-clinical research such as for drug discovery and in silico trials, Abernethy focused her remarks on DHT use in pre- and post-market clinical evidence development. Within this broad use of DHTs, Abernethy highlighted three categories:

- **Data collection support:** DHTs, such as biosensors and remote monitoring technologies, can support the collection of study participant-level and operational data, such as information pertaining to efficacy and safety endpoints within clinical trials.
- **Patient-centricity support:** DHTs, such as telemedicine, can support patient-centricity by reaching patients where they are, bridging gaps in data collection in between clinic visits through continuous data collection, and facilitating the collection of patient-reported outcomes.
- **Data curation and trial management:** DHTs can contribute to the conduct of clinical trials by offering trial management solutions in the clinic as well as by supporting data curation.

When considering how DHTs can be used in clinical research, it is important to take into account the traditional approach of collecting data

for evidence generation, Abernethy emphasized. Digital technologies and data curation could substitute or complement the development of evidence at different points throughout the process of conducting a clinical trial—from following a protocol to generating a dataset and making a decision based on the final results of the study. Rather than replacing traditional clinical trial data, data from DHTs can serve a complementary purpose. For instance, these data could support the generation of real-world datasets and provide longitudinal follow-up data, additional control data, and supplementary information for certain data points. She suggested that it would be useful to consider all features of a clinical trial to find opportunities for DHTs to contribute, either as a complement to the current approach or as the main component in conducting a trial. Abernethy observed that DHTs may drive changes in the infrastructure of clinical trials. A shift in this direction, she noted, has already begun with the advent of telemedicine as well as with the need to adapt the clinical trial infrastructure in the evolving landscape of COVID-19.[2]

Evaluation of Digital Health Technologies for Drug Development

"All datasets have warts; we just have to have a way of measuring and solving for data quality," Abernethy said. When evaluating a DHT, she said the setting of use (e.g., consumer use, adjunct to clinical care, or within the context of a clinical trial) is an important consideration. If they are to be used to collect data on endpoints and biomarkers for clinical evidence generation, DHTs should undergo validity assessments (see Chapter 5 for additional information on analytical and clinical validity). Validity refers to the likelihood that the given output from the DHT will be able to measure the target endpoint (FDA, 2017). As such, validation is related to the endpoint at hand. For example, if the endpoint being assessed is a change in blood glucose, then the validation of a glucometer may involve cross-referencing measurements against other constructs to gain confidence that the sensor performs within that specific setting.

Defining and Optimizing Data Quality

DHTs used for clinical research are often held to a higher standard than currently available tools, Goldsack said. She asked Abernethy if there are strategies for defining and optimizing data quality—or at least identifying limitations so they can be mitigated—in a solution-oriented way that would not compromise regulatory standards. Speaking from her per-

[2] See Chapter 1 for additional details on the impact of COVID-19 on the conduct of clinical trials.

sonal perspective—not as a representative of FDA—Abernethy emphasized the value of developing more standardized approaches to defining data quality across the real-world data space. The field, she observed, may need a consistent way of documenting data completeness, reliability, and different types of validity of individual data elements—specifically face validity, context validity, and construct validity. In the context of DHTs, data quality is shaped by the interrelationships between data outputs, the algorithm used to make sense of that information, and the final endpoint or measurement ultimately used for research analysis.

A structured approach to defining data quality could inform similarly structured approaches to improving data quality, Abernethy said, identifying three strategies that could help: (1) improving the instrumentation; (2) collecting additional data points to triangulate information so that the aggregate data more accurately represents the "truth"; and (3) using analytic methods, such as developing proxies and new analyses. When aggregating a real-world dataset, for example, it will be important to identify data gaps and determine which sources of new data or analyses could be developed to fill them in. A subsequent challenge, Abernethy said, will be determining if those changes have improved the quality of the dataset; use of a standardized assessment of data quality provides a mechanism to monitor the impact of sequential changes. Abernethy predicted that the process of continually improving data will be used increasingly in digital approaches to collecting and using data.

USING DIGITAL HEALTH TECHNOLOGIES TO CAPTURE REAL-WORLD EVIDENCE

Abernethy remarked that there is a tendency to associate DHTs with sensors and other wearable technologies. However, the 21st Century Cures Act[3] catalyzed an increasing focus on understanding real-world data and evidence, including administrative claims data, EHR data, and data collected from DHTs. Commensurately, the language on DHTs has begun to shift from biosensors toward merging with the language of real-world evidence, as the two have sources that are often related. It is important to note that the FDA characterizes data collected from biosensors during a study as clinical trial data and not real-world data because the data are not being collected in a real-world setting (FDA, 2020d).

Goldsack remarked that EHRs and claims data have traditionally been considered the primary sources of real-world data and evidence and inquired if new sources of data, such as from DHTs, could be combined with traditional sources to make the resulting body of real-world evidence

[3] The full text of the 21st Century Cures Act can be found at https://www.congress.gov/bill/114th-congress/house-bill/34 (accessed May 17, 2020).

more valuable. Abernethy highlighted three critical features of data that are relevant when blending different sources of real-world evidence: data linkage, data quality, and longitudinality.

- **Data linkage:** No single dataset can provide all of the variables needed to answer all research questions. While this challenge is addressed in clinical trials by pre-specifying a narrow research question and all variables required to address the question to help ensure that the necessary information will be captured, real-world evidence may require linkages between different data sources to provide additional necessary variables. For example, patient-reported outcomes are often missing in the EHR dataset and clinical variables are missing in administrative claims datasets. Information from biosensors and other digital health solutions could help fill these types of information gaps to build valuable real-world evidence.
- **Data quality:** Real-world evidence is based on data sources of varying quality, Abernethy said. Given that no dataset is perfect, it is important to better understand how to measure the data's limitations and address them. While DHTs, like biosensors, often provide instrumentation data that may be less subjective and have more completeness and reliability than other types of datasets, this information is not immune to data quality limitations. As such, the quality of DHT data should be measured in the same manner as with other types of datasets.
- **Data longitudinality:** Longitudinality, or the length of time a dataset covers, is a valuable feature of datasets, especially in the context of evolving real-world evidence. DHT data (e.g., from biosensors) are often longitudinal and less likely to be episodic and cross-sectional. However, as with every other kind of dataset, it often has limitations. For instance, if patients do not wear a device consistently over the long term, this may lead to missing data and an incomplete assessment of endpoints.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS OF DIGITAL HEALTH TECHNOLOGIES AND CLINICAL RESEARCH

Nebeker said that the ethical, legal, and social implications (ELSI) framework, which has been used in genomics[4] to guide research and protect study participants, can be applied to research using DHTs. Ethical

[4] See the Ethical, Legal, and Social Implications Research Program at https://www.genome.gov/Funded-Programs-Projects/ELSI-Research-Program-ethical-legal-social-implications (accessed June 7, 2020).

implications are rooted in the foundational principles set forth in the Belmont Report (1978),[5] which established a moral framework for biomedical research ethics in the United States. In practical terms, these principles are primarily manifested through the consent process (respect for persons), an evaluation of harms in relation to potential benefits (beneficence), and mitigating undue burden (justice). In research ethics, the normative principle of beneficence holds that research activities should benefit society by contributing new knowledge. While there is no guarantee or expectation that study participants will directly benefit, the principle of beneficence is applied by evaluating the probability and magnitude of potential harms against the possible benefits of knowledge to be gained. Furthermore, this comparison of risks to benefits must consider how risks will be mitigated for the actual research participants, including an evaluation of not only the type of risk, but the intensity, duration, and severity of potential harms to the participant. In the legal and regulatory domain of the ELSI framework, Nebeker focused on regulations that included liability concerns, conflict of interest, human subject protections, and intellectual property laws. She noted that new privacy laws had recently been enacted in Europe (General Data Protection Regulation[6]) and California (California Consumer Privacy Act[7]). Social implications relate to the downstream impacts of DHTs, she said. Mistakes may be inevitable when exploring this new digital health frontier, she added, and it will be important to share resulting lessons learned for the entire DHT community to benefit.

Engaging Stakeholders in Digital Health Research

Nebeker described some of the challenges regarding the various stakeholders in digital health research and how expertise areas could be bridged. She suggested bringing together diverse teams to collectively think through the potential implications of those mistakes for different populations, each of which may be affected in different ways. A variety of stakeholders—including the end users of DHTs—should be engaged in this conversation from the outset. Stakeholders, such as DHT developers, academics, and citizen scientists are now conducting research from a

[5] The full title is the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was published in the *Federal Register* in 1979. The report can be accessed at https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html (accessed May 15, 2020).

[6] More information about the European General Data Protection Regulation is available at https://gdpr.eu (accessed May 17, 2020).

[7] More information about the California Consumer Privacy Act is available at https://oag.ca.gov/privacy/ccpa (accessed May 17, 2020).

range of perspectives. These stakeholders have different goals and varied expertise and levels of formal training. Moreover, they operate within diverse regulatory environments and have different expectations of what is considered acceptable data to demonstrate that a product or process is effective and reliable (Nebeker, 2020) (see Figure 2-1). For example, those within academia, biotechnology, and pharmaceutical sectors tend to have extensive, highly focused training and typically conduct research that is heavily regulated and grounded in ethical principles. In contrast, community health workers have less extensive training, but are instrumental partners in bringing research into community settings. Those who are conducting citizen science or participant-led research are unregulated, may have little to no formal research training, and may be unfamiliar with applying the scientific method and research ethics. To increase community research capacity, Nebeker and colleagues have developed and continue to create educational programs[8] to increase research literacy and awareness of ethical practices among people who are not formally trained as scientists (Grant et al., 2019; Nebeker and López-Arenas; 2016; Nebeker et al., 2020).

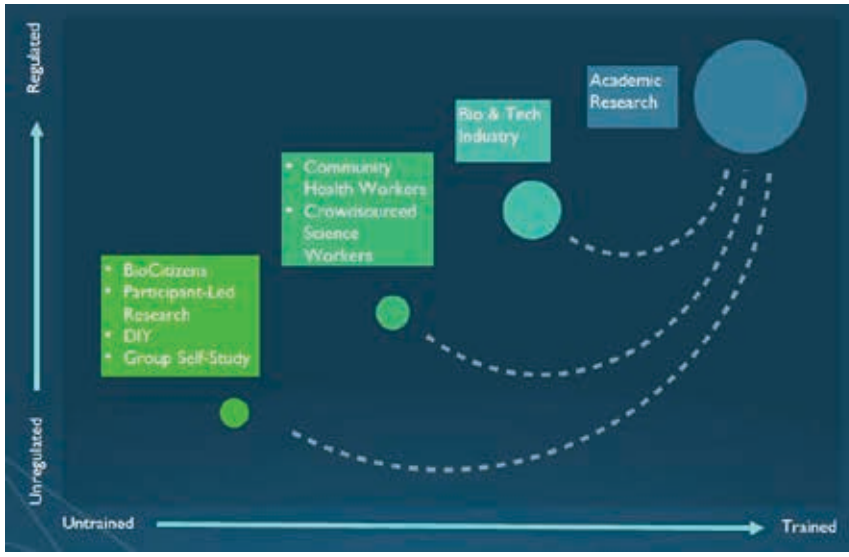

FIGURE 2-1 Variability in regulation and training among diverse stakeholders in the digital health research landscape.
SOURCE: As presented by Camille Nebeker, March 24, 2020.

[8] For more information on ReCODE Health's Building Research & Integrity Capacity course, see https://recode.health/about (accessed June 18, 2020).

Digital Health Decision Support Framework and Checklist

Nebeker and her colleagues developed a digital health decision-making framework and checklist[9] to guide how institutional review boards (IRBs) and researchers think through the ethical considerations (e.g., privacy, access, and risk–benefit analysis) and better protect participants. Ultimately, this framework guides researchers through the cycle of human-centered design (planning, designing, developing, testing, releasing, and applying feedback) to ensure that the right data are used, the right technologies are being developed, the technologies are developed ethically, the beneficiary population is involved in the design process, and the resulting technology fits within the context of the participants' lifestyle.

In developing the framework, Nebeker and her colleagues drew on related work on a clinical decision-making framework that helped clinicians protect their patients from privacy and data management risks when using mobile phone apps for mental health. Nebeker and the ReCODE Health team convened a focus group of ethicists, scientists, legal scholars, and regulatory experts to develop a survey that was deployed with behavioral scientists, and the responses were used to identify key domains of ethical principles for digital health: access and usability, privacy, risks and benefits, and data management (see Figure 2-2 for additional details)—each of which are anchored by the ethical principles of the Belmont Report (Nebeker et al., 2019).

- **Access and usability:** This domain captures product design and whether end users are able to use the technology. Considerations include how a given product works and how that information is communicated to the user, the technology's previous use within the target population, if accessory tools (e.g., smartphone or Internet access) are needed, and whether the product can be used in both the short and long term. Nebeker said that maintaining the participants' long-term engagement with a DHT is emerging as a major challenge.
- **Privacy:** This domain centers on the personal information collected and the participant's expectations that the information will be kept secure. If the information will be shared, then considerations include what information is collected, what is shared and why, and the degree of control afforded to the end user.
- **Risks and benefits:** This domain's goal is to evaluate the types of possible risks as well as the extent of possible harm, severity,

[9] The framework and checklists are available on the ReCODE Health website, available at https://recode.health (accessed May 16, 2020).

FIGURE 2-2 Factors influencing ethical practices in digital health.
SOURCES: As presented by Camille Nebeker, March 24, 2020; from Nebeker et al., 2018.

duration, and intensity. The assessment of risks and benefits is influenced by the evidence available to support the reliability of the DHT, risk mitigation strategies, and recognition of unknown risks.

- **Data management:** This domain addresses how data are collected, stored, and shared, as well as the extent to which the data are incorporated within other systems. Considerations include what data are collected, what data are needed to answer the question, why and how the data are shared, the end user's control over the data, and data interoperability.

Uncertainties Related to Digital Health Technology Use

Nebeker outlined several uncertainties related to data management, governance, health care delivery, and informed consent that she believes should be addressed before the use of DHTs in research can move forward. In terms of data management, questions around data ownership, data anonymity, and the use of data de-identification as a potential solution may require more research. Given the variability in governance, the relevance and responsiveness of existing systems should be considered. These include conventions, norms, and regulations that currently vary across the different disciplines and sectors engaged in this work. In the context of using DHTs to deliver better health care, there remain uncertainties

about whether machine learning and artificial intelligence can improve the effectiveness of clinicians. Finally, it is important to determine if consent can truly be informed in studies using DHTs. Strategies are needed to enhance the consent process so that even people with relatively low technology and data literacy can understand their involvement in a study. It would also be helpful, Nebeker said, to create consent mechanisms that are less onerous to understand than commercial products' terms and conditions of use. These uncertainties have prompted Nebeker, colleagues, and ReCODE Health to conduct studies on an array of considerations in the field of digital health research to bridge the gap between researchers and IRBs on risk assessment, develop a better understanding of concerns about participating in studies using DHTs, and gain further knowledge on terms and conditions participants accept when using DHTs. Nebeker provided further details about each category of research and information gaps to be filled (see Table 2-1).

ReCODE Health is currently partnering with a local retirement community to learn about barriers and facilitators to adopting DHTs; one outcome has been that education is needed on how DHTs work and how they can be beneficial (Wang et al., 2019). Nebeker emphasized that investing time to build trust and channels of communication with communities can enable participants to better understand how their data are used and shared. Goldsack remarked that DHTs have the potential to bring clinical

TABLE 2-1 Digital Health Technology Research and Information Gaps to Be Filled

Category of Research	Research or Information Gaps
Institutional review board (IRB) consent analysis (Nebeker et al., 2015)	• Inconsistent risk assessment • Bystander rights • Data management
IRB focus groups (Nebeker et al., 2017)	• Threats to participant privacy • Expertise within review board • Interest in sharing resources
Participant surveys (Nebeker et al., 2016)	• Device comfort • Consent • Privacy of bystanders and participants
Participant digital divide (Nebeker et al., 2017b)	• Legal risks • Consent • Social implications
Participant terms and conditions (Das et al., 2018)	• Missing privacy policies • Inaccessible reading level • Inaccessible to youth participants

SOURCE: As presented by Camille Nebeker, March 24, 2020.

trials and other research opportunities to communities that have historically been excluded (Khozin and Coravos, 2019) but noted that the digital divide also runs the risk of increasing disparities. Partnering with community health workers can help build trust within communities, Nebeker said, adding that individuals should understand how technologies are used, how data are managed, and who has access to their data. ReCODE Health shares the results of its studies with a broad audience, Nebeker said. In addition to sharing their research results, researchers using digital health technologies also describe how they identified and navigated ethical challenges on the ReCODE Health platform. In many cases, these researchers know more about the potential risks associated with digital health technologies than an IRB. As such, lessons learned from how information is shared with IRBs might help to increase collaboration across the entire research community Nebeker emphasized that the digital health research community needs to support all of its stakeholders in thinking through their respective roles and responsibilities, with the end goal of protecting people who participate in these studies.

CONSIDERATIONS FOR THE FUTURE

In order for digital health research to move forward in an ethical way, Nebeker suggested that the digital heath community be guided by the goal to "move purposefully and fix things" rather than the common refrain of "move fast and break things," echoing remarks of the former U.S. chief data scientist, Dhanurjay Patil. DHTs can be leveraged to answer important and timely research questions, but the risks are great if this work does not proceed thoughtfully and responsibly. Although efforts to date have primarily focused on behavioral health promotion and disease prevention, Nebeker said that work is currently under way to adapt the ReCODE Health Digital Health Checklist for use by clinicians, IRBs, and other communities working on DHTs. ReCODE Health is also looking at ways to support developers who are creating digital health tools (Coravos et al., 2019a).

Tension Between Privacy and Public Health Needs

The requirements related to participant privacy are constantly evolving; for example, privacy protections are now regulated in California with the passage of the CCPR, Nebeker said. In general, greater communication with participants about privacy would be beneficial. Tying privacy and risk of privacy loss to potential improvements in personal and public health could help participants make decisions about using DHTs, Nebeker said. She also suggested that people may be more willing to trade their

privacy if they know what they are getting back. Another consideration is the different preferences that older and younger adults may have regarding their privacy (Wang et al., 2019). In addition to sharing what is being learned from participants' data, it is also important to help participants learn more about themselves. The concept of "return of value" refers to conveying information back to participants in a way that is meaningful to them and represents a true partnership. However, sharing information is a long-term engagement strategy and it takes time to build the necessary trust. It can also be challenging to convey that information back to participants in a clear and useful way (Wang et al., in press).

The COVID-19 pandemic has underscored the tension between data privacy and public health, Nebeker said. For example, discussions are taking place concerning the potential to use digital tools such as cell phone tracking to mitigate the spread of the virus or using wearable devices to improve state-level real-time surveillance (Radin et al., 2020; Servick, 2020). Even prior to the pandemic, overburdened health care systems were relying on large technology companies to sort and analyze large volumes of data, despite the lack of a uniform standard for avoiding the misuse of patient data (Ross and Brodwin, 2020). "We are living in a real-time experiment on balancing privacy and public health," she said, and emphasized that public communication will be critical in forging a path forward in digital health in a way that is responsible and transparent. She added that social media platforms and other technologies could be used for public outreach and the dissemination of science-based information, with the aim of educating the public while also mitigating hype and misinformation.

Regulatory Strategies for Digital Health Technologies

Goldsack remarked that the speed of innovation in the digital health technology space may be escalating at a faster pace than regulatory strategies. Assuming that DHTs are evolving in a direction of providing more high-quality data, Abernethy said that it will be important to evaluate if the current regulatory approach is working before considering mechanisms that enable regulatory strategy to keep pace and introducing flexibilities to allow innovation to occur. Across FDA, approaches are being piloted to identify and pre-ascertain best practices for developing software, algorithms, and digital health technologies that will lead to the highest-quality data outputs (FDA, 2019a). Those running these pilot programs are also coordinating with digital health technology developers to create approaches for technology development that are flexible enough to allow for innovation, but within an appropriate monitoring framework. Balancing innovation with validity expectations will help ensure that

the data outputs of DHTs can contribute to high-risk activities, such as clinical trials and clinical evidence development. A workshop participant reminded the audience about a resource that clarified requirements in digital health technologies research and was released in 2020 by the Health and Human Services Secretary's Advisory Committee on Human Subject Protections.[10]

U.S. Food and Drug Administration's Technology Modernization Action Plan

Abernethy provided an overview of FDA's Technology Modernization Action Plan, which was released in September 2019.[11] The plan was developed to enable FDA to be ready to respond in a flexible way to new, continuously updating, structured and unstructured data acquired from DHTs. In addition to being able to store and analyze this new form of data, FDA needed to be able to interface with the broader community about DHTs. The plan has three parts, the first of which is to ensure that FDA has an internal cloud-forward technology strategy ready to receive and analyze data in a secure and private way. The second part is to create a series of use cases to help propel FDA and the life sciences community forward in terms of thinking about and using these data. For example, FDA is collecting 7- to 15-day safety data for investigational new drugs through an application programming interface that directly provides FDA with ready-to-use structured digital information. The third part involves opening up FDA's communication channels to the larger community of DHT innovators and stakeholders so that those stakeholders can understand what kinds of solutions are needed across the life sciences space. FDA's complementary Enterprise Data Strategy was announced in January 2020, Abernethy added. Its aim is to crystallize FDA's thinking concerning issues related to data sharing, standards, analysis, and "putting data to work." Considerations may include how to use new capabilities such as artificial intelligence and blockchain within the agency and in an integrated way across the industry.

[10] Information about these advisory documents is available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/sachrp-recommendations/index.html (accessed May 16, 2020).

[11] For more information on FDA's Technology Modernization Action Plan, see https://www.fda.gov/about-fda/reports/fdas-technology-modernization-action-plan (accessed June 19, 2020).

3

Digital Health Technologies for Characterizing Disease

Key Messages Identified by Individual Speakers

- Incorporating digital health technologies (DHTs) into research protocols to collect real-world measurements can increase the volume and richness of data, but study context and potential confounders should be taken into consideration. (Omberg)
- Making digital health data widely available to a broad range of stakeholders, with frameworks and initiatives in place, could encourage researchers to collaborate and compare findings using impartial benchmarks. (Omberg)
- Participatory and "people-centered" approaches to research can help ensure that studies better track outcomes that are relevant to patients. (Foschini, Omberg)
- A core advantage of DHTs is their ability to capture information about participants when they are outside of the clinic, allowing for longitudinal, intensive, and repeated measurements that might otherwise be unavailable to researchers. (Lunt)
- "Bring your own device" strategies for capturing digital health data may offer advantages, such as rapid engagement with participants and access to pre-existing data, but this approach can be limited by self-selection bias and device heterogeneity. (Lunt)

- DHTs are often siloed between the clinical care and clinical research domains, but patients tend to view these tools in the broader context of the overall health care journey. These tools can empower people with valuable insights about their own health, but the capacity to easily share health data with clinicians remains a barrier. (Staley)
- Leveraging consumer behaviors that are driving the adoption of commercial mobile health technologies could increase the uptake of these technologies in clinical care and research while also bridging the digital divide. (Staley)
- Person-generated health data (PGHD) can enable participatory discovery and rapid development of health interventions by remotely collecting large volumes of continuous data on people's physiological, functional, and emotional health. (Foschini)
- Optimizing the use of PGHD may require better interoperability, a common analytical framework, and good governance to maintain people's privacy and security. (Foschini)

The first session of the workshop explored pain points and opportunities for using digital health technologies (DHTs) for characterizing disease in pre-clinical research. The speakers offered a range of different perspectives including a nonprofit platform for research, a government-run national data collection project, a patient with lived experience collecting and navigating health data, and a platform for enabling participatory discovery using person-generated health data (PGHD). Larsson Omberg, vice president of systems biology at Sage Bionetworks, discussed how incorporating DHTs into research protocols can capture real-world data that can be used to glean health insights that may be missed by traditional clinical measurements. He also described challenges encountered in collecting data "in the wild," such as confounding factors that can affect the interpretation of the data. Chris Lunt, chief technology officer at the National Institutes of Health's (NIH's) All of Us Research Program[1] (*All of Us*), discussed experiences and lessons learned from the program's efforts to collect digital data on a large scale. Lunt described the value of data collected with DHTs and shared the program's criteria for prioritizing their

[1] The All of Us Research Program was created in 2015 by the National Institutes of Health with the aim of collecting data from 1 million volunteers to accelerate health research and improve the provision of individualized care. Information about the project is available at https://allofus.nih.gov (accessed May 9, 2020).

assessment and device strategies. Alicia Staley, senior director of patient engagement at Medidata Solutions, offered a patient's perspective on the distinction between clinical care and clinical research. She suggested that engaging with patients and more effectively taking into account the consumer mindset could help drive more widespread adoption of DHTs in the research and clinical care domains. Luca Foschini, chief data scientist and co-founder of Evidation Health, described how PGHD can enable participatory approaches to the discovery and development of interventions. The session was moderated by Effy Vayena, director of the Health Ethics and Policy Lab at ETH Zurich.

CHALLENGES IN DERIVING HEALTH INSIGHTS FROM REAL-WORLD SENSOR DATA

Larsson Omberg, Vice President of Systems Biology, Sage Bionetworks

To explore the challenges and opportunities associated with the use of real-world sensor data to derive health insights, Omberg drew on experiences and lessons learned from conducting research using data collected from mobile phones and wearable devices. Incorporating DHTs into research protocols enables the collection of data in a real-world setting—or "in the wild"—and can increase the volume and diversity of the data, Omberg explained. In traditional clinical research protocols, measurements are typically collected intermittently when patients come into a clinic with large time lapses between visits. Research protocols that integrate DHTs allow for more frequent or even continual assessment using sensor measurements and the ability to collect data that captures the interaction between a person's health and their environment. In this type of protocol, the interaction between the research protocol and the participant's life drives the data that are collected. This interaction can lead to data that are more representative of the lived patient experience, but, he cautioned, these data may also be noisier due to a variety of confounders (e.g., geographical location).

Advantages of Measurements Collected "in the Wild"

To illustrate the opportunities of collecting data "in the wild," Omberg compared performance on multiple measurements from mPower,[2] a large Parkinson's disease (PD) study. In this study, the variation in perfor-

[2] mPower was a 3.5 year mobile research study developed by Sage Bionetworks that explored how the progression of PD may be unique to individuals. More information about mPower is available at https://parkinsonmpower.org (accessed May 9, 2020).

mance across time for individuals was greater for people with PD than for healthy controls. To illustrate the consequences for this for a typical clinic-only protocol Omberg showed the measurements of tapping-speed data[3] from a single individual with PD collected through traditional in-person assessment and through a DHT. Over a 6-month period, data on the individual's tapping speed were collected each day using a smartphone app as well as during three in-clinic visits. The data collected through a DHT showed substantial variability in the individual's performance over the study period, with a slight rising trend in the number of taps over time. In contrast, data collected during three clinical visits showed a comparatively drastic upward trend. These results may be partially due to the fact that only three data points were collected in-clinic, he said, but they could also be due to the timing of the data collection. Patients may be more likely to come to the clinic when they are feeling well, as opposed to performing the tapping measurement at home on a daily basis even if they are feeling poorly.

Considering Context to Identify Confounders

It is important to consider contextual factors in research based on remote-sensor data in order to identify and account for potential confounders, Omberg said. For example, when trying to measure the impact of a disease or intervention on a phenotype using a smartphone or wearable device, the phenotype and the disease or intervention can interact and affect each other. Both can also be affected by a range of confounders, such as the location, timing, or duration of the individual's smartphone or device use. Even the weather can be a confounding factor, Omberg explained, and provided an example of a study on multiple sclerosis found that weather has a strong effect on a person's disease phenotype.

The context of the study itself also matters, Omberg said. Compared to well-controlled clinical trials, large-scale observational studies with open recruitment tend to be more vulnerable to selection bias. For instance, an observational study using real-life data from a PD mobile health study, mPower, was intended to build a classifier of PD status, but most of the volunteer participants were young and healthy (Neto et al., 2019). If not accounted for, this type of confounding variable can have a large effect and lead to overestimation of the signal, Omberg said. In mPower, for example, the age distribution of the participants caused a classifier for PD (e.g., a diagnostic algorithm) to primarily learn age-related signals rather than disease signals.

[3] Tapping speed is used as a measure of bradykinesia, a primary symptom of PD characterized by slowness of movement.

Well-designed studies can also be subject to confounding effects, Omberg said. Even if there is no bias at the start of a study, there may be bias when the data are analyzed at the end of the study. One meta-analysis evaluated indicators of participant retention across 8 studies and 109,000 participants and found variation in who enrolled and how long they stayed in the study (Pratap et al., 2020). The group conducting that research found that older people tend to stay in studies longer and that the return of value to participants can affect whether they stay enrolled in a research study (i.e., people with a disease may see more value in participating in a research study than those without a disease). In fact, Pratap et al. (2020) found that participants with the disease being investigated tended to spend roughly twice as long in the study than participants without the disease. The white-coat effect was found to be another potentially confounding factor: people tended to stay enrolled around 4.5 times as long when the idea of participating was introduced to them by a physician.

The identity confounder can also contribute to an overestimation of a study's success. Omberg explained that in protocols that use digital health, much larger volumes of data are collected from single individuals than in other types of protocols that collect measurements more infrequently. Therefore, the possibility of autocorrelation must be considered in DHT datasets that involve repeated measurements from a single individual. Furthermore, each individual measurement cannot be treated as an independent measurement, he said. A review of 47 digital health studies found that half of them had ignored this correlation structure in their data (Saeb et al., 2017) and that this led to a large underestimation of errors (Chaibub Neto et al., 2019). Substantial ethical concerns can also arise when the data are sufficiently high-dimensional to build models and predictors that represent the identity of specific individuals in a study, not just their disease characteristics.

Another contextual consideration relates to validation, Omberg said. Multiple avenues of validation can help to determine whether measurements collected in and out of the clinic are concordant; this is important because not all measurements are translatable, he said. To illustrate how in-clinic and out-of-clinic measurements can differ, he shared findings from a validation study (Webster et al., 2020) that was designed to identify a simple and inexpensive measurement of cardiorespiratory fitness to be deployed in *All of Us*. The validation study used two different VO_2max[4] protocols: a 3-minute step test (3-MST) and 12-minute run test (12-MRT). Both protocols were used to collect data in and out of the clinic, which

[4] VO_2max is a measurement of the maximum rate of oxygen a person consumes during intense exercise.

consisted of a single in-clinic measurement for each protocol and multiple non-supervised, at-home measurements for each protocol collected via smartphone. For the measurements collected in the clinic, the two protocols were relatively concordant (3-MST: 0.61; 12-MRT: 0.66). This level of concordance is not sufficient for basing clinical decisions on, but it is useful in collecting large volumes of survey data from many participants, Omberg said. The at-home measurement using the 3-MST protocol was translatable, with a concordance of 0.61. However, the 12-MRT protocol failed in the at-home measurement component, with a concordance of just 0.25. This demonstrates the importance of testing whether measurements are translatable outside of the clinic, he said.

Opportunities to Improve Health Insights from Real-World Sensor Data

Omberg outlined several opportunities to address challenges related to confounders and validation in order to improve health insights derived from real-world sensor data. Data from digital health research needs to be shared in a way that is ethical but also makes the data available and accessible to a broader set of stakeholders, he said. For example, Synapse[5] is a repository for sharing data collected using smartphones and wearables. Synapse also houses analytical tools for processing and analyzing DHT data and other mobile health resources. The mPower researcher community has benefited from this type of ethical data sharing. The data have been accessed by hundreds of individuals and institutions, leading to several dozen publications thus far (Bot et al., 2016).

Beyond making data more widely available, frameworks should be built to encourage people to work on the data and compare their findings with each other using impartial benchmarking methods, Omberg said. One strategy is to create a challenge for researchers by posing a problem with a new dataset and fostering competition among participants from different sectors, then asking the competitors to collaborate to interpret the differences between their models after the competition. For instance, Sage has hosted a couple of challenges for building methods for predicting disease severity from accelerometer data. The mPower project recently ran a challenge on predicting disease and severity for PD. The performance of the default model was far surpassed by the top winning models, Omberg said. He added that the challenge has changed the way that the participant institutions conduct their processing of this type of data. This illustrates how such open, collaborative methodologies can promote the

[5] The Synapse resource is available at https://www.synapse.org/digitalhealth (accessed May 9, 2020).

development of reusable, broadly accessible tools, code, and pipelines.[6] Another example of this type of effort is the Open Wearables Initiative,[7] a collaboration designed to promote the effective use of high-quality, sensor-generated measures of health in clinical research through the open sharing of algorithms and data. Together with several other institutions, Sage Bionetworks is building a community hub and DHT registry for algorithms and data, and also developing a benchmarking program to evaluate those algorithms.

Value of Participatory Approaches to Research

In studying specific diseases and working with patient communities, it is important, Omberg emphasized, to collaborate with patients before designing a study protocol. Participatory approaches can be used to seek input from patients and the public at large about what sensors could or should measure, which can help to ensure that studies are tracking the outcomes that are most personally relevant to individuals. Participatory approaches might involve convening a patient group to act as advisors and conducting design exercises with patients to understand the burden of disease and the issues that are of the greatest concern for patients. Engaging with research participants can inform a study design and ensure its value to that community, while also obtaining the measurements the clinicians or researchers are seeking. Through this process, researchers typically adapt what they want to measure based on input from the patients, Omberg added.

DIGITAL DATA COLLECTION BY THE ALL OF US RESEARCH PROGRAM

Chris Lunt, Chief Technology Officer, All of Us Research Program

All of Us is an innovative research effort, launched by NIH in 2015 with the aim of collecting data from at least 1 million people in the United States. *All of Us* additionally strives to include participants from races or ethnicities that have been historically underrepresented by medical research. According to Lunt, as of March 2020, more than 250,000 people had joined the project, 80 percent of whom are underrepresented in some respect—for example, based on their access to care or socioeconomic status

[6] Examples of these tools are available at https://github.com/Sage-Bionetworks/mhealth tools (accessed May 9, 2020).

[7] Information about the Open Wearables Initiative is available at https://www.owear.org (accessed May 8, 2020).

(Kaiser, 2019). The ethos of *All of Us* is to engage with participants as partners in the research project. There is a strong focus on returning value to the participants in the program, and the project is built to be a longitudinal study that enables participants to be re-contacted over time. Multiple data types are being collected, including electronic health records (EHRs), surveys, baseline physical measurements, biospecimens, and genomic data. Because *All of Us* is intended to be an open, national-level resource, Lunt and his colleagues are developing open-source software and tools to ensure that the data are accessible to all researchers, including citizen scientists. He emphasized that the project is hypothesis-neutral and broadly useful because it is not intended to serve any particular audience exclusively.

Lunt and his colleagues are working to incorporate DHTs in their data collection as part of *All of Us*. As a starting point for integrating DHTs, *All of Us* created a "bring-your-own-device" (BYOD) program that allows participants to connect a Fitbit or Apple Health app. Pilot projects for specific smartphone-based apps for collecting data on participants' cardiorespiratory fitness and mood are currently under way, Lunt said, with other apps also in development. While *All of Us* started with a BYOD strategy to enable earlier progress, the next step will be to distribute Fitbits to those participants who do not already have a device, Lunt said.

Value of Data Collected Through Digital Health Technology

Lunt discussed the value of data collected through DHT. From his perspective, he said, the greatest value of this type of data is the ability to capture information about participants when they are outside of the clinic. As discussed by Omberg, the intermittent nature of in-clinic data collection and the environment of the clinic can create a host of confounding factors. Because DHTs allow for longitudinal, intensive, and repeated measurements, they enable the collection of greater volumes of data than other strategies. Furthermore, the passive data collection enabled by DHTs can alleviate the burden on participants who are taking part in a longitudinal study that collects large amounts of data on many variables. Another advantage is that DHT data are not as susceptible to the self-reporting biases seen with data collected through survey instruments, Lunt said. Use of DHTs for data collection can also reduce costs, because it builds on an existing and expanding infrastructure of research and device development; integrating DHT data does not necessarily warrant additional investment.

However, the use of DHTs for data collection has several drawbacks, Lunt, said. DHT data tend to be narrow and generally deductive, in that they build on existing hypotheses (e.g., the premise that "steps matter" and thus it is useful to measure a person's step count). The technology

often relies on external infrastructure, such as mobile phone networks, which can skew the data collected. Certain security risks associated with DHTs may require negotiating with technology providers or other external partners in a way that involves yielding some degree of control, Lunt added. For example, participants who wish to share their Fitbit data with *All of Us* are directed through a process of granting consent for data sharing over which Fitbit maintains strict control and is not modifiable in any way by *All of Us*. Similarly, participants can modify the types of data that can be read by program researchers simply by changing the settings within the Apple Health/HealthKit smartphone app. Because *All of Us* has no control over which types of data a participant shares, it is possible for a participant to unknowingly unshare data that the program is specifically focused on collecting.

Criteria for Prioritizing Assessment and Device Strategies

Lunt explained that in considering how to make investments in DHTs, *All of Us* developed a set of prioritization criteria for choosing a particular assessment or device strategy: (1) science, (2) recruitment, (3) engagement, (4) partnership, (5) cost, and (6) logistics. The first criterion is the extent to which the strategy helps advance the scientific agenda of the program. The second, recruitment, evaluates how well the strategy will integrate into an existing audience. For instance, an advantage of working with outside providers, such as Apple and Fitbit, is that participants will often have years of prior data collected by those providers that they may be willing to share with *All of Us*. The engagement criterion assesses whether a strategy will ensure that participants feel valued and stay interested in engaging with the program. Returning information to the participants and providing them with insights about their own health can help foster engagement and interest, he noted.

All of Us has many external partners (e.g., Blue Cross Blue Shield, Walgreens), so DHTs should provide ways for partners to contribute to the program, Lunt said. Costs, the fifth criterion, include monetary costs and the costs of program oversight and program attention (e.g., engaging with institutional review boards and regulatory authorities that can be bottlenecks for the research program). Another cost to consider is the burden on participants in terms of their time and ability to engage in and understand DHT collection. *All of Us* is a national program, so logistical concerns relate to accuracy and the ability to access people in indirect ways, such as through the mail or through a navigator, because the program could never have direct physical access to all participants. Each of these six criteria has been further broken down into sub-criteria by *All of*

Us for considering a strategy, Lunt said. Box 3-1 details the specific questions used by *All of Us* to evaluate the scientific value of a data type.

Value of the Bring-Your-Own-Device Strategy

Lunt described some of the advantages and drawbacks of the initial BYOD strategy adopted by *All of Us*. Around 77 percent of people already have smartphones and about 12 percent of people—and up to 30 percent in some segments—already have their own wearable devices, he said. Smartphones tend to be the primary communication and wearable device for many families regardless of socioeconomic status. Advantages of the BYOD strategy have included the ability to immediately engage with the audience, the lower cost, and the potential for participants to share their preexisting data. As of March 2020, around 7,000 Fitbit users had connected to *All of Us*, Lunt said. Substantial amounts of data are available to the program from around 2018 onward, with some participants sharing data that stretches back to 2011. A disadvantage of the BYOD strategy is that the data collected can be skewed due to participant self-selection and participants' use of different devices. Other drawbacks include a limited audience and the curation costs required to collect a limited set of data.

BOX 3-1
Guiding Questions for Evaluating the Scientific Value of a Data Type

- Is this a novel type of data, hopefully with some prior evidence?
- In terms of context, how many of the data exist from outside of the clinic? For instance, the clinic environment can have many effects on blood pressure; multiple measurements of blood pressure throughout the day and during activities have potential value.
- With respect to the audience, how much of this data type has been collected for populations underrepresented in biomedical research, and how much can be added?
- In terms of volume, has this data type been captured at high frequency or longitudinally, and can it be added to the program's existing dataset?
- From the association perspective, have the data been captured in conjunction with other data? For instance, whole-genome sequence data might be correlated with other data collected, such as time, metabolomic data, and transcriptomic data.
- How much external validation exists for the data type or measure?

SOURCE: As presented by Chris Lunt, March 24, 2020.

Digital Health Technology Strategy for the All of Us Research Program

Lunt outlined five elements of *All of Us*'s core strategy for collecting data through DHTs. Initiating and maintaining participant engagement have been major challenges encountered in attempting to conduct a longitudinal strategy for a diverse audience. The intent is to develop a long-term, cross-component pipeline of pilot studies and tests that can be used over time, while also balancing those efforts with thesis-driven selection. For example, *All of Us* has identified morbidities related to cardiorespiratory fitness as a priority area of focus, so it will be valuable to connect with Apple HealthKit, an app that many people are already using. Another core component is a commitment to using off-the-shelf consumer technology. In part, this is motivated by the size of the research program and the consequent large investment that would be required to develop a new dedicated device for the program.

ADOPTION OF DIGITAL HEALTH TECHNOLOGIES

Alicia Staley, Senior Director of Patient Engagement, Medidata Solutions

Staley's remarks were framed by her perspective as a three-time cancer survivor with more than 30 years of survivorship. Three decades of paper-based and DHT data have been collected from her across different health systems in multiple states, she said, but there is not yet a single, comprehensive way for her to look at her medical record in its entirety. This contrasts with the relative ease with which she has been able to capture her own health data using DHTs over the previous 2 years, she said. Through the use of the Oura Ring,[8] she has collected comprehensive data about her heart rate, respiration, sleep, and activity level, which have strengthened her ability to manage her own health. For instance, based on increases in respiration rate and body temperature, she is able to predict when she is about to develop a cold with a high degree of certainty; this enables her to take preventive action, such as rest and hydration. She drew attention to the ongoing TemPredict Study,[9] which is gathering data collected from Oura Rings used among frontline workers in the COVID-19 pandemic, and could serve as a catalyst to increase the use of DHTs in clinical care settings and in clinical research.

[8] Information about the Oura Ring is available from https://ouraring.com (accessed May 9, 2020).

[9] More information about the TemPredict study at the University of California, San Francisco, is available at https://ouraring.com/ucsf-tempredict-study (accessed May 26, 2020).

A Patient's Perspective on Clinical Care Versus Clinical Research

Staley offered a patient's perspective on the distinction between clinical care and clinical research and reflected that patients who engage with either of those settings tend to view those experiences as a single snapshot of their own care journeys. "They do not see it as clinical research … or clinical care; they view it as health care," she remarked. When DHTs are used in clinical research and in clinical care, the technology's use can seem like fragmented touchpoints to patients. Lack of coordination between these technologies this may contribute to the issues with adoption of DHTs by patients, Staley suggested. Furthermore, the clinical perspective on these technologies tends to be siloed—that is, the technology is considered to be either a care option or a research option. In contrast, patients tend to view the technologies as a single point of interaction with their overall health care team. Historically, major pain points from the patients' perspective have related to accessing, sharing, and transferring their own health data when it is important for not only the patient, but for the clinical care interaction or the clinical research interaction. The expansion of EHRs and the ability to transfer information more easily have helped to reduce those barriers for patients, Staley noted.

Barriers to Patient Use of Digital Health Technologies

To increase the uptake of DHTs in clinical care and research and increase the volume of data collected, Staley suggested finding ways to take advantage of the consumer behaviors driving the adoption of commercial mobile health technologies that are already pervasive. For instance, she said an estimated 120 million Apple Watches[10] have been used at some point in the previous 1.5 years. Similarly, as of January 2020, Fitbit reported that it had sold a total of 100 million devices, with 30 million currently active users.[11] Staley remarked that while it is clear that consumers are buying and using DHTs, these technologies have not yet extended comprehensively into a clinical research setting. *All of Us* and smaller-scale pilots potentially could fill this gap, but larger-scale adoption on the clinical research side is still needed to tap into the mainstream consumer mindset and behaviors, Staley said. The COVID-19 pandemic has exposed the need for more creative ways to capture data and maintain clinical trials in virtual settings. She suggested that consumers and

[10] More information about the Apple Watch device is available from https://www.apple.com/watch (accessed May 9, 2020).

[11] More on Fitbit's sales and active user figures is available in a press release. See https://investor.fitbit.com/press/press-releases/press-release-details/2019/Fitbit-to-Be-Acquired-by-Google/default.aspx (accessed June 22, 2020).

patients should be engaged to identify additional points at which data could be captured for building on pervasive technologies as a way to help to support clinical research. Innovative strategies for policy adoption and consumer adoption will be needed if these tools are to be used to their full potential, however.

In addition to the lack of full-scale adoption in clinical research, Staley said that another current barrier is the lack of data sharing from consumer mobile health technologies to health care providers. For instance, she cannot easily and directly share critical information from her Oura Ring about her respiration with her primary care physician or oncologist. Instead, she must track her own data, analyze it herself, and bring the data profiles to her providers.

The technology divide poses another barrier, Staley said. In her experience as a member of the breast cancer patient community, she said, she has long been aware of the digital divide and its potential to create a bias toward healthier populations with higher education levels when data are collected from consumers in BYOD studies. She cautioned that with the advent of so many new tools, it is important to be mindful of populations that may be left behind. Many households and even entire communities lack consistent, reliable internet access. "We need to be able to educate our users on these tools, make sure that they have access to these tools, and utilize them in a way that makes sense for their life," she said. One strategy is to find patients who are well respected in their communities and are willing to step forward, use tools, and take advantage of clinical research opportunities. These patients can then become beacons of hope and information for other patients in efforts to integrate DHTs into clinical trials and to promote clinical trial awareness in general. Empowering those patients to be voices for their own communities can also help bridge the technical and community divides that have been evident in clinical trial settings, Staley said.

Integrating Digital Health Technologies into Clinical Trials

Staley explained how Medidata is working to adapt the clinical trial platform to include patient data. An entire team at the organization is focused on integrating mobile sensors and other types of digital technologies into clinical trials. There is value in working with organizations that have existing, validated tools that can be integrated into a clinical trial, she said, adding that that more companies are beginning to conduct pilots or smaller-scale studies that are integrating FDA-approved technologies. Another positive trend is increasing buy-in among consumers and patients as companies such as Apple are starting to launch their own studies that use DHTs. Medidata has also conducted a number of stud-

ies on the use of DHTs in clinical trials, with the results made publicly available.[12] As more companies conduct trials designed around patient-focused outcomes and goals, DHTs will increasingly be integrated into larger-scale clinical trials, Staley predicted.

DISCOVERY THROUGH PERSON-GENERATED HEALTH DATA

Luca Foschini, Chief Data Scientist and Co-Founder, Evidation Health

To explore opportunities for PGHD to inform participatory approaches to the discovery and development of health interventions, Foschini offered examples of research conducted by Evidation Health. He explained that PGHD enables continuous monitoring of health outcomes at the individual level so as to make it possible to better understand and measure a person's experience. PGHD typically comprises a dataset that is collected either by a person or their caregiver to qualify and address the person's health. The acronym is often defined as "patient-generated health data," but because much data can be collected from the individuals before they become patients, Foschini said he prefers "person" to "patient," he said. This type of long-term data collection can be drawn from a variety of sources, including smart clothing, wristbands, and smart houses and automobiles (see Figure 3-1). He added that a large component of the PGHD that can be collected today comes from the voice of the person, through the direct articulation of subjective feelings and experiences.

Leveraging Person-Generated Health Data to Inform Public Health Interventions

PGHD makes it possible to carry out universal research on how individuals feel, function, and survive, Foschini said, because the data can be collected remotely and on a large scale. He suggested that collecting PGHD should be the first step in building health interventions—from the development of drugs and devices to public health policies—and in understanding how those developments affect the people they are ultimately intended to serve. He used the COVID-19 Pulse study[13] as an example of how this type of participatory discovery and development can inform public health interventions in real time. As of March 2020, Evidation had recruited more than 100,000 participants from among its Achievement pro-

[12] More information about the studies is available from https://www.medidata.com/en (accessed May 17, 2020).

[13] Information about the COVID-19 Pulse study is available from https://Evidation.Com/News/Covid-19-Pulse-First-Data-Evidation (accessed May 17, 2020).

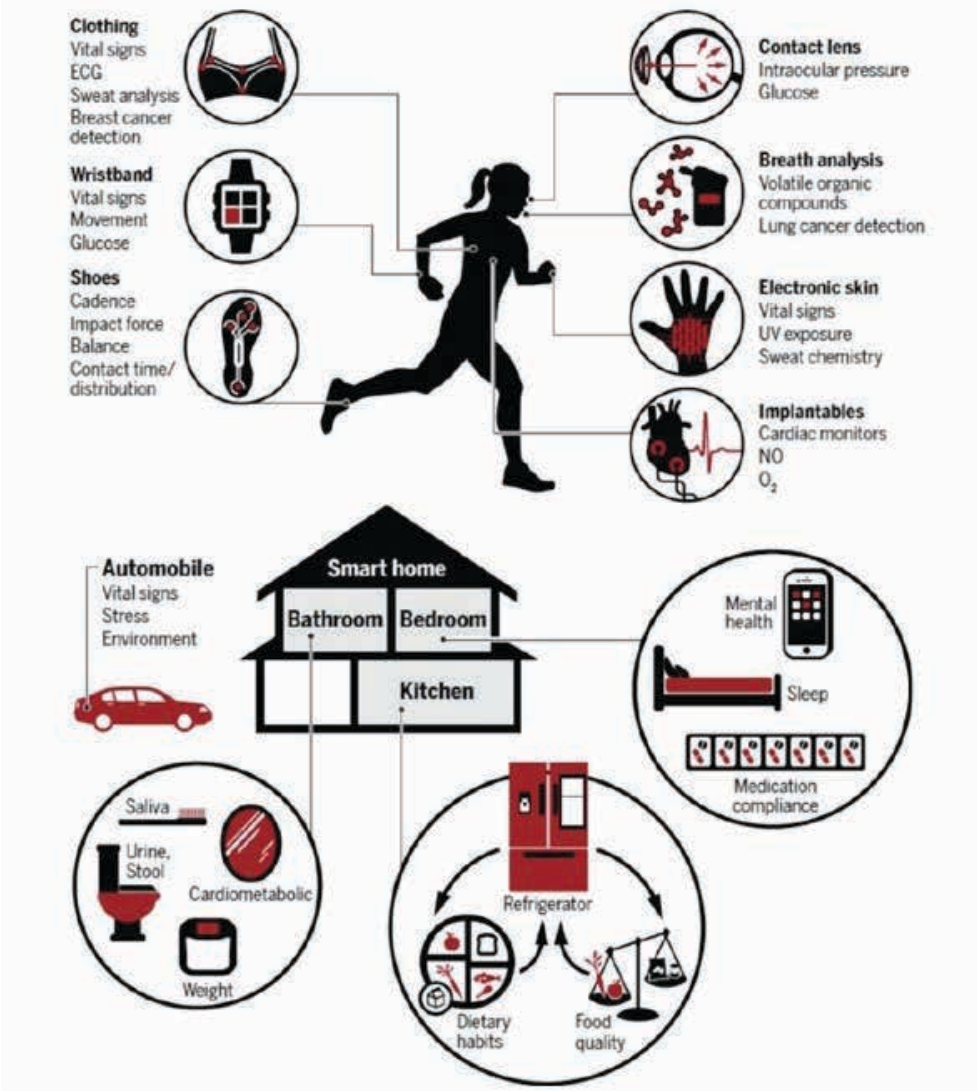

FIGURE 3-1 Sources of person-generated health data.
SOURCES: As presented by Luca Foschini, March 24, 2020. Originally from Gambhir et al., 2018.

gram participants for an ongoing longitudinal study covering almost 90 percent of counties in the United States (see Box 3-2 for more information about the program). The aim of the study is to understand how people in the United States are coping with the COVID-19 pandemic by collecting data about how their behaviors are disrupted and how their perceptions are changing. These data can offer insights into whether interventions are working as well as into how they are perceived to be working. As of March 18, 2020, about two-thirds of participants reported washing their hands more frequently over the previous week, but only about one-third reported avoiding large gatherings. Around 40 percent reported increased anxiety over the previous week. Financial anxiety is generally mediated by social determinants of health, Foschini said, and in the United States, people without health insurance tend to have much greater levels of anxiety. Uninsured individuals are also more likely to present at an emergency room if they have symptoms of COVID-19 than are patients with insurance, who tend to visit their primary care providers first. Understanding how populations will react based on their health insurance status is important for building interventions to curtail contagiousness at the point of care, he said. This PGHD can also be used to visualize the impact of the mitigation strategies being deployed across the country. For instance, Evidation was able to access wearable device data of respondents who consented, and to plot those data over time. The analysis of those data revealed variability in the impact of public health strategies in different states. In some states, participants' data indicated decreased mobility (as measured as Fitbit steps) compared to baseline in the days after the United States declared COVID-19 a federal emergency.

BOX 3-2
Evidation Health's Achievement Program

Evidation Health's Achievement program allows any adult in the United States to connect health sensors from consumer and clinical-grade devices and apps, participate in research opportunities in a virtual, privacy-safe, and secure way, and receive rewards for doing so. Participants receive ongoing phenotypic labeling via digital and self-reported methods. Consent is obtained from participants each time their data points are used for any research opportunity, even retrospectively, to build trust and transparency. Around 4 million members were using the app as of March 2020.

SOURCE: As presented by Luca Foschini, March 24, 2020.

Using Person-Generated Health Data to Complement Real-World Data

PGHD from a commercial wearable device can also serve as a complement to traditional real-world data, Foschini said. For instance, continuous data from a commercial wearable can be used to monitor post-operative recovery from surgery. Foschini described a study that surveyed almost 51,000 people enrolled in the Achievement program about whether they had received a medical procedure or surgery in the previous year (Ramirez et al., 2020). Of the 1,203 respondents who reported having undergone a weight loss procedure, 675 had some Fitbit data and 118 had high-quality, high-density Fitbit data that they consented to share. There is a large decrease in available data when data-quality constraints are applied, he noted, suggesting that researchers should be mindful and standardized in defining what "data quality" means in the context of PGHD. The researchers found large changes in patients' activity levels at 12 weeks compared with baseline (pre-surgery) in the measures captured by the patients' Fitbit devices. Overall, the patients' mobility increased to above baseline levels after the expected dip in mobility immediately after the surgery. Interestingly, the patients' resting heart rate dropped drastically by six to eight beats per minute over the 12 weeks. Total sleep time increased as expected and then decreased back down to baseline, but sleep efficiency as measured by Fitbit increased and was maintained over a longer time. This illustrates how real-world measures can contribute to a broader understanding of how patients feel about their recovery from surgery, Foschini said. Currently, the main measures of success for a weight loss procedure, beyond weight loss itself, are outcomes related to insulin resistance reversal or complications. However, the patient may care more about outcomes such as sleeping better, walking more, or better fitness conditioning that can be captured using real-world PGHD.

Ways Forward for Person-Generated Health Data

Foschini outlined opportunities to expand the use of PGHD to inform participatory discovery and rapid development of interventions that have the individual at the center, ranging from public health policies to drugs, devices, and digital therapeutics. The current ability to build trusted relationships with individuals to collect PGHD is unprecedented, he said. For instance, enrollment recently started in the Heartline study,[14] which will look at how DHTs such as the Apple Watch and a health program delivered through an iPhone app can improve cardiovascular disease

[14] More information on Johnson & Johnson's Heartline study is available from https://www.heartline.com (accessed May 17, 2020).

outcomes in 140,000 older people in the United States. Experiences and lessons learned in trying to deploy and run large-scale efforts involving DHTs have identified several strategies for moving forward, Foschini said. The first is to ensure interoperability. Although The Office of the National Coordinator for Health Information Technology and the Centers for Medicare & Medicaid Services recently released its Interoperability and Patient Access final rule,[15] no equivalent standard has been set for PGHD specifically, Foschini said. All stakeholders—including individuals, providers, and regulators—should have a common data format for storing and transmitting PGHD in order to share data collected using DHTs (e.g., sharing Oura Ring data with a provider). He noted that the Smart Markers[16] domain is working to include PGHD into the Smart Framework and urged the community to support this effort while the setting is still precompetitive. PGHD is as identifiable as DNA, he said, so good governance will be needed to maintain people's privacy and security. Ethical concerns will abound because PGHD straddles research, care, and consumer experiences, he added. Ensuring representativeness and striving to reduce the technological divide will help to ensure that all people can share in the benefits of PGHD. Developing a common analytical framework will also be important, he said. To improve the quality and density of data, there should be a standardized analytic pipeline that allows researchers to evaluate whether data collected in the real world is fit-for-purpose for a given type of analysis.

DISCUSSION

Developing Operational and Analytical Standards for Digital Health Technologies

Given the diversity of tools and activities under way in this space, Vayena asked the panelists if it would be beneficial to work toward developing a novel set of standards for digital technologies, either for the way that they operate or how they are used. The raw accelerometry data collected by a Fitbit device is not shared with the user, Lunt noted, and instead the user receives information that has been curated by Fitbit. He suggested that instead of focusing narrowly on a single measure—which is necessarily reductive of the underlying raw data—it could be useful to

[15] More information about the Centers for Medicare & Medicaid Services Interoperability and Patient Access final rule can be found at https://www.cms.gov/Regulations-and-Guidance/Guidance/Interoperability/index (accessed May 31, 2020).

[16] Information about the Smart Markers domain is available from https://smarthealthit.org/smart-markers-a-framework-for-patient-generated-data (accessed May 17, 2020).

create an environment that encourages multiple stakeholders to interpret that raw accelerometry data in different ways.

The large body of data collected from digital tools over the past several decades is largely inaccessible to the public, partly due to the financial value of these data, Omberg said. This makes it difficult to evaluate the accuracy of the algorithms and outputs of DHTs commonly in use and underscores the need to establish methods for independent benchmarking. For instance, he said, in his experience using the Garmin and Fitbit accelerometers, he has found that their step counts can be discrepant by up to 30 percent. He noted that the actual algorithms also have value, not just the data. His organization is working with the Open Wearables Initiative[17] to develop independent benchmarks of algorithms by running them on subsets of data. This type of modeling does not require an entire dataset to be shared publicly.

There is an opportunity for adding a layer of standardization for data storage and data sharing, Foschini said. Currently, different platforms for data collection (e.g., Apple HealthKit, Fast Healthcare Interoperability Resources within EHR systems, or Clinical Data Interchange Standards Consortium/Clinical Data Acquisition Standards Harmonization) do not have a common way to represent data collected in a multivariable time-series format. Developing a common way to store and transport that data would make it easier for platforms to run their own algorithms and conduct their own analytical validation on the data that are being collected by a third party, Foschini said. He suggested that an abstraction layer could be built into analytical validation to foster collaboration in this domain as has happened in other research communities, such as the genetics community. That community took 20 years to reach a consensus on the pipeline from raw sequencing data to single-nucleotide polymorphism studies, but it is now an established standard.

Given the large volume of data collected through digital modalities, Lunt suggested shifting the paradigm from "moving the data around and keeping the tools in place to moving the tools around and keeping the data in place." This transition is already under way, although developing the necessary structures and ensuring data privacy will require substantial effort. A workshop participant asked if there is an ultimate authority that can advise the community about whether a given DHT is validated. Lunt said his organization works closely with the UK Biobank,[18] which has shared useful lessons gleaned from its long history of doing this type

[17] More information about the Open Wearables Initiative can be found at https://www.owear.org (accessed May 31, 2020).

[18] Details about the UK Biobank resource can be found at https://www.ukbiobank.ac.uk (accessed May 17, 2020).

of work. One takeaway is to engage earlier with different audiences to gain various perspectives on which measures are considered to be the gold standard. For instance, the UK Biobank ran a study for 10 years before granting any access to its data, at which point the cardiology community suggested that a more appropriate measure should have been used for certain of the data. A challenge will be finding a way to query across an entire community of researchers to understand what measures the various researchers consider to have the greatest predictability, which will likely be in constant flux as sensors and devices improve.

4

Digital Health Technologies for Recruitment and Safety

Key Messages Highlighted by Individual Speakers

- In the regulatory review process, a digital health technology can qualify as a Drug Development Tool if it has value in meeting an unmet need, measures a concept of interest, and contributes to meaningful improvement in a person's life. (Leptak)
- Digital health technologies can help surmount traditional research barriers and bring research to the general public through large-scale decentralized trials that collect a broad range of real-world data from participants. (Chan)
- Retention is the Achilles' heel of clinical research that uses digital health technologies, but it can be improved by gaining buy-in from health care providers and creating platforms to foster connections among study participants. (Chan)
- Human connection is an important element of recruitment, retention, and engagement with digital technologies, but it can be difficult to scale. Researchers should learn from voices in the patient community about how to best manage these interactions. (Chan, Kapur)
- Continuously collected data could shed light on factors that may be affected by participants' real-world activities in a way that cannot be captured from participants living a controlled setting such as a clinical pharmacology unit; however,

more work will be needed to better understand, interpret, and validate measurements of vital signs collected via remote monitoring. (Benko)

- Shifting conventional clinical assessments to remote monitoring could help protect clinical trial participants during infectious disease outbreaks by reducing the need for participants to visit clinical settings where they could be put at risk, put others at risk, or otherwise place additional burdens on health care systems. (Benko)
- Expanding the body of research on functional status in a way that uses digital technologies for data collection will require addressing a substantial change management problem within the oncology therapeutic area leadership at many of the major drug development companies. (Benko)
- Digital health technologies could support a comprehensive system for patient-centered care, in which standardized remote data collection facilitates clinical research and continuous learning as well as returning value to patients through better clinical care. (Perakslis)
- Ideal system capacities for collecting data remotely, picking up samples, monitoring people at home, and propagating data in a reasonable way have not yet been achieved in real-world systems; achieving this vision in the COVID-19 crisis will require "big thinking" at the federal level. (Perakslis)
- Crisis settings require swift and strong leadership to take control and ensure that the right data are collected from the outset—this involves convening the right experts to rapidly develop standardized data collection protocols and propagate them downstream appropriately. (Perakslis)

During the second session of the workshop, the role of digital health technologies (DHTs) in recruitment and safety trials was explored. Christopher Leptak, director of the Regulatory Science Program in the Office of New Drugs at the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration (FDA), provided an overview of how FDA uses Drug Development Tools (DDTs) as part of its drug development programs and discussed how DHTs may offer an opportunity to inform the development of DDTs. He also described FDA's regulatory approach to defining and determining whether tools are fit-for-purpose as well as the conceptual framework for biomarker acceptance. Yvonne Yu-Feng Chan, senior director of medical affairs for digital medicine at Otsuka Pharmaceutical, explored the use of DHTs for engaging the

public in research. She described a large-scale decentralized trial as a case example of how to modernize clinical trials and explained how the study enabled the acceleration, democratization, and standardization of certain research methods. Chris Benko, chief executive officer at Koneksa Health, discussed the roles of DHTs and remote monitoring as part of the drug development process during early-stage clinical trials; he shared findings from the company's validation studies to evaluate the use of remote technologies for assessments in early-stage clinical studies. He also suggested some potential uses for digital technologies to address the COVID-19 pandemic. Eric Perakslis, Rubenstein Fellow at Duke University, described how layers of data and communication overlay the interaction of clinical care and research. He presented his vision for the structure of a telehealth-based learning health system. The session was moderated by Deven McGraw, chief regulatory officer at the Ciitizen Corporation.

REGULATORY PERSPECTIVE ON DRUG DEVELOPMENT TOOLS

Christopher Leptak, Director, Regulatory Science Program, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Leptak explained that FDA's DDT program[1] currently operates under a statute that was included in the 21st Century Cures Bill[2] at the end of 2016 (see Box 4-1). The statute broadly defines a DDT as any material, method, or measure that aids in drug development regulatory review, as determined by the Secretary of Health and Human Services, and calls out two specific types of DDTs: biomarkers and clinical outcome assessments (COAs). In addition to playing a role in the collection of information for biomarkers and COAs, he said, DHTs themselves can serve as standalone, independent tools. In fact, FDA is beginning to explore a pathway for DHTs to lay the groundwork for regulatory discussions, Leptak said.

Components of a Drug Development Tool

Although the definition of a DDT in the statute is beneficial for innovation and flexibility, its breadth can make it difficult to provide generalizable advice or describe a specific approach. To clarify the concept of

[1] For more information on the Drug Development Tool Qualification Programs, see https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs (accessed June 7, 2020).

[2] The full text of the 21st Century Cures Bill is available at https://www.congress.gov/bill/114th-congress/house-bill/34 (accessed May 17, 2020).

BOX 4-1
21st Century Cures Section 3011 Drug Development Tool Qualification

The term "drug development tool" includes—
- (A) a biomarker;
- (B) a clinical outcome assessment; and
- (C) any other method, material, or measure that the Secretary [of Health and Human Services] determines aids drug development and regulatory review for purposes of this section.

The term "biomarker"—
- (A) means a characteristic (such as a physiologic, pathologic, or anatomic characteristic or measurement) that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention; and
- (B) includes a surrogate endpoint.

The term "clinical outcome assessment" means—
- (A) a measurement of a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions; and
- (B) includes a patient-reported outcome.

SOURCES: As presented by Christopher Leptak, March 24, 2020; 21 USC § 357(e).

a DDT, Leptak highlighted three tangible components: (1) the concept of value to the drug development context, (2) the measurement of concept or how information is gathered, and (3) the interpretation of concept. In the case of a biomarker, value would be a defined biologic response, an assessment of a physiologic organ function, or a finding on a radiography assessment, Leptak said. Measurement of concept is the domain in which many proposals for DDTs can contribute information. For example, for a disorder that affects movement ability (e.g., muscular dystrophy), the concept of interest is how a patient moves. DDTs, such as sensor arrays or other means of assessing movement, could be used to measure this concept, perhaps in real time in a patient's home environment. From a regulatory point of view, he said, the most important component is the interpretation of the concept. Beyond simply collecting data, a proposal for a DDT should indicate whether it contributes to improvement for an individual's daily life—specifically, if the DDT is beneficial to the extent that the change is substantial and of personal value to people, or if the change is so small that it does not improve people's lives to a large extent. In some respects, the interpretation of concept is subjective and is largely based on what patients perceive to be a meaningful improve-

ment. Another consideration for novel DDTs pertains to which parts of the proposal are new and which already exist or could be repurposed: (1) an existing concept with existing measurement, (2) an existing concept with new measurement, (3) a new concept with existing measurement, or (4) a new concept with new measurement.

Integrating Drug Development Tools

DDTs can come to FDA through several pathways, Leptak said. These pathways do not exist in isolation, and in many cases parallel efforts are under way within or between pathways (Daniel et al., 2016). All of the pathways share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data. One pathway is a direct submission to FDA as part of a pharmaceutical company's investigational new drug (IND) application. Through this approach, the company can bring forward technological ideas and negotiate with subject matter experts in FDA's clinical division about the utility of the DDT and how it might be used in a clinical trial setting. Another pathway is scientific community consensus, typically through publications in scientific journals or consensus statements put forth by professional societies. This approach can be useful for hypothesis generation, but in many cases it does not make primary data as readily available to FDA as the IND pathway does. Consequently, the DDTs that come through this pathway do not tend to be as "regulatory ready." The third pathway is through DDT qualification programs, through which tools are developed independently of a drug program that—if successful—can be used in drug programs. This process generally involves presenting the data to FDA for rereview, he added.

Regulatory Perspective on Digital Health Technologies as Biomarkers

For FDA, a biomarker is a defined characteristic that is measured as an indicator of normal or pathogenic biological processes or as a response to an intervention, Leptak said. In contrast to a COA, a biomarker is not a clinical assessment of how a patient feels, functions, or survives. Biomarker considerations include the reproducibility of data, the adequacy of the analytic device to assess a biomarker's reliability, and the feasibility of the biomarker should a drug be approved—that is, whether the analytic will be widely available and suitable for integration into clinical practice paradigms.[3]

[3] The National Institutes of Health–FDA Biomarker Working Group has published a glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care. This resource can be found at http://www.ncbi.nlm.nih.gov/books/NBK326791 (accessed May 10, 2020).

Determining Biomarker Fit-for-Purpose

Biomarkers need to be matched with a specific drug development goal in a way that is supported by data, Leptak said. For example, susceptibility and risk biomarkers are fit-for-purpose for monitoring changes in a person's normal, non-diseased physiology.[4] There is much variability in this concept of normalcy, from variation in a specific person over the course of a day or a lifetime to variation between patients with different characteristics. Understanding this normal variability helps in the assessment of whether a change from normal is beneficial to a given person.

Pathologic changes in the body over time can be used to develop clinical findings about the symptoms of diseases. A different set of biomarkers—diagnostic, monitoring, and prognostic—are fit-for-purpose here. Once a therapeutic intervention is initiated, then pharmacodynamic, predictive, and safety biomarkers are fit-for-purpose for monitoring changes in a person's physiology. The aim of therapy is to slow or stop the progression of the disabling characteristics of a disease or, in a best-case scenario, reverse the progression to a more normal physiological state. At this point, a response biomarker might be an endpoint in a clinical trial. A small subset of biomarkers that are predictive of clinical benefits might become surrogate endpoints, he added.

Digital Health Technologies as Biomarkers from a Regulatory Perspective

A common question is whether certain DHTs might be considered biomarkers by default or whether they are considered to be another type of drug development tool in addition to COAs and biomarkers, Leptak said. The field is struggling with the use of the term "digital biomarkers," which took hold early on but may not adequately capture the regulatory distinction between a concept of interest and how it is measured. There are many different types of biomarkers that, in and of themselves, may either be the source material of the biomarker or how the biomarker is measured. In most cases, proposed digital tools are methods of measurement or data collection, and, as such, the tool itself is not the biomarker. It is the concept of interest of the tool that is the primary concern for regulators. Although DHTs for data collection are essential, they do not typically constitute a biomarker from a regulatory perspective. Benko added that in the experimental space, biomarkers are often developed to satisfy the requirements of large sponsors that have vast amounts of resources at

[4] The concept of "fit-for-purpose" in this context refers to the regulatory acceptability of using a specific tool for a specific purpose in drug development. For more information on FDA's Fit-for-Purpose Initiative, see https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative (accessed May 20, 2020).

their disposal to make their decisions. Although they may be conscious of FDA's guidance, these organizations tend to be more concerned with commercializing a DDT or making a case concerning registration. Often, they have a more informal engagement with FDA through type B and type C meetings to explain the work.[5] Adhering to the right methods is important, Benko said, but in many cases this work does not necessarily need to be oriented around the more well-known validation frameworks.

Conceptual Framework for Regulatory Acceptance of Digital Health Technologies in Biomarker Development

Leptak discussed a conceptual framework for biomarker development for regulatory acceptance (see Figure 4-1). Within the framework, the process of proposing a novel tool or technology begins with a need statement that is independent of the tool itself. The need statement should specify how current drug development is stymied due to current challenges or barriers—for example, the heterogeneity of the patient population or the lack of patients who have a rare disease. It should also clearly express the targeted need that the tool intends to address and how the tool will help to address it. The next step is to establish the context of use for the tool, such as its outcome in a clinical trial, its benefit for patients of a certain subtype, or its contribution to the better management of safety signals. Many safety concerns relate to off-target effects, so the context of use for some tools might be differentiating the possibility of those effects. Subsequent stages in the framework are to evaluate the benefits and risks to patients compared with the status quo, which informs the stringency of the evidentiary criteria that will be required to gain regulatory approval.

Improving Drug Development Through the Use of Drug Development Tools

Several components of a DDT contribute to the success of drug development and approval, Leptak said. These include the DDT itself, how the DDT is measured, the targeted patient population for which the DDT is indicated to have value, and other elements of the clinical trial design, such as the input. Any of these elements can lead to failure, he said, so it is important to optimize as appropriate and feasible. Designing a clinical trial that introduces a novel tool or technology requires consideration of

[5] Type B (e.g., pre-IND meeting) and C meetings (including anything outside of the purview of Type A and Type B meetings) are informal meetings that occur between a sponsor or applicant and FDA staff. A Type A meeting is a formal meeting immediately necessary for a stalled drug development program to proceed.

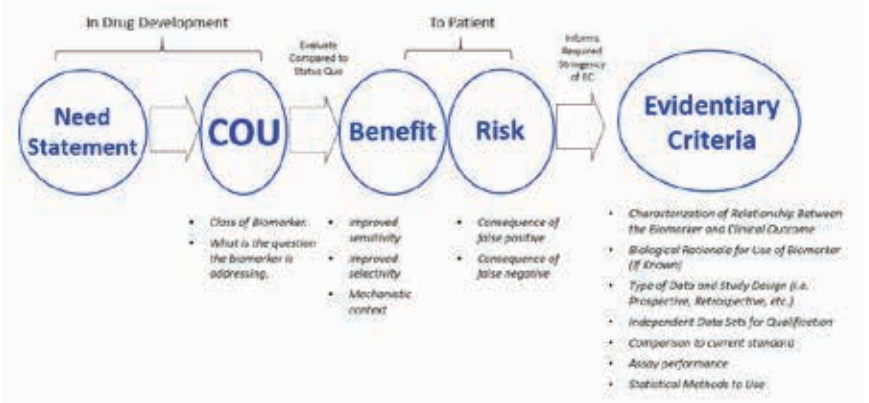

FIGURE 4-1 Conceptual framework for biomarker development for regulatory acceptance.
NOTE: COU = context of use; EC = evidentiary criteria.
SOURCES: As presented by Christopher Leptak, March 24, 2020. Originally from FNIH, 2016.

the current scientific understanding and how the tool would improve on it. This in turn depends in large part on how the science is understood. Because science—especially biology—is subjective in many respects, he said, it is helpful for a trial designer to carefully consider the assumptions that are involved and how the current state of the science is being interpreted. Devoting time to those conversations at the outset can be useful because it allows for learning from negative results in situations in which the trial design or data collection process do not go as predicted.

Addressing Unmet Drug Development Needs

Proposals for DDTs typically include an explication of the unmet drug development need that will be met by the tool, Leptak said. This may include an overview of the current approach used in drug development for the intended population that highlights the challenges and limitations of this approach. Examples of the types of unmet needs the DDT could address include the need to apply new technology or knowledge providing measures of disease severity; the lack of treatments for a specific condition for which a new diagnostic tool could aid in patient identification; the lack of a system for characterizing subtypes of a condition that may exhibit different responses to the same therapy; or identification of toxicity resulting from exposure to an investigational drug. Generally, the proposal will also include descriptions of the nature, severity, and prevalence of the disease or condition and other characteristics of the target population as well

as any other justifications for the need to be addressed. It is also useful to describe the added value that the DDT could provide to the current drug development and regulatory review processes and how it might address any other potential public health benefit. There are several safety biomarkers in development within FDA's biomarker program, he said, referring participants to FDA's biomarker qualification submissions website (FDA, 2020c). Digital technology may be beneficial for some of them, although not all of those tools will necessarily be novel. The DDT qualification program provides many resources online to support this process, he added.[6]

ENGAGING THE PUBLIC IN RESEARCH USING MOBILE HEALTH

Yvonne Yu-Feng Chan, Senior Director, Medical Affairs for Digital Medicine, Otsuka Pharmaceutical

To explore how DHTs can help accelerate and democratize research, Chan described experiences and lessons learned while she and her team at the Icahn School of Medicine at Mount Sinai were involved in conducting the Asthma Mobile Health Study, a large-scale decentralized trial for which she was the principal investigator (Chan et al., 2018).

Overcoming Research Barriers to Digital Health Technologies

Clinical studies have been conducted for centuries in a way that is inaccessible for many members of the public, Chan said. Mount Sinai, where Chan previously worked, was one of the five original launch partners for Apple's ResearchKit,[7] a framework that helped address this barrier of bringing research to the masses. The initial pilot for the Asthma Mobile Health Study used the iPhone iOS platform because it was the first such technology available to allow anyone interested in participating to

[6] Resources include list of qualified biomarkers, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm; biomarker qualification submissions, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535881.htm; table of surrogate endpoints, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636.htm; list of qualified COAs, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm450689.htm; and COA qualification submissions, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm625989.htm. All resources accessed May 17, 2020.

[7] Apple's ResearchKit is an open source framework designed to help researchers and developers create apps for medical research. More information is available at https://www.apple.com/researchkit (accessed May 11, 2020).

download the app. Participants could register for the study if they met the study criteria, which included having doctor-diagnosed asthma and using prescription medicines; the study had no controls. Despite the relatively stringent recruitment criteria, around 3,000 patients were recruited within 3 days of the launch, and this grew to around 10,000 participants recruited from Ireland, the United Kingdom, and the United States within about 1 year. This is indicative of the feasibility and promise for this type of mobile health recruitment paradigm, she said. This type of strategy is able to surmount historical barriers to participation in research studies, such as geography, work-life challenges, and psychosocial factors.

A common criticism of research strategies using DHTs is that only a single platform is prioritized, which can exclude some participants, Chan said; offering the app through iOS and Android platforms when feasible can help to overcome some of those generalizability issues. Despite using a single platform, the Asthma Mobile Health Study was able to reach patients with severe baseline disease—around 13 percent of participants had a history of intubation, a marker for severe disease. More traditional methodologies would be less likely to reach those patients or others who would be less likely to participate in a study, such as people living outside of large academic hubs and in rural areas. In Chan's study, 90 percent of the participants recruited lived outside of the New York City metro area.

When conducting a study that exclusively uses a smartphone to collect multidimensional data, Chan said, it is important to demonstrate the feasibility of the approach and to evaluate the validity and usefulness of the data collected. Just because a technology is new does not mean that it intrinsically has value, she said, so she and her colleagues rigorously assessed the various types of patient-generated and patient-reported information that were being collected. To evaluate the quality and validity of the study data, Chan and her colleagues assessed if data collected had similar intervariable correlation as has already been established in the medical literature. For example, it had already been established that men with good baseline asthma control who are tall should have higher peak flow relative to other subgroups of the patient population. Demonstrating these types of correlations in the study data was helpful in demonstrating the value of the study data, she said.

Chan outlined some of the different types of data that can be collected "in the wild" using DHT. In addition to electronic patient-reported outcomes, it is possible to collect geolocation data, environmental data, and data from connected devices. An example of a sub-analysis performed using the study data illustrates the importance of designing studies that appropriately obtain a consent from patients that is broad enough to ensure that data collected could be used in a future sub-analysis and other uses. For example, the study team was able to analyze data from participants who lived in the affected areas during the 2015 wildfires in

Washington State. Information such as environmental data, patients' self-reported triggers, and patients' clinical status enabled the researchers to perform analyses to better understand how the disaster had affected the study participants.

DHTs can also make it possible to integrate datasets that have historically been siloed and separated into a common platform, Chan said. In terms of data analysis, mobile health allows researchers to collect prospective, granular data that can facilitate time-series analyses, cluster analyses, and the discrimination of patient subtypes. The current capacity to categorize patients, she said, is relatively crude. Using mobile health data to refine patient subtypes for specific conditions could help lay the groundwork for more personalized treatments.

Digital Health Technologies to Promote Recruitment and Retention

DHTs can promote recruitment and retention in research studies, Chan said. For example, the Asthma Mobile Health Study benefited from the involvement of Apple ResearchKit and its introduction at a large Apple event. Most traditional research efforts do not enjoy such advantages, she said. Some of the traditional methods of recruitment have moderate effectiveness, but a promising new approach is to use social media in recruitment strategies. Different approaches can be used to target and engage specific types of patients, and digital platforms can also be used to reach out to patients more effectively than traditional methods of conducting research via postal mail or phone calls—forms of communication that are no longer an integral part of many patients' lifestyles today. Relying on those traditional methods can yield a study population that is even less representative. Understanding how to reach customers and patients is an evolving process and a useful principle is to strive to be where your patients are, she said.

"Retention is the Achilles' heel of mobile health," Chan said. To help promote better patient retention, she suggested encouraging health care providers to endorse or advocate for the use of digital tools as well as creating communities or other types of platforms to foster connections among study participants when possible or appropriate. DHTs will never obviate the need for human contact in the clinical and research realms, she said; however, a strategy for combining the two elements might involve letting digital technology do most of the "heavy lifting" of more mundane tasks and using the scarcer resource—human contact—on a strategic and periodic basis. Kapur agreed that human connection is an important element of recruitment, retention, and engagement with digital technologies but is often difficult to scale. Learning from the individuals who participate in research about what elements help them feel connected can help inform future technology development, she added.

DIGITAL HEALTH TECHNOLOGIES AND REMOTE MONITORING IN DRUG DEVELOPMENT

Chris Benko, Chief Executive Officer, Koneksa Health

DHTs and remote monitoring could be used in early-stage clinical studies to address some of the barriers encountered in traditional clinical study protocols, Benko said. His organization, Koneksa Health, focuses on the development and implementation of digital biomarkers for patient-centric assessments of novel investigational products. Koneksa Health primarily works on products not yet fully proven in terms of safety and efficacy.

Use of Clinical Pharmacology Units in Early-Stage Clinical Trials

Early-stage clinical trials in many therapeutic areas—excluding oncology—are conducted among healthy volunteers with the aims of establishing the pharmacokinetic, pharmacodynamic, and safety profiles of an investigational drug. The healthy volunteers are typically confined to a clinical pharmacology unit (CPU) while the pharmacokinetic, pharmacodynamic, and safety data are collected. The CPU is a protected health care setting that allows volunteers to be evaluated and monitored for any adverse safety effects. The duration of confinement depends on the anticipated safety profile of the drug being investigated.

There are some drawbacks to relying on CPUs, Benko said, and it can be one of the most expensive and rate-limiting components of the drug development process. Furthermore, confinement in the CPU for extended periods of time is inconvenient for study participants, and it may not provide data that are reflective of normal day-to-day activities. Because the drugs are unproven and potentially risky at this point in the development process, it is important to limit the volunteers' exposure to the drug to no longer than is necessary to answer the research question. Furthermore, little or no safety information about the drug—other than the participant's memory recall—is available after the participant is discharged from the CPU and in between follow-up visits. This can make it difficult to interpret potential safety findings, he added.

Digital Health Technologies for Assessments in Early-Stage Clinical Trials

Given the disadvantages associated with the reliance on CPUs in early-stage clinical trials, there is growing interest in the potential role of remote technologies for the assessment of pharmacokinetics, pharmaco-

dynamics, and the safety of new drugs, Benko said. Two of the sponsors of Koneksa Health, Merck & Co., Inc., and Takeda Pharmaceutial, have expressed interest in the logistical potential to gather more data without necessarily confining study participants in CPUs and to potentially to develop deeper phenotypes or better baselines to understand normal human variability by gathering continuous data outside the clinic. The latter type of data could shed light on factors that may be affected by participants' real-world activities in a way that could not be captured from participants living a controlled setting.

The COVID-19 pandemic has given rise to a new set of challenges specific to phase I drug development that are likely to cause substantial disruption to that stage of the process, Benko said. Traditionally, phase I studies require bringing people into health care facilities, which can compromise social distancing and introduce other possible risks that can cast doubt on whether phase I studies should be initiated at all during the pandemic (Upadhaya et al., 2020). Despite the pandemic there will be an impetus to continue the clinical studies of drugs at later stages of development to the extent possible. At that point in the development process, drugs will have already demonstrated lifesaving or significantly health-altering potential. In contrast, most drugs in phase I of development outside of oncology—by definition—do not yet offer an established health benefit to the study participants. In addition, phase I units are being considered as excess capacity for health systems across the world as many become increasingly overburdened in the pandemic response. As a result, CPUs with the capacity to monitor vital signs will not likely be allocated toward studies of new unproven medicines for some time.

DIGITAL HEALTH TECHNOLOGIES AND THE COVID-19 PANDEMIC

In dealing with the COVID-19 pandemic, there are emerging areas of interest related to using DHTs and the remote monitoring of vital signs and potential COVID-19–related symptoms as a proxy for disease incidence prior to confirmation with laboratory testing, Benko said. DHTs such as sensors and digital biomarkers connected to the body could be used to monitor vital signs and symptoms remotely using software; this could be complemented with electronic patient-reported outcomes collected via mobile phones or other devices. In March 2020, FDA released rapid guidance to support the adaptation of clinical trials during the COVID-19 emergency.[8] The guidance identifies several types of non-invasive remote

[8] The FDA guidance document is available at https://www.fda.gov/media/136238/download (accessed June 19, 2020).

devices that could be helpful in monitoring patients' body temperature, cardiovascular function, respiration, and pulse oximetry.

These types of remote measures and monitoring technologies could also help facilitate the continuity of other types of clinical studies ongoing in various disease areas that are at risk of being disrupted by the pandemic, Benko said. Shifting conventional clinical assessments into a remote mode could help protect clinical trial participants by reducing the need for participants to visit clinical settings where they could be put at risk, put others at risk, or otherwise place additional burdens on health care systems. For example, pulmonary function tests typically require a person to breathe into a machine during an in-hospital assessment, potentially promoting the spread of disease. Providing a patient with a Bluetooth-enabled individual spirometer, he said, could enable the patient to measure pulmonary function in the home without risking exposure or transmission in a hospital.

Interpreting and Validating Measurements Collected via Remote Monitoring

More work will be needed to better understand, interpret, and validate measurements of vital signs collected through continuous monitoring using remote devices, Benko said. Body temperature appears to be a useful indicator of the progression and severity of COVID-19, so there is interest in the use of continuous remote temperature monitoring through a device such as a patch worn on the chest. Although continuous monitoring can generate rich datasets, the measurements can be challenging to analyze in the context of traditional standards. For example, it can be difficult to interpret measurements and establish alert thresholds for continuous temperature monitoring because of the poor correlation between those measurements and measurements of body temperature taken in body cavities (Izmailova et al., 2019). Regular spot checks with digital thermometers that measure body temperature in the oral cavity have well-established reference ranges and intervals, which makes the measurements relatively simple to interpret. If a person who appears healthy has very low oral temperature measurement, then the person would typically be asked to repeat the measurement with the thermometer in an adjusted position in the mouth—or some other adjustment—until a reference value is attained that is better aligned with the person's presentation. However, continuous temperature monitors are more prone to generating aberrant values than traditional methods. Benko and his colleagues looked at data from a single healthy individual using a continuously worn temperature monitoring device outside of a controlled setting, and this demonstrated how variable those measurements can be, with excur-

sions well outside of healthy ranges—from 34°C to more than 38°C. It can be difficult to control for these types of deviations, because the data are affected by a variety of factors such as ambient temperature, clothing, and physical activity. More normative studies may be required to better understand measurements collected through the continuous monitoring of temperature or other vital signs before they can be integrated into a clinical development program, he added.

To illustrate how data collected using DHTs can be validated, Benko described a well-controlled crossover study that Koneksa Health designed with Merck to examine the potential for DHTs to detect meaningful real-world changes in cardiovascular and vital activity (see Box 4-2). The measurements captured by the wearable technology were concordant with traditional in-clinic approaches, and the technology was able to detect the expected changes in the participants' vital signs during in-home use. The results of the study, he said, build confidence in the use of DHTs to capture real-world data on vital signs with sufficient sensitivity to detect the kinds

BOX 4-2
Evaluation of Digital Health Technology for Cardiovascular Monitoring

An open-label randomized clinical trial was conducted to evaluate a mobile device for cardiovascular monitoring in healthy male volunteers. The first part of the study began with a side-by-side comparison of wearable mHealth devices (the 1-Preventice BodyGuardian® Single Lead ECG and the A&D UA-767PBT-Ci Blood Pressure Monitor) with in-clinic devices measuring heart rate, blood pressure, respiratory function, and activity. The researchers found that the mHealth measurements of heart rate and blood pressure were similar to the corresponding measurements by standard methods. During the second part of the study, the goal was to assess whether relatively modest changes in heart rate could be detected using remote technologies. Detecting such changes in vital signs is clinically important. Subjects went home with the wearable devices and started either on placebo or one of the two study drugs: either bisoprolol, which lowers blood pressure and heart rate in healthy individuals, or salbutamol, an inhaler that causes an elevated heart rate during the first several weeks of adapting to the drug. The placebo was designed to have neither of those effects. Investigators hypothesized that changes in heart rate as measured by the wearable device would be greater in the treatment groups than in the placebo group. The results of the study bore this out; the expected heart rate changes were observed in the treatment groups taking the drugs that were designed to decrease and increase heart rate (bisoprolol and salbutamol, respectively).

SOURCES: As presented by Chris Benko, March 24, 2020; Huang et al., 2020.

of treatment effects of concern with respect to safety. Vital signs can also be interpreted in other meaningful ways, he added. Significant changes in vital signs often indicate other changes in functional status. In settings such as oncology, for example, changes in vital signs can serve as a dynamic predictor of hospitalization or other decompensation—or the deterioration of an organ or organ system to maintain adequate physiological function.

Incorporating Digital Health Technologies into Oncology Research and Care

DHTs do not play a prominent role into oncology research and care, Benko said, although a recent study found activity level to be a significant predictor of hospitalization for patients with locally advanced non-small-cell lung cancer (Ohri et al., 2019). However, oncology drug developers in general are still resistant to adopting endpoints beyond progression-free and overall survival, which Benko said is short-sighted. To differentiate long-term benefit and long-term survival outcomes of targeted therapies from traditional chemotherapy and radiation, especially relative to cost, a patient's functional status needs to be considered, he added. Measuring real-world components of functionality such as activity, satisfaction, and sleep are meaningful for those types of long-term analyses. However, drug development teams at pharmaceutical companies tend to focus on short-term milestones. An often-neglected consideration is that, over the long term, payers will have to choose between different therapies that may have been developed using different endpoints. In many cases the differentiation between those traditional endpoints either has not been established or is not compelling enough to justify the cost of one treatment over the other. Furthermore, there has not yet been a market force to drive this, he said. Benko highlighted another study that looked at patient satisfaction and activity among people with myeloma over the course of a long-term therapy (Chari et al., 2019), but he said that this type of work remains uncommon. Expanding the body of research on functional status in a way that uses DHTs for data collection will require addressing a substantial change-management problem within the oncology therapeutics leadership at many of the major drug development companies.

DEPLOYING DIGITAL HEALTH TECHNOLOGIES AT THE INTERSECTION OF CLINICAL CARE AND RESEARCH

Eric Perakslis, Rubenstein Fellow, Duke University

The use of DHTs should begin with the idea that necessity is the mother of invention, Perakslis said. "If you bring the right problem, you

are going to find a reason to bring the right technology to it," he said. A focus of his own work is the dichotomy between data used for research and data used for care. Clinicians are often asked to work with bad data, as evidenced by those who report struggling with electronic health records or being unable to find a comprehensive history on a patient during a case review. If data are not considered to be good enough for research, they should not be considered good enough for clinical care, he said, adding that the opposite also holds true. Although data for research and data for care have different purposes and functions, he questioned how different the two types of data actually need to be.

Envisioning a Telehealth-Based Learning Health System

Perakslis described his vision of how a telehealth-based learning health system might function during an infectious disease outbreak, based on his own experience in the field during the previous two Ebola virus disease outbreaks (see Figure 4-2). In this vision, there is a complex network of data, learning, and communication that intersect across the domains of clinical care and research. Each clinical interaction should be able to support cycles of learning and clinical research. Within this system, for example, a family would receive a telehealth visit in which they are guided through layers of data collection supported by standard case definitions, standard protocols, and trusted sources for information; the information would then be fed back into the provision of clinical advice and care. During an outbreak, Perakslis said, the most important conversation to be had is to reassure people at home who are wondering if they are taking the right steps to protect their health and the health of their loved ones. However, these ideal system capacities for collecting data remotely, picking up samples, monitoring people at home, and propagating data in a reasonable way have not yet been achieved in real-world systems. Some of the individual elements and connections are functional and may connect with each other in a given system, but the entire enterprise does not function as a whole. "If you think big, you can always act small," he said. "If you are thinking small, you are not going to trip and fall into big." Those leading the federal-level response to COVID-19 should "think big" in their efforts to address the deep-rooted systemic problems that the pandemic has exposed.

Supporting Patients and Ensuring Data Privacy Outside of Traditional Clinical Settings

To more effectively incorporate DHTs into clinical care and research, Perakslis suggested working with community health workers (e.g., nurses

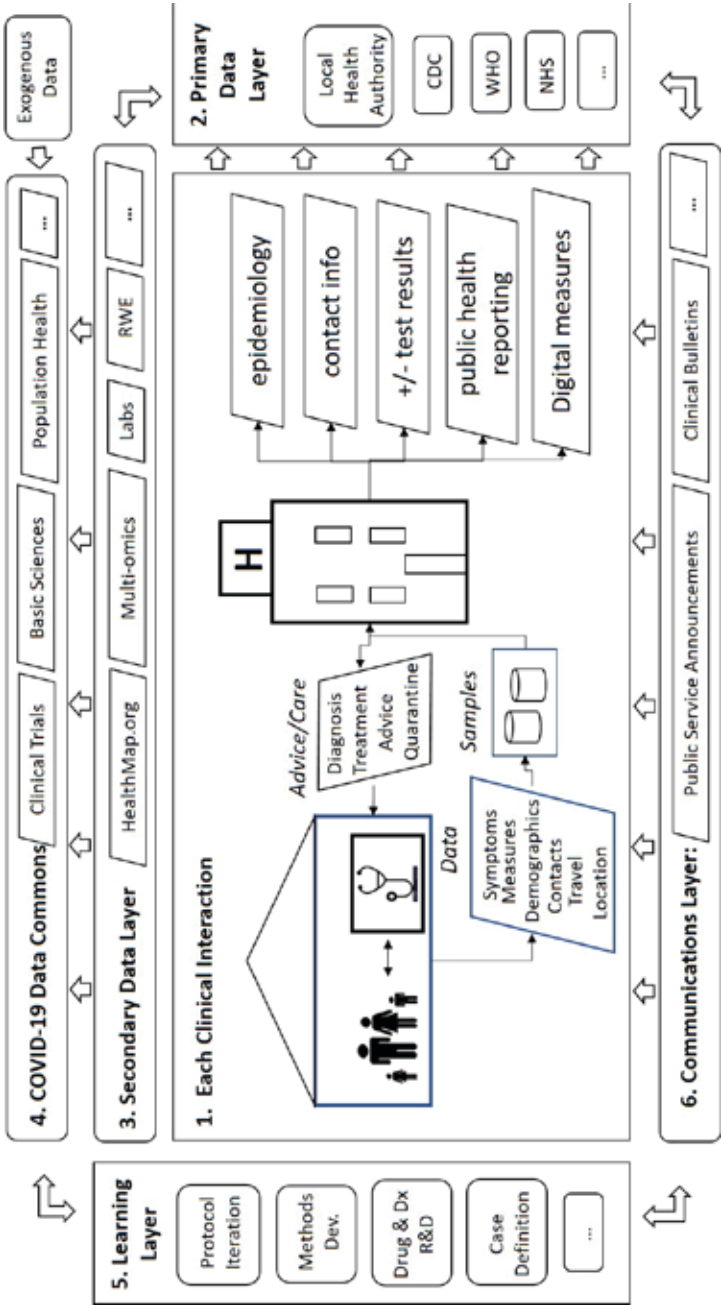

FIGURE 4-2 Telehealth-based learning health system during an infectious disease outbreak.
NOTE: CDC = Centers for Disease Control and Prevention; Dev = development; Dx = diagnostic; NHS = United Kingdom National Health Service; R&D = research and development; RWE = real-world evidence; WHO = World Health Organization.
SOURCE: As presented by Eric Perakslis, March 24, 2020.

or clinical trial managers), who play a critical role in delivering health care within the "last mile." He emphasized that efforts to engage community health workers should ensure that there are fewer protocol deviations, the appropriate data are being propagated, the drugs are reaching the sites where they are needed, and people understand how to appropriately use DHTs. Community health workers may serve an important role in the implementation of "click-and-mortar" solutions, which mix the old paradigm of using brick-and-mortar sites with new DHT applications to fill gaps in clinical care and research. Another important consideration for the use of DHTs is data privacy, he added. He suggested that a proactive approach to data privacy could help ensure the security of data as increasing volumes of information are collected and integrated across multiple layers of the health care system. Starting with "privacy by design" to obtain appropriate consent and communicate clearly is important, he said.

Ensuring data standards and data validity when collecting data outside of traditional clinical settings requires high-level coordination, standardization, and organization, Perakslis said. During the Ebola outbreak in West Africa, the World Health Organization (WHO) served as the coordinator to support Guinea, Liberia, and Sierra Leone. WHO established a single case definition and a single set of triage forms. The degree of standardization that was achieved across the countries during the outbreak is something that many hospitals in the same U.S. cities have difficulty achieving, he said. Strong organization up front is also critical during a crisis such as an infectious disease outbreak. For example, it would be unsafe to recruit older populations with mild disease into a clinical trial by bringing them into a clinical setting. In those situations, a community health worker could visit patients in their homes to introduce the trial and lead them through the consent forms. Simple "click-and-mortar" solutions can enable the collection of clean data on the front end, even if there is variability downstream at the patient level. A single case report form could be developed for every COVID-19 patient, or a standard set of 10 questions could be asked at the beginning of every telehealth session. Crisis settings require swift and strong leadership to take control and ensure that the right data are collected from the outset, he added. This involves convening the right experts to rapidly develop standardized data collection protocols and propagate them downstream appropriately. All of the necessary technologies already exist, he said, but deploying them effectively depends on strong organization.

How, McGraw asked, can researchers ensure that privacy is not sacrificed in efforts to aggressively pursue data collection that could help to understand and halt the COVID-19 pandemic? The first priority should be to act appropriately without making avoidable mistakes, Perakslis said. For example, the appropriate patient consent and institutional review

board approval should be obtained early so that valuable data are not lost. Every COVID-19 test result could be immediately tokenized so the data can be shared in a way that preserves privacy up front, he said. This is an example of existing technology that is simple, inexpensive, and widely available. It is important to take advantage of every opportunity for data collection, even in the midst of a crisis, he said. Each clinical interaction offers a unique and irreplaceable opportunity to capture information from that patient; the technology to collect data rapidly, securely, and comprehensively is already available and should be employed to its full extent.

DISCUSSION

Streamlining Regulatory Approval During Crises

The pharmaceutical industry, a workshop participant said, is entirely dependent on the rules and regulations established by governing bodies, while other industries have seen a paradigm shift in which consumers and manufacturers are compelling regulators to change more swiftly. Given that the COVID-19 pandemic demands rapid action, he asked, how could industry demonstrate the value of DHTs and drive change at an accelerated pace? The actions taken by regulators to expedite the pace of approval might continue long after this pandemic is under control, another participant suggested. The crisis has created a situation in which clinical providers and patients may be more likely to try out DHTs, such as telemedicine, Chan said, which could potentially drive demand and adoption of DHTs over the longer term. As telemedicine has taken off, she added, the Centers for Medicare & Medicaid Services and some payers have adapted by changing their approach for reimbursement. Perakslis suggested thinking about how DHT development and incorporation into the standard of care might differ in crisis versus non-crisis environments. For example, he pointed out that in non-crisis situations, it might be typical for safety and risk to be evaluated through the course of clinical research. However, in an accelerated-approval or crisis scenario, there may be a shift toward more risk assessment in post-market settings. Experience based on previous outbreaks has indicated that crises can be used to spur forward momentum when it comes to technology development and implementation, he added.

5

Digital Health Technologies for Pivotal Trials

Key Messages Highlighted by Individual Speakers

- In the expanding universe of big data, digital health technologies (DHTs) can be used to leverage multiple data types with complex characteristics in terms of velocity, volume, variety, and veracity. (Khozin)
- DHTs can enable the collection of high-velocity data about patients' experiences in clinical trials and pivotal studies, but these measurements need to be verified, analytically validated, and clinically validated with sufficient rigor that they can be relied on to demonstrate safety and effectiveness. (Kapur, Khozin, Sacks)
- Common methodologies and standard performance criteria are needed to evaluate digital metrics. (Kapur)
- For regulators, DHTs can add value to clinical trials by enabling remote data collection in decentralized trial settings, broadening access for participants, and capturing novel data (e.g., continuous physiological measurements, measures of functionality). (Sacks)
- Creative, collaborative approaches could improve interoperability among DHTs and establish strategies for the analytical validation of novel measures. (Kapur, Sacks)

The workshop's third session focused on the use of digital health technologies (DHTs) in pivotal trials,[1] a crucial phase in the drug development process that generates the evidence upon which regulatory approval decisions are based. Sean Khozin, global head of data strategy at Janssen Research & Development provided an industry perspective on the potential impact of DHTs on the velocity, volume, variety, and veracity of data. He also described technical and procedural challenges encountered when incorporating data collected from DHTs into pivotal trials. Ritu Kapur, head of biomarkers at Verily Life Sciences, provided a practical overview of the processes of signal verification, analytical validation, and clinical validation for novel DHTs. She also highlighted several opportunities to improve the measurements captured by those technologies going forward. Leonard Sacks, associate director of clinical methodology in the Office of Medical Policy at the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration (FDA), offered a regulatory perspective on ways that DHTs could enable decentralized clinical trials, as well as on their potential to capture novel measurements. The session was moderated by Husseini Manji, global therapeutic head of neuroscience at Janssen Research & Development, LLC.

INDUSTRY PERSPECIVE ON DIGITAL HEALTH TECHNOLOGIES IN PIVOTAL TRIALS

Sean Khozin, Global Health of Data Strategy, Janssen Research & Development, LLC

Khozin said that the expanding universe of big data presents complexities regarding four computational dimensions (see Figure 5-1):

- **Volume:** Dataset size (e.g., computing storage sizes—megabyte, gigabyte, terabyte, and petabyte);
- **Variety:** Data type (e.g., tables, databases, clinical trial data, electronic health records);
- **Veracity:** Data noise and uncertainty (i.e., where data lie on the continuum of being structured to undefined); and
- **Velocity:** Data flow and processing speed (e.g., batch, intermittent, near real time, and real time).

The expanding complexity that big data poses is depicted in Figure 5-1. Whereas data in the center of the concentric circles represents a hypotheti-

[1] A pivotal trial is held to the highest standards of rigor and quality control; it requires prespecification of all components (e.g., study design, enrollment, dosages, comparators, measures, endpoints, statistical plan) in discussion with regulators prior to conducting the trial.

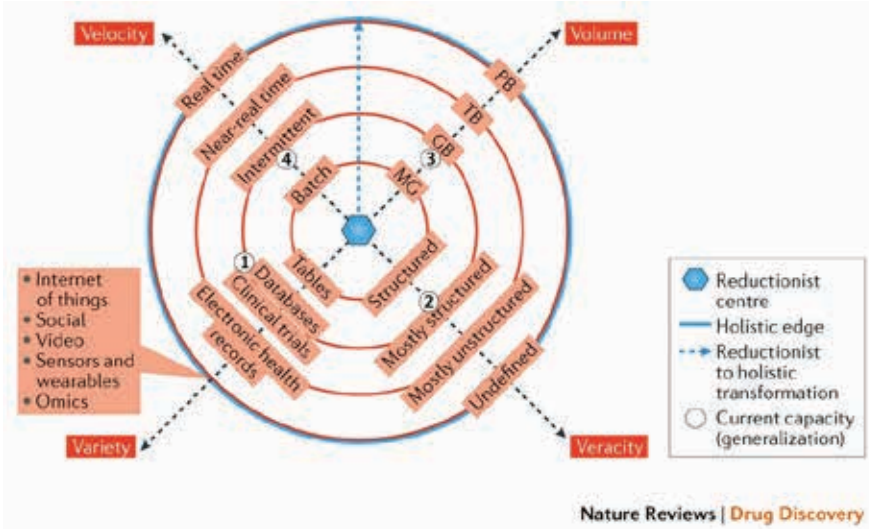

FIGURE 5-1 Conceptual map of technical and organizational capacity for biomedical big data.
NOTE: GB = gigabyte; MG = megabyte; PB = petabyte; TB = terabyte.
SOURCES: As presented by Sean Khozin, March 24, 2020; from Khozin et al., 2017.

cal reductionist center where biomedical research does not take advantage of big data, DHTs fall on the outer edge of the concentric circles. As such, Khozin noted that the "holistic" edge of big data represents emerging opportunities to leverage multiple data types that, despite having complex characteristics with respect to data standards, quality, size, and veracity, are fundamental building blocks of developing a new generation of precision therapies with near-real-time velocity. In some cases, he added, data from digital health technologies (e.g., wearables) close to the holistic edge of big data can also be used to capture patients' experiences in pivotal trials, using novel trial designs that accommodate more decentralized data collection. Due to the unique nature of data assets emerging from DHTs, he explained, it is important to consider the technical and procedural issues associated with incorporating those modalities into clinical trials.

Technical Considerations for Using Digital Tools in Clinical Trials

Khozin explained that measurements, verification, and validation are used to assess the technical features of digital tools (Coravos et al., 2019b). In order to trust the data that are captured by DHT measurements, the software and hardware specifications must be standardized and clearly understood. Such measurements typically involve three layers: an input layer (e.g., a camera, microphone, or sensor); a processing layer (i.e., an algorithm that pro-

cesses the input); and an output layer (i.e., a digital biomarker). The output layer might be a familiar clinically validated measurement (e.g., heart rate). However, an advantage of using DHTs is the ability to quantify outputs that are currently unfamiliar or unquantifiable. For example, performance status is a subjective assessment used to understand the patient's daily activities which is used in oncology to determine participant trial eligibility and the intensity of treatment regimens (Kelly and Shahrokni, 2016). Work is ongoing to use digital tools to better quantify the assessment of performance status using digital sensors that can track a patient's daily activities.

Verification and analytical validation are additional technical components to consider when evaluating and using DHTs in pivotal trials, Khozin said. This process includes engineering benchmarks to ensure that a product is measuring and storing values accurately. He noted that a tool's accuracy, precision, and reliability are three related yet nearly mutually exclusive concepts. In some cases, it is possible to extrapolate experiences from how companion diagnostics are developed and analytically validated in terms of accuracy, precision, and reliability.[2] For example, a heart rate sensor should be able to faithfully convert electrical signals into an accurate, clinically relevant measure—in this case, heart rate in beats per minute. Such a device would then need to be analytically validated to ensure that it is accurately measuring what it is supposed to measure.

Devices that have been verified and validated analytically still need to be clinically validated, be it prospectively in a clinical trial or separately as part of a qualification program. Clinical validation addresses whether the measurement is applicable in the target population and whether the context of use renders the digital biomarker fit-for-purpose (see Christopher Leptak's presentation in Chapter 4). Further expanding on his example of a heart rate sensor, Khozin explained that clinical validation would entail ensuring that the output of the sensor is a meaningful endpoint and could replace, for example, the traditional tactile measurement of a patient's pulse for a clinical trial.

Digital Health Technologies as Diagnostic Tools

Khozin spoke about how the issue of false negatives and positives could be addressed when using clinically validated DHTs for diagnostic purposes. Established methods for addressing false negatives and positives in traditional diagnostic tests will also apply to DHTs. All tests used in the clinical setting, Khozin noted, have false negative and false positive rates, which are generally managed by purposely administering tests to

[2] Accuracy refers to how close a captured measure is to the true value of an endpoint. Precision refers to how consistent repeated measures are to each other. Reliability is a similar concept to precision and refers to the degree to which a measurement instrument is consistent and free from error (Trajkovic, 2008).

patients who, based on the patient's data and the provider's clinical judgment, have a high probability of having a target disorder. This practice, known as increasing pretest probability, can also be employed when using digital health technologies to make them more predictive.

Procedural Considerations for Using Digital Tools in Clinical Trials

Khozin discussed procedural considerations related to the use of these DHTs in pivotal clinical trials, including clinical validation and the design and conduct of clinical trials (Coravos et al., 2019b). To illustrate the process, he drew an analogy with how biomarkers are validated in oncology clinical trials. Biomarkers are typically validated clinically prospectively during a clinical trial and are paired with a targeted therapeutic using an analytically validated assay, rather than being separately evaluated as part of FDA's Biomarker Qualification Program, Khozin said. The same methods can be applied to clinically validate digital biomarkers prospectively in a clinical trial, he added.

Further procedural considerations relate to the novel clinical trial design opportunities that the use of digital tools can allow, Khozin said. Decentralized clinical trials have garnered interest in recent years as a strategy for scaling studies (Khozin and Coravos, 2019). Because they are decentralized, these types of clinical trials have unique features in terms of where the data are being captured and who is collecting the data. He noted that there is a continuum of decentralization in the sense that most traditional clinical trials already have decentralized components, such as collection of data on the phone or via home visits (instead of a research facility) and outsourcing of testing to commercial laboratories rather than having it done at a centralized laboratory. Khozin said that in appropriate cases, DHTs today could allow data to be collected completely remotely, perhaps even in the absence of any intermediaries. This would create opportunities to collect data from patients where they live. Hybrid approaches could also be deployed, he added. An example of a siteless, completely decentralized clinical trial is the Heartline study, which is exploring how commercial technologies (e.g., Apple iPhone and Watch) can facilitate the early detection of atrial fibrillation.

PERFORMANCE REQUIREMENTS FOR DIGITAL HEALTH TECHNOLOGIES IN PIVOTAL TRIALS

Ritu Kapur, Head of Biomarkers, Verily Life Sciences

Verily is currently developing means to use digital measurements and emerging DHTs to improve the success of drug and medical device development. Specifically, Kapur explained, the goal is to create endpoints that

increase the efficiency of clinical trials and that are useful in the context of pivotal studies. To this end, digital measurements need to undergo a process of verification and validation to reliably demonstrate the safety and efficacy of investigational products. Specifically, this involves a three-step process of signal verification, analytical validation, and clinical validation. Kapur defined each term and gave examples of each:

1. **Signal verification** tests whether a sensor is working, which typically requires bench testing. Challenges can depend on the diversity of devices being used in a study. For example, a "bring-your-own-device" strategy can create a prohibitively large number of permutations of devices and operating systems for analysis.
2. **Analytical validation** tests whether the DHT is measuring what it is intended to measure. This usually involves measuring the underlying algorithm's performance against a trusted corroborative device. In some cases, this can be performed through comparison with a score from a human rater. Challenges can include collecting enough naturalistic data for comparison because these tend to be noisy and variable. Furthermore, in cases where human observations are the benchmark, the accuracy of corroboration is pinned to a subjective measure.
3. **Clinical validation** tests a digital measurement's predictive power in the context of its intended clinical use. This generally relies on testing a tool with datasets in which the clinical outcome of interest varies in order to see how well the test predicts a given clinical outcome, Kapur said. A challenge frequently encountered is the lack of common methods for evaluating digital metrics against traditional clinical ratings.

To further explore this three-step process, Kapur illustrated hypothetical examples of digital tools used to measure the symptoms and severity of Parkinson's disease (PD) (see Box 5-1).

Improving Measurement by Digital Health Technologies

Kapur highlighted several opportunities to improve measurements captured by DHTs. Establishing a common approach for evaluating digital measures against subjective clinical ratings would be helpful, although how to do so remains an open question. Transitioning from subjective to objective measurements may require an agreed-upon set of performance criteria for quantitative measurements that are not pinned to subjective ratings. In the verification and validation of digital metrics, a foundational step will be to establish what counts as "good enough" performance. A common approach that is established should be agreed upon by a wide set of stakeholders, she said.

BOX 5-1
Verification and Validation of Digital Tools for Measuring Parkinson's Disease Severity

Measuring Step Count with a Wearable Device

A wrist-worn accelerometer device can be used to measure step count and evaluate the disease severity among people with Parkinson's disease (PD). Signal verification of the accelerometer is conducted through bench testing of the accelerometer. Analytical validation determines whether the accelerometer is actually measuring steps and can be done by comparing the digital measure to a manual step count or using a corroborative device on people in a real-world setting to generate naturalistic datasets for comparison. Clinical validation would evaluate the association between step counts and disease severity among people with PD. This might involve comparing the step count between those with PD and those without PD. Another approach would be to determine if step count decreases with disease severity.

Measuring Bradykinesia with a Wearable Device

A wrist-worn accelerometer may also be used to measure bradykinesia (slowness or difficulty in initiating movement), a primary symptom of PD. Digital health technology could be used in a pivotal trial to investigate whether an investigational product has an effect on bradykinesia. Signal verification can again be accomplished through bench testing. However, the analytical validation of a measurement of slowness of movement would be complicated by the lack of an existing "gold standard" metric for comparison purposes. Currently, the only option is to compare the digital metric to subjective observations made by a human rater. The current scale to measure severity of bradykinesia has neither high sensitivity nor good inter-rater reliability. As a result, using this rating as a comparator establishes a ceiling for the accuracy of a new digital measure, Kapur explained.

Clinical validation for this type of metric is also challenging, and the line between analytical and clinical validation can become blurred because both are testing against a clinical score. The lack of consensus about the appropriate methodological approach, the variation in measurements among raters, and the lack of a standard methodology with consensus scores that the digital measures can be evaluated against can make clinical validation especially challenging.

Measuring Geosocial Quality of Life with a Smartphone App

A smartphone app could be used to measure geosocial quality of life and evaluate it against the severity of PD. This app could use smartphone sensors to combine measurements of activity, spread of geospatial location, and frequency of social interaction into a digital endpoint for quality of life. While study participants generally have higher levels of engagement when using their own smartphone (a "bring-your-own-device" study protocol), such an approach can make it prohibitively difficult to perform signal verification for each combination of device, operating system, and varying standards for performance. This scenario is another example in which the lines between analytical and clinical validations can blur, Kapur added. Both of these are subject to challenges due to existing clinical ratings being subjective and due to a lack of common methods for cross-evaluating digital metrics. Similarly, there is no existing gold standard that can be used to demonstrate that a novel measurement is measuring what it is posited to be measuring.

SOURCE: As presented by Ritu Kapur, March 24, 2020.

Scalability is a related issue, Kapur said. Each new digital measurement could potentially be taken through a regulatory process for approval through either a drug development pathway or a tool development pathway. However, it is not yet clear how this process could be scaled if it consisted of increasing numbers of metrics simultaneously built and combined. Balancing accuracy of validation with speed when scaling will also be important, Kapur said. In the context of building entirely new measurements, Kapur wondered whether testing an algorithm's performance on a clinical dataset could substitute for prior analytical validation. She noted that this would require sound methodological approaches—such as appropriately separating training and testing datasets—and the ability to demonstrate that the analyses yield consistent results across multiple independent datasets.

Leveraging Digital Health Technologies for Recruitment, Retention, and Engagement

Kapur shared some of Verily's experiences in using digital technology for recruitment, retention, and engagement. Creating a sense of human connectedness when operating at scale is a challenge encountered when DHTs are incorporated into clinical trials. Although it may seem counterintuitive in the context of digital technology, human connection should be at the core of these efforts. For example, finding ways for participants to feel connected, such as providing help lines for people to call, can be useful when structuring rollouts. Another approach is to work with communities and learn about what helps people feel connected—particularly within successful initiatives—and incorporate those lessons learned into the technology. Kapur explained how this could be valuable by describing a collaboration that Verily had with the Radboud University Medical Center and ParkinsonNet in the Netherlands. The joint initiative enrolled participants using wearable devices to monitor their symptoms (Bloem et al., 2019). This initiative held a participant event during the study to allow participants to hear about progress of the study and allow participants to learn about each other's experiences. This event appeared to increase engagement and after 1 year in the study timeline, an average of 20 hours wear time per day and a dropout rate of less than 1 percent was achieved—both of which are highly successfully results for a wearable initiative.[3]

[3] For more information on the Personalized Parkinson's Project, see https://blog.verily.com/2019/04/visiting-personalized-parkinsons-project.html (accessed June 19, 2020).

REGULATORY PERSPECTIVE ON THE USE OF DIGITAL HEALTH TECHNOLOGIES IN PIVOTAL TRIALS

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

Sacks noted that DHTs provide two opportunities from a regulatory perspective:

- **Supporting decentralized trials:** DHTs can support the remote collection of data from patients in decentralized clinical trial settings. In addition to helping ensure the continuity of clinical trials during a pandemic (see Chapter 1 for more information on the impact of COVID-19 on clinical trials) or another disaster, decentralized clinical trials provide access to patients who are unable to travel to clinical sites, offer improved patient convenience, and can address access issues among people with impaired mobility, such as people with Duchenne's muscular dystrophy. Furthermore, decentralized trials provide access to people with rare diseases (e.g., inborn errors of metabolism), who may be widely distributed across the country or world.
- **Supporting capture of novel measurements:** Traditional clinical trials typically rely on sporadic or intermittent measurements, but DHTs can facilitate continuous measurements to capture information from participants during interim periods that would otherwise be lost (e.g., hypoglycemic episodes, falls, or seizures). Novel technologies also offer the opportunity to objectively and quantitatively measure clinician- and patient-reported outcomes, such as functional status. Functional status can now be measured by DHTs. The use of interactive task-based tests on mobile devices holds promise for enabling more frequent testing of vision, hearing, cognition, and fine motor coordination, Sacks said. DHTs can also be used to capture physiological measurements (e.g., continuous electrocardiograms, pulse oximetry, and lung function) and enable other types of novel measurements using photography.

Uses of Digital Health Technologies in Clinical Trials

Sacks described how DHTs can fit into the design of clinical trials. For example, they could be used to improve participant screening and enrichment strategies by selecting patients based on levels of disease severity or activity levels. Furthermore, DHTs could be used to refine

how performance is evaluated. During a trial, DHTs can also be used to monitor treatment adherence and drug safety as well as to provide pharmacodynamic impressions of how study drugs are working relative to their dosing. Another exciting opportunity DHTs provide in clinical trials is the potential to shape endpoints.

To explain how DHTs can contribute value in this respect, Sacks provided an overview of endpoints used in FDA pivotal trials for 280 new drug applications between 2007 and 2015. About 30 percent were approved based on clinician- or patient-reported outcomes, clinical events, or clinical signs. From a regulatory perspective, the dearth of objective ways to measure functional status represents a substantial opportunity for DHTs. Additional opportunities that DHTs provide beyond the dimension of functional status include such physiological measurements as continuous blood pressure monitoring, electrocardiograms, electroencephalograms, and pulse oximetry. Digital tools are also beginning to be used for biochemical testing, such as continuous glucose monitoring (Hirsch et al., 2019).

Measuring Functionality

Sacks explained that functional status (in terms of movement and activity) is a valuable yet challenging measure to assess across many product development areas, such as cardiorespiratory conditions (e.g., heart failure and pulmonary hypertension) and neuromuscular diseases (e.g., Duchenne's muscular dystrophy). Functionality has traditionally been measured using a 6-minute walk test, which, Sacks noted, is a relatively crude metric that has many potential confounders. DHTs are already being used to capture more precise and quantifiable measurements of functional status. Sensors could also be used to measure functional status in the home environment through smartphone-based interactive tests of vision, hearing, cognition, and coordination, Sacks observed.

Sacks described the results of a study that measured functional status among people with heart failure (Snipelisky et al., 2017) to illustrate the capabilities that DHTs could provide. The study compared participants' average daily accelerometry units (ADAUs) to traditional parameters (e.g., 6-minute walk test and the Kansas City Cardiomyopathy Questionnaire or KCCQ).[4] Results of study found a statistically significant correlation between ADAU and the 6-minute walk test, as well as between ADAU and KCCQ, across all three tertiles of study participants.

[4] The Kansas City Cardiomyopathy Questionnaire is available at https://www.fda.gov/media/108301/download (accessed May 17, 2020).

Measuring Movement Disorders

The use of DHTs for imaging purposes also holds promise from a regulatory perspective, Sacks said. To illustrate how video technology can be applied to measure symptoms of movement disorders, he compared key results from two double-blinded, placebo-controlled studies for the approval of valbenazine, a drug for tardive dyskinesia,[5] both of which used a 12-item clinician-rated Abnormal Involuntary Movement Scale to rate participants. While one of the studies was conducted in a traditional clinical trial setting and used a single dose of valbenazine, the other study tested two doses of valbenazine and incorporated DHTs by sending video recordings of participants to independent adjudicators who were blinded to the sequence of the video recordings and to the study drug allocations. In the first study, investigators blinded to treatment allocation who made successive subjective assessments on their patients reported improvement from baseline in placebo-treated patients. However, when investigators using video recordings were blinded to treatment allocation and to the sequence of visits, no change from baseline was observed in placebo recipients. Sacks speculated that the blinding of the sequence of visits using DHT may have removed a subjective bias in successive evaluations.

Regulatory Considerations

Sacks outlined some of the regulatory considerations that pertain to using DHTs in clinical trial settings. Verification and validation data are important for understanding whether a DHT has met its technical specifications and provides precise and accurate results in the study population. The verification and validation process could involve comparison with measurements made visually or other reference methods. Sacks said that it would be important to identify potential confounders of measurements made by DHTs. User testing would be critical to preempt operational problems during the trial and to ensure that participants are comfortable using a particular DHT. Another consideration is the justification of novel endpoints made possible by DHTs, he added. This will likely involve comparisons with existing benchmarks of drug efficacy and consultations with patients, caregivers, disease experts, and regulators. In general, he said, determinations of the suitability of a given DHT in a clinical trial are made independently of whether that technology has been cleared by FDA's Center for Devices and Radiological Health. Informed consent dis-

[5] Tardive dyskinesia is a condition that affects the nervous system and causes repetitive involuntary movements; it is often caused by long-term use of neuroleptic drugs to treat psychiatric conditions.

cussions with participants will also be important to determine their expectations of privacy, potential physical risks, and considerations related to real-time safety monitoring. Issues related to data custody, access controls, audit trails, and the preservation of source information may also need to be addressed, Sacks added.

DISCUSSION

Analytical Validation Without a Gold-Standard Reference

Kapur and Sacks discussed approaches that could be used to perform analytical validation on DHTs in the absence of a gold-standard reference measurement. Kapur suggested a combined approach to addressing this challenge—particularly for novel measurements—before the widespread introduction of a tool. Internal work within a company could involve validation in the clinical setting as well as testing using different datasets to demonstrate whether a novel measurement has less variability than current metrics. Kapur noted that data from some populations are variable in expected ways that must be taken into account. For example, people with more advanced PD are less mobile than those with early-stage disease. External work may involve convening stakeholders, such as FDA, the National Institutes of Health, and patient advocacy groups, to agree upon standards for establishing the reliability of novel measurements. Sacks remarked that dealing with a novel measurement in the absence of a gold standard, or any standard at all, is a multidimensional endeavor that requires creativity and offers opportunities for progress and collective thinking. A new measurement must be evaluated by a broad variety of constituents—including patients, caregivers, doctors, and regulators—so that a community-based decision about whether it is valid can be made. Certain features captured by a new measurement may add richness to the data. In situations where an already approved drug is known to be effective, it may be helpful to evaluate whether a new measurement could provide greater discrimination of the treatment effect than existing metrics.

Collaborative Approaches to Improving Interoperability

The panelists considered collaborative approaches to improve interoperability among DHTs and address the challenge of device heterogeneity. Kapur emphasized that addressing this issue will require an ecosystem-based solution rather than a technical one. She highlighted the benefit of having stakeholders from across sectors and disciplines coming together to collaboratively define a set of clearly outlined standards or values for DHT development. If there were a set of clear standards or values in

place, then there would be an impetus for DHT developers to make their products compliant, she added. As of now, smaller start-up companies trying to develop DHTs are often left guessing about what the standards and values should be because these have not been clearly established. The clearer the standards and values for what DHT developers should be aiming to achieve, the easier it will be for all stakeholders to participate at scale, she added.

While standards would be welcomed by the DHT developer community, Kapur made the point that standards may vary depending on the technology itself and the context of use. Sacks suggested that key stakeholders could identify specific areas of opportunity. For example, certain technologies, such as mobile phones, have clearly defined standards and are highly interoperable. Sacks added that common standards are also useful because they make it possible for the digital health community to evaluate which technologies might be suitable for a proposed use and which are not. For example, technological standards for mobile phones and smart watches may allow study participants to use their own devices rather than using a study-assigned mobile phone or wearable devices.

6

Digital Health Technologies for Enhancing Real-World Evidence Collection, Patient Centricity, and Post-Market Studies

Key Messages Highlighted by Individual Speakers

- Real-world data captured by digital health tools (DHTs) contribute to post-market surveillance by enabling the development of novel digital endpoints, engagement of more diverse participants, and remote monitoring of product safety among different subtypes of patients. (Crouthamel)
- Collecting real-world longitudinal digital health data can empower participants throughout the drug development process, including the post-market phase, by illuminating lived experiences and amplifying the voices of patients. (Okun)
- Partnering with patients as "citizen scientists" to inform people-centered study design and product development can enable continuous, shared learning to optimize patients' use of digital tools. (Okun)
- DHTs could help address clinicians' concerns about post-market products through assessments of comparative effectiveness, more nuanced understanding of a product's tolerability and toxicity profile, and better insights into the drivers of adherence. (Robinson)
- DHTs can provide a platform for collective communication that allows an entire care team—not just an individual physician—to "wrap their arms digitally around the patient." (Robinson)

The fourth session of the workshop explored digital health technologies (DHTs) for post-marketing surveillance. Michelle Crouthamel, director of digital health and innovation at AbbVie Inc., discussed industry motivations for conducting post-marketing research and explored how the industry can leverage DHTs to collect real-world data and generate insights. Sally Okun, director of policy and ethics at UnitedHealth Group Research & Development, described opportunities for digital technologies to empower patient participation and illuminate the patient experience in drug development. She discussed strategies for maximizing the impact of patient-generated health data and for applying patient-centered principles in study design. Edmondo Robinson, chief digital innovation officer at the Moffitt Cancer Center, explored how DHTs for post-marketing surveillance can help address clinician concerns about the effectiveness, tolerability, and adherence to drugs. The session was moderated by Christina Silcox, managing associate at the Duke-Margolis Center for Health Policy.

DIGITAL HEALTH TECHNOLOGIES FOR POST-MARKETING RESEARCH AND SURVEILLANCE

Michelle Crouthamel, Director of Digital Health and Innovation, AbbVie Inc.

There are three major factors that compel industry to conduct post-marketing research, Crouthamel said. A primary reason is that companies may be required to do so by law for reasons of safety surveillance. The U.S. Food and Drug Administration (FDA) may require additional safety and efficacy studies to be conducted on certain products that are approved under accelerated approval or under efficacy rules or have prior pediatric studies (FDA, 2019b). Studies and clinical trials that FDA requires sponsors to conduct under one or more statutes or regulations are referred to as post-marketing requirements (PMRs). Post-marketing commitments (PMCs) are studies or clinical trials that a sponsor has agreed to conduct.[1] In other cases, companies may choose to conduct post-marketing studies to explore the optimum uses of their products or to seek a label expansion and sometimes for label extension (FDA, 2020a). However, an increasingly common rationale is to collect real-world evidence to support product differentiation or to perform cost-effectiveness analyses for payers. Crouthamel said that real-world data collection is garnering increased interest due to the rapid expansion of DHTs. This

[1] More information on FDA's PMRs and PMCs is available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments (accessed May 17, 2020).

is evident in the growing number of phase IV trials—particularly in the areas of cardiorespiratory health and neurology—that are incorporating wearable sensors and other DHTs to collect real-world data and develop novel digital endpoints (Johnson & Johnson, 2020; NIH, 2020).

Use of Digital Health Technologies for Real-World Data Collection

The use of mHealth apps for real-world data collection can be traced back to the introduction of the first iPhone by Apple in 2007, Crouthamel said. This breakthrough catalyzed the development of more than 2 million iOS apps in the years since. The 2015 launch of the Apple ResearchKit as a joint collaboration between Apple and academic institutions was an effort that laid the groundwork for the possibility of a fully digitized clinical trial. In 2016 GlaxoSmithKline began to explore and test this open-source platform, which led to the first industry-sponsored real-world study using the Apple ResearchKit: the Patient Rheumatoid Arthritis Data From Real World study. Almost 400 people living with rheumatoid arthritis were recruited in just 30 days. Investigators were able to collect electronic consent forms, disease insights, and sensor data directly from the participants' smartphones. Through this effort, the investigators were also able to develop a novel digital measure of functionality called wrist range of motion, which enabled them to capture information about participants' pain at a more granular level (Crouthamel et al., 2018).

One advantage of the ResearchKit is that it can provide easy access to clinical trials, Crouthamel said, but it can be challenging to authenticate the potential participants. To address this challenge, particularly in the context of PMRs and PMCs, she suggested incorporating telehealth visits, creating study-specific access codes, and using facial recognition and fingerprints for authentication. Another benefit offered by ResearchKit is the capability to crowd-source patient insight in a cost-effective way. However, to avoid platform bias from a sampling perspective, it is helpful to use both ResearchKit for iOS and ResearchStack for Android to collect insights from a broader range of participants. Although using a virtual platform can enable the rapid recruitment of participants, a high dropout rate is a known disadvantage of this type of digital engagement. For longitudinal PMR and PMC studies, Crouthamel suggested creating incentives for participants, such as financial compensation, sharing data, and even providing medical benefits. Integrating human interactions into the study design is critical for participants who may be in a vulnerable state, she added. Through the ResearchKit platform, iPhone sensors can be used to create novel endpoints. While this is a powerful tool, it can be challenging to control for variability across users and how they provide their data. She emphasized that for industry developers, "good data [are] more

important than big data." Analyzing large volumes of unlabeled data can be difficult; however, including clear instructions and providing supervised training can substantially improve the quality of data collected. The most recent version of FDA's MyStudies[2] app largely addresses some of these challenges, and Crouthamel urged sponsors to adopt this platform to help standardize data collection and facilitate easier data review.

Returning Digital Health Data to Study Participants

With regard to DHTs, the pharmaceutical industry has focused more on the application of technologies than on building them, Crouthamel said. She suggested that one approach to consider is engaging with patients to seek their insights about how to better design a technology's interface to capture the measurements that are most meaningful. Crouthamel further emphasized the importance of applying DHTs in a way that is user-friendly and not intrusive. Behavioral elements will also be important to consider when applying DHTs, she observed. While mobile phones have become ubiquitous and indispensable for many people on a broad scale, other devices, such as wearables and sensors, are not yet fully integrated into daily life and thus may be less useful for driving changes in behavior.

Returning data to study participants can be an important incentive to motivate engagement. Patients often report that they would like to see how well they are doing throughout the course of a study. However, whether data should be returned to study participants depends on the data type and study design, she added. For example, patients who receive a pain relief medication might like to know how well the medication has improved their ability to move around. As such, receiving data could influence a participant's daily life activities due to the Hawthorne effect—behavioral modification in response to a participant's awareness of being observed. The balance of protecting study integrity and providing data feedback at appropriate times is a critical consideration of study design, which must avoid compromising resulting statistical analyses.

Integrating Digital Health Technologies into Post-Market Study Design

Integrating DHTs into post-marketing study design can enable surveillance and the monitoring of product safety among different subtypes of the study population, Crouthamel said. A hypothetical product for rheumatoid arthritis would have several subtypes of patients—such as males, females, and different age groups—that each have distinct needs.

[2] The MyStudies app is available at https://www.fda.gov/drugs/science-and-research-drugs/fdas-mystudies-application-app (accessed May 17, 2020).

An advantage of DHTs is their potential to measure individual participants' baselines and better understand the degrees of improvement in clinical outcome. However, this capacity has not yet been realized because study design is largely still constrained by the traditional focus on using control groups and homogeneous study populations that may not accurately reflect the real world. Shifting the focus toward individuals and using digital technologies to capture personalized measurements would be a breakthrough for the field, she said.

Case Example: Digital Pregnancy Registry for Post-Marketing Research

Post-marketing research has become an active space for trials supported by DHTs, offering sponsors an opportunity to use their platforms to redesign traditional PMR, PMC, and real-world studies and collect higher-quality data in more efficient ways, Crouthamel said. To illustrate, she described how a digital platform could be used to re-design a post-marketing research and pregnancy registry study. The potential impact that a medication or other intervention can have on a pregnancy—such as miscarriage or birth defect—underscores the value of rapidly collecting and disseminating this type of data to patients and stakeholders. If such an effort were carried out with a traditional clinical trial design, it might take up to a decade to collect results, which would risk losing important data. For example, a patient who is prescribed a new medicine might become pregnant in the future, at which point she might go back to the same physician who may or may not remember that there is a pregnancy registry available for this patient to be enrolled in and monitored. The application of DHTs has the potential to sharply curtail the time it takes to collect results in a pregnancy registry by maximizing the clinical touch points digitally, she said. A DHT can remind patients who become pregnant about the registry and provide a channel for the patient to engage with the registry study coordinator. The coordinator can then encourage the patient to download the dedicated study app, which allows them to virtually engage with the investigator. The patient is engaged and does not have to travel while pregnant, and investigators can collect high-quality data.

USE OF DIGITAL HEALTH TECHNOLOGIES TO EMPOWER PATIENT PARTICIPATION

Sally Okun, Director of Policy and Ethics, UnitedHealthGroup Research & Development

Okun began by underscoring the importance of patient participation in the drug development process from start to finish. Empowering patient

participation is a process of continuous and shared learning across drug development, Okun said, and this is especially true in the surveillance and post-approval stages. This process has the potential to open up a range of opportunities, from real-time longitudinal data collection to expanding the notion of surveillance beyond the traditional view of gathering information solely around safety to include effectiveness and outcomes from the real-world use of data and an understanding of patients' lived experiences. It also presents opportunities for the broader inclusion of populations not previously represented in pre-approval clinical trials in order to better understand the impact on people who have not previously been studied. Furthermore, partnering with patients as "citizen scientists" in real-world evidence generation is an opportunity that has not yet been fully harnessed for continuous and shared learning. To make progress toward empowering patient participation, she suggested considering information that can be gleaned from patients and consumers to inform the principles that will help guide tool design, data protection, and privacy. For instance, new social contracts with patients may need to be put in place in order to develop a better understanding of what factors drive them to want to participate in research efforts. Patient-centric strategies should be incorporated to ensure that new knowledge and insights are shared broadly, she added.

Use of Digital Tools to Illuminate the Patient Experience

DHTs can be used to help illuminate the patient experience, Okun said. She described a hypothetical patient–clinician scenario in which the clinician is focused on the positive impact of a treatment based on certain indicators. In contrast, the patient is more concerned with—but does not express—other consequences of the treatment. Perhaps the patient is having trouble sleeping, is unable to exercise, and no longer enjoys food as much. All of those unexpressed factors will affect the patient's adherence to the drug or even the patient's interest in taking the drug at all. An open dialogue between the patient and clinician might be easier and more effective if the patient used a wearable device that was collecting data longitudinally about sleep cycles and other types of biometric measures, she said. This could also enable the visit with the clinician to take place virtually. Furthermore, if the biometric data were streamed to the clinician in advance of the virtual visit, it would free up more time for the clinician to discuss the patient's concerns in ways that are more concrete and engaging for the patient as an active participant.

Collaborating with Patients to Optimize Digital Solutions

DHTs also provide opportunities for working with patients to explore ways to optimize their use of digital tools. For example, by helping patients

identify variables that interfere with their interest in or ability to maintain treatment, DHTs can provide new solutions to familiar problems. A recent qualitative study by Herrmann et al. (2020) investigated digital competencies and attitudes toward digital adherence solutions among elderly patients treated with novel anticoagulants. The study demonstrated that gaining a better understanding of the reasons for non-adherence can help inform possible digital solutions as well as improve understanding of the digital competencies that particular populations may need to take advantage of these digital tools. In collecting information during the post-marketing period, digital tools have value in helping to identify factors that may put a patient at risk of not using the medication as prescribed or otherwise compromising his or her health and safety.

Developing Patient-Informed Principles

Across the drug development cycle, information should be gathered from the patients themselves about the things that matter to them, Okun said. This is even more critical during the post-marketing period, she said, when patients are generally left to manage their daily lives with drugs and other products as part of their experience. During that stage, there is an opportunity to collect information from patients to better understand what motivates them to participate in a certain type of data collection model. In her experience, Okun said, patients value being seen as a whole person and desire opportunities to feel in control by contributing in an active way to the data being collected—for example, by prioritizing the things that matter most to them. Applying patient-informed measurement and design principles can provide guidance in this respect (see Box 6-1).

Harnessing Existing Systems to Maximize Patient-Generated Health Data

To maximize the value of patient-generated health data, Okun suggested harnessing existing systems and bringing in information to address gaps not currently being filled by other data sources. For example, the comprehensive Sentinel Initiative launched by FDA in 2008 recently expanded its capacity beyond its data partners' environments by establishing a coordinating center, an innovation center, and a community-building and outreach center.[3] If patients were broadly empowered to directly generate their own data in the post-marketing arena—through developers and apps deemed trustworthy—then patients themselves would become new

[3] For more information on the Sentinel Initiative, see https://www.sentinelinitiative.org (accessed May 29, 2020).

BOX 6-1
Patient-Informed Measurement and Design Principles

Measurement Principles

- Clear
- Answerable
- Efficient
- Relevant
- Educational
- Harmless
- Actionable

Design Principles

- Caregivers exist to:
  - Get the data that makes a difference
  - Help people achieve better outcomes
- Patients want caregivers to:
  - See [them] as a whole person
  - Come with [them] on [their] journey
  - Help [them] capture [their] truth
  - Let [them] define who is like [them]
  - Help [them] feel in control
  - Put [their] needs first
  - Inspire confidence
  - Build on what [they] already want to do
  - Prioritize
  - Minimize [their] work

SOURCES: As presented by Sally Okun, March 24, 2020; Okun and Goodwin, 2017.

data partners within the Sentinel system. Repurposing FDA's MyStudies app for the post-marketing arena as a MyTreatment app could provide an opportunity for clinicians and researchers to gather information about the patient experience, she said. If such an app were pre-populated with a patient's prescription(s), then they could easily input information about their experiences and potentially connect to other sensor data already being collected from them.

Using Digital Health Technologies to Inform Patient-Focused Drug Development

DHTs have the potential to exponentially amplify the voice of patients and bring patient-focused product development full circle, Okun said.

There are existing funding mechanisms such as the Prescription Drug User Fee Act that could be used to support FDA's patient-focused drug development initiative (FDA, 2020b). Expanding this mechanism by using digital tools from trustworthy sources could help illuminate what daily life is really like for patients, she said. This body of data could offer valuable continuous learning opportunities about patients' real-life experiences in real time. This type of information could offer new insights and ways to better assess safety and tolerability, including relevant measures for outcomes that matter most to patients. By learning from patients and sharing that information broadly across systems, clinicians and researchers collecting this information could also benefit stakeholders who are not directly engaging with digital tools but would benefit from the insights gained from those who are.

Okun said that efforts to capture real-time data from people using digital tools during the post-market surveillance period benefit from considering the types of patients who would typically be using the tool for its intended purposes, how they will use the tools, and how mechanisms within the tool will address the specific needs of certain subpopulations of patients, such as those who speak a different language or those with digital literacy issues. For example, Herrmann et al. (2020) highlighted an opportunity to consider how the potential tools are fit-for-purpose, whether for regulatory decision making or for gathering data for point-of-care decision making.

Digital tools might also be used to further enhance or expand patient–provider communication, while also minimizing or being mindful of the burden on providers. The successful adoption of digital tools depends on obtaining and applying feedback from patients, Okun said. If the digital tools are to be used at the point of care, incorporating feedback from providers will also be helpful in gaining their buy-in and maintaining their interest in using the tools. For example, a study of veterans with epilepsy who were engaged with the platform PatientsLikeMe asked the participants' neurologists about information the neurologists would be interested in learning at the point of care about their patients' epilepsy experiences (Hixson et al., 2015). Three priorities emerged: the frequency of a patient's seizures, whether the patient lost consciousness during the episode, and whether there had been any triggers. Using this feedback, the digital tool was updated to include these questions and capture the patients' responses; this enabled the clinicians at the point of care to obtain the information they felt was most important. In addition to providing value to the clinicians, the patients demonstrated significant increases in self-management and self-efficacy within just 6 weeks.

CLINICIAN PERSPECTIVE ON DIGITAL HEALTH TECHNOLOGIES FOR POST-MARKETING RESEARCH AND SURVEILLANCE

Edmondo Robinson, Chief Digital Innovation Officer, Moffitt Cancer Center

DHTs should facilitate communication between patients and their entire care team, not just between individual patients and physicians, Robinson said. Furthermore, it should be done in a way that is comfortable for each patient, he added. When a care team is able to "wrap their arms digitally around the patient," patients may feel more supported and individual physicians may feel less overwhelmed. However, he added, this type of approach will require a better understanding of how care teams interact with DHTs. Maximizing the use of DHTs can help clinicians answer questions related to new drugs that their patients may be taking as well as support their efforts to increase innovation in care delivery.

Digital Health Technologies to Understand Drug Effectiveness in Real-World Settings

When clinicians consider a drug's effectiveness in the post-market context, Robinson said, a primary concern is whether the drug will work for their own patient population, which may include individuals who are older, sicker, more diverse, and affected by more comorbidities than the population that participated in clinical research. Another question that clinicians often have is whether a new drug is better than the current standard of care, particularly given that new treatments are frequently more costly. DHTs provide several opportunities to help answer these types of questions about effectiveness, Robinson said. For example, endpoint monitoring can be facilitated by digital technologies for activity tracking and for capturing physiological measurements (e.g., heart rate, blood pressure, pulse oximetry). Depending on a patient's disease state and the intervention, digital technologies can also facilitate remote monitoring of the endpoint that a specific intervention should be improving, such as continuous blood glucose monitoring. Conducting surveys about symptom improvements or quality of life can be facilitated online, via a smartphone app, text messaging, or even through voice recognition modalities. Opportunities now exist to use a combination of digital approaches to evaluate effectiveness, he said. For example, a new intervention for rheumatoid arthritis could be monitored using a combination of an activity tracker and a voice-administered quality-of-life survey. This could contribute to a practical and comprehensive understanding of whether the

treatment is achieving the types of results that actually matter to a specific patient population compared with the current standard of care.

Digital Health Technologies to Assess Safety and Tolerability

Given that new treatments may have associated safety and tolerability issues that are more or less pronounced in special populations, Robinson said, it can be difficult for a clinician to determine which of these issues are more relevant than others for patient populations that are not typically included in clinical trials (e.g., older adults or people with comorbidities). A more nuanced understanding of a drug's toxicity profile should be developed during the post-marketing period in order to begin refining the patient population for whom that particular intervention is better suited, he added. Another common consideration for clinicians is whether the side effects of a treatment are impairing a patient's quality of life. The risk–benefit ratio may need to be reconsidered, particularly in patients dealing with difficult conditions, to determine if the incremental gains offered by the new treatment over the standard of care are worth managing the new side effect profile.

Opportunities for DHTs to help answer these types of questions about tolerability include digital survey modalities to evaluate side effects and quality of life, while DHTs for activity tracking, physiological measurements, and remote monitoring can be used to look at side effect endpoints. The increasing use of oncological immunotherapies has created a need to monitor the significant neurological side effects associated with immunotherapy, such as delirium. DHTs provide an opportunity to better understand how those side effects manifest in different populations, such as in older patients. For example, voice-analysis technology could be used to screen for delirium potentially caused by an intervention. Another opportunity is to use gamification, he suggested. Developing a mobile or online game with an endpoint linked to a prize or some other type of strategy to engage the user could also allow for measuring the user's ability to engage over time at sequential points. There may be some benefit to understanding how people navigate through a game, he said, which could be correlated with the neurological side effects from an intervention such as immunotherapy.

Digital Health Technologies to Improve Patient Adherence

One concern from a clinician perspective, Robinson said, is patient adherence to a treatment regimen. Adherence may vary by patient population, as the drivers of adherence are complex and may be shaped by social determinants and other factors. Robinson suggested that DHTs

may help clinicians better understand how an intervention varies with respect to adherence as well as how patient adherence could be improved. Opportunities in this domain could include digital reminders and engagement with patients through apps and wearables. For example, digitally enabled medication dispensers and the use of "digital pills" that can track medication ingestion could be used in place of directly observed therapy to track the number of times that a patient dispenses a medication, Robinson suggested. This type of application could be helpful for supporting adherence for high-risk medications that patients need to take consistently (e.g., anti-tuberculosis medication). Additionally, Robinson suggested that a medication adherence strategy could apply gamification—extracting game design elements and game principles and using them to drive adherence—along with digital monitoring approaches.

7

Reflections and Key Takeaways

The workshop concluded with reflections and consideration of key next steps for the use of digital health technologies (DHTs) in drug development. Jennifer Goldsack, executive director at the Digital Medicine Society, and Joseph Menetski, associate vice president of research partnerships at the Foundation for the National Institutes of Health, discussed the risks associated with the use of new modalities for collecting digital health data, the importance of patient-centricity and education, the need for standards and frameworks for evaluation, and other barriers and opportunities.

CHALLENGES ASSOCIATED WITH THE USE OF DIGITAL HEALTH TECHNOLOGIES

With the new methods enabled by DHTs come novel data, but also concomitant new risks, Goldsack said. She emphasized the importance of finding ways to mitigate those risks while also taking advantage of these new data to their fullest potential. As new DHTs become more powerful and pervasive, it is important to consider whether the data they generate are being appropriately analyzed and correctly interpreted. Care should be taken to ensure that these new technologies are being deployed in an ethical manner. The need to apply an ethical lens to this work was introduced by Camille Nebeker and echoed by participants throughout the workshop. Strategies are also needed to deploy existing technologies without reinventing the wheel, given the large number of tools and the

volume of digital data already available. The COVID-19 pandemic has underlined the need to deploy new digital technologies in practical ways. Goldsack described the COVID-19 pandemic as a pressure test for the current state of digital measures. While there are a variety of capabilities available for DHTs, she said, these may not be ready for prime time. The workshop participants helped to shed light on some of the reasons why DHTs have not been instantly deployed and immediately ramped up in the same way that telehealth has, for example.

DIGITAL HEALTH TECHNOLOGIES TO ENABLE PATIENT-CENTERED DRUG DEVELOPMENT

Patient centricity was a consistent theme running through the workshop, Goldsack said. Multiple workshop participants emphasized that patients are at the heart of the development and deployment of digital measures. For these measures and tools to be equitably deployed, they should be developed in ways that ensure they perform equally well and are universally available across the entire population. Education also is foundational in improving equity and accessibility, she said. All stakeholders—from study participants to clinical trialists to institutional review boards—need to clearly understand the benefits, risks, and opportunities associated with these DHTs. She reiterated a call to action that was issued by Amy Abernethy and then echoed through the rest of the workshop's discussions: the need to bridge the divide between data generated through clinical care and clinical research. Digital measures of real-life phenomena warrant commensurately practical strategies for collecting that evidence in the real world, in ways that are perhaps less controlled than traditional methods. There is often a forced conflict between privacy of participants and speed of data collection, Goldsack said, echoing remarks earlier in the day from Nebeker. Although the escalating pace of innovation in DHTs poses certain barriers to maintaining ethical standards in this space, it also heightens the need to do so from the outset of any study design or product development efforts. Participants dispelled myths around regulatory barriers being a limiting factor to rapid progress in the field—in fact, existing regulatory frameworks can provide solid foundations to build upon.

Opportunities, challenges, and solutions for better engagement with patients were also discussed throughout the workshop. DHTs provide opportunities to build trusted relationships with patients and illuminate the patients' experiences. However, the adoption of those technologies is hindered by the lack of capabilities to easily share data onward with clinicians and researchers and then return value to patients in a meaningful way, Menetski said. Potential solutions to these engagement chal-

lenges, which were highlighted by Yvonne Yu-Feng Chan and Camille Nebeker, may include (1) building trust and educating patients through health provider advocates, (2) using digital technologies to foster a community for participants to connect with each other, (3) using digital tools judiciously in specific contexts that are supported by human contact, and (4) educating the general public to build trust in the outcomes of DHT use.

STANDARDS AND EVALUATION FRAMEWORKS

Goldsack outlined several gaps that emerged throughout the workshop related to standards for evaluating DHTs. The field is currently lacking the standards and evaluation frameworks needed to perform the necessary verification, analytical validation, and clinical validation of DHTs (see Box 7-1). The dearth of well-established, gold-standard reference measures is also a challenge for verification and validation. This is a particular concern in cases where no reference measure exists at all, as no standard method is consistently applied in those situations. More broadly, methodological approaches have not yet been standardized across the field. This undercuts the effectiveness of comparative analyses of the tools and technologies themselves, as well as the quality of the data that are captured and the interpretations that are derived from those data. Similarly, better standards are needed to define, describe, and understand the data collected by these technologies. In addition to fostering common understanding among stakeholders across the field, better data standards would enable more consistent and accurate reporting, evaluation, and sharing of the data. Goldsack noted that another critical missing component is a single "source of truth" that would facilitate linkages across datasets and allow actors in this space to infer meaning from each other's work.

BOX 7-1
Standards Needed for Evaluating Digital Health Technologies

- Verification
- Analytical validation
- Clinical validation
- Defining, describing, and understanding the data collected by these technologies
- Shared methodological approaches
- Data capture and interoperability

SOURCE: As presented by Jennifer Goldsack and Joseph Menetski, March 24, 2020.

Although DHTs provide opportunities to expand and standardize the capture of data in clinical research, Menetski said that strategies will be needed to work within the current existing limitations of data quality while also developing methods to improve the data quality (e.g., instrumentation improvements, supplemental data points, normative studies) and interoperability. Reflecting on comments heard earlier in the day, he suggested that the quality, validity, and reliability of data would benefit from community-wide standards for data capture and interoperability, a repository for digital health data, greater population diversity in data collected, and strong frameworks for data governance, and common methodologies for validating DHTs and for comparing digital metrics to clinical ratings.

Goldsack reiterated that these efforts to propel and expedite progress in digital technologies should not be reinventing the wheel; instead, they should learn from and build upon the work that has already been done. For instance, the pharmaceutical industry has instituted several initiatives for driving standards and using devices and data in noncompetitive ways, such as the Metrics Champion Consortium[1] and TransCelerate.[2] She suggested several other initiatives that might be useful resources, including the Digital Medicine Society,[3] the Clinical Trials Transformation Initiative, and the Open Wearables Initiative.

"PAIN POINTS" ACROSS THE DRUG DEVELOPMENT PROCESS AND SOLUTIONS DIGITAL HEALTH TECHNOLOGIES CAN PROVIDE

Menetski reflected on the differing "pain points" across the drug development lifecycle that speakers presented, and he summarized the opportunities that DHTs provide as well as the unique challenges that arise when they are used in clinical research. In discussions about disease characterization in the early stages of development, the lack of interoperability was a commonly cited barrier (see Chapter 3). The challenge of retaining study participants emerged as a substantial barrier in the contexts of recruitment, safety trials, and post-market surveillance. As put by Yvonne Yu-Feng Chan, "the Achilles' heel of digital health technologies is retention." Speakers in session 2 (see Chapter 4) highlighted the value of understanding what matters to patients and participants and reporting it

[1] Information about the Metrics Champion Consortium is available at https://metricschampion.org/mcc-risk-quality-scoring-tools (accessed May 17, 2020).

[2] TransCelerate can be found at https://transceleratebiopharmainc.com (accessed May 17, 2020).

[3] Information about the Digital Medicine Society is available at https://www.dimesociety.org (accessed May 17, 2020).

back to them in order to help increase adherence and improve consistency. Challenges related to the lack of benchmarks and gold-standard reference measurements for demonstrating that a new measurement is actually measuring what it is intending to measure were discussed in the context of pivotal trials (see Chapter 5). Speakers discussed a concrete solution to this barrier; rather than waiting passively for a single entity to take the initiative, the entire community should take collaborative action to develop gold standards. Speakers also emphasized the importance that these efforts to convene around community-wide standards be inclusive of all stakeholders, from product developers to regulators to the teams of health care providers on the ground who are caring for people's health and to patients and their representatives. At the same time, the bottleneck around validation standards could be addressed through a collective decision to accept the best available standards—and work to refine them—rather than allowing "perfect to be the enemy of the good" and continuing to operate without any standards at all.

Goldsack encouraged participants to be involved in the process of implementing the learnings from the workshop and help build an action-oriented body of work to advance the field. We are the community, she said, and we need to be the ones who develop the standards as soon as possible.

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Appendix A

Workshop Statement of Task

Digital health technologies (e.g., smartphone apps, wearable sensors, and other remote, sensor-based tools that combine hardware and software) have become increasingly available to consumers, providers, and researchers. They offer new opportunities to address critical challenges or pain points, better connect patients and health care providers, and incorporate patient input throughout the drug research and development (R&D) lifecycle. This workshop will provide a venue to discuss challenges and opportunities in using digital health technologies to improve the probability of success in drug development. Workshop participants may consider key components for an evidence-based framework for applying digital health technologies toward drug R&D.

WORKSHOP OBJECTIVES:

- Highlight critical barriers or pain points along the drug R&D lifecycle for which digital health technologies may be uniquely suited to address;
- Consider lessons learned from currently validated digital health technology applications that could be generalizable for newer digital health technologies;
- Consider opportunities to enable the practical application of digital health technologies for improving drug development (e.g., sharing best practices for the validation and use of digital health technologies, harmonizing guidelines across sectors);

- Consider strategies for evaluating and selecting digital health technologies that are fit-for-purpose in drug development (e.g., examining existing frameworks, establishing appropriate evidentiary criteria); and
- Discuss privacy, ethical, and regulatory issues related to the use of digital health technologies.

Appendix B

Workshop Agenda

The Role of Digital Health Technologies in Drug Development:
A Workshop

TUESDAY, March 24, 2020

10:00 a.m. (EST) Welcome
Robert Califf, Verily Life Sciences
Geoffrey Ginsburg, Duke University School of Medicine

Opening Remarks
Jennifer Goldsack, Digital Medicine Society
Joseph Menetski, Foundation for the National Institutes of Health

Briefing: Ethical Considerations

10:15 a.m. Ethicist Perspective
Camille Nebeker, University of California, San Diego

Session I: Digital Tools for Characterizing Disease
Effy Vayena, Health Ethics and Policy Lab, ETH Zurich, *Moderator*

10:45 a.m. Nonprofit Perspective/Platform Research Perspective
Larsson Omberg, Sage Bionetworks

National Institutes of Health Perspective
Chris Lunt, All of Us Research Program, National Institutes of Health

Patient Engagement Perspective
Alicia Staley, Medidata Solutions

Developer Perspective
Luca Foschini, Evidation Health

11:25 a.m. Panel Discussion with Speakers and Workshop Participants

11:45 a.m. Break

Session II: Digital Tools for Recruitment and Safety Trials
Deven McGraw, Ciitizen Corporation, Moderator

12:00 p.m. Regulatory Perspective
Christopher Leptak, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Industry Perspective
Yvonne Yu-Feng Chan, Otsuka Pharmaceutical

Developer Perspective
Chris Benko, Koneksa Health

Academic Perspective
Eric Perakslis, Duke University

12:40 p.m. Panel Discussion with Speakers and Workshop Participants

1:00 p.m. Break

Fireside Chat
Jennifer Goldsack, Digital Medicine Society, *Moderator*

1:30 p.m. Regulatory Perspective
Amy Abernethy, U.S. Food and Drug Administration

Session III: Digital Tools for Pivotal Trials
Husseini Manji, Janssen Research & Development, LLC, *Moderator*

2:00 p.m. Industry Perspective
Sean Khozin, Janssen Research & Development, LLC

Developer Perspective
Ritu Kapur, Verily Life Sciences

Regulatory Perspective
Leonard Sacks, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

2:30 p.m. Panel Discussion with Speakers and Workshop Participants

2:50 p.m. Break

Session IV: Digital Tools for Post-Market Surveillance
Christina Silcox, Duke-Margolis Center for Health Policy, *Moderator*

3:00 p.m. Industry Perspective
Michelle Crouthamel, AbbVie Inc.

Patient Engagement Perspective
Sally Okun, UnitedHealth Group Research & Development

Clinician/Health System Perspective
Edmondo Robinson, Moffitt Cancer Center

3:30 p.m. Panel Discussion with Speakers and Workshop Participants

Key Reflections and Next Steps

3:45 p.m. Key Reflections and Next Steps
Jennifer Goldsack, Digital Medicine Society
Joseph Menetski, Foundation for the National Institutes of Health

4:15 p.m. Adjourn

Appendix C

Planning Committee Biographical Sketches

Jennifer Goldsack, M.Chem., M.A., M.B.A. (*Co-Chair*), is the interim executive director at the Digital Medicine Society (DiME), a new professional organization promoting the adoption of digital technologies for health. Previously, Ms. Goldsack spent several years at the Clinical Trials Transformation Initiative (CTTI) where she led the development and implementation of several projects within CTTI's mobile program and was the operational co-lead on the first randomized clinical trial using the U.S. Food and Drug Administration's Sentinel System. Ms. Goldsack spent 5 years working in research at the Hospital of the University of Pennsylvania, first in Outcomes Research in the Department of Surgery and later in the Department of Medicine. More recently, Ms. Goldsack helped launch the Value Institute, a pragmatic research and innovation center embedded in a large academic medical center in Delaware. Ms. Goldsack earned her master's degree in chemistry from the University of Oxford, England, her master's degree in the history and sociology of medicine from the University of Pennsylvania and her M.B.A. from The George Washington University. Additionally, she is a certified Lean Six Sigma Green Belt and a Certified Professional in Healthcare Quality. Ms. Goldsack is a retired athlete, formerly a Pan American Games Champion, Olympian, and World Championship silver medalist.

Joseph P. Menetski, Ph.D. (*Co-Chair*), received his Ph.D. from the Northwestern University Feinberg School of Medicine with Dr. Stephen Kowalczykowski and completed his postdoctoral training at the Laboratory

of Molecular Biology at the National Institutes of Health with Dr. Martin Gellert. He then started his career in industry in 1993 in the immunopathology department at Parke-Davis (later Pfizer), where he established a discovery research program in cellular inflammation that eventually transitioned to the molecular study of osteoarthritis. Dr. Menetski moved to Merck in 2004. His first position was in the Department of Immunology, where he was involved in the osteoarthritis new targets and biomarker program. While at Merck he has been a member of the molecular profiling group, a member of the knowledge discovery and knowledge management group, and, finally, a director in global competitive intelligence. Over the years he has been a key contributor to many basic research and clinical programs in the areas of arthritis, sarcopenia, osteoporosis, and asthma. He has served as a core research team member on several external basic research projects for the identification of new targets and molecular biomarkers. His industry research and development experiences include target identification, compound selection, translational biomarker identification, clinical study design and analysis, and external scientific collaborations. In the commercial space he has been intimately involved in opportunity and asset identification and qualification and in assessing the competitive landscape of disease areas that he is supporting. During this time, he has been recognized by multiple research and development awards for his contributions.

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) at the National Institutes of Health (NIH). 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 and has 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 Central Nervous System 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 to 2013, she co-led the Molecular Libraries and Imaging Program, a trans-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 completed her Ph.D. at the Emory University School of Medicine, followed by postdoctoral 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.

Ray Dorsey, M.D., M.B.A., is a professor of neurology and the director of the Center for Human Experimental Therapeutics at the University of Rochester Medical Center. Dr. Dorsey is investigating new treatments for movement disorders and is working on ways to improve the way that care is delivered for individuals with Parkinson's disease (PD) and other neurological disorders. Using simple web-based video conferencing, he and his colleagues are seeking to provide care to individuals with PD and neurological diseases. Dr. Dorsey's research has been published in leading medical and neurology journals and has been featured on National Public Radio and in *The New York Times* and *The Wall Street Journal*. He previously directed the movement disorders division at Johns Hopkins and worked as a consultant for McKinsey & Company. He completed his undergraduate studies at Stanford University, business school at the Wharton School, and medical school at the University of Pennsylvania.

Deborah Estrin, Ph.D., M.S., is the Robert V. Tishman '37 Professor at Cornell Tech and in the Computer Science Department at Cornell University and currently serves as the associate dean for impact at Cornell Tech. She is the founder of the Health Tech Hub and directs the Small Data Lab at Cornell Tech, which develops new personal data application programming interfaces and applications for individuals to harvest the small data traces they generate daily. Dr. Estrin is also the co-founder of the nonprofit startup Open mHealth.

Previously, Dr. Estrin was on the University of California, Los Angeles, faculty where she was the founding director of the National Science Foundation Center for Embedded Networked Sensing, pioneering the development of mobile and wireless systems to collect and analyze real-

time data about the physical world and the people who occupy it. Dr. Estrin was chosen as a 2018 fellow of the MacArthur Foundation.

Geoffrey Ginsburg, M.D., Ph.D., is the founding director for the Center for Applied Genomics & Precision Medicine at the Duke University Medical Center. He is also the founding director for MEDx, a partnership between the schools of medicine and engineering to spark and translate innovation. He is a professor of medicine, pathology, and biomedical engineering and a professor in the Duke University School of Nursing.

While at Duke, Dr. Ginsburg has pioneered translational genomics, the development of novel diagnostics, and precision medicine, initiating programs in genome-enabled biomarker discovery, longitudinal registries with linked molecular and clinical data, biomarker-informed clinical trials, and the development of novel practice models and implementation research for the integration of genomic tools and digital health technologies into heath care delivery systems.

In 1990 he was recruited to the faculty of the Harvard Medical School, where he was the director of preventive cardiology at Beth Israel Hospital and led a laboratory in applied genetics of cardiovascular diseases at Boston Children's Hospital. In 1997 he joined Millennium Pharmaceuticals Inc. as the senior program director for cardiovascular diseases and was eventually appointed the vice president of molecular and personalized medicine, where he was responsible for developing pharmacogenomic strategies for therapeutics as well as biomarkers for disease and their implementation in the drug development process.

He has received a number of awards, including the Innovator in Medicine Award from Millennium in 2004, the Basic Research Achievement Award in Cardiovascular Medicine from Duke in 2005, and the ILCHUN Molecular Medicine Award from the Korean Society for Biochemistry and Molecular Biology in 2014. In 2015 he was an honored speaker at the White House Champions for Change in Precision Medicine. He received Duke's Research Mentoring Award in 2017. He is a founding member and a former board member of the Personalized Medicine Coalition, a section editor for the *Journal of the American College of Cardiology* and an editorial advisor for *Science Translational Medicine*. In addition, he is the editor of *Genomic and Personalized Medicine* (Elsevier), whose third edition was published in 2016. He is a member of the Faculty of 1000. He has been a member of the Department of Veterans Affairs' Genomic Medicine Program Advisory Committee; a member of the National Institute of General Medical Sciences External Scientific Panel for the Pharmacogenomics Research Network; the Board of External Experts for the National Heart, Lung, and Blood Institute; the National Advisory Council for Human Genome Research at the National Institutes of Health (NIH); the Advisory

Council for the National Center for Advancing Translational Sciences at NIH (where he was the vice chair for the Cures Acceleration Network Board); and the World Economic Forum's Global Agenda Council on The Future of the Health Sector. He is the co-chair of the National Academies of Sciences, Engineering, and Medicine's Roundtable on Genomic and Precision Health and the co-chair of the Global Genomic Medicine Collaborative and is a member of the Advisory Committee to the Director of NIH.

Husseini K. Manji, M.D., FRCPC, is the global therapeutic head for neuroscience at Janssen Research & Development, LLC, one of the Johnson & Johnson pharmaceutical companies. He is also a visiting professor at Duke University. Dr. Manji was previously the chief of the Laboratory of Molecular Pathophysiology & Experimental Therapeutics at the National Institutes of Health (NIH) and the director of the NIH Mood and Anxiety Disorders Program, the largest program of its kind in the world.

The major focus of Dr. Manji's research is the investigation of disease- and treatment-induced changes in gene and protein networks that regulate synaptic and neural plasticity in neuropsychiatric disorders. His work has helped to conceptualize these illnesses as genetically influenced disorders of synaptic and neural plasticity and has led to the investigation of novel therapeutics for refractory patients. Notably, Dr. Manji's research demonstrated that AMPA- and NMDA-mediated synaptic plasticity may underlie the pathogenesis of depression and that targeting these pathways may produce robust and rapid antidepressant effects. Under his leadership this has led to the approval by the U.S. Food and Drug Administration of the first novel antidepressant mechanism (NMDA-antagonism) in decades. Spravato (an NMDA antagonist) was demonstrated to produce robust and rapid antidepressant effects and is approved for treatment resistant depression. Phase 3 studies investigating its efficacy in the treatment of suicidal ideation are under way.

Dr. Manji has received a number of prestigious awards, including the National Institute of Mental Health Director's Career Award for Significant Scientific Achievement, the A.E. Bennett Award for Neuropsychiatric Research, the Ziskind-Somerfeld Award for Neuropsychiatric Research, the National Alliance for Research on Schizophrenia & Depression Mood Disorders Prize, the Mogens Schou Distinguished Research Award, the American College of Neuropsychopharmacology's (ACNP's) Joel Elkes Award for Distinguished Research, the Depression and Bipolar Support Alliance Klerman Senior Distinguished Researcher Award, the Briggs Pharmacology Lectureship Award, the American Federation for Aging Research Award of Distinction, the Caring Kind Alzheimer's Disease Leadership Award, and the Global Health & the Arts Award of Recog-

nition. He has received Pharmaceutical Research and Manufacturers of America's Research & Hope Award for Excellence in Biopharmaceutical Research and has also been recognized as one of 14 inaugural "Health Heroes" by *Oprah* magazine.

Dr. Manji has been inducted into the National Academy of Medicine (NAM) and the World Economic Forum (WEF) Global Future Councils and has held numerous leadership positions within the NAM, the Foundation for the National Institutes of Health Biomarkers Consortium executive committee, ACNP, and the Society of Biological Psychiatry.

Throughout his career, Dr. Manji has also been committed to undertakings related to medical and neuroscience education and has worked with the National Board of Medical Examiners, the Howard Hughes Medical Institute Research Scholars Program, and numerous national curriculum committees. He founded and co-directed NIH's Foundation for the Advanced Education in the Sciences graduate course in the Neurobiology of Neuropsychiatric Illness and has received several teaching and mentoring awards. He has also served as the editor and on editorial boards of numerous scientific journals.

Dr. Manji has published extensively on the molecular and cellular neurobiology of severe neuropsychiatric disorders and the development of novel therapeutics, with more than 300 publications in peer-reviewed journals, including *Science*, *Science Translational Medicine*, *Nature Neuroscience*, *Nature Reviews Neuroscience*, *Nature Reviews Drug Discovery*, *New England Journal of Medicine*, *Journal of Clinical Investigation*, *Proceedings of the National Academy of Sciences of the United States of America*, *Journal of Neuroscience*, *JAMA Psychiatry*, and *Molecular Psychiatry*.

Deven McGraw, J.D., M.P.H., LLM, is the chief regulatory officer for Ciitizen. Prior to joining Ciitizen, she directed U.S. health privacy and security policy through her roles as the deputy director for health information privacy at the Department of Health and Human Services' Office for Civil Rights (the office that oversees Health Insurance Portability and Accountability Act [HIPAA] policy and enforcement) and the chief privacy officer (acting) of The Office of the National Coordinator for Health Information Technology. Ms. McGraw also advised the Patient-Centered Outcomes Research Network as well as the federal All of Us Research Program Initiative on HIPAA and patient-donated data research initiatives.

Lauren Oliva, Pharm.D., is the global regulatory policy lead for new technologies at Biogen. She oversees the development and execution of the research and development policy roadmap for digital health tools and gene therapy to enable Biogen's neuroscience portfolio. In her time at Biogen she launched a widely used regulatory intelligence service

and served as a policy lead and regulatory strategy manager. Dr. Oliva received her Pharm.D. from the Rutgers University Ernest Mario School of Pharmacy and has previously served as adjunct faculty and a lecturer at the Massachusetts College of Pharmacy and Health Sciences in Boston, Massachusetts.

Bray Patrick-Lake, M.F.S., is the director of strategic partnerships at Evidation Health. She develops collaborations to support the design and implementation of participant-centered studies, and serves on the All of Us national advisory panel, the Digital Medicine Society scientific leadership board, and the Board on Health Sciences Policy at the National Academies of Sciences, Engineering, and Medicine. Previously, Ms. Patrick-Lake led engagement for the Duke Clinical Research Institute Project Baseline Study Coordinating Center and served as the co-chair on the advisory committee to the National Institutes of Health director that authored the Precision Medicine Initiative's cohort program. Ms. Patrick-Lake holds a B.S. from the University of Georgia and an M.F.S. from National University.

Leonard Sacks, M.D., received his medical education in South Africa, moving to the United States in 1987, where he completed fellowships in immunopathology and infectious diseases. He worked as an attending physician in Washington, DC, and South Africa, and he joined the U.S. Food and Drug Administration in 1998 as a medical reviewer in the Office of New Drugs. Subsequent positions included the acting director of the Office of Critical Path Programs and the associate director for clinical methodology in the Office of Medical Policy in the Center for Drug Evaluation and Research. In this capacity he has led efforts to support the use of electronic technology in clinical drug development. Besides his involvement in the design and analysis of clinical trials, he maintains a special interest in tuberculosis and other tropical diseases and has published and presented extensively on these topics. He is board certified in internal medicine and infectious diseases and holds an academic appointment as an associate clinical professor of medicine at The George Washington University.

Joyce Tung, Ph.D., joined 23andMe in 2007 and manages the 23andMe research team, which is responsible for consumer health and ancestry research and development, academic and industry collaborations, computational analyses for therapeutics, and new research methods and tools development. While a postdoctoral fellow at Stanford University, Dr. Tung studied the genetics of mouse and human pigmentation. She graduated from Stanford University with honors and distinction with a B.S. in

biological sciences and a minor in computer science, and she earned her Ph.D. in genetics from the University of California, San Francisco, where she was a National Science Foundation graduate research fellow.

Effy Vayena, Ph.D., studied medical history and bioethics at the University of Minnesota and completed her habilitation in bioethics and health policy at the University of Zurich. From 2000 to 2007 she worked at the World Health Organization (WHO). In 2007 she joined the Institute of Biomedical Ethics and History of Medicine at the University of Zurich, with which she remains affiliated. She is a consultant to WHO on several projects and visiting faculty at the Harvard Center for Bioethics at the Harvard Medical School. In 2015 she was named a Swiss National Science Foundation Professor of Health Policy and leads the newly established Health Ethics and Policy Lab in the Department of Public Health at the University of Zurich. Her current research focus is on ethics and policy questions in personalized medicine and digital health. At the intersection of multiple fields, she relies on normative analyses and empirical methods to explore how values such as freedom of choice, participation, and privacy are affected by recent developments in personalized medicine and in digital health. She is particularly interested in the issues of ethical oversight of research uses of big data, ethical uses of big data for global health, and the ethics of citizen science. Using the ethics lens in innovative ways, she aims to provide concrete policy recommendations and frameworks that facilitate the use of new technologies for a better and more just health.

Appendix D

Workshop Speaker Biographical Sketches

Amy Abernethy, M.D., Ph.D., is an oncologist and internationally recognized clinical data expert and clinical researcher. As the principal deputy commissioner of food and drugs at the U.S. Food and Drug Administration (FDA), Dr. Abernethy helps oversee FDA's day-to-day functioning and directs special and high-priority cross-cutting initiatives that affect the regulation of drugs, medical devices, tobacco, and food. As the acting chief information officer, she oversees FDA's data and technical vision and its execution. She has held multiple executive roles at Flatiron Health and was a professor of medicine at the Duke University School of Medicine, where she ran the Center for Learning Health Care and the Duke Cancer Care Research Program. Dr. Abernethy received her M.D. at Duke University, where she did her internal medicine residency, served as chief resident, and completed her hematology/oncology fellowship. She received her Ph.D. from Flinders University and her B.A. from the University of Pennsylvania and is boarded in palliative medicine.

Chris Benko, M.B.A., is the chief executive officer and the co-founder of Koneksa Health, the leader in developing and implementing patient-focused digital biomarkers for drug development. By unlocking the potential of real-world data from remote, wearable, and other digital technologies, Koneksa speeds up the time required to understand how a drug is working, requiring fewer patients, and develops real-world evidence for how medicines can affect their daily lives. Prior to founding Koneksa, Mr. Benko was a vice president in Merck's corporate strategy

office, working with its Global Health Innovation venture capital fund. He began his career at Merck in 1995 and progressed through roles in information technology as well as talent and organizational development, working in research and development, commercial, and at the corporate level as vice president for global talent management.

Yvonne Yu-Feng Chan, M.D., Ph.D., FACEP, is the senior director of medical affairs for Digital Medicine at Otsuka America Pharmaceutical, Inc. (Otsuka), a national leader in digital medicine research, and is a board-certified emergency physician. At Otsuka, Dr. Chan develops advanced methods, digital tools, and technology platforms to derive real-world clinical and health economics evidence in collaboration with internal and external collaborators. She provides medical input to all aspects of product development at Otsuka's digital medicine division. Dr. Chan leverages her 15-plus years of medical and digital health experience as a physician–scientist to help lead Otsuka's pioneering work in digital medicine in support of patients, physicians, and caregivers.

Previously, Dr. Chan was the founding director of the Center for Digital Health at the Icahn School of Medicine at Mount Sinai. The mission of her Center for Digital Health was to drive large-scale patient participation in biomedical research and clinical care by applying the latest digital technology and advanced analytic techniques to uncover novel insights and actionable results.

Dr. Chan is an editorial board member of the Nature Partner Journals (npj) *Digital Medicine* and *Digital Biomarker*. She is also a member of the Digital Medicine (DiMe) Society's scientific leadership board and the National Institute of Neurological Disorders and Stroke Common Data Elements for Stroke Group. Dr. Chan received her B.A. and M.D. from Rutgers University (New Jersey Medical School) and completed her emergency medicine training at Albert Einstein School of Medicine, Long Island Jewish Medical Center. At the conclusion of her NINDS T32 Cerebrovascular Research Fellowship at Mount Sinai, she was granted the Mount Sinai Institutional KL2 Clinical and Translational Research Career Development Ph.D. Candidate award.

Michelle Crouthamel, D.B.A., is an industry thought leader in digital health with a broad spectrum of research and development experience spanning drug discovery, clinical development, project management, and digital health initiatives. Her passion for driving patient-centricity/precision medicine in the pharmaceutical industry led her to become an "intrapreneur" at GlaxoSmithKline and the founding member of its clinical innovation unit, which focuses on harnessing digital technologies and platforms to improve clinical evidence generation and opti-

mize trial operation. Ms. Crouthamel is currently the director of digital health and innovation at AbbVie Inc. leading digital health strategy and implementation. She is also involved in the industry-wide consortium, including TransCelerate, IMI, and the Digital Medicine Society. Over the past 15-plus years, Ms. Crouthamel led many successful programs in discovery and development. She is an inventor who holds multiple patents and has published extensively in the areas of neuroscience, oncology, and digital health.

Ms. Crouthamel has a bachelor's degree in nursing, a master's degree from the Institute of Neuroscience, and a doctorate from the Temple University Fox School of Business, with a research focus on measuring the firm performance of patient-centricity in the pharmaceutical industry.

Luca Foschini, M.S., Ph.D., is the co-founder and the chief data scientist at Evidation Health, responsible for data analytics and research and development. At Evidation he has driven research collaborations resulting in numerous publications in the fields of machine learning, behavioral economics, and medical informatics. Previously, Dr. Foschini held research positions in industry and academic institutions, including Ask.com, Google, ETH Zurich, and the University of California, Santa Barbara. He has co-authored several papers and patents on efficient algorithms for partitioning and detecting anomalies in massive networks. He holds an M.S. and a Ph.D. in computer science from the University of California, Santa Barbara, and an M.E. and a B.E. from the Sant'Anna School of Advanced Studies Pisa, Italy.

Rita Kapur, Ph.D., is the head of digital biomarkers at Verily Life Sciences (formerly Google Life Sciences), a translational research and engineering organization focused on improving health care by applying scientific and technological advances to significant problems in health and biology. She serves as a cross-functional lead across hardware, software, clinical operations and data science to develop and implement initiatives that use wearable and passive sensing technology to help better diagnose, monitor, and intervene in disease. Dr. Kapur received a bachelor's degree (cum laude) in human biology from Stanford University and a doctorate in neuroscience from the University of California, San Francisco, where she specialized in using in vivo awake behaving electrophysiology and signal processing to study the brain systems underlying reward and learning. Prior to joining Verily, she served as a senior clinical research scientist focused on the analysis of biosensor (electrocorticographic) and clinical trial data to provide support for physicians in selecting, implanting, and optimizing therapy with an implantable closed-loop brain stimulator for the treatment of epilepsy.

Sean Khozin, M.D., M.P.H., is an oncologist, a physician–scientist, and a research affiliate at the Massachusetts Institute of Technology. Dr. Khozin is the global head of data strategy for Janssen/Johnson & Johnson, focusing on the incorporation of data science and advanced quantitative methods (including artificial intelligence and machine learning) into research and development (R&D) activities. He joined the company from the U.S. Food and Drug Administration (FDA) Oncology Center of Excellence, where he built and led the center's bioinformatics capabilities and efforts. He was also the founder of Information Exchange and Data Transformation, FDA's first data science and technology incubator for de-risking solutions through internal R&D and strategic partnerships for improving global biomedical research and advancing national public health priorities. Prior to his tenure in federal government, Dr. Khozin was the cofounder of Hello Health, developing an integrated telemedicine, point-of-care data visualization, and analytical platform for optimizing patient care and clinical research. The company's core technology offerings were first operationalized in a multidisciplinary network of clinics called SKMD, which he founded and for which he served as the chief medical officer.

Christopher Leptak, M.D., Ph.D., completed his M.D. and Ph.D. in microbiology/immunology at the University of California, San Francisco. After a residency in emergency medicine at Harvard's combined Mass General and Brigham program, he joined the U.S. Food and Drug Administration in 2007 as a primary reviewer in the Office of New Drugs (OND) division of gastroenterology products, focusing on immunomodulators for inflammatory bowel diseases. In 2010 he joined OND's guidance and policy team and became OND's biomarker and companion diagnostics lead. His focus is on biomarker and diagnostic device utility in clinical trials and drug development, both for drug-specific programs. Dr. Leptak is the director of the Center for Drug Evaluation and Research's biomarker qualification program, which is intended to improve regulatory consistency and policy development in areas of emerging science and technology.

Chris Lunt is the chief technology officer for the All of Us Research Program at the National Institutes of Health (NIH). *All of Us* is an effort to build a national, large-scale research enterprise with 1 million or more volunteers to extend precision medicine to all diseases. He has 20-plus years of experience designing web services and data platforms. He joined NIH from GetInsured, where he served as the vice president of government solutions. There, he worked with the federal government, states, and the vendor community to improve health insurance shopping and enrollment systems. He also worked as an entrepreneur for the Department of Health and Human Services. Earlier in his career he led an initial

public offering, and he invented more than 10 social networking patents now owned by Facebook.

Camille Nebeker, Ed.D., M.S., is an associate professor of behavioral medicine in the Department of Family Medicine and Public Health in the School of Medicine at the University of California, San Diego. Her research and teaching focus on two intersecting area: community research capacity building (e.g., citizen science and community engaged research) and digital health research ethics (e.g., consent, privacy expectations, data management). She co-founded and directs the Research Center for Optimal Digital Ethics and leads the Building Research Integrity and Capacity programs and the Connected and Open Research Ethics initiative. Dr. Nebeker's research has received continuous support from government, foundation, and industry sources since 2002.

Sally Okun, R.N., M.M.H.S., joined UnitedHealth Group Research and Development (UHG R&D) in 2020 to focus on policy and ethics with an emphasis on patient and consumer participation in care, research, and policy. Prior to joining UHG R&D, Ms. Okun was the vice president for policy and ethics at PatientsLikeMe. In her 12-year tenure she led the development of the company's health data integrity, patient voice taxonomy, drug safety, and pharmacovigilance monitoring platform; the research collaboration agreement with the U.S. Food and Drug Administration; and the ethics and compliance advisory board. Ms. Okun advances the science of patient participation and integration of patient perspective into diverse health policy initiatives at the national and global level. She is a member of numerous expert and advisory boards, including the National Academy of Medicine's Leadership Consortium for a Value and Science-Driven Health Care System; Public Responsibility in Medicine and Research Public Policy Committee; Duke-Margolis Center for Health Policy Real World Evidence Collaborative Advisory Group; and the International Consortium for Health Outcomes Measurement Patient-Reported Outcome Measures National Steering Committee. Prior to joining PatientsLikeMe she practiced as a community-based palliative and end-of-life care specialist. Ms. Okun completed her graduate studies at the Heller School for Social Policy and 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.

Larsson Omberg, Ph.D., as the vice president of systems biology at Sage Bionetworks, oversees a research agenda that focuses both on genomics and participant-centered research where data are being collected using

remote sensors and mobile phones. The group focuses heavily on using open and team-based science to get a large number of external partners to collaborate on data-intensive problems. Dr. Omberg has a background in computational biology and has been developing computational methods for genomics analysis and disease modeling. Dr Omberg obtained an M.Sc. in engineering physics from the Royal Institute of Technology in Stockholm Sweden and a Ph.D. in physics from The University of Texas at Austin before performing a postdoctoral fellowship in computational biology and biostatistics at Cornell University.

Eric Perakslis, Ph.D., is a Rubenstein Fellow at Duke University, where his work focuses on collaborative efforts in data science that span medicine, policy, engineering, data science, information technology, privacy, and security. Dr. Perakslis is also a lecturer in the Department of Biomedical Informatics at Harvard Medical School and a strategic innovation advisor to Médecins sans Fontières. Prior to his current role, Dr. Perakslis served as the chief science officer at Datavant and was the senior vice president and head of the Takeda Research and Development Data Science Institute. Prior to Takeda, he was the executive director of the Center for Biomedical Informatics and the Countway Library of Medicine, and before that he served as the chief information officer and chief scientist (informatics) at the U.S. Food and Drug Administration (FDA). In this role, Dr. Perakslis, authored the first information technology (IT) strategic plan for FDA and was responsible for modernizing and enhancing the IT capabilities as well as in silico scientific capabilities at FDA. Prior to his time at FDA, Dr. Perakslis was the senior vice president of research and development (R&D) information technology at Johnson & Johnson Pharmaceuticals R&D. Dr. Perakslis has a Ph.D. in chemical and biochemical engineering from Drexel University. He also holds a B.S.Ch.E. and an M.S. in chemical engineering.

Edmondo Robinson, M.D., M.B.A., F.A.C.P., serves as the senior vice president and the chief digital innovation officer for Moffitt Cancer Center. Dr. Robinson is responsible for expanding Moffitt's ecosystem from within and outside of health care to deliver on consumer-oriented, real-world solutions for clinical practice, research, and administrative processes essential to support growth and competitive advantage. He also oversees Moffitt's portfolio of digital innovation, including the development and commercialization of health products, tools and technology. With this role, Moffitt aims to create and test new services, programs, partnerships and technologies that apply digital innovations, while challenging the status quo to reduce the cost of care, improve quality, increase access to care, and enhance the patient experience. Previously, Dr. Robinson was the chief

transformation officer and the senior vice president of consumerism at ChristianaCare, one of the largest health systems in the mid-Atlantic. He was responsible for the transformation of health care delivery to advance population health initiatives and the move from volume-based to value-based care with a special focus on developing and managing ChristianaCare's consumerism and digital strategies. Dr. Robinson is an associate professor of medicine at Thomas Jefferson University's Sidney Kimmel Medical College and an adjunct senior fellow in the Leonard Davis Institute of Health Economics at the University of Pennsylvania. He is also a fellow of the American College of Physicians and a senior fellow of the Society of Hospital Medicine. He holds a medical degree from the David Geffen School of Medicine at the University of California, Los Angeles; an M.B.A. with an emphasis in health care management from the Wharton School at the University of Pennsylvania; and a master's degree in health policy research from the University of Pennsylvania.

Christina Silcox, P.h.D., is a managing associate at the Duke-Margolis Center for Health Policy, working on policy solutions to advance innovation in health and health care and improve the regulation, reimbursement, and long-term evaluation of medical products. Dr. Silcox's portfolio includes multiple areas in digital health policy and real-world evidence, with a focus on medical devices. Currently, she is concentrating on challenges to regulating and adopting artificial intelligence–enabled software as a medical device, using mHealth to collect real-world data, and characterizing real-world data quality and relevancy. Her projects have included the use of patient-generated health data in medical device evaluations, the exploration of value-based payments for medical devices, and convening the National Evaluation System for Health Technology planning board.

Before she joined Duke-Margolis, Dr. Silcox was a senior fellow at the National Center for Health Research, focused on federal regulation of and policies for medical products. She earned an M.S. from the Massachusetts Institute of Technology (MIT) in electrical engineering and a Ph.D. in medical engineering and medical physics from the Harvard–MIT Division of Health Sciences and Technology.

Alicia Staley, M.B.A., M.S.I.S., is the senior director of patient engagement for mHealth at Medidata. She has more than 20 years of experience in software design and information systems management and works to infuse the patient perspective throughout the product development lifecycle and help engage patients in novel ways. Ms. Staley is also a three-time cancer survivor, first diagnosed with Hodgkin's disease as a sophomore during college. Over the past 10 years she has applied her engineering background to improve the patient experience for those deal-

ing with cancer. With an extensive network of patient advocates and nonprofit organizations, she collaborates with a wide range of stakeholders to improve processes and policies that affect patient care and clinical trials. She has co-led several research studies on how patients share information in online forums and seek out clinical trial opportunities. An early adopter of social media, she co-founded #BCSM, which attracts more than 250 global participants each week to its scheduled online discussions. This foundational online social media support channel is recognized as the gold standard for disease-specific social media networks. Prior to joining Medidata, Ms. Staley worked at Cure Forward and Science 37, leading their patient recruitment and engagement initiatives to help advance clinical research. As a champion of patient advocacy and engagement, she understands the critical issues facing patients looking to engage in clinical research. With a keen focus on improving access to clinical trials, Ms. Staley is passionate about making a difference for all patients searching for information about clinical trials.