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Real-World Evidence Generation and Evaluation of Therapeutics

PROCEEDINGS OF A WORKSHOP

Autumn Downey, Amanda Wagner Gee, and Anne B. Claiborne,
Rapporteurs

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

Health and Medicine Division

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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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Mark Pletcher, University of California, San Francisco
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Lewis Sandy, UnitedHealth Group
Patrick Vallance, GlaxoSmithKline
Jon White, Office of the National Coordinator for Health Information Technology

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 **Daniel R. Masys,** University of 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.

Contents

Boxes and Figures

BOXES

FIGURES

Acronyms and Abbreviations

ACC	American College of Cardiology
ASPE	Office of the Assistant Secretary for Planning and Evaluation
CDC	Centers for Disease Control and Prevention
CDRN	clinical data research network
CMS	Centers for Medicare & Medicaid Services
COPD	chronic obstructive pulmonary disease
CTSA	Clinical and Translational Science Awards
EHR	electronic health record
FDA	U.S. Food and Drug Administration
MDUFA	Medical Device User Fee Amendments
NEST	National Evaluation System for health Technology
NIH	National Institutes of Health
OHDSI	Observational Health Data Sciences and Informatics
ONC	Office of the National Coordinator for Health Information Technology
PCORI	Patient-Centered Outcomes Research Institute
PCORnet	The National Patient-Centered Clinical Research Network

PMI	Precision Medicine Initiative
pRCT	pragmatic randomized controlled trial
PROMIS	Patient-Reported Outcomes Measurement Information System
RCT	randomized controlled trial
STS	Society for Thoracic Surgeons
TAVR	transcatheter aortic valve replacement
TVT	transcatheter valve therapy
VA	U.S. Department of Veterans Affairs

1

Introduction[1]

The volume and complexity of information about individual patients is greatly increasing with use of electronic records and personal devices. Potential effects on medical product development in the context of this wealth of real-world data[2] could be numerous and varied, ranging from the ability to determine both large-scale and patient-specific effects of treatments to the ability to assess how therapeutics affect patients' lives through measurement of lifestyle changes. However, mechanisms to facilitate efficient use of real-world data to meet the decision-making needs of myriad stakeholders have not been established. Traditional efficacy clinical trials are designed to test novel medical treatments in ideal, controlled circumstances. Clinical practice is much more diverse, and efficacy in practice (i.e., effectiveness) is affected by patient adherence, co-morbidities, concomitant

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

[2] Real-world data are "data collected from sources outside of traditional clinical trials. These sources may include large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and health care claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries (e.g., device, procedural, or disease registries). The data [are] typically derived from electronic systems used in health care delivery, data contained within medical devices, and/or in tracking patient experience during care, including in home-use settings" (FDA, 2016, p. 4).

treatments, and other factors. Real-world evidence, which the U.S. Food and Drug Administration (FDA) has characterized as health care information aggregated from sources outside traditional clinical research settings (Sherman et al., 2016), has been touted as a way to generate a more complete understanding of treatment usage, effectiveness, and value.

In the current drug development paradigm, however, real-world evidence has primarily been applied in early discovery and in the postmarket phase for safety surveillance and comparative effectiveness evaluations (see Figure 1-1). Although this has led to many valuable insights, the larger promise of real-world evidence has not yet been fulfilled. On October 19, 2016, the Forum on Drug Discovery, Development, and Translation (the Forum) of the National Academies of Sciences, Engineering, and Medicine (the National Academies) held a workshop to facilitate dialogue among

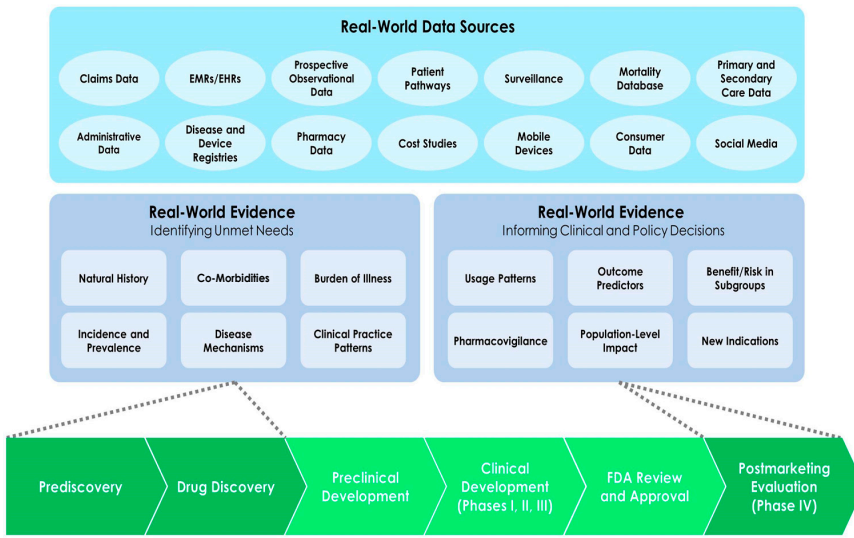

FIGURE 1-1 Examples of current uses of real-world evidence derived from diverse and complex sources.
NOTES: Real-world evidence could inform all phases of treatment discovery and development, although thus far has been more commonly used to inform early development decisions and postmarketing safety surveillance or comparative effectiveness studies. By contrast, clinical development and review have tended to use more idealized and tightly controlled data sources for efficacy trials. EHR = electronic health record; EMR = electronic medical record.
SOURCE: Galson and Simon, 2016.

BOX 1-1
Statement of Task

An ad hoc committee will plan and conduct a 1-day public workshop that will examine opportunities and challenges for incorporating real-world evidence into evaluation of medical products. Subject-matter experts will be invited to participate in the workshop through presentations and discussions that will consider:

- Quality of data from real-world sources, including
  - Relevance and validity of different sources of real-world data (e.g., user-collected, practice-based) in the context of different clinical/scientific questions; and
  - Strengths and limitations of different data sources at different stages of treatment development and licensing process.
- Methodologies and best practices for high-quality real-world evidence generation and application, including
  - Innovations in clinical trial design to maximize value of information for the full range of stakeholders;
  - Considerations of how evidence generation from existing studies could potentially inform the design of future clinical trials and amplify understanding of product efficacy;
  - Discussion of how shared goals of payers and regulators can better align evidence generation processes used for regulatory evaluation and decisions on use by payers; and
  - Re-evaluation of traditional distinctions between goals and methods of preapproval and postapproval research.
- Other novel methodologies and approaches to improve development and evaluation of products using real-world evidence, including
  - Use of Web-based or digital technologies to enhance clinical trial evidence collection and participation, and
  - Techniques and case-studies for effectively using electronic health record data.

The committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate or identify moderators for the discussions. A summary of the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

stakeholders about the opportunities and challenges for incorporating real-world evidence into all stages of the process for the generation and evaluation of therapeutics (see Box 1-1 for the full Statement of Task). This workshop builds on previous workshops sponsored by the Forum that in

BOX 1-2
Potential Additional Uses of Real-World Evidence as Outlined by Individual Speakers

- Conducting pragmatic clinical trials (Roddam, Rothman)
- Conducting comparative effectiveness and postmarketing studies (Mack, Rothman, Shah)
- Collecting more complete patient care data through linking data sources (Dore)
- Improving patient accessibility, subpopulation recruitment, virtual patient engagement, and study efficiency through mobile health devices (Foschini)
- Tracking long-term patient outcomes through registry data (Carroll)
- Assessing quality of an intervention on patient outcome through use of registries (Mack)
- Informing decisions about a patient's care in real-time (Fiore)
- Reporting adverse events and safety surveillance (Curtis)

SOURCES: Speaker presentations, 2016.

recent years have focused on clinical trials, data sharing, and regulatory science.[3]

The potential applications of real-world evidence are numerous (see Box 1-2), and there are many remaining challenges surrounding its generation, accessibility and distribution, and use. To focus the discussions, presenters were asked not to delve into detailed technical aspects such as statistical methodologies, but instead, to share their perspectives on unmet stakeholder needs and opportunities to generate new kinds of evidence that meet those needs.

[3] Publications from previous National Academies workshops with particular relevance to the topic of real-world evidence include

- *Large Simple Trials and Knowledge Generation in a Learning Health System: Workshop Summary* (IOM, 2013b), which focused on opportunities to advance a learning health system and improve the efficiency of drug development by integrating research at the point of care through large simple trials;
- *Sharing Clinical Research Data: Workshop Summary* (IOM, 2013c), which examined the benefits, barriers, and strategies to enhancing the sharing of clinical research data; and
- *Advancing the Discipline of Regulatory Science for Medical Product Development: An Update on Progress and a Forward-Looking Agenda: Workshop Summary* (NASEM, 2016), which touched on the integration and use of "big data" (e.g., data from electronic health records, registries, social media) in clinical research and regulatory decision making.

ORGANIZATION OF THE PROCEEDINGS OF A WORKSHOP

This Proceedings of a Workshop was prepared by the rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual workshop participants and have not been endorsed or verified by the Forum or the National Academies, and they should not be construed as reflecting any group consensus. The workshop was webcast live and online participants were able to contribute to the discussions through the hashtag #RealWorldEvidence. The slide presentations and videos are archived on the Forum website.[4]

The proceedings is organized as follows:

- Chapter 2 introduces the topic of real-world evidence in greater detail by describing some priorities for improving evidence generation to support decision making on approval and use of therapeutics as proposed by several diverse stakeholders, including regulators, patients, health care providers, payers, and industry.
- Chapter 3 characterizes some sources of real-world data and what can be learned from them.
- Chapter 4 summarizes discussion of four case studies that highlight how real-world evidence has been incorporated into medical product development and evaluation processes, and the opportunities and challenges to build from these successful use cases. The four case studies were as follows:
  1. Salford Lung Study
  2. Transcatheter Valve Therapy (TVT) Registry
  3. Sentinel Initiative
  4. Observational Health Data Sciences and Informatics
- Chapter 5 summarizes some practical strategies for expanding the incorporation of real-world evidence into the generation and evaluation of therapeutics, including potential key next steps.

[4] For more information, see https://www.nationalacademies.org/hmd/Activities/Research/DrugForum/2016-OCT-19.aspx (accessed November 16, 2016).

2

Improving Evidence Generation for Decision Making on Approval and Use of New Treatments: Some Stakeholder Priorities

Key Messages Identified by Individual Speakers

- Technology advances and health care reform efforts are creating opportunities to reshape the current system by which evidence is generated to better meet stakeholder needs. However, the reliability of those data should be considered. (Califf, Carroll, Vallance)
- Stakeholders lack the evidence needed to make real-world decisions on approval, coverage, and use of treatments because current evidence generation processes focus narrowly on questions of safety and efficacy. (Califf, Carroll, Chin, Robinson Beale, Sherman, Simon, Vallance)
- Real-world evidence has the potential to improve efficiency across the drug development paradigm and, in certain situations, may address questions that can only be answered with real-world evidence. This implies that ensuring that such data are reliable is paramount. (Vallance)
- FDA has the flexibility to use real-world data to support decisions on approval and labeling of medical products. (Califf)
- Improved communication from leadership within the biopharmaceutical industry and regulatory sectors may be needed to overcome the resistance to change that currently impedes the generation and use of real-world evidence. (Califf, Vallance)

- The traditional demarcation between pre- and postapproval phases is not fit-for-purpose for many medical products. Regulatory approval decisions could be informed by the same evidence that informs use and coverage decisions, although the criteria for regulatory and coverage decisions based on that evidence should be different. (Califf, Chin, Sherman)
- Clinical usage decisions often rely on individual practitioners' experience and perceptions, or trial-and-error experimentation, because data available at approval are limited. This results in a more expensive health care system, and many patients do not receive the best treatment. (Califf, Carroll, Chin, Robinson Beale)
- Validated and facile tools, based on large datasets, to help inform real-time decision making in clinical practice would be invaluable, yet are currently limited. (Carroll, Robinson Beale)

Greg Simon, an investigator with Group Health Research Institute and workshop co-chair, laid out the basic premise for the workshop: that our current system of generating evidence is not meeting our needs. When new treatments are released into the real world, he said, we often lack the information we need to make real-world decisions. Randomized controlled trials (RCTs) have been the gold standard for answering questions of safety and efficacy, but they have not adequately addressed the fundamental questions of how well a new treatment works, particularly in comparison to other options, or when and for whom it should be recommended. Although this realization has not yet led to significant changes in the pipeline for the production of new therapeutics, a number of advances that are underway offer opportunities to reshape the current evidence generation paradigm.

THE CURRENT LANDSCAPE FOR EVIDENCE GENERATION PROCESSES

FDA Commissioner (at the time of the workshop) Robert Califf, who was also the workshop keynote speaker, described the landscape in which medical product development is occurring as one undergoing rapid and profound changes. A technology revolution is happening that, while exciting in terms of its potential, will also increase demands on the current system. Novel techniques such as gene editing raise questions regarding safety and effectiveness that will need to be addressed, he said. Additionally, devices have proliferated that enable consumers to continuously monitor and col-

lect health-related data. Califf emphasized that, if the full potential of these technology advances is to be realized, data sharing is important.

Califf also acknowledged the opportunities arising as a result of health care reform efforts, which are driving a shift from traditional fee-for-service to a value-based reimbursement model. A desire to achieve better value in health care has incentivized movement toward what the National Academies has called a learning health system,[1] in which large amounts of electronic health data can be shared rapidly across systems and rapid cycle improvement can be achieved by understanding what works, then measuring impact following implementation. The digital capture, aggregation, and analysis of health care data with the goal of improving quality of care and cost-effectiveness represents a fundamental change in evidence generation processes, with significant implications for medical product development. Califf stressed that with this new model for knowledge generation, there would be less need for a completely separate, and consequently inefficient, clinical research infrastructure. The integration of research with clinical care and use of existing data has the potential, therefore, to drastically reduce the cost of evidence generation.

Overall, Califf concluded, leveraging available data sources is more widespread and commonplace than ever. Yet, he said, "the current system is not delivering adequate evidence in the face of an explosion of new medical products and increased understanding of how to evaluate products already in clinical use," and many clinical treatment decisions are not supported by evidence (Tricoci et al., 2009; Han et al., 2015). Now is the time, he said, to build on the foundation of recent advances and take them to the next level (see Box 2-1).[2]

STAKEHOLDER PERSPECTIVES ON PRIORITIES FOR IMPROVING REAL-WORLD DECISION MAKING

During the first workshop session, Califf's keynote was accompanied by a diverse panel of stakeholders who provided remarks about the most pressing challenges and priorities for improving evidence generation to support real-world decision making. These individual speakers noted that the traditional processes for evaluating new therapeutics focus too narrowly on efficacy and safety outcomes and do not adequately address key questions regarding effectiveness, tolerability, and value—questions that matter to clinicians and patients. As a result, these speakers noted, the traditional pathway for medical product development does not produce the evi-

[1] For more information, see IOM, 2013a.
[2] For more information, see Sherman et al., 2016.

BOX 2-1
A Call to Action

Califf concluded his keynote address by laying out a call to action, highlighting five key areas where progress is needed to realize the vision of a system that generates the evidence stakeholders need to support real-world decision making. The elements of this call to action, outlined below, framed many of the discussions throughout the rest of the workshop:

- Organize operational systems that bring together research networks embedded in practice and focus on standardizing operations across health systems for implementing prospective protocols.
- Establish a robust framework for privacy, confidentiality, and security.
- Adopt a common approach to configuring, storing, and reusing digital health care data to enable use in care, research, safety surveillance, and public health.
- Develop and test new methods to reliably answer research questions.
- Ensure the development of novel approaches focused on streamlining and harmonizing processes in ways that eliminate barriers that promote unnecessary complexity, while ensuring safeguards that are truly needed.

SOURCE: Califf presentation, 2016.

dence needed to inform real-world clinical, regulatory, and reimbursement decisions.

Industry

Patrick Vallance, president, Pharmaceuticals Research and Development, GlaxoSmithKline, observed that the medical product development industry is actually becoming less efficient. The cost of clinical trials is increasing sharply (Berndt and Cockburn, 2014) and the failure rate of the clinical research enterprise is profound. As Califf noted, more than 90 percent of drugs that enter Phase I trials do not make it to market because of issues related to effectiveness, toxicity, or reliable production. Vallance remarked that the incorporation of real-world data into the evaluation of therapeutics has the potential not just to improve the efficiency of clinical trials, but to actually answer different questions that, in some cases, can only be answered with real-world evidence. As one example, Vallance cited that real-world evidence is particularly suited to answering questions not about safety and efficacy, but instead about how well a particular treatment

works in comparison to other possible treatments (i.e., comparative effectiveness). He also stated that questions about determining compatibility, dosage, and usage indications for combination treatments, and increasingly even for combinations during development rather than postmarketing studies, can be assessed with real-world evidence. Although postmarket evaluations have been moving in this direction, he said, evidence generation processes earlier in the product development life cycle must be able to account for the complexities seen in real-world populations. He cited an example in the increasing number of medications that will need to be tested in combination during the development phase. What is really going to change the way that industry thinks about clinical trials going forward, said Vallance, is the opportunity to incorporate the vast amount of information from electronic health records and devices that continuously collect data directly from patients and consumers outside the clinical setting. Consequently, it will be important to focus more on ensuring that such data are reliable.

Regulators

Addressing the escalating costs of bringing new treatments to market, Califf emphasized the need for a drug development system that winnows out failures as quickly as possible and, for the promising candidates, ensures that the right clinical trials are undertaken to inform decision making by all stakeholders. While maintaining that very early clinical trials will still need to be conducted in highly controlled environments so that the safety, pharmacology, and systems biology of new treatments can be carefully assessed, Califf stressed the later stage research can be integrated within the real world of clinical practice, the better the system will be at yielding results that give doctors and patients the information they need to understand what treatment options are best for them. "Sticking to the old model is a recipe for an escalating cost (of research) at a time when we need more efficient research because the questions are far outnumbering our ability to answer them," he said.

Califf highlighted common misperceptions that FDA has encountered in discussions on the use of real-world evidence for regulatory decision making, which the agency is working to correct in its communications with stakeholders. First, he said, the source of the data should not be confused with the design of the study. A common assumption is the generation of real-world data is synonymous with observational study design; however, randomization in the context of the real world is both possible and critical. The system will not change until that distinction is broadly understood, echoed Rachel Sherman, Deputy Commissioner for Medical Products and Tobacco, FDA. Second, both Califf and Sherman emphasized that FDA's

role does not end after approval. For example, FDA is charged with writing labels that provide accurate, instructive information on how to use approved products safely and effectively in medical practice. Continued evidence generation on effectiveness in the postmarket phase can inform FDA labeling changes as well as new indications. Indeed, Sherman noted, the demarcation between pre- and postmarket represents an outdated way of thinking about the drug development paradigm. Real-world evidence will increasingly be embedded across the process of drug discovery and development and through to the market, informing regulatory decisions across all of those phases. Finally, Califf sought to dispel the misperception that FDA regulations or guidance prohibit or inhibit use of real-world evidence for regulatory approval of new treatments.[3] Real-world evidence, when considered appropriate in the views of competent experts in the field, could legitimately contribute to the legally required demonstration of substantial evidence of effectiveness of new treatments.[4] As the evidence system changes, Califf said, a process will be needed for driving agreement on what constitutes substantial evidence and quality for different purposes.

Payers

When new treatments are approved, health care payers—including the Centers for Medicare & Medicaid Services (CMS), private insurers, and, increasingly, providers who participate in shared savings and capitation arrangements—base coverage determinations on their value, which is calculated by examining the net costs and evidence of benefit. While this can create tension between payers and industry, Rhonda Robinson Beale, chief medical officer, Blue Cross of Idaho, underscored the fact that when

[3] The 21st Century Cures Act, signed into law on December 13, 2016, requires FDA to evaluate the use of real-world evidence to help support the approval of a new indication for a previously approved drug and to help support or satisfy postapproval study requirements. Under the direction of the Secretary of Health and Human Services, a guiding framework will be developed to implement a program within FDA that details the circumstances, standards, and methodologies for which real-world evidence can be used in medical product evaluation. This program will then guide the development of draft guidance for industry to be released for public comment, and final guidance on the use of real-world evidence for medical product evaluation by FDA (21st Century Cures Act, Public Law 114-255, 114th Cong., 2d sess. [December 13, 2016]).

[4] Substantial evidence is defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(d)) as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

there is a limited pool of resources, overspending on high-cost treatments shifts the financial balance, noting that high spending on some patients could result in inadequate resources being available for the remainder of the population being serviced. In this context, payers must make coverage decisions based on limited evidence because traditional clinical trials are not designed to answer questions regarding the comparative value. Joseph Chin, deputy director, Coverage and Analysis Group, CMS, pointed out that some types of patients, such as Medicare beneficiaries, are often excluded from clinical trials, making it challenging to make coverage determinations for those populations. Chin noted that the incorporation of real-world data into evidence generation processes could assist CMS coverage determinations by rendering clinical research results more immediately translatable to the beneficiary population, both by incorporating data from a more general population than typically seen in clinical trials and by potentially creating the opportunity to apply the results obtained during approval at FDA without further need to request additional studies on efficacy for CMS. This could also motivate CMS to work with FDA on harmonizing evidence requirements.

Robinson Beale said payers see a lot of off-label use and experimentation that have little practical evidence or recognized guidelines demonstrating treatment effectiveness in clinical practice for disease areas with high mortality or morbidity. She suggested that these disease areas could be prioritized. When high-cost treatments are involved, the trial-and-error methodology often used by providers who must apply those treatments to real-life populations that do not completely match the clinical trial population is simply unaffordable and drives up health care costs, she said. She noted that this expense is affecting patients in particular, with current insurance premiums closer in cost to a house payment than a car payment.

Health Care Providers

John Carroll, professor of medicine and co-medical director of the Cardiac and Vascular Center, University of Colorado Hospital, described the completion of RCTs not as an endpoint, but as the start of a new phase of learning. Health care providers then determine how best to apply the results from RCTs, with heterogeneity of treatment effect, to individual patients, who will have different characteristics and preferences. The individualizing of care calls for experience, skills, and judgment gathered over years of practicing medicine. Carroll also pointed out that regulatory approvals are often narrowly focused, but medical products can be used by medical providers on label, near label, or off label to address patients' needs. He emphasized the importance of learning from all of these different uses.

The process of gathering evidence to improve decision making about treatment options by clinicians and patients is limited by the slow and anecdotal process of experience acquisition from relatively small numbers of patients. Tools such as registries that enable learning from tens of thousands of patients receiving the same treatment throughout the United States have the potential to significantly accelerate knowledge generation. Tools to help health care providers and patients translate knowledge into actionable information were noted as a gap by a number of workshop participants. Even when evidence to support clinical treatment decisions exists, that evidence may not be reaching frontline providers. As a result, many patients are receiving the wrong treatment, said Robinson Beale, who characterized the existing tools providers have to support decision making, such as written clinical guidelines, as antiquated. To close the translation gap, clinical decision support tools could be embedded in the process of care to support decision making in real time. The availability of such tools could drive a shift toward more evidence-based decision making in health care. However, Carroll said, it will be important to understand their validation and what can be expected from them in terms of capturing the key elements that go into decision making.

Carroll suggested that priority focus areas to facilitate such learning health systems include the improvement of data quality and reduction of the magnitude of effort and cost currently required to gather data and translate them into actionable information. Several individual panelists agreed with Carroll that engaging health care providers in prospective research activities will add a significant burden in addition to their clinical responsibilities and thus will present a challenge to embedding research in the clinical care infrastructure.

Patients and Consumers

Naftali Zvi Frankel, a patient and consumer advocate, recognized that methodologies that generate real-world evidence are not a replacement for traditional clinical trials, but can instead be viewed as supplementing them. Such real-world studies offer new opportunities for patients with co-morbidities who are often excluded from traditional clinical trials. He illustrated this with a quote from a collaborating clinical trial investigator: "The requirement to have a clean cohort of patients in clinical trials creates a reality where drugs are tested on a universe of patients that does not reflect patients commonly seen." He stressed that engagement with patients and consumers needs to be reciprocal. Patients and consumers can be partners in the evidence generation process by sharing their data with providers and investigators, and greater efforts are needed to give information back to them as well. Patients too often feel isolated when faced with

choosing among therapies with little awareness of available data, such as comparative effectiveness data, that could inform their treatment decisions. Frankel said a greater effort is needed to improve transparency and patient engagement throughout the product development life cycle.

POTENTIAL CROSSCUTTING PRIORITIES FOR IMPROVING REAL-WORLD DECISION MAKING

Several crosscutting priorities emerged from the Session I discussion.

Communicating Leadership Support for New Approaches to Evidence Generation

Resistance to change was noted by Vallance as a major barrier to more systematic incorporation of real-world data into evidence generation processes. Given the significant costs associated with moving new treatments through the drug discovery and development process, the adoption of new methods for evidence generation represents a real risk. Reluctance to diverge from what has worked in the past has slowed change efforts in industry and on the regulatory side. Vallance suggested that although there may be support at the top of organizations for use of real-world evidence when it is appropriate to answer a specific question, that support may not be fully communicated throughout organizations. As a result, there is a sustained misperception that real-world evidence is not acceptable to support regulatory decision making, and, he remarked, leadership intervention within industry and regulatory agencies will be needed to encourage risk taking. Califf agreed that efforts to improve communication within and outside FDA could give companies more confidence about incorporating real-world data sources and pursuing alternative endpoints.

Harmonizing Evidence Generation Processes Across Stakeholder Groups

There is a great deal of interest across the biopharmaceutical industry, regulatory agencies, and payers in harmonizing evidence generation processes as a means of improving the efficiency of the drug development process and simultaneously generating the kinds of evidence needed to support real-world decision making. Although different stakeholders might use different criteria for decision making, it could be possible for them to use the same source of evidence. For example, explained Califf, FDA and CMS might use different criteria in determining whether a treatment should be approved and whether it should be covered, respectively, but thoughtfully designed studies that yield data on effectiveness and resource usage could inform both sets of decisions, reducing the number of studies that

industry needs to undertake. This is a goal that FDA and CMS are actively pursuing. However, Sean Tunis, founder, president, and chief executive officer, Center for Medical Technology Policy, said that there are a number of other decision makers (e.g., private payers, formulary committees, guideline developers, health technology assessment organizations) who will be assessing quality and relevance of evidence in the postmarket context and therefore should be engaged on the front end of discussions on evidence generation processes.

Addressing Privacy and Confidentiality Concerns

Embedding research into the clinical care infrastructure depends on the ability to share, aggregate, and analyze patient data. But in the current cybersecurity environment, it is not possible to absolutely guarantee the security of those data, cautioned Califf, who advocated instead for a participatory environment that is endorsed by patients and consumers and includes robust procedures for ensuring data security and protecting confidentiality. These concerns could discourage patients from permitting use of their data for secondary purposes such as clinical research. There is also a common, yet unfounded, fear among patients that health-related data could be used against them, for example, in life insurance coverage decisions, explained Robinson Beale. She stressed that it would help for those collecting the data to fully explain to patients and consumers the kinds of safeguards that are in place to minimize risks, such as de-identification methods. Sherman added that stakeholders need to think more creatively about ways to protect data other than keeping it sequestered. Frankel was optimistic about the willingness of patients and consumers to share their data despite the risks, but again stressed the importance of transparency and receiving clear consent from patients, so they understand how the data may be used and the benefits and risks of those uses.

3

Opportunities for Real-World Data

Key Messages Identified by Individual Speakers

- Electronic health records and databases containing other health-related data (claims, pharmacy) can support observational studies and pragmatic clinical trials, both of which can be important sources of real-world evidence. (Dore, Rothman)
- Integrating data from different sources creates a richer, more robust dataset than any one source alone can yield. However, combining data from different sources is currently a labor-intensive process due to challenges with data standardization and interoperability. (Dore, Rothman)
- Patients and consumers have a significant role to play in the collection of real-world data and generation of real-world evidence, but to be effective, patient and consumer engagement approaches would include considering them partners and capturing outcomes that are important to them. (Foschini, Robinson Beale, Rothman, White)
- Big data bring a number of challenges (high volume, high velocity, high variability). Greater investment in data science could support the health industry in realizing the potential of big data for health care and clinical research purposes. (Berger, Roddam, Shah, White)

Following the identification of stakeholder needs in the first workshop session, the second session was focused on answering a framing question: What can we learn from real-world data? The growing availability of rich clinical data provides opportunities to address a broad range of real-world questions on effectiveness and value. However, as noted by Simon, concerns regarding the quality of clinical data have impeded efforts to incorporate real-world data into the traditional clinical research paradigm. Panelists in this session discussed opportunities to leverage the "data exhaust" from clinical practice (e.g., data captured in electronic health records [EHRs] and claims and pharmacy databases during the course of clinical care) and mechanisms to overcome the challenges that arise when applying those data for the secondary purpose of research. The panelists also discussed the potential of data streams originating from mobile devices and other digital health technologies that capture data outside the clinical setting. Setting the tone for the session's discussions, Marc Berger, vice president, Real-World Data and Analytics, Pfizer Inc., stressed that it is "not a question about [whether] [these] real-world data [are] good enough. It's about how . . . we move to a learning health care system and use the data . . . for an appropriate purpose that drives us to where we want to get." He reminded the audience that "real-world evidence is good evidence and people are using it every day to make decisions."

LEVERAGING ELECTRONIC HEALTH RECORDS

The promise of a learning health system is dependent on the ability to digitally capture, aggregate, and analyze health data for research and quality improvement purposes. Over the past 15 years, significant progress has been made toward the vision set out in the 2001 Institute of Medicine report *Crossing the Quality Chasm* (IOM, 2001), which underscored the importance of a robust health information technology infrastructure, observed Jon White, deputy national coordinator for health information technology, Office of the National Coordinator for Health Information Technology (ONC). In 2015, 96 percent of hospitals and 78 percent of office-based physicians used certified EHR technology. Califf emphasized that it is important to take advantage of this infrastructure to move the evidence generation system to a much more efficient model and to answer questions that are critical for people to make the right decisions about their health and health care.

Several workshop participants discussed barriers that arise when using EHRs for research. Andrew Roddam, vice president and head of Real-World Evidence, GlaxoSmithKline, noted that EHRs might not contain all of the data that researchers want, so it is important to consider whether the EHR can be expanded to become the repository of all desired information

or, instead, to use what is there and then collect the missing information using simple data collection tools.

Other challenges noted by individual workshop participants included the following:

- missing data
- need for computable phenotypes
- lack of standardization (e.g., data schemes and data transfer protocols)
- interoperability issues with proprietary health information systems

Addressing the limitations of EHRs, Califf asked, "How much energy do you spend on the upfront regimentation of data collection versus curating data on the back end?" Several workshop participants noted a need for balance. Good evidence can come from back-end curation, although it may not be perfect, replied Sherman. This can help demonstrate the value of those data for other purposes, which can help drive improved data quality and collection for secondary use. Vallance suggested that some effort to improve quality of data entry on the front end is needed to improve back-end curation, citing as an example a study that found 120 different definitions of myocardial infarction. Califf observed that changing reimbursement practices may incentivize entry of more accurate data by providers, who will increasingly require such data to demonstrate the quality and value of care they are delivering.

The promise of EHRs inspires excitement, but also frustration, about the technology's unfulfilled potential. White noted that providers report to ONC not that they want to return to paper-based records systems, but that EHR systems need to work better for them. ONC is actively working on many of the barriers that are frequently noted, he said, including lack of standards and interoperability issues. Certified EHR technology is now required for participation in the Medicare incentive program and the newly released quality payment program, and in October 2015, ONC released the final version of its interoperability roadmap, *Connecting Health and Care for the Nation: A Shared Nationwide Interoperability Roadmap Version 1.0* (ONC, 2015). The private sector is also advancing opportunities to leverage EHR data for quality improvement and research, said Berger, citing as an example Pfizer's use of natural language processing to create very rich datasets by mining the wealth of EHR data residing in free text notes.

THE POWER OF LINKING AND MINING DISPARATE DATA SOURCES

The linking of multiple datasets provides a richness of data that cannot be achieved with any single data source. Combining EHR data with claims and pharmacy data, for example, captures a more complete picture of the continuity of care for a patient and a record of that person's interaction with the health care system, said David Dore, vice president, Epidemiology, and principal epidemiologist, Optum Life Sciences. Linking in data from other sources also may help to address data-quality issues by filling in missing data and validating data through checks for consistency across data sources. However, Califf pointed out, inconsistencies are not always an indicator of bad data. Inconsistencies may be real, reflecting different perceptions of different providers or variability in lab testing results, and may only be detectable by comparing across datasets. For example, it is possible to identify a patient population prescribed a particular drug using EHR data while claims data show that a certain percentage of those patients never filled the prescription. This has significant implications for any safety or effectiveness analyses conducted on those data and is a question that can only be answered with linked EHR and claims datasets, said Berger. The datasets that need to be linked depend on the question that must be answered, added Dore. One data source may be better at capturing certain data, but may miss others. This is why understanding the inherent biases of different datasets is important, cautioned Luca Foschini, co-founder and chief data scientist, Evidation Health. For example, claims datasets often tend to be more complete because payment serves as the incentive to enter data, but claims data have their own biases—for example, more expensive things are more likely to be captured there.

Patient-level linking of datasets remains a challenge when there are no unique patient identifiers. Although this is an area of significant interest and some work has been done in the private sector, federal efforts to implement unique patient identifiers are currently prohibited by law,[1] explained White. Other efforts to facilitate data linking and aggregation include the use of claims data to link patient records across EHR systems and the development of common data models, which map concepts from different data sources into a common format with common definitions. As discussed by two panelists in this workshop session, these methods have enabled the

[1] See Sec. 510, Consolidated Appropriations Act, 2016. Public Law 113, 114th Cong. (December 18, 2015): "None of the funds made available in this Act may be used to promulgate or adopt any final standard under section 1173(b) of the Social Security Act providing for, or providing for the assignment of, a unique health identifier for an individual (except in an individual's capacity as an employer or a health care provider), until legislation is enacted specifically approving the standard."

development of large linked datasets to support both public-sector research and private-sector analyses.

PCORnet's Clinical Data Research Networks

The Patient-Centered Outcomes Research Institute (PCORI) supports health-related decision making by patients, providers, payers, and policy makers by generating and examining evidence on the effectiveness of various medical treatments. Russell Rothman, director, Center for Health Services Research, Vanderbilt University, described how the National Patient-Centered Clinical Research Network (PCORnet), funded by PCORI, is advancing real-world evidence research by leveraging existing electronic health data sources to support national comparative effectiveness studies and pragmatic clinical trials. In addition to its 20 patient-powered research networks, PCORnet consists of 13 clinical data research networks (CDRNs) representing more than 100 health care systems and organizations across the country. PCORnet currently has EHR data from more than 110 million patients, and CDRNs are also working to link EHR data to data from other sources, including claims, vital statistics, registries, state health data, Medicare and Medicaid, and private health plans, in an effort to capture a more complete picture of patients for research purposes.

Because it incorporates standardized data from different sources using a common data model, the PCORnet infrastructure can now be used to identify potentially thousands of patients across the networks with particular conditions, to conduct observational studies that follow patient cohorts over time, and for interventional clinical research, including comparative effectiveness trials. Rothman also described tools that have been developed for PCORnet to support clinical trials, including electronic processes for patient identification and recruitment, consenting, and collecting patient-reported outcomes. These tools, along with some administrative simplification, have enabled the conduct of large pragmatic trials with great efficiency, he said. Rothman cited the ADAPTABLE trial on optimal aspirin dosing for patients with coronary heart disease as an example of the potential of the PCORnet infrastructure for conducting faster, cheaper, and more informative clinical research in the real-world space. In this pragmatic trial, which is still ongoing, patients were identified, recruited, and consented electronically and randomized to baby or regular strength aspirin. Data for follow-up were captured from EHRs and claims, and from patients directly using electronic survey tools. "The front door for PCORnet is now open," said Rothman, for investigators interested in running queries or using the network for observational or interventional research.

Development and Use of Centralized Data Repositories in the Private Sector

In the private sector, efforts to aggregate and analyze data from EHRs, claims, and other sources are driven, in part, by demands from provider networks as they try to control financial risks for managing patient populations. Dore outlined how Optum, part of UnitedHealth Group, compiles data from electronic records (including medical, claims, and pharmacy records) for provider networks into a centralized repository. Data are linked using encrypted data linkage methods so that patient-identifying information is not shared across parties. To address interoperability issues across different record systems within provider networks, Optum uses an intensive manual process to extract information; validates, maps, and normalizes it; and iterates it to get to a standardized data format. Following a series of data quality checks at the end of the process, the company has generated a centralized repository containing data for those patients within a particular provider network. That repository can then be used for a range of analytics, including predictive modeling, quality benchmarking, and risk stratification (e.g., identifying patients who have high risk of rehospitalization). This process can be scaled up so that data from many provider networks are aggregated under a single ontology, capturing more than 70 million patients in a single centralized dataset (see Figure 3-1). Dore said Optum is

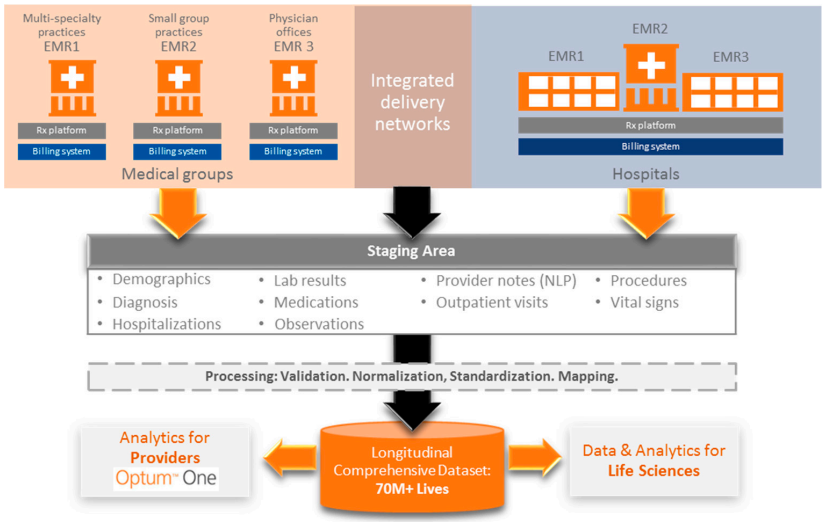

FIGURE 3-1 Optum's process for aggregating data from multiple provider networks into a centralized data repository.
NOTE: EMR = electronic medical record; NLP = natural language processing.
SOURCE: Dore presentation, 2016.

in the process of onboarding other data, including those from clinical trials, registries, and wearables. He emphasized that, beyond supporting clinical decision making for provider networks, these data repositories also have value for clinical research and have been used for observational studies evaluating comparative effectiveness.

COLLECTING REAL-WORLD DATA OUTSIDE THE CLINICAL SETTING USING DIGITAL HEALTH TOOLS

Speaking on the opportunities to engage and collect real-world data directly from patients and consumers outside of the clinical setting, Foschini described the tremendous recent growth of digital health technology in the consumer space. Not only has there been a proliferation of devices on the market, but the measurement capability of these devices is also expanding. Collectively, he estimated, wearables and other consumer devices can now measure physiological parameters at a level that is approaching what might be seen in a hospital intensive care unit.

Because many mobile health devices are commonly worn throughout the day and sometimes even during sleep, excitement regarding their potential stems from the ability to capture data from the 99 percent of patient and consumer activity that occurs outside the health care setting. This allows researchers to track the progression of an individual over time at a much finer level of resolution than ever before. Although these devices can be used to compare pre- and postevent or intervention data at the individual level, it is also possible to develop population-level outcome measures. Foschini cited as an example the measurement of recovery of mobility following surgery. Using data from a mobile health device, it is possible to calculate a mobility index and compare postsurgery levels to baseline to determine the time to recovery of full mobility following surgery. With population-level data, an outcome of interest may be the time it takes for an individual who received the surgery to return to 90 percent of his or her presurgery mobility level; in addition, the impact of variables such as age on the outcome measure can be examined to identify individuals at higher risk of not regaining full mobility.

In the context of clinical trials, the broad, consumer-driven distribution of digital health devices across large and diverse populations has important implications for trial design. For example, said Foschini, these devices can enable virtual study recruitment, which has the potential to increase the efficiency of clinical trials and reach subpopulations that might not be reached through traditional recruitment practices. When considering their use for data collection, however, Foschini emphasized that investigators should remember that these devices will be used in unsupervised settings

and may therefore necessitate a more user-oriented approach than is typical in traditional trial design.

Although there is a great deal of interest in the emerging potential of digital health tools, as demonstrated by an exponential increase in the number of publications featuring analyses of data collected using these devices, a number of workshop participants raised questions about the reliability of data collected using these tools, both in terms of their accuracy and their ability to engage consumers over the long term. A lot of scientific work is needed to validate results from wearables and define wearable-oriented endpoints that will support regulatory approval, cautioned John Hernandez, head of Health Economics, Value, and Access, Verily Life Sciences.

CONSIDERATIONS FOR REALIZING THE POTENTIAL OF REAL-WORLD DATA

The ability to use real-world data to answer research questions regarding effectiveness and value is contingent on access to the full spectrum of health data and capability to transform the data into evidence using analytic tools. In discussions on realizing the potential of real-world data, two key themes emerged: partnering with patients and consumers, and investing in data science capabilities.

Partnering with Patients and the Public

A number of levers can be applied to realize the potential of real-world evidence, including certified EHR technology and regulations, but the fulcrum, said White, is patients and consumers, and specifically, their data and information. Several individual workshop participants commented that the research enterprise needs to do a better job of engaging those individuals as partners. Patients can be a source of important data not routinely collected for purposes of care—socioeconomic, cultural, and educational background factors—that significantly affect treatment outcomes. They can also help to link their own longitudinal care data (e.g., data from surgery and rehabilitation services), said Frankel, who suggested that proactively engaging patients and consumers to obtain such data needs to be part of a data strategy for any research study.

Several examples of patient engagement mechanisms were provided by workshop participants. Rothman described efforts at his institution to make it easy for patients to share their data and participate in research by offering research portals within patient portals. These portals can be used to upload information that could be used for research purposes or to enable patients to sign up to participate in research studies. Robinson Beale highlighted the success of PatientsLikeMe, a patient-powered effort to make data avail-

able for the purposes of finding similar patients and comparing outcomes of different treatments. More broadly, though, said Nigam Shah, associate professor of medicine, Stanford University, a culture of data sharing needs to be promoted to advance the public's understanding that to benefit from a learning health system, patients need to contribute their data.

Investing in Data Science

Data are increasingly becoming an asset for health care providers, with incentives for leveraging "big data" coming from CMS and pay-for-performance opportunities. These drivers are also generating opportunities to apply big data to clinical research, but expertise is a key component to support the necessary aggregation and curation of data and analytics. Several individual workshop participants discussed the creation of a culture of data science within organizations and the importance of investment in data science experts to transform health care data into meaningful information. The health care industry is lagging behind others already adept at working with big data, like many of the dominant American corporations such as Amazon and Walmart, said Califf, who added that efforts are needed to recruit that talent into the health care industry.

4

Generating and Incorporating Real-World Evidence into Medical Product Development and Evaluation: Building from Successful Case Studies

Key Messages Identified by Individual Speakers

- Significant progress has been made with real-world evidence in the medical device world. Drug development processes could be improved by applying lessons learned and best practices from those experiences. However, payment reform and reducing physician burden may be important elements to realize meaningful changes in applying similar methods to drugs. (Califf, Carroll, Mack, Robinson Beale)
- Preapproval pragmatic trials have been carried out in the United Kingdom, where the National Health System infrastructure enables the real-time monitoring of safety outcomes. Clear guidance from FDA on whether such studies would be acceptable in the United States would be helpful. (Roddam, Rothman)
- Reusing infrastructure from past pragmatic trials could achieve greater efficiencies for future studies. (Dember)
- Registries (based on diseases, procedures, or devices) are useful tools for pulling together data that can be used to generate real-world evidence on effectiveness, safety, quality of care, and value of different treatments on real-world patient types. Successfully scaling this approach would be aided by the development of methods to overcome the challenges with registry

operations and data collection, which is currently labor and cost intensive. (Carroll, Hernandez, Mack, Robinson Beale)
- Keys to successful population-based surveillance methods include partnership, transparency, and careful attention to data quality and validation of methods. (Curtis)

Building from the discussions of stakeholder needs and the potential applications of real-world data in the two preceding workshop sessions, discussions during Session III focused on opportunities and challenges for broadly adapting promising practices. Four successful use cases were discussed that showcased how alternative data sources can be used to answer real-world questions. The case studies fell into three categories of real-world evidence approaches—randomization in the clinical setting, research embedded in registries, and population-based surveillance using health system data.

RANDOMIZATION IN THE CLINICAL SETTING

Pragmatic randomized controlled trials (pRCTs) address limitations in the generalizability of results from traditional RCTs by embedding clinical research in the care delivery setting and randomizing interventions at the point of care. The Salford Lung Studies, described by Roddam, are notable as the world's first preapproval pRCTs. The studies, which were initiated in 2012 and conducted in the Salford area of Greater Manchester in the United Kingdom, were designed to evaluate the effectiveness of medication using a once-daily combination inhaler in comparison to existing maintenance therapy for chronic obstructive pulmonary disease (COPD) and asthma. The question drove the approach: Because the comparator arm was continuing treatment with usual care, which would have involved multiple inhalers, it would not have been possible to conduct this evaluation through a traditional RCT in a controlled setting, observed Roddam. The investigators adopted broad inclusion criteria and, importantly, no other aspects of the care being rendered were changed, so the study provided a truly representative assessment of real-world effectiveness in the clinical setting in which the medication would be used. Roddam emphasized that partnerships with local health care entities (e.g., general practitioners, pharmacies) were critical to success, reiterating a point made earlier in the workshop regarding the importance of engaging providers in research. The study involved only two visits—at initiation and again at the end of the study. Between the two visits was a 12-month follow-up period, during which there was continuous real-time collection of data from EHRs and daily safety monitoring. Although the effect of the medication on asthma

is still under investigation, results for COPD endpoints have been publicly reported and a significant reduction in moderate to severe exacerbations was observed for the intervention group, with no increase in the rate of serious adverse events, as compared to usual care (Vestbo et al., 2016). Thus, through this real-world evidence approach, the first Salford Lung Study provided information that could be used to have meaningful conversations with patients about treatment options for COPD.

The pragmatic nature of the trial enabled efficiencies in patient recruitment, by leveraging the clinical system to identify eligible patients, and in data collection. The more data that can be collected from the EHR (versus an independent collection effort), the more efficient the trial becomes, said Roddam. However, although the United Kingdom has a single unique identifier for patients, there were still multiple data streams for each patient (representing different interactions with the health care system, including primary care visits, after hours/emergency care, and pharmacy data), and data collected by different health care entities varied significantly. As a result, Roddam noted, significant effort to combine data on the back end was required.

Discussing how additional efficiencies could be achieved, Laura Dember, professor of medicine, University of Pennsylvania, suggested that consideration should be given to opportunities to reuse the infrastructure for future trials. The Salford Lung Studies, for example, necessitated the training of 3,000 individuals in good clinical practice—these trained individuals now represent a resource that could be leveraged, and doing so could reduce costs for future trials.

Addressing the question of adaptability, John Hernandez of Verily Life Sciences queried Roddam on the potential for doing this kind of preapproval study in the United States. Roddam admitted that the National Health Service infrastructure in the United Kingdom, including identifiers that enabled the linking of patient records, was key to the feasibility of the study, particularly for the real-time monitoring of safety outcomes. Investigators were confident that any serious adverse event would be captured in the system. "If you need to do that in the U.S., it's really hard," he said. Rothman observed that Phase IV (postapproval) pragmatic trials for comparative effectiveness have been successfully carried out in the United States. However, it is not clear whether these kinds of trials would be acceptable to FDA in the preapproval setting and for labeling changes, suggesting that more regulatory guidance is needed. Sherman indicated that FDA is actively working on producing this kind of guidance, reiterating that the sharp distinction between pre- and postmarket in terms of requirements for evidence generation is outdated. There is no reason, Sherman said, "that the evidence we need to know how to use something should be any different than the evidence that we need to know whether or not to approve it or to license it."

RESEARCH EMBEDDED IN REGISTRIES

Registries represent an efficient mechanism of collecting data for specific analytic purposes and can bring discipline to upfront data collection. Device registries have helped to advance the use of real-world evidence in the medical device world and may offer lessons for the drug development field. Michael Mack, chair, Cardiovascular Service Line, Baylor Scott & White Health, described how a public–private partnership led to the creation of a registry-based infrastructure for real-world evidence generation on the effectiveness and safety of transcatheter aortic valve replacement (TAVR). TAVR allows replacement of heart valves without surgery by delivering the valve by a catheter from an artery in the leg to the heart. In 2011, FDA developed an initiative for strengthening postmarket surveillance for devices using national device registries (FDA, 2012). The Society for Thoracic Surgeons/American College of Cardiology (STS/ACC) Transcatheter Valve Therapy (TVT) Registry evolved from that effort as a product of a partnership among FDA, STS, ACC, the Duke Clinical Research Institute, and CMS (Carroll et al., 2013). Discussing the importance of incentives, Mack underscored the critical role CMS played in the success of the TVT Registry. In its national coverage determination, CMS approved the TAVR treatment with coverage under evidence development, whereby CMS requires that services or items be provided in the context of clinical study participation or that additional clinical data be collected to support further evidence development (CMS, 2014). It also mandated participation in the TVT Registry. As a result of these conditions, data from virtually all U.S. patients receiving the device (approximately 75,000 to date) have been captured in the registry. Additionally, linkage to CMS claims data enabled evaluation of long-term (i.e., 1 year and longer) patient outcomes.

Mack outlined a number of ways the TVT Registry has supported real-world evidence generation:

- **Postmarket regulatory purposes—**safety reports are generated and sent to FDA quarterly, supporting postmarket surveillance, and the registry has also supported nested postapproval studies[1] with three different device manufacturers.
- **Premarket regulatory decision making—**registry data on off-label use of the device has supported label expansion, and several inves-

[1] FDA can impose at the time of device approval a requirement for medical device manufacturers to conduct postapproval studies to generate additional evidence on product safety and effectiveness in the postmarket context. For more information see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostApprovaStudies/ucm135263.htm#q5 (accessed November 25, 2016).

tigational device exemption studies have been nested within the TVT Registry.

- **Quality improvement—**quarterly reports generated from registry data have enabled risk-adjusted benchmarking across TAVR sites.
- **Research—**registry data are being incorporated into several different research studies, including an evaluation of volume-to-outcome relationships that may inform the optimal number of TAVR sites, and a comparative effectiveness study comparing outcomes for surgical and non-surgical interventions.

Workshop participants discussed opportunities and challenges to scaling the TVT Registry model as a mechanism for real-world evidence generation. A primary identified challenge was sustainability, given how expensive and burdensome it is to populate and maintain a registry. The TVT Registry is populated manually, and data are collected using a case study form with 400 data fields. Mack noted that a budget of $6 million per year is required to run the registry, and that does not include the cost of full-time employees at each of the 420 TAVR sites who enter the registry data. In the case of TAVR, the device was expensive (approximately $32,000/device) and CMS was the only payer, so the agency was able to condition reimbursement on participation in the registry. How this model would work without the CMS mandate for registry participation is unclear, he said. Without the reimbursement incentive, clinicians would probably not be willing to take on this level of burden. Carroll suggested that increasing the efficiency of the process by which key data elements are extracted from the EHR will be critical to scaling the registry model. Automatic population of a registry with data from EHRs could reduce the burden and cost associated with collecting and entering data, although, Mack cautioned, given the current state of EHRs, autopopulation would likely only be able to be used to populate 20 percent of data fields. Reducing the number of required data elements would also help improve efficiency but, Mack emphasized, it can be challenging to get agreement from all stakeholder organizations, each of which has its own specific interests in the data. Jesse Berlin, vice president and global head of epidemiology, Johnson & Johnson, stressed that to overcome this issue it is important to demonstrate the value of a data field before it can be required.

An expansion of the registry model may be incentivized by payment reform efforts, observed Califf. Bundled payment might encourage the capture of long-term follow-up data in a registry-type database, but, as Carroll noted, providers entering the initial diagnosis/treatment information do not always have access to long-term follow-up data. Therefore, that kind of longitudinal data capture relies on partnerships similar to the one described for the TVT Registry, where CMS data were linked to provide 1-year out-

come data. Robinson Beale added that a shift to measuring true outcomes would be required, rather than just process measures. Additionally, she emphasized that the full potential of registries in a learning health system depends on their ability to provide actionable information to providers in real-time, for example, by connecting to decision support tools.

In the context of bringing use cases to scale, Mack showed a model proposed by John Laschinger, medical officer, FDA, representing a vision for a tiered national device registry infrastructure (see Figure 4-1). In this model, the complexity of the dataset captured in the registry and the level of multistakeholder support would vary across the tiers, depending on the intended use of the registry. The registry at each site would be fit-for-purpose, and sites would apply for a specific level of certification based on the desired level of participation. For those sites in the outermost tier where the registry would be used primarily for local quality improvement work, only the minimum dataset would be collected. This minimum dataset would be common across all tiers (captured through a standard case report form), but additional "modules" would be added sequentially as the desired capability to support studies increased (moving toward the innermost tier).

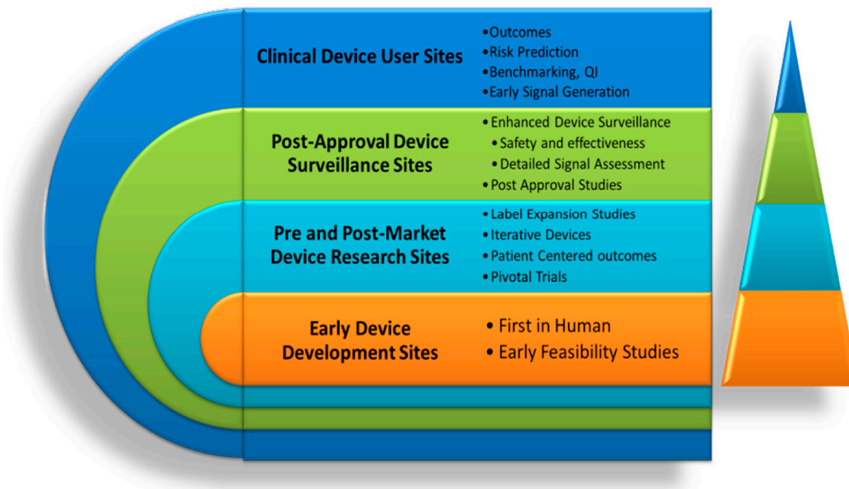

FIGURE 4-1 A model for a tiered national device registry infrastructure.
NOTE: QI = quality improvement.
SOURCE: Mack presentation, 2016.

POPULATION-BASED SURVEILLANCE USING HEALTH SYSTEM DATA

The ability to aggregate data from EHRs and link health-related data from other sources (e.g., claims) has enabled the conduct of large-scale observational research that is answering real-world questions about safety and effectiveness and providing information that informs clinical trials. As examples of the kinds of studies that can be conducted using these large linked datasets to generate real-world evidence, Lesley Curtis, professor of medicine and director for Pragmatic Health Services Research, Duke Clinical Research Institute, shared her experiences with the FDA Sentinel Initiative and Shah discussed the Observational Health Data Sciences and Informatics (OHDSI) program. Workshop attendees also heard a summary from Louis Fiore, executive director, Massachusetts Veterans Epidemiology Research and Information Center on the U.S. Department of Veterans Affairs' framework for gathering and applying data gathered from the population of veterans in their system (see Box 4-1).

BOX 4-1
Knowledge Generation with EHR Data at VA

Louis Fiore, executive director, Massachusetts Veterans Epidemiology Research and Information Center, outlined the U.S. Department of Veterans Affairs' (VA's) approach to using real-world data to inform patient treatments within its system. He emphasized that electronic health records (EHRs) data can be used to glean information at both a population and an individual patient level, but that the ultimate goal should be to inform decisions about an individual patient's care in real-time. This infrastructure needs to be in place before any pragmatic trial begins in order to maximize its utility. Fiore outlined the sequential steps needed for "Local Learning Through Experiments":

1. A patient gets a diagnosis.
2. Those data are aggregated with that of other patients with similar diagnoses.
3. An analysis is performed with a predetermined algorithm.
4. An individualized treatment recommendation is made.
5. The patient can then be entered into a randomized, pragmatic trial embedded within routine clinical care.
6. Patient outcomes are fed back into the disease-specific database, and the prediction algorithm is updated.

SOURCE: Fiore presentation, 2016.

FDA Sentinel Initiative

The impetus for the Sentinel Initiative was the FDA Amendments Act of 2007, which mandated the creation of an active surveillance system for continued safety evaluation of marketed medical products. Sentinel uses private health plan data (clinical, administrative claims, and registry data) for near real-time active safety surveillance. Rather than aggregating the data into a centralized repository, Sentinel uses a distributed data network architecture so that health plans are able to keep their data behind a firewall. Executable code is sent to FDA Sentinel's 19 health plan partners to run behind their firewalls against a common data model similar to the one used by PCORnet. Summarized data are provided to FDA. Through this approach, Sentinel has been able to access data from approximately 190 million individuals, all with private health insurance, resulting in a defined population with longitudinal data. Highlighting Sentinel's impact, Curtis cited 4 FDA drug safety communications; 48 methods papers; 70 peer-reviewed articles; and more than 100 assessments of products, conditions, and product outcome pairs. In discussing opportunities to build from the lessons learned from Sentinel, Curtis laid out three ingredients she believed were critical to its success: engaged partners, attention to data quality, and reusable tools (see Box 4-2). Several workshop participants noted that efforts to adapt the Sentinel model are already under way. In the United States, the new National Evaluation System for health Technology (NEST) initiative will use real-world evidence to conduct postmarket evaluations of safety and performance of medical devices. Additionally, distributed data networks for safety surveillance across Europe are being considered under the auspices of the Innovative Medicines Initiative, a public–private partnership involving the European Medicines Agency and the European pharmaceutical industry.

Observational Health Data Sciences and Informatics Initiative

The OHDSI community is a multistakeholder, interdisciplinary group of investigators working collaboratively to bring out the value of observational research and generate evidence that will improve health decision making through building open-access tools, best practice methods, and a large data network. Currently, 94 different sites from across the world contribute data to the OHDSI network. Although not all sites will participate in every study, that equates to potential access to data from approximately 650 million individuals. The OHDSI suite of tools enables clinical characterization, patient-level prediction, and population-level effect estimation (causal inference). Shah described two of the tools that have been developed by the OHDSI community:

BOX 4-2
Critical Elements in the Success of the Sentinel Initiative

1. **Partnership**—The operation center for FDA Sentinel is led out of the Harvard Pilgrim Health Care Institute, but the health plans that contribute their data and expertise are critical partners. The ability to engage in dialogue with experts in those institutions who have a deep understanding of their data is vital to generating evidence able to support regulatory decision making. The establishment of the partnership called for an understanding of the needs of the various data partners. Recognizing the proprietary interests and competitive nature of these businesses, the decision was made not to create a centralized data repository. Instead, data are extracted via distributed query. Health plans are asked to share only the minimally necessary information and could opt not to respond to requests. In addition to the data partners, other scientific partners bring additional expertise.
2. **Attention to Data Quality**—When analyzing data from a multitude of sources, it is important to have a good understanding of those data sources, how the data are generated, and their associated biases. Mini-Sentinel* employed data validation methods and rigorous data checking to ensure the integrity of the evidence they were generating. For example, each data refresh from health plan partners resulted in approximately 1,500 data checks to confirm the data were transformed according to the common data model and did not change in an unexpected way over time. This was found to be important because data sources are dynamic and data can change between refreshes. By looking at differences across data partners, FDA Sentinel has created opportunities for sharing best practices across that community.
3. **Reusable Tools**—Recognizing that the kinds of queries the Mini-Sentinel operation center would need to run to extract data from health plans for safety surveillance would take a fairly standard form, efficiencies were created by generating a library of reusable tools as part of the Sentinel infrastructure.

* Mini-Sentinel was a pilot program launched in 2009 to inform development of the full Sentinel program. FDA began transition from Mini-Sentinel in 2014, and Sentinel was officially launched in early 2016.
SOURCE: Curtis presentation, 2016.

- **Achilles—**a database profiling tool for characterization of databases (e.g., demographics, subpopulations, and data quality assessment).
- **Atlas—**an integrated platform for building cohorts (e.g., for observational studies), as well as for database exploration and population-level analysis.

In addition to these and other tools, the OHDSI community provides recommendations on methods to improve quality of evidence. This includes both standard diagnostics, such as propensity models used to ensure that comparisons are valid (e.g., two drugs being compared are actually likely to have been prescribed for a given set of patients), and calibration methods using controls that should be used when looking at drug adverse-event associations.

As an example of the potential of OHDSI, Shah discussed a recently published analysis that used the data network to characterize the complement of drugs (e.g., first line, second line) prescribed for three diseases—hypertension, depression, and diabetes (Hripcsak, 2016). This kind of large-scale, real-world characterization of practice can only be done empirically. The results of such analyses can be used to inform future clinical studies—for example, comparative effectiveness studies of different second-line treatments (Vashisht et al., 2016). Figure 4-2 depicts a model that

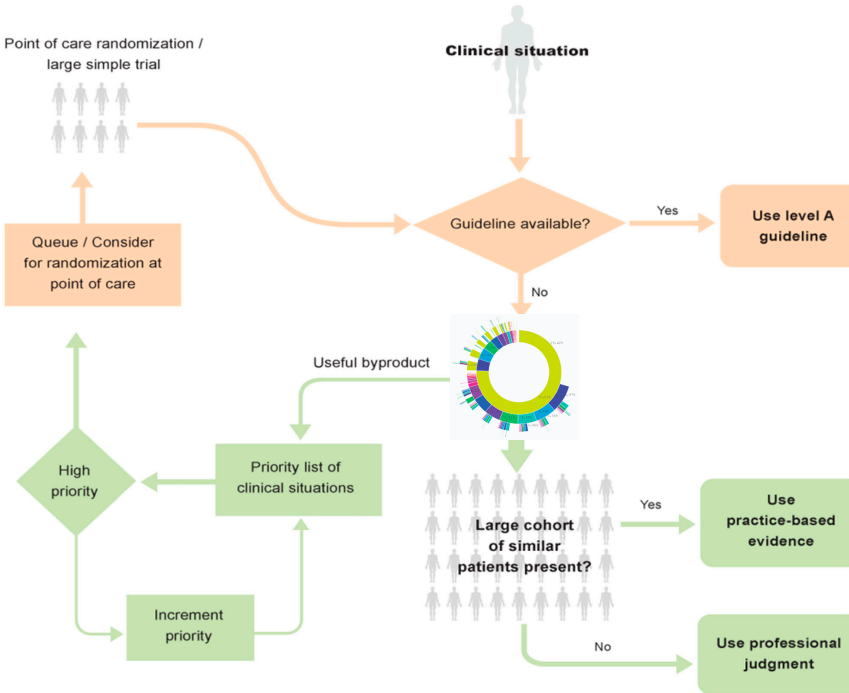

FIGURE 4-2 Schema for leveraging OHDSI resources to inform patient care decisions and clinical studies.
SOURCE: Shah presentation, 2016.

shows how OHDSI can inform both clinical practice and research. In the practice setting, OHDSI's toolsets and data networks could be leveraged to support both clinical practice and research for such a comparative effectiveness study (Longhurst et al., 2014). This model describes three distinct, yet potentially interactive, levels where questions about care are asked in OHDSI: for individual patients (top right), in practice-based or large cohorts (bottom right), and for large populations (left side). In the practice setting, there may be situations for an individual patient where an obvious first-line treatment exists, as depicted by availability of a clinical guideline at the top of the flow chart in Figure 4-2. However, for that same patient, there may not be an obvious second-line treatment, and evidence generation becomes necessary, as depicted by central rings. Thus, when no clinical guideline based on high-quality RCT data is available, health care providers could use a decision support tool, represented by the flow chart shown in Figure 4-2, that leverages OHDSI's existing data networks to aggregate data sources—such as EHRs, claims data, and even social media data—and conduct analyses of treatment results for large cohorts of similar patients (when available in OHDSI databases) and draw on the resultant practice-based evidence to inform care decisions, depicted on the right half of Figure 4-2. As shown on the left half of Figure 4-2, continuous monitoring of such analyses being conducted by clinicians using OHDSI could, as a byproduct, inform a priority list for generating higher quality evidence through pragmatic or large simple trials.

5

Potential Strategies for a Way Forward

Key Messages Identified by Individual Speakers

- Partnership and transparency through data sharing will help leverage the full potential of real-world evidence in a learning health system, as will standardization and harmonization of data elements and outcome measures. However, for progress to be achieved, the perfect need not be the enemy of the good. (Berlin, Lewis-Hall, Shah, Sherman)
- Although significant progress in the generation of robust real-world datasets has been achieved through the use of common data models, standards and improved interoperability could improve front-end data collection and aggregation, reducing the labor-intensive curation of data. (Hernandez, McClellan, Shah)
- Although randomization is an important tool for generating real-world evidence, some questions cannot be answered through randomized trials. With proper controls, calibration, and demonstrated repeatability using independent datasets, observational studies can yield robust evidence that can be used for causal inference in specific circumstances. (Berger, Califf, McClellan)
- Incentives would help to promote the collaboration of health care providers and health care systems in collection and use of clinical care data for research. (Tunis)

- To engage patients and consumers as meaningful partners, researchers could measure outcomes that are important to them, be open about how their data will be used, and share the results of research studies that could inform patients' health care decisions. (Lewis-Hall, White)
- Some individual workshop participants suggested straightforward next steps: connecting existing initiatives and databases; developing and iterating an idealized test case for using real-world evidence throughout product development; and standardizing inputs for stakeholder engagement.

During the closing session of the workshop, individual panelists reflected on the day's presentations and discussions, and identified practical strategies to generate momentum toward the evidence generation paradigm of the future, in which real-world evidence is systematically incorporated into processes for the development and evaluation of medical products. Summarizing workshop participants' comments on factors that would be critical to achieving what Hernandez called "a vibrant ecosystem for real-world evidence," Mark McClellan, director, Margolis Center for Health Policy, Duke University, and moderator of this final session, framed these critical elements for success in the context of four themes: data availability, data methods and quality, study design, and incentives. Highlights from workshop discussions focused on each of these thematic areas are summarized in the sections below.

DATA AVAILABILITY

The systems currently in place are not yielding enough data of high enough quality to be broadly usable for research, stated McClellan. Addressing this issue of data availability, Freda Lewis-Hall, chief medical officer and executive vice president, Pfizer Inc., underscored the need for a fully digitized EHR platform that is interactive and can provide data to:

- patients—to inform decisions on how best to improve their own health;
- providers—to guide treatment decisions;
- health systems—to improve the quality of care they deliver; and
- the research community—to answer questions that can drive improvements in the system.

Achieving this vision of a learning health system could benefit from enhanced integration of the research and clinical care enterprises. Despite the opportunities to leverage synergies and improve efficiency through an

integrated system, however, the potential of practice-based systems for research has yet to be realized. Although a number of technical hurdles remain, many individual workshop participants observed that the main barriers are cultural. Califf noted that "learning in [clinical] practice doesn't seem to be one of the fundamental attributes that's being valued right now." Califf's comments were echoed by Simon, who asserted that the biggest challenge to incorporating data from health care into research is not the quality of the data, but a fundamental problem with the way health care is currently practiced and, specifically, with the recording of information on the delivery of care. Simon expressed his belief that realizing the potential of a learning health system will ultimately require health care systems and providers to be held accountable for systematically and accurately capturing a record of treatment decisions, along with the rationale for those decisions, and for evaluating the impact of the treatment approach on patient outcomes. Also underpinning the system is data sharing, as discussed in more detail in Chapters 2 and 3. The ability to share data seamlessly across systems involves broad stakeholder engagement and a commitment to transparency. It was emphasized by several individual workshop speakers, however, that robust engagement of stakeholders in a learning health system will be bolstered if data partners, whether they are patients, consumers, providers, health plans, or health systems, trust that their data will be protected and that their confidentiality and privacy needs will be responsibly addressed. Califf noted that the privacy and trust principles and data security framework developed under the auspices of the National Institutes of Health's (NIH's) Precision Medicine Initiative (PMI) serve as a strong foundation on which to build going forward to maintain trust in the system.

Partnership

Broadening Stakeholder Engagement

Many individual workshop participants commented that a broadening of the stakeholder engagement process would support a pivot toward an evidence generation system designed to address the needs of multiple stakeholders simultaneously. As end users, patients, clinicians, and health systems could inform the processes that will be used to generate the evidence they ultimately depend on for treatment decisions. One workshop participant observed that in initiatives funded by PCORI, representatives from these stakeholder groups participate in advisory roles, as co-investigators, or on oversight committees, ensuring that their perspectives are incorporated into the design, execution, and dissemination of research. Another workshop participant added that there are a number of other "postregulatory decision makers" (e.g., payers, formulary committees,

guidelines developers, and health technology assessment organizations) that address the quality and relevance of the evidence; there are benefits to ensuring they are at the table for early discussions on evidence generation processes (e.g., methodology, data sources).

Several individual workshop participants noted that bringing to scale the kinds of successful initiatives highlighted at the workshop will be bolstered by a significant investment in infrastructure. In discussions on how such an infrastructure could be supported, one participant asked whether those investments would be made by the government, by advocacy organizations, or by industry groups. In response, Sherman expressed her belief that the federal government can be a partner but, given the current fiscal climate, it is not going to finance the development of the infrastructure on its own. Another participant stressed that the kind of public–private partnership approach that worked for the TVT Registry needs to be expanded. In such partnerships, federal agencies can use policy tools to develop opportunities to generate and use real-world evidence, but also have the leverage to bring stakeholders (including patients and patient organizations) together in a precompetitive way to discuss infrastructure needs, priorities, and how to move beyond approaches that are obsolete and ineffective. With multiple private stakeholders, infrastructure costs can be shared, said Berlin, but conveying the value of the infrastructure to industry partners will be critical to making the business case for their participation.

Engaging Patients and Consumers as Partners

Beyond identifying the kinds of stakeholders that need to be engaged in evidence generation processes, additional points of emphasis from individual workshop participants focused on redefining what engagement means, particularly for patients and consumers. "We have really got to change the way we think about how we engage with people," said White, noting that in the PMI's All of Us Research Program, there are no research subjects, only research participants. Lewis-Hall outlined three aspects of meaningful partnerships with patients: engaging them in the collection of data, giving data back to them, and assessing outcomes that are meaningful to them. One workshop participant observed that measuring outcomes important to patients (e.g., improved quality of life) enables the incorporation of those outcomes into value calculations. Although patient-centric outcomes like functionality traditionally have not been a focus, it was noted that progress has been made in this area in recent years. The Cancer Moonshot Blue Ribbon Panel set as 1 of its 10 priorities the incorporation of patient-reported outcomes and quality-of-life measures into EHRs, and PCORnet has endorsed many patient-reported outcome measures from the Patient-Reported Outcomes Measurement Information System (PROMIS).

Transparency

The importance of transparency arose in two different contexts during the workshop discussions. The first was transparency with regard to those whose data are collected and analyzed. In addition to reciprocal data sharing and forthright conversations about data security discussed in Chapters 2 and 3, ethical issues arise with secondary uses of data when research is embedded into the clinical care infrastructure. One participant noted that at his institution, possible secondary uses of data are explained upfront and patients are given the option of excluding themselves.

The other area where a need for improved transparency was noted is sharing of study methods and outcomes. Progress in data sharing for clinical trials represents a model that can be more broadly applied to improve transparency, said Berlin. In addition to sharing protocols, making available the code used to generate an analysis would not only improve transparency by showing the approach investigators took, but would also help demonstrate reproducibility by enabling the testing of methods on different datasets. Both are important to building the credibility of real-world evidence, added Shah.

STUDY DESIGN, DATA METHODS, AND DATA QUALITY

When is real-world evidence good enough and for what purposes? This framing question, posed by Berger, set up a series of discussions on the use of appropriate methodological approaches focused on study design, validating data methods, and improving data quality. In the context of these discussions, a number of individual participants emphasized that evidence should be fit-for-purpose, and the optimal methodology will depend on the research question.

Study Design

Discussing the relative value of different study designs, Califf emphasized that although RCTs are not the answer to every question, randomization has a critical role to play in ensuring that clinical trials provide definitive results. Novel designs that employ randomization at the point of care, Califf continued, can advance the generation of real-world evidence while shielding results against bias. Acknowledging that pragmatic trials are a valuable means of addressing many of the methodological concerns about real-world evidence, Berger pointed out that such trials are still expensive to conduct and cannot meet all of the needs of a learning health system. In fact, results from RCTs and observational studies often are comparable, he said, citing a Cochrane report that found little evidence for significant effect

estimate differences between observational studies and RCTs (though the authors of this report also note that factors other than study design should be considered when examining reasons for lack of agreement between RCTs and observational studies) (Anglemyer et al., 2014). On the other hand, Rothman noted that pragmatic trials may increase in efficiency and decrease in cost over time with advances in technology, as evidenced by the success of the ADAPTABLE trial. For example, technological advances will take advantage of how patients are identified, contacted, and recruited, noted Rothman, as well as how data are collected and standardized. To strengthen the reliability of observational studies, Berger suggested that many of the same approaches used to ensure the validity of RCT data be adopted, including

- preregistration of studies in public registries with prespecified protocols and data analysis plans;
- checks to ensure best methodological practices were followed; and
- ensuring repeatability through multiple studies on different datasets.

McClellan added that, for validation purposes, results from observational studies can be compared to RCT results if available, as was done during the early years of FDA's Sentinel Initiative. Recognizing that the strength of evidence from observational studies falls short of that from well-controlled clinical trials, Berger and McClellan emphasized that with proper controls, calibration, and demonstrated repeatability using independent datasets, secondary data can nevertheless be used for causal inference. Moreover, observational studies are being used when RCTs are infeasible, as in the case of rare diseases.

Data Methods and Data Quality

Data from the health care enterprise are extraordinarily complex, said McClellan, and can mean different things when coming from different sources. Thus, it is important to have a robust understanding of the sources and characteristics of data being used to generate real-world evidence on the effectiveness and value of medical products. Many individual workshop participants noted that a lack of common standards and interoperability issues necessitate labor- and cost-intensive efforts to combine information from different records (e.g., manual data entry to populate registries or time-consuming curation efforts to generate linked datasets). Hernandez pointed out that health care lags far behind other industries in terms of the capability to share and generate insights from "big data" and stressed that policy makers need to be thinking about how to ensure, and potentially even mandate, the seamless interoperability of real-world data so they can

be shared across multiple data systems in a plug-and-play fashion using tools like standard application programming interfaces. While the challenge was identified by participants as one of the more tractable ones, interoperability issues were noted as a source of great inefficiency and lost potential for electronic health data.

Several individual workshop participants pointed to the increasing use of common data models to transform data into a standard format on the back end as a partial solution. Although there can be variability in the models themselves, this can be attributed to the different purposes for which the models were created, and reflects ongoing innovation. Common data models need to evolve to accommodate new kinds of data being generated. Once data have been mapped to a common data model, however, it is much easier to map those data to each other. Significant progress has been achieved using such back-end data curation methods, but considerable opportunity remains for the implementation of standards and common terminology for prospective data collection, as called for in the Nationwide Interoperability Roadmap published recently by the ONC (2015). Standardization on the front end has the potential to dramatically reduce the effort required for back-end data curation.

Shah elaborated on the importance of method validation given the higher standard of evidence and level of rigor required for causal inference. Stakeholders need confidence in the data models, statistics, and comparison methods that go into generating the evidence they will use to inform their decisions. Noting that common data models have been validated by application to a wide range of datasets used to conduct real-world studies, Shah suggested that a shared standard dataset—on the scale of millions of patients—could be used for benchmarking to facilitate more rapid progress in methods development in the real-world evidence realm. McClellan added that with more validated methods, there may be less need to share or aggregate sensitive raw data and more evidence could be generated using "cloud-based" approaches as described for Sentinel and OHDSI, where patient-level data are retained behind the firewalls of data partners.

INCENTIVES

Incentives are powerful drivers of change. Lewis-Hall observed that a shift from traditional separate evidence generation systems for clinical practice and research to an integrated model that addresses the real-world questions of all stakeholders will require a realignment of incentives, adding that it will be important to consider the different kinds of incentives that will work for different stakeholders. Shah added that the infrastructure for a real-world evidence generation platform should include a data strategy

that defines the incentives to ensure data are made available for clinical research over time.

Incentivizing Patients and Providers to Participate in Clinical Research

Many individual workshop participants emphasized that if the path forward for real-world evidence is to embed research in the clinical care infrastructure, the key elements of incentivizing health care providers and health systems to capture high-quality data and participate in prospective research will require a significant culture change. Tunis underscored the need to understand what motivates clinicians to engage. The following possible incentives for health care providers were suggested by individual workshop participants:

- **Communicate the importance of provider participation—**If health care providers are asked to take on additional responsibilities beyond their clinical burden to assist with patient recruitment and data collection for research purposes, it will be important for them to understand why their participation is critical and how the research could benefit their patients.
- **Ask questions that interest providers and health systems—**Providers and health systems will be more willing to engage in studies that are interesting to them and address the real-world questions they face, such as how to provide better care for their patients and how to reduce costs. Engaging providers in the development of questions early in the process can improve the relevance of the study to their needs. Asking questions that health systems care about could provide more opportunities to leverage the clinical care infrastructure and resources for research. For example, health system administrators may encourage providers to participate in research that helps answer questions related to performance improvement. Feeding information on study results back to providers could bolster their ongoing participation in research.
- **Emphasize prestige—**It is unethical to offer financial incentives to health care providers or institutions for participating in research studies, but recognition and prestige can be a powerful driver. Opportunities for recognition as a primary investigator and publication in peer-reviewed journals may be attractive to providers, particularly for those in academic institutions.

Similar incentives were suggested as possible motivators for engaging patients in research. Patients may be more likely to enroll in studies or share their data if researchers are asking questions and measuring outcomes

that matter to them and communicating how the results can help them make better decisions on treatment options. One participant reminded the audience of the simple power of a thank you and added that even in cases where there is no direct benefit to the patient, many patients will be willing to participate if they can understand how the research may help others.

The Role of Regulators

Steven Galson, senior vice president for Global Regulatory Affairs and Safety, Amgen Inc., noted that regulators have a number of tools that could be employed to incentivize the incorporation of real-world evidence into evidence generation processes. A relatively simple means of encouraging industry to take the risks perceived to be associated with real-world evidence generation is through improved communication and coordination efforts. Guidance on the use of real-world evidence for regulatory purposes like that recently published by FDA for medical devices (FDA, 2016) can help to increase confidence in expanding beyond traditional evidence collection processes. Furthermore, the 21st Century Cures Act, signed into law on December 13, 2016, directs FDA to produce a framework, program, and guidance on the use of real-world evidence to help support the approval of a new indication for a previously approved drug and to help support or satisfy postapproval study requirements (21st Century Cures Act, Public Law 114-255, 114th Cong., 2d sess. [December 13, 2016]). Sherman noted that, in addition to guidance, shifting the dialogue between FDA and industry to earlier in the development pathway would provide more opportunity for FDA to influence decisions on use of real-world data sources and capture of patient-centric outcome measures. FDA is also working on internal education regarding the appropriate use of real-world evidence. Another key leverage point FDA has, Sherman pointed out, is its labeling authority. Companies may be incentivized to generate real-world evidence if they knew it would be going into FDA labeling. As an example of how FDA is using many of its tools (e.g., grants, guidance, and coalition building) to advance the use of real-world evidence for the evaluation of medical devices, McClellan cited the NEST initiative.

The Role of Payers

Aligning payments for drugs and devices with payment reforms that are taking place in the health care industry would put drug and device manufacturers "on the hook" along with providers for demonstrating better patient population outcomes and lower total cost of care, said McClellan. Payers can employ a number of levers to realign payment-based incentives, including pay-for-performance and pay-for-certification. Robinson Beale

added that payers can pay for provider participation within organized and sound entities using big data for decision support. To facilitate this, it is important that payers know which of those big data products and methodologies are sound and will produce the best evidence to drive practice-level outcomes and help providers to be more effective, stressed Robinson Beale.

SOME PRACTICAL NEXT STEPS

McClellan brought the workshop to a close by asking panelists to identify practical next steps that can be initiated now that would significantly advance the generation and application of real-world evidence and our understanding of how medical products—those on the market today and those in the pipeline—perform in the real world.

Connecting Existing Systems and Initiatives

At the federal level, different agencies are spending significant energy and resources creating separate systems and initiatives to address similar and connected goals (see Box 5-1). Several individual workshop participants suggested that an important next step is to connect these existing systems into a national evidence generation platform. Califf emphasized that this is not about creating a single system, but rather a federation that works together under a common set of rules and facilitates data sharing to answer questions efficiently. Galson added that in the process, some systems and initiatives may need to be abandoned so that the limited resources available are being directed to those that are going to result in the greatest advances.

Developing End-to-End Use Cases

The reshaping of a national evidence generation system is a systems problem to be examined in an end-to-end fashion, so that standards, methods, and incentives are aligned across the whole. Instead of attempting to address each element of the system piecemeal, one practical next step, suggested Lewis-Hall, could be the development of end-to-end use cases. The process would start by asking the question: What would be the plan for using real-world data at discrete points and under specific circumstances for developing a new therapeutic? Such use cases would enable, for example, the identification of points in the process where incentives are not optimally aligned so that decisions could be made on how best to incentivize the stakeholders at those points. Iterated several times, the process will start to solve the system problem, observed Lewis-Hall.

BOX 5-1
Federal Systems and Initiatives Related to Evidence Generation

- U.S. Food and Drug Administration (FDA)—Sentinel, National Evaluation System for health Technology (NEST), Medical Device User Fee Amendments (MDUFA) data standardization
- National Institutes of Health (NIH)—Clinical and Translational Science Awards (CTSA), Health Care Systems (HCS) Collaboratory, multiple Institute/Center networks
- Centers for Disease Control and Prevention (CDC) Vaccine Surveillance Network
- Office of the Assistant Secretary for Planning and Evaluation (ASPE)—Patient-Centered Outcomes Research (PCOR) Trust Fund
- Patient-Centered Outcomes Research Institute (PCORI)—The National Patient-Centered Clinical Research Network (PCORnet)
- Centers for Medicare & Medicaid Services (CMS)—Enclave, Coverage with Evidence Development
- U.S. Department of Veterans Affairs' Million Veterans' Program
- NIH's Precision Medicine Initiative (PMI)

SOURCE: Califf presentation, 2016.

Creating a Standard Process for Stakeholder Engagement

Several workshop participants expressed frustration with the current sequential process for evidence generation, which is inefficient and does not meet the needs of all stakeholders, often necessitating post-hoc efforts to address gaps. The evidence generated to support regulatory approval, for example, may not meet payer requirements for coverage determinations, resulting in a need for additional studies. Hernandez suggested that a formal process for stakeholder engagement be developed to guide efforts on working together in a collaborative fashion end to end. The goal of companies soliciting input from stakeholders (including patients, providers, payers, and regulators) early in the process would be to generate a single development plan that meets multistakeholder needs.

Appendix A

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Appendix B

Workshop Agenda

REAL-WORLD EVIDENCE GENERATION AND EVALUATION OF THERAPEUTICS: A WORKSHOP

October 19, 2016
National Academy of Sciences Building, Room 120
2101 Constitution Avenue, NW, Washington, DC 20418

BACKGROUND AND WORKSHOP OBJECTIVES

The traditional process for evaluating new therapeutics does not produce the evidence that patients, clinicians, and payers need for real-world decisions. The volume and complexity of information about individual patients is greatly increasing with use of electronic records and personal devices. Possibilities for medical product development in the context of this wealth of real-world data are great, ranging from the ability to determine both large-scale and patient-specific effects of treatments to assessing how therapeutics affect patients' lives through measurement of lifestyle changes. However, mechanisms to facilitate efficient use of real-world data to meet the decision-making needs of myriad stakeholders have not been established. An ad hoc committee will plan and conduct a 1-day public workshop that will examine opportunities and challenges for incorporating real-world evidence into evaluation of medical products.

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

- Quality of data from real-world sources, including
  - Relevance and validity of different sources of real-world data (e.g., user collected, practice based) in the context of different clinical/scientific questions; and
  - Strengths and limitations of different data sources at different stages of treatment development and the licensing process.
- Methodologies and best practices for high-quality, real-world evidence generation and application, including
  - Innovations in clinical trial design to maximize value of information for the full range of stakeholders;
  - Considerations of how evidence generation from existing studies could potentially inform the design of future clinical trials and amplify understanding of product efficacy;
  - Discussion of how shared goals of payers and regulators can better align evidence generation processes used for regulatory evaluation and decisions on use by payers; and
  - Re-evaluation of traditional distinctions between goals and methods of preapproval and postapproval research.
- Other novel methodologies and approaches to improve development and evaluation of products using real-world evidence, including
  - Use of Web-based or digital technologies to enhance clinical trial evidence collection and participation; and
  - Techniques and case studies for effectively using electronic health record data.

8:30 a.m. SESSION I: BREAKING THE MOLD: STAKEHOLDER PRIORITIES FOR IMPROVING EVIDENCE GENERATION

Session Objectives:

- Examine different stakeholder evidence needs to support decision making and identify shared goals.
- Discuss priorities for facilitating use of real-world evidence to address stakeholder needs.
- Discuss aligning incentives to maximize generation and sharing of useful evidence.

8:30 a.m. **Opening Remarks and Introductions**

Steven Galson, *Workshop Co-Chair*
Senior Vice President for Global Regulatory Affairs and Safety
Amgen Inc.

Greg Simon, *Workshop Co-Chair*
Investigator, Group Health Research Institute
Chair, Scientific Advisory Board, Depression and Bipolar Support Alliance

8:45 a.m. **Keynote**

Robert Califf
Commissioner
U.S. Food and Drug Administration

9:05 a.m. **Stakeholder Perspectives**

John Carroll
Professor of Medicine
Co-Medical Director, Cardiac and Vascular Center
University of Colorado Hospital

Joseph Chin
Deputy Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services

Naftali Zvi Frankel
Patient and Consumer Advocate

Rhonda Robinson Beale
Chief Medical Officer
Blue Cross of Idaho

Rachel Sherman
Deputy Commissioner for Medical Products and Tobacco
U.S. Food and Drug Administration

Patrick Vallance
President, Pharmaceuticals Research and Development
GlaxoSmithKline

9:30 a.m. **Moderated Discussion with Session I Speakers and Audience**

ROBERT CALIFF, *Moderator*
Commissioner
U.S. Food and Drug Administration

10:45 a.m. **Break**

11:00 a.m. SESSION II: WHAT CAN WE LEARN FROM REAL-WORLD DATA?

Session Objectives:

- Examine different sources of real-world data (e.g., user collected, practice based) and consider their reliability in the context of different clinical/scientific questions.
- Discuss strengths and limitations of different data sources at different stages of treatment development and licensing process.

11:00 a.m. **Background and Session Objectives**

JOHN HERNANDEZ, *Moderator*
Head of Health Economics, Value and Access
Verily Life Sciences

NIGAM SHAH, *Moderator*
Associate Professor of Medicine, Biomedical Informatics Research
Stanford University

11:05 a.m. **Sources for and Practical Use of Real-World Data**

Data Sharing and Linking Records Across Electronic Health Record Vendors

JON WHITE
Deputy National Coordinator for Health Information Technology
Office of the National Coordinator for Health Information Technology

PCORnet and Clinical Data Research Networks

Russell Rothman
Director, Center for Health Services Research
Chief, Internal Medicine and Pediatrics
Vanderbilt University

Potential for Data Analytics

David Dore
Vice President, Epidemiology and Principal Epidemiologist
Optum Life Sciences

Using Data from Activities on Mobile Devices

Luca Foschini
Co-Founder and Chief Data Scientist
Evidation Health

11:45 a.m. **Moderated Discussion with Session II Speakers and Audience**

12:30 p.m. **Lunch**

1:15 p.m. SESSION III: THE PROMISE OF REAL-WORLD EVIDENCE: STRATEGIES FOR BUILDING FROM SUCCESSFUL USE CASES

Session Objectives:

- Discuss examples of successful approaches to generating and incorporating real-world evidence into development and evaluation of medical products.
- Identify opportunities and challenges to scaling up successful practices and adapting them to new purposes.

1:15 p.m. **Background and Session Objectives**

Jesse Berlin, *Moderator*
Vice President and Global Head of Epidemiology
Johnson & Johnson

Cathy Critchlow, *Moderator*
Vice President and Head, Center for Observational Research
Amgen Inc.

1:20 p.m. **Successful Use Cases of Real-World Evidence**

Case Study #1: Salford Lung Study

Andrew Roddam
Vice President and Head of Real-World Evidence
GlaxoSmithKline

Case Study #2: Transcatheter Valve Therapy (TVT) Registry

Michael Mack
Chair, Cardiovascular Service Line
Baylor Scott & White Health

Case Study #3: Sentinel Initiative

Lesley Curtis
Professor of Medicine
Director for Pragmatic Health Services Research
Duke Clinical Research Institute

Case Study #4: Observational Health Data Sciences and Informatics (OHDSI)

Nigam Shah
Associate Professor of Medicine, Biomedical Informatics Research
Stanford University

2:20 p.m. **Moderated Discussion with Stakeholder Reaction Panel**

Marc Berger
Vice President, Real-World Data and Analytics
Pfizer Inc.

Laura Dember
Professor of Medicine
Renal, Electrolyte, and Hypertension Division
University of Pennsylvania

Louis Fiore
Executive Director
Massachusetts Veterans Epidemiology Research and Information Center

Rhonda Robinson Beale
Chief Medical Officer
Blue Cross of Idaho

Sean Tunis
Founder, President, and Chief Executive Officer
Center for Medical Technology Policy

3:30 p.m. **Break**

3:45 p.m. SESSION IV: REAL-WORLD EVIDENCE OF THE FUTURE: POTENTIAL STRATEGIES FOR A WAY FORWARD

Session Objectives:

- Outline an ideal future state for incorporating real-world evidence into evaluation of medical products.
- Identify short- and long-term next steps at any stage of clinical research to achieve seamless use of real-world evidence.
- Discuss incentives that should be explored.

3:45 p.m. **Reflecting on Tactics and Strategies for a Way Forward: Discussion with Workshop Co-Chairs, Session Moderators, Panelists, and Audience**

Mark McClellan, *Moderator*
Director
Margolis Center for Health Policy
Duke University

Steven Galson, *Workshop Co-Chair*
Senior Vice President for Global Regulatory Affairs and Safety
Amgen Inc.

Greg Simon, *Workshop Co-Chair*
Investigator, Group Health Research Institute
Chair, Scientific Advisory Board, Depression and Bipolar Support Alliance

Jesse Berlin
Vice President and Global Head of Epidemiology
Johnson & Johnson

Naftali Zvi Frankel
Patient and Consumer Advocate

John Hernandez
Head of Health Economics, Value and Access
Verily Life Sciences

Freda Lewis-Hall
Chief Medical Officer and Executive Vice President
Pfizer Inc.

Nigam Shah
Associate Professor of Medicine, Biomedical Informatics Research
Stanford University

Rachel Sherman
Deputy Commissioner for Medical Products and Tobacco
U.S. Food and Drug Administration

4:20 p.m. **Moderated Discussion with Session IV Panel and Audience**

5:00 p.m. **Adjourn**

Appendix C

Participant Biographies

MARC BERGER, M.D., is vice president, Real-World Data and Analytics, in the Global Health & Value group at Pfizer Inc. Dr. Berger has held senior-level positions in industry, including executive vice president and senior scientist at OptumInsight; vice president, Global Health Outcomes at Eli Lilly & Co.; and vice president, Outcomes Research and Management at Merck & Co., Inc. He has served on the Medicare Evidence Development & Coverage Advisory Committee for the Centers for Medicare & Medicaid Services; the steering committee for the Agency for Healthcare Research and Quality's Centers for Research and Education on Therapeutics; the board of the International Society for Pharmacoeconomics and Outcomes Research; the Advisory Council for North America of the Drug Information Association; and the editorial advisory board of *Value in Health*. He has chaired the Innovative Technology Advocacy Committee of Pharmaceutical Research and Manufacturers of America. Dr. Berger has written or co-written more than 100 peer-reviewed articles, book chapters, and other publications on a range of topics, including health services research, outcomes research, health economics, and health policy. He co-edited *Health Care, Cost, Quality, and Outcomes—ISPOR Book of Terms*, which was published in 2003 and was subsequently translated into nine languages. His current research focuses on rapidcycle analytics of real-world data, including electronic health records to provide timely insights into the outcomes associated with alternative therapeutic strategies and the use of big data and advanced analytics (including machine learning) to develop predictive models in support of precision medicine drug development. He is also actively

involved in promoting best practices for the leveraging of real-world data to inform health care decision making.

JESSE A. BERLIN, S.C.D., received his Doctorate in Biostatistics from the Harvard School of Public Health. After spending 15 years as a faculty member at the University of Pennsylvania (Penn) Center for Clinical Epidemiology and Biostatistics under the direction of Dr. Brian Strom, Dr. Berlin left Penn to join Janssen Research & Development as a senior director in biostatistics. After 2 years, he was promoted to vice president for epidemiology. He now serves as vice president of epidemiology across all of Johnson & Johnson, with responsibility for pharmaceuticals, devices, and consumer products. He has authored or co-authored more than 250 peer-reviewed publications in a wide variety of clinical and methodological areas, including papers on the study of meta-analytic methods as applied to both randomized trials and epidemiology. He served on an Institute of Medicine committee that developed recently released recommendations for the use of systematic reviews in clinical effectiveness research, and currently serves as chair of the Scientific Advisory Committee to IMEDS (Innovation in Medical Evidence Development and Surveillance), part of the Reagan-Udall Foundation. IMEDS is aimed at understanding methodology for assessing drug safety in large, administrative databases. Dr. Berlin co-chairs the Scientific Oversight Committee (with Greg Pappas from the U.S. Food and Drug Administration) for the Medical Device Epidemiology Network Initiative (MDEpiNet), a public–private partnership that is working toward developing methods and data sources for the evaluation of medical devices. He also serves on the Executive Operations Committee for MDEpiNet. Dr. Berlin serves as a member of working group X for CIOMS (The Council for International Organizations of Medical Sciences), which is developing guidelines for meta-analysis of drug safety data in the regulatory context. He was elected as a Fellow of the American Statistical Association in 2004. In 2013, Dr. Berlin received the Lagakos Distinguished Alumni Award from the Department of Biostatistics at the Harvard School of Public Health.

ROBERT M. CALIFF, M.D., MACC, is the U.S. Food and Drug Administration's (FDA's) Commissioner of Food and Drugs. As the top official of FDA, Dr. Califf is committed to strengthening programs and policies that enable the agency to carry out its mission to protect and promote the public health. Previously, Dr. Califf served as FDA's Deputy Commissioner for Medical Products and Tobacco. In that capacity, he provided executive leadership to the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, and Center for Tobacco Products. He also oversaw the Office of Special Medical Programs and provided direction for crosscutting clinical,

scientific, and regulatory initiatives, including precision medicine, combination products, orphan drugs, pediatric therapeutics, and the advisory committee system. Prior to joining FDA, Dr. Califf was a professor of medicine and vice chancellor for clinical and translational research at Duke University. He also served as director of the Duke Translational Medicine Institute and as founding director of the Duke Clinical Research Institute. A nationally and internationally recognized expert in cardiovascular medicine, health outcomes research, health care quality, and clinical research, Dr. Califf has led many landmark clinical trials and is one of the most frequently cited authors in biomedical science, with more than 1,200 publications in the peer-reviewed literature. Dr. Califf has served on the Institute of Medicine (IOM) committees that recommended Medicare coverage of clinical trials and the removal of ephedra from the market, as well as on the IOM Committee on Identifying and Preventing Medication Errors and on the IOM Health Sciences Policy Board. He has served as a member of the FDA Cardiorenal Advisory Panel and the FDA Science Board's Subcommittee on Science and Technology. Dr. Califf has also served on the Board of Scientific Counselors for the National Institutes of Health (NIH) and the National Library of Medicine, as well as on advisory committees for the National Cancer Institute; the National Heart, Lung, and Blood Institute; the National Institute of Environmental Health Sciences; and the Council of the National Institute on Aging. While at Duke, Dr. Califf led major initiatives aimed at improving methods and infrastructure for clinical research, including the Clinical Trials Transformation Initiative, a public–private partnership co-founded by FDA and Duke. He also served as the principal investigator for Duke's Clinical and Translational Science Award and the NIH Health Care Systems Research Collaboratory coordinating center. Dr. Califf is a graduate of Duke University School of Medicine. He completed a residency in internal medicine at the University of California, San Francisco, and a fellowship in cardiology at Duke.

JOHN CARROLL, M.D., FACC, MSCAI, received his A.B. in biology cum laude from Princeton University and his M.D. (Alpha Omega Alpha) from the University of Chicago. He trained in internal medicine and cardiovascular disease at Tufts New England Medical Center, finishing as the Samuel Levine Cardiology Research Fellow of the American Heart Association. He then became a Cardiology Research Fellow at Universitaetsspital in Zurich, Switzerland. From 1982 to 1996, he was a member of the faculty at the University of Chicago Pritzker School of Medicine and directed the Hans Hecht Cardiac Catheterization Laboratory. In 1996 he moved to the University of Colorado as professor of medicine, director of Interventional Cardiology, and co-medical director of the Cardiac and Vascular Center. He is currently a member of various national and international

editorial and advisory boards, the Society for Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry Steering Committee, and the Steering Committee of the RESPECT trials. Dr. Carroll is an interventional cardiologist with clinical and investigative interests related to structural/valvular heart disease interventions, clinical trials, and the development of advanced cardiac three-dimensional imaging for image guidance.

JOSEPH CHIN, M.D., M.S., is the deputy director of the Coverage and Analysis Group (CAG) in the Center for Clinical Standards and Quality at the Centers for Medicare & Medicaid Services (CMS). He joined CMS in 1992 as a medical officer in the quality improvement component and transitioned to CAG in 1999, focusing on systematic evidence reviews, Medicare translational science, and preventive services. Prior to joining CMS, Dr. Chin practiced full time in occupational and ambulatory medicine. He is board certified in preventive medicine. He completed his M.D., M.S. in epidemiology, and residency at the University of Maryland School of Medicine, and maintains a primary care practice in Maryland.

CATHY W. CRITCHLOW, Ph.D., is head of the Center for Observational Research (CfOR). Dr. Critchlow provides operational and strategic leadership for the design and conduct of observational research within Amgen Inc. The CfOR Real-World Data Platform provides widespread access to patient health data and visualization and analytic tools based on innovative technologies to aid teams in the generation of real-world evidence in support of drug development and commercialization of Amgen products. Dr. Critchlow joined Amgen Inc. in 2004, and led a number of therapeutic areas prior to being named head of CfOR in 2012. Previously, Dr. Critchlow spent several years as a faculty member in epidemiology in the School of Public Health and Community Medicine at the University of Washington. Her past work focused on infectious disease and reproductive epidemiology. She was a member of the Endocrinologic and Metabolic Advisory Committee of the U.S. Food and Drug Administration and has served on a number of Study Sections and Special Emphasis Panels of the National Institutes of Health. Dr. Critchlow earned her bachelor's degree from Stanford University, and both her master's degree in biomathematics and her doctorate degree in epidemiology from the University of Washington. Dr. Critchlow is an affiliate professor of epidemiology at the University of Washington and a fellow of the American College of Epidemiology.

LESLEY CURTIS, Ph.D., is a professor of medicine at the Duke University School of Medicine and directs the Center for Pragmatic Health Services Research in the Duke Clinical Research Institute. A health services researcher by training, Dr. Curtis oversees a portfolio of projects that use

observational data to address questions related to clinical and comparative effectiveness, pharmacoepidemiology, health care delivery, and epidemiological trends. Dr. Curtis has considerable experience analyzing Medicare claims data, large clinical registries, and prescription drug data, and has led the linkage of large clinical registries with longitudinal Medicare claims data. In addition, Dr. Curtis has been responsible for the linkage of those data with longitudinal cohorts in the Cardiovascular Health Study, the Framingham Heart Study, the Jackson Heart Study, and the Multi-Ethnic Study of Atherosclerosis (MESA). Experienced in facilitating large-scale, multi-institutional research through the use of distributed health data networks, Dr. Curtis co-leads the Data Core for the U.S. Food and Drug Administration's Mini-Sentinel Initiative, co-leads the Electronic Health Record Core for the National Institute of Health's Health Care Systems Collaboratory, and co-leads the Data Standards, Security, Networking, and Infrastructure Task Force for the Patient-Centered Outcomes Research Institute's National Clinical Research Network.

LAURA DEMBER, M.D., has more than 20 years of experience as a general nephrologist and has internationally recognized expertise in the systemic amyloidoses, a group of rare disorders that often affect the kidneys. She is a member of the University of Pennsylvania multidisciplinary amyloidosis program that evaluates and treats patients with all types of amyloidosis. Dr. Dember conducts patient-oriented research, including mechanistic studies and clinical trials in chronic kidney disease and end-stage renal disease (ESRD). She has particular interests in hemodialysis vascular access and interventions to improve clinical outcomes in ESRD. Her research is funded by the National Institutes of Health (NIH). Dr. Dember is principal investigator for the Data Coordinating Center of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Hemodialysis Novel Therapies Consortium, which is conducting early-phase clinical trials targeting ESRD-associated inflammation. She is also principal investigator for the "TiME Trial," a large, pragmatic cluster-randomized clinical trial being conducted through the NIH Health Care Systems Research Collaboratory. The TiME Trial will enroll 6,400 participants at 400 dialysis units throughout the United States using a highly centralized and efficient implementation approach leveraging the infrastructure of dialysis provider organizations. Dr. Dember is also a principal investigator for the NIDDK Hemodialysis Fistula Maturation Study, an observational cohort study designed to elucidate predictors and mechanisms of arteriovenous fistula maturation.

DAVID DORE, Ph.D., Pharm.D., is vice president, epidemiology, and principal epidemiologist at Optum Life Sciences, where he leads Optum's epidemiology consulting practice. He has worked continuously for Optum as

a pharmacoepidemiologist since 2007, and from 2010 through 2013 was assistant professor of health services, policy, and practice (tenure track) and assistant professor of epidemiology at the Brown University School of Public Health. Dr. Dore has done a number of studies on the safety of incretin-based antihyperglycemic drugs. His current work also covers electronic health records, natural language processing, medical devices, causal inference, and geriatric pharmacoepidemiology. He is an adjunct faculty member and mentor to several Ph.D. students at the Brown University School of Public Health. Dr. Dore received a Pharm.D. from the University of Rhode Island and a Ph.D. in epidemiology from Brown Medical School. He completed a postdoctoral fellowship at the Center for Gerontology and Health Care Research at Brown University.

LOUIS FIORE, M.D., M.P.H., is the executive director of the Massachusetts Veterans Epidemiology Research and Information Center at the U.S. Department of Veterans Affairs (VA) Boston health care system. He has 25 years of experience in clinical research in the areas of clinical trials, biobanking, epidemiology, and informatics. His current primary focus is on embedding clinical research into the clinical care ecosystem through both the Point of Care Clinical Trials Program and the Precision Oncology Program, both sponsored by the VA Office of Research and Development. He is a proponent of data sharing and strives to reduce silos that isolate researchers from each other and from the clinical care world that they ultimately serve.

LUCA FOSCHINI, Ph.D., is co-founder and chief data scientist at Evidation Health, a company dedicated to defining and demonstrating value in digital health. At Evidation, Dr. Foschini is responsible for data analytics, computing, research, and development. Dr. Foschini has driven research collaborations with machine learning experts at New York University, and behavioral economics departments at Harvard Business School and the Wharton School. Prior to this role, Dr. Foschini worked in research and development at Ask.com and was a visiting scholar at Google Research and ETH Zurich, where he developed efficient algorithms for mining spatial data, partitioning large graphs, and detecting traffic anomalies in computer networks. He has published numerous papers in the broader area of computer science and he co-authored several patents in information clustering and behavior phenotyping. He earned a Ph.D. in computer science from the University of California, Santa Barbara.

NAFTALI ZVI FRANKEL, M.S., is an experienced consumer advocate who has volunteered for research and analysis of scientific studies, available treatments, and specialists for many individuals faced with critical medical

decisions. Mr. Frankel serves on multiple health care advisory boards. He is the consumer representative on the U.S. Food and Drug Administration Circulatory Devices Advisory Board. In 2014, Mr. Frankel published an article in *JAMA Internal Medicine* titled "Surgical Aortic Valve Replacement vs. Transcatheter Aortic Valve Replacement: A Consumer's Perspective Regarding Data Education and Transparency of Hospitals." The article highlighted the need for increased hospital outcomes data transparency. Mr. Frankel graduated from Johns Hopkins University with an M.S. in regulatory science.

STEVEN K. GALSON, M.D., M.P.H. (*Planning Committee Co-Chair*), is senior vice president for Global Regulatory Affairs and Safety at Amgen Inc. From 2010 until 2014, he was vice president for Global Regulatory Affairs at Amgen Inc. Prior to this, he was the senior vice president for Civilian Health Operations and chief health scientist at Science Applications International Corporation and a consultant for Warburg Pincus. In 2009, he completed 23 years of government service, most recently, for 2 years, as Acting Surgeon General of the United States. From January to September 2009, he was also the Acting Assistant Secretary of Health. As Acting Surgeon General in 2008, Dr. Galson launched the Healthy Youth for a Healthy Future Initiative, which brought national attention to the complex issue of childhood obesity prevention, and prompted hundreds of community-based actions. This initiative included visiting 38 states and personally modeling healthy behaviors directly with children. Dr. Galson also convened, with the National Institutes of Health, the Surgeon General's Workshop on preterm birth in 2008, to jump-start national activities to reduce the incidence of these births. In addition, Dr. Galson published two Surgeon General's Calls to Action, on Deep Vein Thrombosis and Pulmonary Embolism to bring renewed attention and prevention efforts to a health problem that kills more than 100,000 Americans every year, and on how to Promote Healthy Homes, to bring attention to the connection between housing and health and outline a blueprint for national action. Dr. Galson furthered the nation's evolution toward personalized medicine by releasing a new My Family Health Portrait, a Web-based tool to enable individuals and families to create, store, and share their family health histories. He also highlighted the importance of preventing underage drinking by visiting states to encourage local efforts on this persistent challenge. Dr. Galson created the Surgeon General's Perspectives, a column in the journal *Public Health Reports*, and published eight columns on various prevention topics, bringing a leadership viewpoint to this widely read publication. In addition, Dr. Galson started a regular column for dieticians in the *Journal of the American Dietetics Association*, and published six columns on topics of interest to this key professional organization. As

Acting Assistant Secretary of Health, Dr. Galson led a U.S. Department of Health and Human Services (HHS)-wide effort to prepare a plan for the $650 million Prevention and Wellness section of the American Recovery and Reinvestment Act of 2009. He also managed 12 core public health programs for HHS. Previously, he served as deputy director and director of the U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research from 2001 until 2007. In that role, he provided leadership for the center's broad national and international programs in pharmaceutical regulation. Dr. Galson began his Public Health Service career as an epidemiological investigator at the Centers for Disease Control and Prevention after completing a residency in internal medicine at the Hospitals of the Medical College of Pennsylvania. In addition to his high-ranking positions at HHS, he has held senior-level positions at the U.S. Environmental Protection Agency (EPA) and the U.S. Department of Energy, where he was chief medical officer. Prior to his arrival at FDA, he was director of the EPA's Office of Science Coordination and Policy, Office of Prevention, Pesticides, and Toxic Substances. Dr. Galson is the recipient of numerous awards, including the Surgeon General's Medallion, three Secretary of Energy Gold Awards, and The Founders Medal from the Association of Military Surgeons of the United States. Dr. Galson has been a board member of the National Board of Medical Examiners, a Regent of the Uniformed Services University of the Health Sciences, and a peer reviewer for medical journals. Dr. Galson is currently professor-at-large at the Keck Graduate Institute of Applied Life Science, and a member of the Board of Directors of Vanda Pharmaceuticals. He holds a B.S. from Stony Brook University, an M.D. from Mount Sinai School of Medicine, and an M.P.H. from the Harvard School of Public Health and is board certified in preventive medicine and public health and occupational medicine.

JOHN B. HERNANDEZ, Ph.D., M.A., is a health care executive with broad experience in engaging with leading payers, hospital systems, physician organizations, researchers, and others to improve health care value. Dr. Hernandez has demonstrated success in growing businesses with disruptive technologies and driving market expansion. He is widely published in scientific journals, and lectures frequently on diverse topics ranging from health care reforms to real-world evidence strategies. Dr. Hernandez has more than 25 years of specialized research, consulting, and advocacy expertise, with a particular interest in generating evidence to show the value of transformative health care innovations. He has extensive clinical and commercial strategy experience in the life sciences industry and he has been directly involved in more than 30 major product launches. He is skilled at building and leading global teams to generate clinical and economic evidence across the product life cycle and executing market access strategies to obtain fund-

ing and develop markets in the Americas, Europe, and Asia. Dr. Hernandez is currently engaged in numerous research initiatives and public–private partnerships leveraging digital health data from multiple sources, including electronic medical records, claims databases, and registries to track and improve health care costs, quality, and outcomes. The goal of these efforts is to support a radical transformation of the U.S. health care system by dramatically expanding real-world evidence collection and embedding research on health care value into mainstream practice.

FREDA LEWIS-HALL, M.D., is chief medical officer and executive vice president of Pfizer Inc. Dr. Lewis-Hall is the senior physician in the company, responsible for enterprise-wide medical, patient safety, regulatory affairs, and quality assurance as well as outreach to doctors and other medical professionals. Dr. Lewis-Hall will serve on Pfizer Inc.'s Executive Leadership Team, its most senior leadership group. She will shape Pfizer Inc.'s regulatory and medical policy during a time of fast-changing expectations for health care companies and a wave of new therapies in development, especially as information technologies change the ways companies develop medicines, clinicians prescribe them, and patients and payers value them. Prior to joining Pfizer Inc., Dr. Lewis-Hall was executive vice president, Medicines Development, Vertex Pharmaceuticals. In that role, she was responsible for clinical and non-clinical development as well as both medical and regulatory; she also served as senior vice president of Medical Affairs at Bristol-Myers Squibb, vice president of Research and Development at Pharmacia, and product team leader at Eli Lilly & Co. Dr. Lewis-Hall is a fellow of the American Academy of Psychiatry. She received her B.A. from Johns Hopkins University and her M.D. from Howard University Hospital and College of Medicine.

MICHAEL MACK, M.D., has practiced cardiothoracic surgery in Dallas since 1982. He is board certified in Internal Medicine, General Surgery, and Thoracic Surgery and is currently the director of the Cardiovascular Service Line for Baylor Scott & White Health, chair of the Baylor Scott & White Cardiovascular Governance Council, and director of Cardiovascular Research at The Heart Hospital Baylor Plano. He also co-founded the Cardiopulmonary Research Science and Technology Institute. He has authored more than 500 peer-reviewed medical publications. He is on the Steering Committee of the Cardiothoracic Surgery Network of the National Institutes of Health and is a member of the American College of Cardiology (ACC) Foundation Board of Trustees, the ACC Interventional Scientific Council, and the Society of Thoracic Surgeons (STS)/ACC National Transcatheter Valve Therapy Registry Steering Committee. He is a member of the U.S. Food and Drug Administration (FDA) Medical Device

Epidemiology Network Initiative (MDEpiNet) Advisory Committee. He is a director of the American Board of Thoracic Surgery and a member of the National Medical Device Planning Board of the FDA/Duke Margolis Institute. Dr. Mack was STS president in 2011 and is past president of the Thoracic Surgery Foundation for Research and Education, the Southern Thoracic Surgical Association, and the International Society for Minimally Invasive Cardiothoracic Surgery. He is an honorary member of the German Society for Thoracic and Cardiovascular Surgery and the Indian Association of Cardiovascular and Thoracic Surgery. He has received the Presidential Citation of the ACC and the Transcatheter Cardiovascular Therapeutics Lifetime Achievement Award.

MARK McCLELLAN, M.D., Ph.D., is the Robert J. Margolis Professor of Business, Medicine, and Policy, and director of the Duke-Margolis Center for Health Policy at Duke University, with offices at Duke University and in Washington, DC. Dr. McClellan is a physician and an economist, and his work has addressed a wide range of strategies and policy reforms to improve health care, including payment reforms to promote better outcomes and lower costs, methods for development and use of real-world evidence, and approaches for more effective drug and device innovation. Dr. McClellan is a former administrator of the Centers for Medicare & Medicaid Services and former commissioner of the U.S. Food and Drug Administration, where he developed and implemented major reforms in health policy. He was also a senior fellow at Brookings Institution and a professor of economics and medicine at Stanford University.

RHONDA ROBINSON BEALE, M.D., is a seasoned health care executive with more than 30 years of experience in health care systems, managed care, and quality improvement in behavioral health and medical care. She is the senior vice president and chief medical officer for Blue Cross of Idaho, overseeing the Medical and Quality Management Division responsible for medical and behavioral service management for all market segments. Dr. Robinson Beale has served in the past as the chief medical officer/physician executive within several large, national and local health care organizations, such as Optum, a subsidiary within UnitedHealth Group, PacifiCare, Cigna, Blue Cross Blue Shield of Michigan, and Health Alliance Plan in Michigan. She has been involved with many national organizations as a subject-matter expert, including the National Institute of Mental Health, Institute of Medicine (IOM), National Quality Forum, American Psychiatric Association, American Psychological Association, American Society of Addiction Medicine, National Committee for Quality Assurance, and others. Dr. Robinson Beale has served on many national boards, has engaged with key committees and work groups, and has been significantly involved in

influencing changes in the system. She was on the IOM committees that created *Crossing the Quality Chasm* and *To Err Is Human*. She was involved in influencing local and national legislation, particularly around parity and Patient Protection and Affordable Care Act issues. She has testified before the Senate's Committee on Health, Education, Labor and Pensions on the state of behavioral health care. Dr. Robinson Beale has experience in health care as a health plan administrator, a hospital medical director, and a capitated provider of care to commercial and public-sector populations. She has been able to use the experience as a capitated provider for more than 18 years to help organized systems of care restructure their operations to be successful in managing populations within capitation and alternative payment arrangements. Dr. Robinson Beale received her M.D. from Wayne State University and her psychiatric training at Detroit Psychiatric Institute. She is a Diplomat to the American Board of Psychiatry and Neurology and, when in practice, she was a certified addictionologist through the American Society of Addiction Medicine.

ANDREW RODDAM, Ph.D., is currently vice president and head of Epidemiology & Real World Evidence at GlaxoSmithKline, is a member of the HL7 advisory council, and is a renowned expert in epidemiological research, with specific interest in the use of routine data for research purposes. He was a senior researcher at the Cancer Research United Kingdom Cancer Epidemiology Unit at the University of Oxford before starting at Amgen Inc., where he was most recently Regional Head (the European Union and Europe, the Middle East, and Africa) in the Center for Observational Research. Dr. Roddam obtained his Ph.D. in statistics at the University of Oxford, working with Sir David Cox, and he also completed a postdoc in infectious disease epidemiology.

RUSSELL L. ROTHMAN, M.D., M.P.P., is a professor of internal medicine, pediatrics, and health policy, and the vice president for Population Health Research at Vanderbilt University Medical center. He also serves as the director of the Vanderbilt Center for Health Services Research and chief of the Internal Medicine/Pediatrics Section. Dr. Rothman's current research focuses on improving care for adult and pediatric patients with diabetes, obesity, and other chronic diseases. As director of the Vanderbilt Center for Health Services Research, Dr. Rothman oversees a Center that engages more than 140 faculty across the university who are engaged in more than $50 million of funded research annually related to health services research, implementation science, behavioral research, health disparities research, quality improvement research, and other areas aimed at improving health outcomes. He has been the principal investigator on more than $35 million in extramural funding and has authored more than 120 manu-

scripts. He is currently the principal investigator of the Patient-Centered Outcomes Research Institute (PCORI)-funded Mid-South Clinical Data Research Network, which engages more than 50 hospitals and thousands of ambulatory practices reaching patients across the nation. He is also the principal investigator of the new Centers for Medicare & Medicaid Services (CMS)-funded Mid-South Practice Transformation Network, which engages 4,000 clinicians in quality improvement. Dr. Rothman also serves on the PCORI National Patient-Centered Clinical Research Network (PCORnet) Executive Steering Committee, which is overseeing the development of a national network to support comparative effectiveness research and pragmatic clinical trials, with more than $250 million committed from PCORI to date. Dr. Rothman serves as the co-chair of the Steering Committee of the ADAPTABLE study, an $18 million pragmatic clinical trial enrolling 20,000 patients to evaluate the optimal dose of aspirin in secondary prevention.

NIGAM SHAH, Ph.D., is an associate professor of medicine (biomedical informatics) at Stanford University, assistant director of the Center for Biomedical Informatics Research, and a core member of the Biomedical Informatics Graduate Program. Dr. Shah's research focuses on combining machine learning and prior knowledge in medical ontologies to enable use cases of the learning health system. Dr. Shah received the American Medical Informatics Association New Investigator Award for 2013 and the Stanford Biosciences Faculty Teaching Award for outstanding teaching in his graduate class on Data-Driven Medicine. Dr. Shah was elected into the American College of Medical Informatics in 2015 and inducted into the American Society for Clinical Investigation in 2016. He holds an MBBS from Baroda Medical College, India, and a Ph.D. from Pennsylvania State University. He completed his postdoctoral training at Stanford University.

RACHEL E. SHERMAN, M.D., M.P.H., is the Deputy Commissioner for Medical Products and Tobacco at the U.S. Food and Drug Administration (FDA). On behalf of the Commissioner, she provides leadership, management, and policy direction in planning and implementing major crosscutting medical product policy and programmatic initiatives that are clinical, scientific, or regulatory in nature. She brings more than 25 years of dedication to public health. Areas of focus include medical product development, communication of medication information, and clinical care. Her areas of focus include establishing the Oncology Center for Excellence and the Combination Products Policy Council as well as oversight for the EvGen initiative, the Offices of Good Clinical Practice, Orphan Products Development, and Pediatric Therapeutics; and modernization of Advisory Committee practices. Most recently, Dr. Sherman served as Associate Deputy Commissioner for Medical Products and Tobacco from October 2015 until Septem-

ber 2016. During her previous tenure at FDA (1989 to 2014), she served in a variety of roles, ranging from primary FDA medical reviewer during the AIDS crisis to member of the Executive Leadership Team in FDA's Center for Drug Evaluation and Research (CDER). From 2009 to 2014, Dr. Sherman served as CDER's associate center director for medical policy and directed CDER's Office of Medical Policy. She established and led a large, multidisciplinary staff charged with developing and implementing high-priority policies and programs, including the Sentinel Initiative; FDA's program for regulating biosimilars; and FDA's expedited drug development and breakthrough therapy designation programs. She organized multistakeholder public–private partnerships; oversaw development of regulations and guidance for industry; and played a key role in enhancing clinical trial quality and good clinical practice. Her achievements contributed directly to more effective prescription drug promotion and to the modernization of professional drug labeling, generic drug labeling, and medication information for patients. From 2014 to 2015, Dr. Sherman continued her focus on the development of innovative therapies in her role as principal, drug and biological drug products, at Greenleaf Health LLC, a consultancy that provides strategic and technical assistance, with an emphasis on medical product development. Dr. Sherman is an Internist with a subspecialty in Infectious Diseases. She has served over the years as attending physician, Division of Infectious Diseases, at the Veterans Affairs Medical Center; clinical assistant professor of medicine (infectious diseases) at Georgetown University; and volunteer physician with Montgomery Mobile Health. She received her B.A. in mathematics from Washington University in St. Louis, her M.P.H. from Johns Hopkins University, and her M.D. from Mount Sinai School of Medicine.

GREGORY SIMON, M.D., M.P.H. (*Planning Committee Co-Chair*), is an investigator at Kaiser Permanente Washington Health Research Institute and a psychiatrist in Group Health's Behavioral Health Service. He is also a research professor in the Department of Psychiatry and Behavioral Sciences at the University of Washington and chair of the national scientific advisory board of the Depression and Bipolar Support Alliance. Dr. Simon completed residency training in internal medicine at the University of Washington, residency training in psychiatry at the Massachusetts General Hospital, and fellowship training in the Robert Wood Johnson Clinical Scholars program at the University of Washington. Dr. Simon's research focuses on improving access to and quality of care for mood disorders, both unipolar depression and bipolar disorder. Specific areas of research include improving adherence to medication, increasing the availability of effective psychotherapy, evaluating peer support by and for people with mood disorders, suicide prevention, cost-effectiveness of treatment, and co-morbidity of mood disorders

with chronic medical conditions. Dr. Simon currently leads the Mental Health Research Network, a cooperative agreement funded by the National Institute of Mental Health that supports population-based mental health research across 13 large health systems.

SEAN TUNIS, M.D., MHSR, is president and chief executive officer of the Center for Medical Technology Policy (CMTP) in Baltimore. CMTP is an independent, nonprofit organization that provides a neutral platform for multistakeholder collaborations that promote high-value innovation by improving the quality, relevance, and efficiency of clinical research. Through 2005, Dr. Tunis was director of the Office of Clinical Standards and Quality and chief medical officer at the Centers for Medicare & Medicaid Services. He also served as the director of the health program at the Congressional Office of Technology Assessment and as a health policy advisor to the U.S. Senate Committee on Labor and Human Resources. Dr. Tunis serves as vice president of Health Technology Assessment International, a member of the Health Sciences Policy Council for the International Society for Pharmacoeconomics and Outcomes Research, and on several other public and private governing and advisory boards. He received a B.S. in biology and history of science from the Cornell University School of Agriculture and an M.D. and a master's in health services research from the Stanford University School of Medicine. Dr. Tunis did his residency training at the University of California, Los Angeles, and the University of Maryland in emergency medicine and internal medicine.

PATRICK VALLANCE, M.D., is president of research and development at GlaxoSmithKline (GSK) and a member of the GSK Corporate Executive Team. Prior to joining GSK in 2006, Dr. Vallance was a clinical academic. He was a professor of medicine who led the Division of Medicine at University College London (UCL) and consultant physician at UCL. His academic work was in the field of cardiovascular biology and ranged from chemistry through to use of large electronic health records. Dr. Vallance is a Fellow of the Academy of Medical Sciences. He has been on the Board of the U.K. Office for Strategic Co-ordination of Health Research since 2009. He is also a director of Genome Research Limited.

JON WHITE, M.D., Deputy National Coordinator, is a family physician who has dedicated his career to improving health and health care quality through the use and sharing of electronic health information. Dr. White has been working in partnership with the Office of the National Coordinator for Health Information Technology (ONC) since 2004. ONC is at the forefront of the nation's efforts to adopt and meaningfully use health information technology, and achieve health information technology interoper-

ability, as a foundational element of better health for everyone in America. Before his service at ONC, Dr. White was director of the Division of Health Information Technology at the Agency for Healthcare Research and Quality (AHRQ). In his role at AHRQ, Dr. White directed hundreds of projects in 48 states, including research, demonstration, and implementation projects on a wide variety of health information technology (IT) applications and issues. Dr. White has extensive experience working with federal government partners (including the Centers for Medicare & Medicaid Services and the U.S. Department of Veterans Affairs) as well as key health care professional, patient, policy, and health IT stakeholder groups to implement major health care initiatives. Dr. White trained in Family Medicine at the University of Virginia and Lancaster General Hospital in Pennsylvania. He is a recipient of the national American Academy of Family Physicians Award for Excellence in Graduate Education.

Appendix D

Discussion Paper: *Real-World Evidence to Guide the Approval and Use of New Treatments*[1,2]

[1] This appendix was added after the prepublication release.

[2] The views expressed in this Perspective are those of the authors and not necessarily of the authors' organizations, the National Academy of Medicine (NAM), or the National Academies of Sciences, Engineering, and Medicine (the National Academies). The Perspective is intended to help inform and stimulate discussion. It has not been subjected to the review procedures of, nor is it a report of, the NAM or the National Academies.

DISCUSSION PAPER

Real-World Evidence to Guide the Approval and Use of New Treatments

Steven Galson, Amgen, and **Gregory Simon,** Group Health Research Institute

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Current State

The Focus of Traditional Evidence Generation on Narrow Questions Regarding Efficacy and Safety

Research regarding new treatments (drugs, biological products, and high-risk devices) often begins with a broad assessment of disease epidemiology, disease burden, and shortcomings of existing treatments. That research may draw from diverse data sources, including real-world data generated by health system operations (see Figure 1).

The clinical research phase of treatment development typically follows a well-established pathway from initial evaluation of safety to preliminary evaluation of therapeutic efficacy to pivotal trials intended to support regulatory approval for marketing. Those pivotal trials focus on key questions of efficacy (typically in comparison to placebo or some analogous control condition) and safety (especially serious or previously unrecognized adverse effects). This focus is consistent with the responsibility of the U.S. Food and Drug Administration (FDA) for assuring the safety and efficacy of drugs, biological products, and medical devices at the time of approval.

Regulatory approval is sometimes followed by systematic postmarketing evaluation to address a wider range of practical or real-world questions. This more pragmatic research again draws from more varied sources of data drawn from diverse clinical settings.

A Lack of Information for Stakeholders (Patients, Providers, and Health Systems) to Guide Real-World Decisions

Evidence generated by traditional clinical research often fails to address key questions of patients, physicians, and health systems regarding the appropriate role of new treatments. Those unaddressed concerns include the following:

Effectiveness

Traditional efficacy trials typically aim to evaluate a single treatment rigorously. In contrast, patients, providers, and health systems choose among alternative treatments on the basis of net benefit in real-world practice. Real-world effectiveness may differ substantially from efficacy detected in the traditional clinical trial setting. Factors contributing to that efficacy–effectiveness gap include variation in practice settings, provider decision making, patient adherence, co-occurring conditions, and concomitant treatments. In a clinical trial designed to assess efficacy, these factors would be considered sources of noise or error, and trial design would attempt to minimize variation. In everyday clinical practice, these sources of variation are directly relevant to practical decisions by patients and providers and are central to the information stakeholders need to inform practical decisions. Many treatments would be expected to show some slippage or loss of benefit between efficacy trials and real-world practice. But we cannot presume that slippage is consistent across treatments, patient populations, or practice settings. Consequently, findings from efficacy trials regarding differences (or lack of differences) in efficacy do not necessarily translate to the same differences in real-world performance.

Tolerability

While patients and physicians are certainly concerned about less common and more serious adverse effects of new treatments, they are equally concerned about more common adverse effects—such as nausea, tremor, fatigue, weight gain, or interference with sexual function. Even when traditional efficacy trials evaluate these effects, the resulting evidence is rarely adequate to guide patients' and physicians' decisions regarding alternative treatments—especially if those treatments are to be continued for months or years.

DISCUSSION PAPER

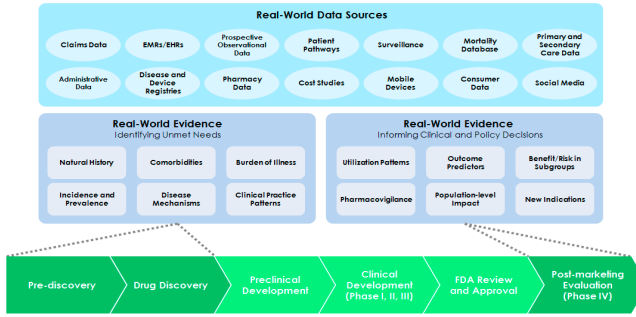

Figure 1 | Real-world evidence is derived from curating, standardizing, and analyzing real-world data to obtain high-quality and reliable information from diverse and complex sources. Real-world evidence could inform all phases of treatment discovery and development, although thus far has been more commonly used to inform the questions and data in early development decisions and in postmarketing safety surveillance or comparative effectiveness studies. In contrast, clinical development and review has tended to more use idealized and tightly controlled data sources for efficacy trials.

Value

Health care payers base coverage and reimbursement decisions regarding new treatments on the balance of net cost and benefit, although payers may not consider long-term factors, such as the benefits of prevention, over a typical lifespan. Given the increasing prevalence of high insurance deductibles and coinsurance arrangements, patients and families must also consider the value of alternative treatments. True net cost of a new treatment depends not only on its price but also on the net impact on overall cost of care. Traditional clinical trials, in which treatment protocols are highly controlled, usually offer little information on how new treatments affect overall or downstream use of health services.

Heterogeneity of Treatment Effects

An individual patient and his or her physician are naturally most interested in person-specific effects ("What are the expected benefits and harms of this treatment for someone like me?"). Traditional clinical trials focus instead on assessment of average effects. Particularly in the early phases, heterogeneity of effects is more often a source of error to be minimized rather than an important signal to be detected.

Current Incentives Do Not Promote Necessary Innovation

Our current evidence-generating process has evolved to fit our traditional regulatory and business environment. Business imperatives of new treatment development drive research toward a relatively narrow focus: producing the data essential for regulatory approval. Traditional clinical trials are optimized to efficiently address key questions in the regulatory process: Is a new treatment superior to a placebo or other appropriate control treatment with respect to a specific clinical outcome? Is there evidence of a specific danger or harm—especially a harm not previously recognized?

Bringing a new treatment to market involves significant time and expense. For developers of new treatments, broadening research to address real-world questions may introduce additional uncertainty or delay and, in addition, require data not readily

available to industry. Expanding the evidence-generating process to address real-world effectiveness, value, tolerability, and heterogeneity of treatment effects would almost always require more flexible treatment protocols and more heterogeneous clinical populations. The "noise" introduced by that flexibility and heterogeneity could certainly interfere with the detection of primary "signals" regarding efficacy and safety.

Ideally, developers of new treatments would be rewarded for generating evidence more relevant to real-world decisions. Those rewards might include approval for labeling regarding improved effectiveness, tolerability, or value. Some European regulators may consider evidence regarding cost-effectiveness or value in regulatory or pricing decisions. In the United States, research to support those claims has been impeded by uncertainty regarding the types of evidence that will be acceptable to support approval of novel therapies and new indications (Bipartisan Policy Center, 2016).

Enabling Developments

The Increasing Use of Electronic Health Records and Development of Linked Data Resources

Data generated from research and practice have historically been siloed. However, as the concept of a learning health system continues to take hold, such distinctions are increasingly being reexamined. The nation's electronic health information infrastructure has continued to mature over the past decades, and, as a result, a wealth of clinical data—residing in electronic health records, patient registries, and administrative claims databases—now provides an opportunity to generate evidence on the effectiveness of medical products directly from clinical experience, complementing the data generated through traditional randomized controlled trials. Electronic records systems can certainly facilitate the traditional clinical trials, expanding the scale and lowering the cost of participant recruitment and recording of clinical outcomes. In addition, the "data exhaust" of ordinary (nonresearch) health care has the potential to inform regulatory and reimbursement decisions. However, ensuring that the data are fit for the purpose of research will require thoughtful consideration. Most real-world data, including those from electronic health records and claims databases, are not currently generated for the purpose of research.

Leveraging the full potential of these data sources will depend on data integration capabilities. Analytic processes enabling patient-level linking of disparate clinical data sources are helping to address data quality issues (e.g., filling in missing data and vetting data by searching for inconsistencies across data sources). Networked systems (e.g., the Observational Health Data Sciences and Informatics [OHDSI] Collaboration) are enabling data aggregation on a scale not previously possible and are yielding information on patient population characteristics and health care utilization that may significantly impact future trial design and improve the generalizability of results (Hripcsak et al., 2016).

A key challenge of leveraging clinical data to support the evaluation of medical products resides in the fact that providers and health systems are not systematically assessing the impact of treatment. The routine collection of standard outcome measures is an important but tractable barrier.

The Increasing Use of Standard Patient-Reported Outcome Measures

In addition to traditional clinical data, patient experiences and perspectives are increasingly being incorporated as essential aspects of the medical product evaluation process. Patient-reported outcomes may include symptoms, quality of life, and functional status. Patient-centered outcomes research is a primary focus of the Patient-Centered Outcomes Research Institute (PCORI), which has initiated the development of minimum standards for patient-reported outcomes data. PCORI has also established PCORnet, a centrally coordinated network of research networks, to improve the speed and efficiency of clinical research by leveraging existing large data sources, including patient-powered research networks.

The Use of E-Health and M-Health Tools to Collect Real-World Data

The increasing popularity of wearable and other mobile devices that collect health-related data from individuals has opened new avenues for consumer and patient engagement and the collection of real-world data. Of course, such data only have value if they are meaningful. Mobile devices such as medical wearables that can passively and accurately collect data on

DISCUSSION PAPER

primary clinical endpoints can help to demonstrate the benefit of a particular intervention—a capability that is of great interest to not only patients and providers but also health systems and manufacturers of medical products. Online patient communities and consumer search behavior, too, may be sources of data on effectiveness, safety, use, and compliance. However, in addition to technical barriers related to data capture and integration, a number of legal and regulatory challenges must be addressed prior to routine integration of these real-world data sources with more traditional structured clinical datasets.

Promising Practices

Population-Based Surveillance Using Health System Data

The linkage of health system records has enabled large-scale observational research including representative samples of patients treated in under real-world conditions. Research to date has focused primarily on outcomes detectable through traditional insurance claims data, including billing diagnoses and procedures. The increasing availability of rich clinical data from electronic health records should enable research regarding a broader range of effectiveness outcomes, including laboratory results, vital signs, and standardized patient-reported outcomes.

Example: FDA Sentinel Initiative

The FDA Sentinel initiative was created with the goal of establishing an integrated, national, electronic system that monitors the safety of medical products, including small molecule drugs and biologics. The initiative was taken in response to recommendations of the Institute of Medicine (IOM) (IOM, 2006) and the 2007 FDA Amendments Act that mandated FDA to have a system in place for active postmarket risk identification and analysis (Food and Drug Administration Amendments Act of 2007). The Sentinel initiative for medical product safety surveillance was launched in 2008. In 2009, the Mini-Sentinel program was established as a pilot effort to test the core function of the future system—mainly the analysis of health care information obtained from multiple and varied data sources and the utilization of the data to inform FDA decision making (Sentinel Program Interim Assessment—FY15, 2015). A main goal for the program was to enable real-time queries while maintaining the privacy of patients and to build a system that would rely on existing infrastructure and require minimal data transfer from data sources that would remain under the control and maintenance of their owners (Kuehn, 2016). Beginning in late 2014, FDA has been transitioning from the Mini-Sentinel system to the full Sentinel initiative. Along with the Harvard Pilgrim Health Care Institute, which was chosen as a data analytics partner to the program, the initiative has established relationships with 19 data partners that cover a combined 178 million lives.

Example: Observational Health Data Sciences and Informatics Program

The OHDSI program was created with the aim of facilitating better health decisions by using collaboratively generated evidence (1). OHDSI builds on the 5-year Observational Medical Outcomes Partnership (OMOP), a public–private partnership that focused on the use of observational datasets for investigating medical products. The program was relocated to the Reagan-Udall Foundation for the FDA and is the basis of the Innovation in Medical Evidence Development and Surveillance (IMEDS) program, in which the OHDSI information model was developed (Hripcsak et al., 2015). OHDSI now operates as an international collaborative that utilizes open-source data analytic tools applied to a network of databases contributed to by 90 participants for population- and patient-level analyses. In a recent demonstration of the potential for using the OHDSI system in large-scale, international observational research, the disease treatment pathways for type 2 diabetes mellitus, hypertension, and depression were investigated using data aggregated from 11 sources providing electronic health records of 250 million patients across four countries (Hripcsak et al., 2016).

Research Embedded in New Product Registries

Systematic registries of patients exposed to new treatments are more common for the postmarketing evaluation of medical devices than for drugs or biological products. These registries can support both observational research and randomized trials to evaluate the effectiveness and tolerability of new products.

Example: Transcatheter Valve Therapy Registry

The Society for Thoracic Surgeons and the American College of Cardiology collaborated with FDA and the Centers for Medicare & Medicaid Services to create the Transcatheter Valve Therapy (TVT) Registry (2) of

patients undergoing valve repair or replacement surgery. The registry was launched in 2011 to track patient safety and outcomes from transcatheter aortic valve replacement in real-world settings, enrolling nearly all patients receiving a device. One important reason for establishing the registry was to support gaps both in premarket trials of medical devices, which are typically held only in specialized centers and on a carefully selected patient samples, and in the postregulatory approval period. Postregulatory approval is aimed at optimizing outcomes, patient selection criteria, device safety monitoring, and possible expansion of device indications. While traditionally different stakeholder groups collected data to support such efforts in disparate ways, a collaboration among professional societies, regulators, payers, the medical device industry, clinicians, and patient groups enabled the selection and harmonization of the data elements comprising the TVT Registry as well as patient selection criteria (Carroll et al., 2013; Carroll et al., 2015).

In 2011 the TVT Registry began a partnership with the Duke Clinical Research Institute for registry data analytics, and in 2013 the first results from the TVT Registry were published, reporting on outcomes from 7,710 patients. By 2015, more than 319 medical centers participated in the TVT Registry involving more than 18,500 cases of transcatheter aortic valve replacement (Rumsfeld et al., 2015). As an example of the TVT Registry's role as an infrastructure for conducting postapproval studies, in 2013 FDA approved expanded labeling for a transcatheter heart valve (Edwards SAPIEN), allowing its use among a larger segment of patients with aortic stenosis; the decision was based partially on data provided from the TVT Registry (Society of Thoracic Surgeons, 2013).

Randomization Embedded in Real-World Practice

Despite common misperceptions, real-world evidence need not be generated solely through retrospective analysis of existing data. Increasingly, clinical trials are being conducted in real-world settings to improve the generalizability of results and to reduce inefficiencies related to separate research infrastructures. These pragmatic clinical trials use an existing clinical infrastructure to prospectively test interventions in everyday situations and enable randomization at the point of care (FOCR, 2016).

Example: Salford Lung Study

Initiated in 2012, the Salford Lung Study was a 12-month, open-label, phase III pragmatic randomized controlled trial (pRCT) sponsored by GlaxoSmithKline and conducted in the Salford borough of the greater Manchester area in the United Kingdom (3). The study represents the first time a pRCT was conducted before the registration of the treatment being investigated (New et al., 2014). The study included a series of trials that evaluated a new once-daily-administered dry-powder inhaler containing both the corticosteroid fluticasone furate and the long-acting β2 agonist vilanterol (FF/VI). Previous studies demonstrated that a combined administration was more effective in treating chronic obstructive pulmonary disease (COPD) than each of the components administered separately (Bakerly et al., 2015). The trials were specifically designed to compare the real-world effectiveness of FF/VI to existing treatments for asthma and COPD in a large segment of the population of patients during routine clinical care. The primary outcomes measured in the trials were the rate of moderate and severe exacerbations and measured improvement in asthma control for COPD and asthma, respectively.

Patients were randomized and received the usual care for the duration of their study, including dispensing of trial medication at local pharmacies. The local technological and clinical infrastructure in Salford facilitated the implementation of this pRCT. While more than 60 primary care clinics were involved in the trial, patients in the study area are served by one regional hospital, and both primary and secondary health providers share one integrated electronic health record system. The Salford Integrated Record, originally created in 2001, is updated in real time and allowed the necessary safety monitoring required from a phase III trial. Additional data feeds into the system were created to capture information on mortality and access to health care services outside the region. Furthermore, all community pharmacies in the Salford area also participated in the study and provided information on medication adherence and prescriptions delivered. Following the Salford Lung Study pRCT, the European Commission granted marketing authorization to FF/VI treatment for asthma and COPD in November 2013 (Woodcock et al., 2015).

DISCUSSION PAPER

Desired Future State

Evidence Generation Driven by the Needs of Real-World Stakeholders

Real-world evidence regarding new treatments should address the practical questions of various stakeholders:

- For patients and physicians: When is this new treatment preferred over existing alternatives? Does effectiveness or tolerability vary in a predictable way among different groups of patients or different health care settings?
- For payers: How does the value of this new treatment compare to existing alternatives? What coverage or reimbursement policies will maximize overall value to taxpayers or insurance plan members?
- For industry: Where and when is this treatment likely to deliver the greatest value to our customers?
- For regulators: How can labeling be more informative for patients and clinicians?

Incentives Realigned to Promote Relevant and Efficient Research

If developers of new treatments are expected to broaden clinical trials to address real-world questions, they must be appropriately rewarded for bearing the additional expense and not burdened by additional delay in the approval process. Creating appropriate incentives for real-world evidence generation will require the following:

- Guidance regarding appropriate data sources, research methods, and analytic methods to support labeling regarding effectiveness, tolerability, value, and heterogeneity of treatment effects; and
- Consensus among payers regarding the role of real-world evidence and more specific labeling in decisions regarding coverage and reimbursement.

Guidance on the use of real-world data from regulatory agencies—such as that recently released for medical devices (FDA, 2016)—can help to define a new paradigm for evidence generation that improves the impact of research efforts.

More Flexible Boundaries between Premarket and Postmarket Research

A new model for medical product development may see the blurring of current demarcations between premarket and postmarket evaluation. Continued assessment for effectiveness, not just safety, in the postmarket setting using real-world data will enable continuous reevaluation of risk–benefit profiles and generate labeling changes and new indications. Premarket, real-world evidence may augment evidence from traditional RCTs, and increased use of pragmatic trials may improve external generalizability of results. Premarket and postmarket evaluations can form a feedback loop, enabling a rapid learning cycle.

Improved Public Health through More Widely Shared Real-World Data

Data from industry-sponsored clinical trials are increasingly available for secondary analyses by a wide range of users. Ironically, data from not-for-profit health care systems are typically not as freely shared. Many real-world questions (especially those involving cost and heterogeneity of treatment effects) require large samples only achievable with pooling of data across institutions. Data sharing and more open data access will certainly require appropriate protections for patients' privacy and health systems' proprietary information. Open access will also require researchers to set aside proprietary interests in order to facilitate more efficient learning.

True Integration between Research and Practice

Ultimately, the evidence necessary to guide policy decisions regarding new treatments overlaps substantially with the evidence necessary to guide everyday clinical decisions for individual patients. If we are to use data generated from everyday practice to create generalizable evidence, then we would need systematically recorded data regarding patients' risk factors or prognostic characteristics, providers' rationale for treatment choices, patients' actual treatment exposures, and a range of clinically relevant outcomes. More systematic collection and recording of those data would not only facilitate practice-based research but also significantly improve the quality and effectiveness of everyday health care.

Realizing this promise will necessitate an evolution to a true learning health system approach, as described by the IOM (IOM, 2013), where the traditional boundaries between clinical research and practice are blurred and where knowledge is generated as a by-product of each care experience.

Notes

1. For more information on the OHDSI program, see http://www.ohdsi.org (accessed September 23, 2016).
2. See https://www.ncdr.com/WebNCDR/tvt/home (accessed September 23, 2016).
3. For more information, see https://clinicaltrials.gov/ct2/show/NCT01551758 (accessed September 23, 2016).

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DISCUSSION PAPER

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