



Using Real-World Evidence to Accelerate Safe and Effective Cures

Advancing Medical Innovation for a Healthier America

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FDA: ADVANCING MEDICAL INNOVATION EFFORT

The Bipartisan Policy Center's initiative, FDA: Advancing Medical Innovation, is developing viable policy options to advance medical innovation and reduce the time and cost associated with the discovery, development, and delivery of safe and effective drugs and devices for patients in the United States. Key areas of focus include the following:

- Improving the medical product development process;
- Increasing regulatory clarity;
- Strengthening the Food and Drug Administration's (FDA) ability to carry out its mission;
- Using information technology to improve health and health care; and
- Increasing investment in medical products to address unmet and public health needs.

This effort is chaired by former Senate Majority Leader William H. Frist, MD and former Representative Bart Gordon. Members of the advisory committee include Marc Boutin, CEO, National Health Council; Mark McClellan, MD, PhD, director, Robert J Margolis Center for Health Policy, Duke University and former FDA commissioner; Patrick Soon-Shiong, MD, chairman and CEO, Institute for Advanced Health; and Andrew von Eschenbach, MD, president, Samaritan Health Initiatives and former National Cancer Institute director and former FDA commissioner. Janet Marchibroda, BPC's Health Innovation director, serves as the staff director for the effort.

The initiative also taps into the expertise and views of a broad range of experts and stakeholders through one-on-one interviews and roundtable discussions.

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DISCLAIMER

The findings and recommendations expressed herein do not necessarily represent the views or opinions of the Bipartisan Policy Center's founders or its board of directors.

Letter from the Co-Chairs

We are fortunate to live in an age of continuous discovery and scientific breakthroughs, especially when it comes to treatments for disease. New and highly effective medications are available today that treat conditions considered incurable just a decade ago, such as Hepatitis C.

But while scientific discovery is moving ahead rapidly, the pace of moving new drug discoveries to patients in need remains quite slow. It takes an average of ten years and two billion dollars to bring a new drug to the marketplace. With so many diseases and conditions that still lack effective treatments—such as Alzheimer’s disease, which affects more than five million Americans—the need to accelerate the search for tomorrow’s cures is clear.

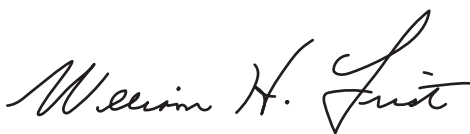
Modernizing the entire life cycle of drug development and regulatory review is the focus of this report. Congress and the administration are moving forward with efforts that demonstrate their strong support for improving the development and delivery of medical products. This report includes recommendations to inform this progress.

Bringing safe and effective cures and treatments to patients in a timely and cost-effective manner will require new processes and new policies to support them. Using real-world evidence—data that reflects the actual experience of patients during real-world situations—in addition to relying on data derived from conventional randomized controlled trials will enhance the nation’s ability to advance the safety and effectiveness of drugs in a wider population.

Real-world data is available through electronic medical records, claims databases, laboratory and pharmacy systems, registries, and even from patients’ own health-monitoring devices.

Our recommendations focus on defining how real-world data can be used to support more efficient and effective drug development and strengthen the FDA’s ability to oversee such progress.

Improving and streamlining the process of bringing new drugs to market will enhance U.S. global competitiveness. But more importantly, an approval process that maintains the highest standards of safety and brings new medications to the market faster will help tens of thousands of Americans who are waiting for treatments and cures. Many cannot wait much longer. For these patients especially, it is time to act.



Senator William H. Frist, MD

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FDA: Advancing Medical Innovation



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Table of Contents

| | |
|----|--|
| 6 | Introduction |
| 8 | Today's Drug Approval Process |
| 8 | An Overview of Today's Drug Approval Process |
| 11 | Current Methods for Conducting Clinical Trials |
| 12 | Current Post-Market Surveillance Efforts |
| 13 | Real-World Data: A New Opportunity to Strengthen the Process |
| 13 | An Overview of Real-World Data |
| 14 | Current Uses of Real-World Data Within the Drug Approval Process |
| 14 | Benefits of Real-World Evidence |
| 15 | Gathering Real-World Evidence Through Close-Monitoring |
| 15 | Issues that Need to be Addressed |
| 16 | Integrating Real-World Evidence into the Drug Development Process |
| 18 | Recommendations for Modernizing the Drug Development Process Through the Use of Real-World Evidence |
| 18 | Improve Regulatory Clarity Regarding Use of Real-World Evidence |
| 19 | Improve Methods and Data Quality for the Generation and Use of Real-World Evidence |
| 21 | Improve Policies for Information Sharing to Support Clinical Research |
| 22 | Explore New Adaptive Pathways to Modernize Drug Development and Support a New Era of Personalized Medicine |
| 24 | Conclusion |
| 25 | Exhibit I: List of Interviewees and Roundtable Participants |
| 27 | Endnotes |

Introduction

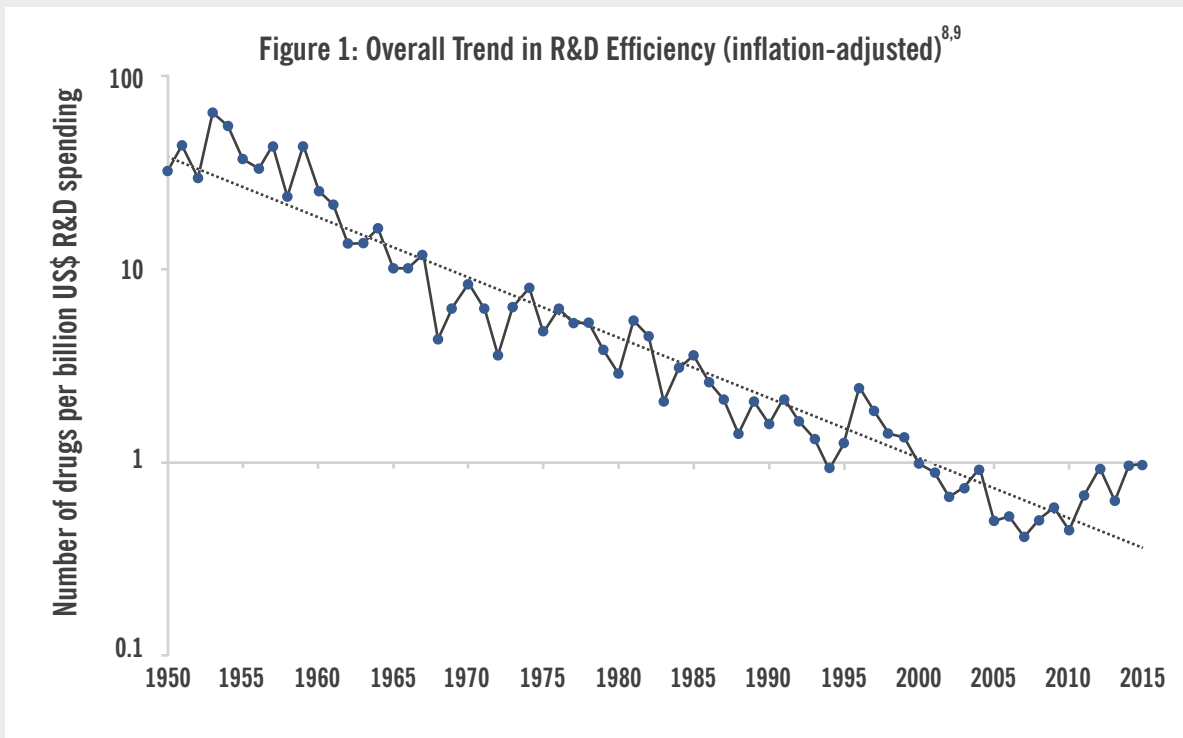
Unparalleled advances in science and technology during the past two decades have resulted in some stunning medical breakthroughs, such as the cure for Hepatitis C and new, more effective cancer treatments based on patients' genetic profiles.

Science is moving swiftly, but there are still significant unmet needs. An estimated 5.3 million Americans suffer from Alzheimer's disease, for which there is still no prevention or cure.¹ Heart disease remains the No. 1 cause of death in the United States, killing nearly 800,000 people in 2011 alone.²

In fact, for the approximately 10,000 known molecular-based diseases, there are approved treatments for only 500 of them.³ The urgency of finding the next generation of cures is clear.

Modernizing the drug discovery, development, and approval of new cures and treatments plays a critical role in addressing this issue and should be a key priority for the United States. It takes too long and costs too much to bring treatments and cures to patients in need. The most reliable studies suggest that on the average it costs approximately \$2 billion and takes more than a decade for a new drug to reach the market.^{4,5,6,7}

While the United States has invested more than \$1.5 trillion in research and development (R&D) over the past two decades, the level of R&D efficiency (number of drugs approved per billion dollars of R&D spending) has declined.



Both Congress and the administration have taken steps to address this issue. The U.S. House of Representatives nearly unanimously passed the 21st Century Cures Act in 2015. The Senate Health, Education, Labor, and Pensions (HELP) Committee completed its mark-up of bipartisan legislation earlier this year and is negotiating to advance a medical innovation package in the Senate in 2016. Negotiations between industry and the Food and Drug Administration (FDA) are now well underway in preparation for the reauthorization of drug and device user fee legislation in 2017. Finally, the administration's Precision Medicine Initiative is making considerable progress, as is the vice president's Cancer Moonshot launched earlier this year.

Modernizing the drug discovery, development, and approval process was also the focus of the Bipartisan Policy Center's July 2015 report, *Advancing Medical Innovation for a Healthier America*.¹⁰

The digitization of biology and the vast increase in the amount of electronic data captured during routine care, or by patients themselves, creates an unprecedented opportunity to modernize and augment clinical trials and improve the post-market monitoring process. The need to advance the generation and use of real-world evidence was one of the key recommendations of BPC's July 2015 report. This report highlights opportunities to modernize and improve the current drug development process through the use of real-world evidence, as well as the policy actions needed to realize those opportunities.

The findings and recommendations in this report were developed by BPC based on a review of the literature and interviews and roundtable discussions with 30 experts and practitioners, a list of which is provided in Exhibit I.



Today's Drug Approval Process

The FDA oversees the process of developing, testing, and approving new drugs. There are multiple stages and milestones in this years-long process, beginning with laboratory-based research and analysis and progressing through clinical-trials testing in human subjects, starting with very small groups and expanding to larger patient populations, to evaluate both safety and effectiveness.

An Overview of Today's Drug Approval Process

The current drug approval process is composed of four primary phases, summarized in Figure 2.

Figure 2: Current Drug Development Process

| Phase | Description of Activities ^{11, 12} |
|--|---|
| Pre-Clinical Phase | <ul style="list-style-type: none"> ▪ The drug sponsor develops (or buys or licenses) a new drug compound and goes through animal testing to assess toxicity. ▪ The sponsor submits an investigational new drug application (IND) to the FDA based on the results of initial testing and develops a plan for testing on humans. The FDA reviews the IND to assure that the clinical studies do not place human subjects at unreasonable risk of harm. |
| Clinical Trials | <p>Ordinarily, drugs go through three phases of clinical trials:</p> <ul style="list-style-type: none"> ▪ Phase I trials provide the first human studies of a new drug in individuals. This phase is designed to furnish greater understanding of the drug’s safety, including side effects in relation to drug dose. ▪ Phase II trials evaluate the effectiveness of a drug for a specific therapeutic use in patients, and continue to evaluate safety. The primary goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. ▪ Phase III trials involve relatively larger numbers of patients and are designed to gather enough information on safety and effectiveness to meet the FDA’s requirements for adequate assessment of the benefit/risk ratio for the drug, as well as preparation of information for drug labeling. |
| New Drug Application (NDA) Review | <ul style="list-style-type: none"> ▪ After meeting with the FDA, the sponsor submits an NDA, which includes all animal and human data and analyses, as well as how the drug behaves in the body and how it is manufactured. ▪ The FDA reviews drug labeling and assures appropriate information is communicated to health care professionals and consumers. ▪ The FDA inspects the facilities where the drug will be manufactured. ▪ The FDA either approves the drug or issues a response letter. |
| Post-Market Activities | <ul style="list-style-type: none"> ▪ Once a drug is approved, the Phase IV post-market monitoring process begins, whereby the sponsor is required to submit periodic updates to the FDA. ▪ The FDA has also established an ongoing post-market surveillance system to detect serious, unexpected adverse events and take actions if needed. |

Congress has authorized and the FDA has implemented several programs designed to facilitate early patient access to safe and efficacious drugs under certain conditions. Demands from patients with serious conditions and unmet medical needs have stimulated the development and implementation of these more flexible approaches to drug approval in the United States. Figure 3 provides an overview of expedited programs in the United States.

Figure 3: Overview of Expedited Drug Approval Programs in the U.S.¹³

| | Qualifying Criteria | Other Features |
|-----------------------------|---|---|
| Accelerated Approval | <ul style="list-style-type: none"> ▪ Intended to treat a serious condition ▪ Provides a meaningful advantage over available therapies ▪ Demonstrates effect on surrogate endpoint reasonably likely to predict clinical benefit | <ul style="list-style-type: none"> ▪ Approval based on surrogate or intermediate clinical endpoint ▪ Confirmatory trials required to verify benefit |
| Breakthrough Therapy | <ul style="list-style-type: none"> ▪ Intended to treat a serious condition ▪ Preliminary clinical evidence indicates drug may demonstrate substantial improvement on clinically significant endpoints over available therapies | <ul style="list-style-type: none"> ▪ Intensive guidance on efficient drug development ▪ Rolling review |
| Fast Track | <ul style="list-style-type: none"> ▪ Intended to treat a serious condition ▪ Data demonstrate potential to address unmet medical need, or the drug is designated as a qualified infectious disease product | <ul style="list-style-type: none"> ▪ Actions to expedite development and review ▪ Rolling review |
| Priority Review | <ul style="list-style-type: none"> ▪ Application for drug that treats serious condition ▪ Provides significant improvement in safety or effectiveness or the following: <ul style="list-style-type: none"> – Proposes labeling change pursuant to report on pediatric study – Is for a drug designated as qualified infectious-disease product – Is for drug submitted with priority review voucher | <ul style="list-style-type: none"> ▪ Shorter clock for review of marketing application (six months compared with the ten-month standard review) |

The European Medicines Agency (EMA) also has several expedited programs in place, including conditional approval, accelerated assessment, and the adaptive pathways approach. The EMA’s adaptive pathways program is a life-cycle approach to drug approval. Instead of a one-time approval that provides all patients access to a drug after completion of large randomized controlled trials (RCTs), adaptive pathways allow for early and progressive patient access to a medicine. New products are approved for a targeted population, evidence is continuously gathered, and the treatment population is progressively expanded. The EMA also assures early involvement of stakeholders who have a role in determining patient access, including the regulatory agency, industry, health technology assessment bodies, and patients.¹⁴

Current Methods for Conducting Clinical Trials

Clinical trials are the most critical, expensive, and time-consuming phase of the drug development process, taking on average nearly seven years and \$1.6 billion of the approximately \$2 billion spent on bringing a new drug to market.¹⁵ The FDA’s ultimate approval decision is largely based on data from clinical trials.

Figure 4: Average Time and Cost Associated with the Drug Approval Process

| Factors | Pre-Clinical Studies | Clinical Trials | | | FDA Review | Post-Market Monitoring |
|------------------------|----------------------|---|----------------|----------------|------------|------------------------|
| | | Phase 1 Trials | Phase 2 Trials | Phase 3 Trials | | |
| Time ¹⁶ | 1 year | 1.65 years | 2.53 years | 2.56 years | 1.33 years | Indefinite |
| | | Total average time for clinical trials: 6.74 years | | | | |
| Cost ^{17, 18} | \$182M | \$375M | \$542M | \$689M | \$129M | \$312M |
| | | Total average cost for clinical trials: \$1.6B | | | | |

Researchers in the United States have conducted clinical trials for FDA submissions in essentially the same way for more than 50 years.¹⁹ These clinical studies are largely based on RCTs, which are usually placebo-controlled, randomized, double-blind investigations in which patients are randomly assigned to a drug treatment group or a placebo group and neither the patient nor the investigator knows—until the end of the trial—which option the patient received. While known as the gold standard of clinical research, RCTs do have some limitations. Many experts agree that real-world evidence used in conjunction with more manageable clinical testing protocols can help address some of these limitations.

The tightly controlled nature of RCTs brings strong evidence, but only in relatively small and narrowly defined populations, limiting generalizability. Often missing from trials are representative samples of patients with multiple comorbidities, concomitant use of other drugs, varying races and ethnicities, ages at both the low and high ends of the spectrum, and different practice settings. Because they are conducted with a narrowly defined group of patients, RCTs often do not reflect the realities that would be present if the drug was used in a real-world population of patients for whom the treatment is intended.

For example, a trial to test a new diabetes drug will generally not include patients who also have other conditions, so that researchers can assess the drug’s effect on the target condition without additional complications. But in the real world, many patients with diabetes do have other conditions, such as heart disease. For the most part, clinical trials cannot reveal whether or not the drug would affect these patients differently or how it might interact with other drugs the patient may be taking.

RCTs will not be able to generate sufficient data in a new era of precision medicine. Precision medicine is an emerging approach for prevention and treatment that takes into account individual variability in genes, environment, and lifestyle.²⁰ The administration launched the Precision Medicine Initiative in 2015, seeking to leverage advancements in genomics, technology, and policies that empower patients in order to accelerate biomedical discoveries and advance individualized care.²¹ While large-scale RCTs have always played a key role in demonstrating the safety and efficacy of block-buster drugs, they are less likely to be able to provide the type of data needed in an era of personalized medicine, in which drugs and diagnostics are developed to treat subsets of patients who may respond to one treatment but not another, due to genetic or other factors.²²

The challenges associated with recruiting patients for RCTs are well-documented. The National Institutes of Health (NIH) estimates that up to 80 percent of clinical trials fail to meet their patient-recruitment timelines.²³ These challenges are especially significant in smaller patient populations with rare diseases. Only 4 percent of eligible people actually participate in clinical trials, and professionals who run large clinical trials attribute half of the delays encountered to the difficulty of enrolling volunteers.²⁴ The high cost of clinical trials is also a concern and is often prohibitive for smaller companies. The inability to sponsor these trials can lead to loss of competition in the marketplace, and adds to the high cost of medications. Finally, the very long duration of clinical trials—six to seven years—delays access to promising treatments and cures.

Current Post-Market Surveillance Efforts

Because it is not possible to predict all of a drug's effects during clinical study periods, the FDA has established a post-marketing safety system to detect serious, unexpected adverse events and take actions if needed.²⁵ FDA, under certain circumstances, including expedited review programs, permits use of a drug based on shorter or smaller clinical studies, based on a commitment to conduct a larger or longer-term Phase IV study following approval.

Once the FDA grants approval for a sponsor to market a drug in the United States, Phase IV—post-approval monitoring—ordinarily begins. During this phase, the sponsor is required to submit periodic safety updates to the FDA so that it can monitor the long-term effects of new drugs and treatments in larger and more diverse groups of patients. The post-marketing phase can require considerable resources—on average, \$312 million, as noted in Figure 3.

The FDA uses the FDA Adverse Event Reporting System (FAERS), a computerized database that contains information on adverse event and medication error reports submitted to the FDA, to support its post-marketing safety surveillance program for drugs and therapeutic biologic products. Health care professionals and consumers can voluntarily report adverse events and medication errors to the FDA.²⁶ Most reporting is conducted electronically through the MedWatch system. Manufacturers are required by law to send to the FDA any adverse event reports received.²⁷

If a potential safety concern is identified, further evaluation is performed by the FDA. Such evaluation might include conducting studies using other large databases, such as those available in the Mini-Sentinel System. Based on its evaluation, the FDA can take regulatory actions to improve safety and protect the public health. This may include requiring a sponsor to update a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or in rare cases, removing a product from the market.²⁸



Real-World Data: A New Opportunity to Strengthen the Process

An Overview of Real-World Data

Data gathered from sources outside of randomized controlled trials reflecting the actual experiences of patients during routine patient care is often referred to as real-world data. Real-world evidence is derived from real-world data sources. Sources of real-world data include electronic health records (EHRs) used within provider settings, laboratory information systems, pharmacy and radiology systems, administrative claims systems, and registries. Other sources include patient-generated data captured on home-based and wearable monitoring devices, as well as patient information-sharing networks and social media.

The significant increase in the use of EHRs within the clinical setting, combined with the surge in the number of Americans recording health information through devices and information-sharing applications, is producing unprecedented amounts of information useful for regulatory decision-making. About 83 percent of office-based physicians and 84 percent of hospitals now use some type of EHR, making more clinical data available every day.^{29, 30}

In addition, seven in ten American adults say they track at least one health indicator for themselves or for someone else.³¹ Fifty-eight percent of U.S. smartphone owners have downloaded a fitness or health app, and about 65 percent of those individuals open the app at least once a day.³² Many of these apps connect to wearable devices that track activity and vital signs. All of these are sources of potentially useful health data that can complement data generated through controlled trials.

Real-world data is already being used to support a number of efforts to improve health and health care. Data derived from EHRs, claims, and laboratory systems are being used to measure and improve quality, cost, and health outcomes, supporting new payment and delivery system reforms.

Real-world data is also being used in outcomes and comparative effectiveness research to compare current health care interventions and determine which work best for which patients. The Patient-Centered Outcomes Research Institute (PCORI) has awarded more than \$1.7 billion in funding for comparative clinical effectiveness research projects, including provider and patient-centered research networks that leverage real-world data.³³ The NIH Health Care Systems Research Collaboratory is also investing in new infrastructure for collaborative research and supporting the design and rapid execution of pragmatic clinical trial demonstration projects.³⁴ Real-world data is also expected to be used for the national research cohort of more than one million American participants in the administration's Precision Medicine Initiative.

Current Uses of Real-World Data Within the Drug Approval Process

The FDA is already using real-world data to support post-market surveillance efforts. In response to the FDA Amendments Act of 2007, which required the FDA to develop a system for post-market risk identification and analysis of drugs, the FDA implemented the Sentinel Initiative.³⁵ Mini-Sentinel was launched in 2009 to serve as a pilot program of the Sentinel Initiative, designed to test the feasibility of accessing and analyzing health care information from a variety of data sources and using that data to improve FDA decision-making. A recent assessment conducted by the Government Accountability Office indicates that Mini-Sentinel inquiries to date have resulted in two label changes, three safety communications, and no medical product withdrawals or recalls.³⁶ Traditional adverse event reporting from clinicians, patients, and manufacturers remains the primary source of safety information at the FDA.³⁷ There is considerable opportunity to further leverage real-world evidence to support post-market surveillance efforts.

Use of real-world data is less common when generating evidence through clinical trials to support drug approval. While the use of real-world data in pre-market evidence development is not specifically prohibited by law, it is not widely used due to the lack of clarity regarding evidence requirements associated with its use and long-standing perceptions that only RCTs will be accepted by the FDA to support drug approvals.

The use of pragmatic randomized clinical trials is one way to begin to build experience with the use of real-world evidence within clinical trials. Pragmatic clinical trials are trials that take place in settings where routine care occurs, such as community clinics, hospitals, and health systems and they involve diverse, representative populations and multiple, heterogeneous settings.³⁸

Benefits of Real-World Evidence

Through review of research and reports, and interviews and roundtables with experts and practitioners, BPC identified several benefits and opportunities for using real-world evidence during the drug development process.

Real-world evidence can support many activities during the clinical trials phase of drug development. It can expedite the generation of hypotheses to inform the design of clinical studies and enable identification of subpopulations with higher risk-benefit ratios to target development efforts. Real-world evidence can enable more efficient and targeted recruitment of patients for clinical trials. It can also reduce the burden of data collection and reporting and enable the collection of patient-reported outcomes. Real-time monitoring of trials can help sponsors identify safety and operational issues requiring action sooner, to help avoid adverse events and unnecessary delays. The use of real-world evidence can improve the generalizability of trials by augmenting RCTs with data from a broader, more diverse group of patients in different practice settings than is currently gained through targeted, tightly controlled populations, to gain better insights on safety and effectiveness. Real-world evidence can make studies and their findings more relevant to patients and provide information on long-term outcomes. Finally, earlier generation of effectiveness data can help inform decision-making regarding value and reimbursement sooner, which is a goal of both sponsors and payers.

Real-world evidence also provides considerable opportunity to improve post-market activities, by reducing the time and cost of conducting Phase IV post-market monitoring through more efficient methods of data collection and improving the timeliness and effectiveness of ongoing post-market surveillance efforts. Real-world evidence can also improve the efficiency of studies that confirm clinical benefit for drugs approved under FDA's expedited programs.

Gathering Real-World Evidence Through Close-Monitoring

The rapid increase in and now widespread use of technology creates new opportunities for monitoring the safety and efficacy of drugs prior to and after their approval. New technology and the real-world data that it produces can support a new concept of “close-monitoring.” In this new paradigm, patients, researchers, and regulators could benefit from real-time monitoring of patients—with their consent—during clinical trials, during a post-approval commitment phase, or after approval to a subset of patients, through a combination of personal monitoring devices, smartphone apps, phone calls and virtual visits, all with patient consent.

- Monitoring would move from a population-based model to a personalized medicine approach, where almost every single patient exposed to the new medication is monitored.
- Monitoring would occur much more frequently, without disrupting the patient's lifestyle and without incurring excessively high costs.
- Patients would be monitored proactively and individually, not just reactively and statistically.
- Development cycles and regulator as well as payer review cycles would be shortened.
- Ongoing close support of patients would likely improve compliance.
- Post-marketing monitoring for safety would be strengthened.

The close-monitoring model could also be leveraged to support Risk Evaluation and Mitigation Strategies (REMS) requirements.

In addition to the near-real-time safety monitoring of individuals using the medication, a close-monitoring program could also address one of the FDA's major concerns: how to reliably communicate safety information to a subset of patients who are among the first to take a drug or who are in a drug registry program that is part of a REMS. If a safety concern were to arise during such programs, every patient using the drug, and his or her physician and pharmacist, could be notified immediately—something that is impossible to accomplish in the current Phase IV post-marketing program.

Issues that Need to be Addressed

As real-world evidence is increasingly used to support the drug development life cycle, more research, collaboration, and transparency is needed to support improvements in both statistical methods and data analytics.

Also, several difficult—but surmountable—data challenges exist, including lack of data completeness for clinical research, the lack of adoption of standards to support effective interoperability and use of the data across disparate systems, the lack of agreement on methods for accurate patient matching, and the lack of traceability of data or data provenance. Work is currently underway to help address many of these challenges, but more action will be needed to support the generation and use of real-world evidence.



Integrating Real-World Evidence into the Drug Development Process

There is growing consensus that real-world data can and should play a significant role in supporting and even strengthening the evidence base for safety and effectiveness—across the life cycle of drug development—encompassing both pre- and post-market regulatory decision-making.

Review of the research and interviews with experts and leaders revealed a number of opportunities for the use of real-world evidence to improve the drug development process.

Circumstances under which real-world evidence can make an immediate impact include supporting regulatory decision-making associated with a label extension or a new indication for an approved drug, supporting confirmatory studies for drugs approved under the FDA's existing expedited programs, and improving the efficiency of Phase IV post-market monitoring and ongoing post-market surveillance. The use of pragmatic clinical trials to support RCTs is also ripe for implementation.

Finally, given the growing science and focus on personalized medicine approaches that do not lend themselves to traditional one-size-fits-all large clinical studies, regulators and those who pay for health care should begin to explore new approaches for clinical trials that are more adaptive in nature and can take into account smaller sub-populations. The integration of individualized close-monitoring—as described above—as well as other types of data capture of real-world evidence, can support an adaptive drug approval approach in a new era of precision medicine.

Figure 5: Opportunities for the Use of Real-World Evidence

| | |
|--|---|
| <p>Near-Term Opportunities for Use of Real-World Evidence</p> | <ul style="list-style-type: none"> ▪ Implement new, more flexible, pragmatic models of clinical trials which combine the benefits of collecting data from more real-world settings while incorporating elements of randomization typical in RCTs, referred to as pragmatic clinical trials ▪ Utilize real-world evidence to expand upon previous studies using RCTs to inform regulatory decision-making: <ul style="list-style-type: none"> – Label revisions or expansions – New indications for existing drugs – Confirmatory studies for drugs approved under the FDA’s expedited programs – Phase IV post-marketing studies ▪ Utilize real-world evidence in certain cases where randomization is unethical ▪ Expand upon current efforts to use real-world evidence to support ongoing post-market surveillance. |
| <p>Opportunities to Use Real-World Evidence Under a New Paradigm of Drug Development</p> | <ul style="list-style-type: none"> ▪ Explore new, adaptive approaches that use continuously generated evidence, including that derived from close-monitoring and other real-world studies, to supplement data from RCTs. |



Recommendations for Modernizing the Drug Development Process Through the Use of Real-World Evidence

Integrating real-world evidence into today's drug development process will require improving certainty about the types of evidence that will be accepted and under what circumstances, through greater regulatory clarity. It will also require greater transparency of, as well as agreement on, acceptable methods. Improved data quality and changes in policies for information sharing will make the use of real-world evidence easier and less expensive.

To lay the groundwork for a new era of precision medicine, new adaptive approaches for regulatory decision-making will be needed. As medicine becomes more personalized and drugs become targeted for smaller populations, traditional, large-scale, RCTs will become increasingly less relevant. New approaches will be needed to assure safety and efficacy and to protect the patient's health. Adaptive approaches will be needed that focus on the entire drug life-cycle and that utilize close-monitoring and real-world evidence approaches to augment RCTs conducted within smaller populations.

Recommendation I:

Improve Regulatory Clarity Regarding Use of Real-World Evidence

Evidence requirements for the approval of drugs date back to 1962 when the Kefauver-Harris Amendments to the Federal Food, Drug and Cosmetic Act included provisions requiring manufacturers of drug products to establish a drug's effectiveness by substantial

evidence and adequate and well-controlled investigations before it could be approved for marketing.³⁹ Since then, several regulations and guidances have been published.⁴⁰

Neither definitions for “adequate and well-controlled” investigations included in the law nor in the FDA’s recent guidance preclude the use of real-world evidence for regulatory decision-making.⁴¹ While the statutory basis of regulatory decision-making leaves room for the FDA to consider real-world evidence, to date the statutes and guidance have been narrowly interpreted. Real-world evidence has rarely been used beyond post-market surveillance or to support drug approvals for rare or life-threatening diseases. The broader use of real-world evidence in regulatory decision-making, for example, for label expansions, new indications, or to support new drug approvals, is not yet routinely considered by the FDA.

Sponsors and investigators would pursue the use of real-world evidence to augment and support clinical trials and post-marketing commitments if there were more clarity from the FDA regarding the types of real-world evidence that would be accepted for various decisions, and the methods required to establish confidence in analyses using real-world data.

- 1.** The FDA should develop formal guidance regarding the use of real-world evidence to inform regulatory decision-making, including the circumstances under which real-world data could be used as well as the types of real-world data, methods, and the levels of evidence that would be acceptable for use in regulatory review and decision-making. The guidance should include, but not be limited to, new drug approvals (including approvals under expedited programs), label expansions, new indications, post-market commitments, and post-market study requirements.
- 2.** The FDA should engage representatives of regulated industry, patient and disease research organizations, academia, experts in the use of electronic data, experts in statistical methods, and experts in privacy policy in the development of the guidance.
- 3.** To inform guidance development, the FDA should review the results of research, studies, and pilots associated with the use of real-world data to inform decision-making regarding the types of real-world data that would be acceptable, appropriate statistical and other methods, data quality requirements, and other factors, as appropriate. The FDA should draw upon the experiences of efforts funded by both the public and private sectors, including but not limited to the FDA’s Sentinel Initiative, the NIH Collaboratory, the Agency for Healthcare Research and Quality, the Observational Health Data Sciences and Informatics (OHDSI), previous work of the Observational Methods Outcomes Partnership (OMOP), and PCORI.

Recommendation II: Improve Methods and Data Quality for the Generation and Use of Real-World Evidence

The scope and amount of real-world data potentially available is rapidly expanding, as are the methods to effectively use and interpret the data for regulatory decision-making purposes.

As real-world evidence is increasingly used for regulatory decision-making, there is a need for greater sharing of best practices and transparency of methods used.

The methods and interpretations traditionally used in customized individual study designs ordinarily used within RCTs may not be the appropriate methods to use for understanding much larger data sets, or data drawn from across a network of disparate databases. Studies have shown that similar questions posed to different data sets have drawn very different conclusions. Other studies have shown that different methods applied by different investigators to the same data sets have also drawn different conclusions. Promoting transparency in methods used and public dialogue about best practices for methods will significantly advance the field and provide more confidence in published results using real-world evidence.

Given this, it is imperative that regulatory agencies and those who rely upon such data to inform reimbursement decisions educate themselves and the public about best practices in methods of use and interpretation of real-world evidence for decision-making purposes.

A number of organizations have made great strides in studying methods for using and interpreting real-world data, including OHDSI, OMOP, and PCORI. PCORI has published a set of methodology standards that all grantees are required to use.⁴² OHDSI and OMOP have published the results of extensive testing of methods across a wide range of large data sets and OHDSI is developing open-source tools for large-scale observational studies, including methods for population-level estimation and patient-level prediction, the former of which can be used for safety surveillance and comparative effectiveness studies.⁴³ The Innovation in Medical Evidence Development and Surveillance program of the Reagan-Udall Foundation for the FDA is initiating and facilitating research into methods of safety evaluation in large observational databases.⁴⁴

Many researchers look to the FDA for guidance on interpreting data, leading some to call for full transparency on how the FDA reaches its conclusions. Transparency in the FDA's methods will provide invaluable insight into how regulators deal with problems like missing information, lack of outcomes data, and disparities in sample populations compared with the real world.

The quality and the completeness of real-world data also contributes to its usefulness. Currently the systems that capture data for clinical research are very different from the systems that capture data for clinical care. Often the data required for clinical research does not exist in the EHR or other clinical systems. Poor interoperability among systems, the lack of adoption of common data standards, and the need for more effective methods for matching patient data across disparate systems, also serve as barriers to the effective aggregation and use of real-world data for clinical studies. Also, the FDA requires an audit trail for data used in clinical research. The lack of agreed-upon technological methods and standards to discern the origination of data and who has had access to such data—referred to as the traceability or provenance of the data—can be an obstacle to FDA's acceptance of real-world data for evidentiary purposes in decision-making.

- 1.** The FDA should establish a program to promote sharing and evaluation of methods used in the evaluation of real-world evidence for regulatory decision-making. The FDA should invite a broad spectrum of researchers who are active in the generation and use of real-world evidence and methods development, as well as leaders who rely upon such real-world evidence—including regulators and payers—to participate in this program.
- 2.** The U.S. Department of Health and Human Services (HHS) should support research to improve methods for the use of real-world evidence, which take into account the much larger samples of electronic data now available and enable high-throughput methods that produce accurate and well-calibrated inferences that quantify levels of uncertainty more accurately. Such research should focus on issues that include, but are not limited to, mitigating bias, obtaining solutions to better refine outcomes definitions, understanding implications to analyses for integrating observational data across a number of disparate sources, and understanding the contributions of real-world evidence to causal reasoning.
- 3.** The FDA should require any researchers who receive federal funding or utilize real-world evidence to draw conclusions used for regulatory decision-making to publish and make transparent their methods to support peer-review, promote replicability, and assess validity. Publication should include the specific methods used to evaluate real-world evidence in the study, along with the data sources and intended results, if applicable. FDA should encourage private sector studies to do the same.
- 4.** HHS should continue its efforts to advance the adoption of standards and the interoperability of EHRs and such efforts should extend to other clinical systems beyond the EHR. HHS should develop and publish standards that will improve the accuracy of matching of patient data across health information technology systems. HHS should also continue its efforts to harmonize standards related to data used for clinical research with standards related to data within EHRs and other systems used within health care. FDA should revise and update its guidances to include specific recommendations on technological approaches and modern concepts of data provenance.

Recommendation III:

Improve Policies for Information Sharing to Support Clinical Research

As communication tools have modernized and clinical research has grown more complex, many clinical trials now include patients and participating organizations across multiple health care entities and geographic regions.

Under current law, in order to conduct one real-world study across multiple health care systems, multiple institutional review board (IRB) approvals are required. Regulated by the Office of Human Research Participants (OHRP) within HHS, IRBs are independent groups that review research initiatives to evaluate the potential risks and benefits for human participants and are charged with protecting the rights and welfare of patients involved in research studies.

Given the differences in how IRBs view their remit and what constitutes a clinical trial, a unique and individualized approach is often needed to seek approval from each IRB, leading to delays in trial execution and increased costs.

The idea of creating a centralized IRB for a multi-site trial is not new. The FDA issued guidance in 2006, titled “Using a Centralized IRB Review Process in Multi-Center Clinical Trials.”⁴⁵ In 2010, the OHRP issued a letter to clarify its own 1998 guidance on this topic, stating that it fully supports the FDA’s position on the benefits of relying on a single, central IRB for multi-center research.⁴⁶ The OHRP published a Notice of Proposed Rulemaking (NPRM) on September 8, 2015 for revisions to the Common Rule that would mandate that U.S. institutions engaged in cooperative research rely on a single IRB for that portion of the research that takes place within the United States, with certain exceptions.⁴⁷ The NPRM asked for public comment on the areas of guidance that would be needed for institutions to comply with this requirement. Stakeholders were divided in public comments on the NPRM.⁴⁸ The Secretary’s Advisory Committee on Human Research Protections recommended a compromise approach, suggesting that NIH should use incentives to encourage increased use of a single IRB for multisite studies.⁴⁹

Congress has also recognized the importance of using centralized IRBs. Section 2261 of the 21st Century Cures Act passed by the U.S. House of Representatives in 2015, included provisions that would require the HHS Secretary—through OHRP and FDA—to issue regulations and guidance to facilitate the broader use of central IRBs within 36 months. Such regulations and guidance would clarify the roles of IRBs in multi-site studies, the risks and benefits to human subjects, how to standardize informed consent, and how to incorporate community values through the use of local IRBs while continuing to use central IRBs.⁵⁰ No such language was included in any of the 19 bills included in the medical innovation package approved by the Senate HELP Committee in February, March, and April of 2016.⁵¹

- 1.** Congress should require the HHS Secretary—through the OHRP and the FDA—to issue regulations and guidance to facilitate the broader use of centralized IRBs within 36 months, by clarifying the roles of IRBs in multi-site studies and the risks and benefits to human subjects, standardizing informed consent, and incorporating community values through the use of local IRBs while continuing to use central IRBs.
- 2.** Congress should promote NIH policies to encourage investigators and institutions to voluntarily utilize single IRBs as part of their grant submissions. NIH should provide additional funds to those grants that agree to utilize single IRB arrangements.

Recommendation IV: Explore New Adaptive Pathways to Modernize Drug Development and Support a New Era of Personalized Medicine

A growing number of regulators and researchers across the world recognize the need for a more flexible approach to drug approval, and they understand the role that real-world evidence can play in the process.

As medicine becomes more personalized and drugs become targeted for smaller populations, traditional, large-scale RCTs will become increasingly less feasible. Additional approaches will be needed to assure safety and efficacy and protect the public's health. Adaptive approaches can be an effective method for some types of drugs. They will improve focus on the entire drug life-cycle and utilize close-monitoring and real-world evidence approaches to augment RCTs conducted within smaller populations.

An approach to certain drug approvals using adaptive pathways would use continuously generated evidence—from close-monitoring, as well as observational studies and other real-world evidence, all of which would supplement data from RCTs—to support approval of drugs that have been shown to be safe and effective for well-defined subpopulations. All participating patients would participate in virtual, real-time monitoring through a combination of personal monitoring devices, smartphone apps, phone calls, and virtual visits. This would allow better management of risk because more data, and more timely data, would be gathered from a bigger cohort, leading to earlier and more robust information from which to create risk profiles. This approach is not unlike the EMA's adaptive approval pathway.⁵²

Overseeing this monitoring effort would be a network of both public and private medical professionals. The increasingly consolidation of “patient-centric” medical care now uniquely lends itself to this integration of data. The patient's primary care physician or nurse would enroll in the program, along with the patient's dispensing pharmacist. This network of professionals would follow a carefully designed plan for closely monitoring the patient cohort, and a rapid-response process would be created to quickly address any safety concerns that arise.

Close-monitoring would have the following characteristics:

- Each cohort would have a custom-designed monitoring plan based on the treatment condition, cohort characteristics, drug safety considerations, and the current benefit/risk profile.
- Every single patient in a close-monitoring cohort would be monitored more frequently and more carefully than in the current post-approval model.
- The dispensing pharmacist or other health care professional would receive and monitor information regarding patient compliance, and would alert any non-compliant patients that they risk being dropped from the program.

Rapid advances in technology and personalized medicine would continue to make this level of monitoring easier, more cost effective, and more accurate. In addition, the close-monitoring structure could be used for other purposes—such as large simple trials, REMS requirements, and registries—streamlining processes and saving money.

A flexible, adaptive, life-cycle approach to drug approvals for certain qualifying drugs will:

- Build on the most successful aspects of the FDA's existing expedited review programs;
- Use real-world data together with clinical efficacy and safety data, as appropriate, to support more robust analysis, and allow for more rapid, successive regulatory decision-making; and
- Support the collection of data across the lifecycle of the medicine, for successive assessments and decisions about regulation and reimbursement.

To advance the exploration of this new flexible, adaptive approach to drug approval, several steps must be taken, outlined below.

- 1.** The FDA should develop a new program to develop and test a new adaptive pathway approach to expand the capacity for drug development that has the following key attributes:
 - a.** Iterative phases of development, beginning with initial marketing authorization to a restricted patient population, then expanding to wider populations based on risk-benefit ratios;
 - b.** Gathering evidence through close-monitoring and other real-world evidence, to supplement RCTs; and
 - c.** Early involvement of stakeholders who have a role in determining patient access to the drug, including industry, payers, regulators, clinicians, and patients.
- 2.** The FDA's new program to develop and test a new adaptive pathway approach for drug development should include the following elements:
 - a.** Qualifying criteria for the program, which will determine which types of drugs at what stages could be considered for the adaptive pathway approach;
 - b.** Types and levels of evidence required for initial approval and expansion, including evidence generated from close-monitoring, other real-world evidence, and randomized controlled trials, as appropriate;
 - c.** Methods for early involvement of patients, clinicians, payers, industry, and regulators; and
 - d.** Methods for assuring market removal or label modification of products when follow-up studies and monitoring are not completed or when an unfavorable risk-benefit ratio for certain populations is demonstrated.
- 3.** The FDA should engage experts and stakeholders in developing the program, including representatives of regulated industry, academia, clinicians, patient advocacy and research organizations, and others, as appropriate. The FDA should gain public input on the key attributes and elements of the program.
- 4.** The FDA should launch a pilot program to test the attributes and elements of the new adaptive pathway program for drug development, engaging the participation of multiple consortia and organizations.
- 5.** Upon completion of the pilot program, the FDA should issue guidance for a new adaptive pathway program, including final attributes and elements, that reflects lessons learned from the pilots.



Conclusion

Real-world evidence can play a significant role in modernizing the drug approval process in the United States. The increase in the amount of electronic data available, combined with scientific advances resulting in more personalized and more complex drug regimens, demand a new, modernized approach that spans the entire drug life-cycle.

Implementing the steps outlined in this report will enable the United States to make significant progress in leveraging real-world evidence to help get safe and effective drugs to market faster and more cost-efficiently. Taking these actions will not only improve global competitiveness, but more importantly, will help the hundreds of thousands of patients who are waiting for cures and treatments.

Exhibit I: List of Interviewees and Roundtable Participants

Jeff Allen, MD

Executive Director
Friends of Cancer Research

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Associate Dean for Clinical and Translational Research, Harvard Medical School

Graham Atkinson, D.Phil.

Executive Vice President for Research and Policy
Jayne Koskinas Ted Giovanis Foundation for Health and Policy

L. Charles Bailey, MD, PhD

Assistant Professor of Clinical Pediatrics
Perelman School of Medicine, University of Pennsylvania

Marc Berger, MD

Vice President, Real World Data and Analytics,
Pfizer

Marc M. Boutin, JD

Chief Executive Officer
National Health Council

Jennifer DeVoe, MD, DPhil

Chief Research Officer
ADVANCE Project, OCHIN

Theodore Giovanis

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Robert Harrington, MD

Arthur L. Bloomfield Professor of Medicine and
Chairman of the Department of Medicine, Stanford University
Director of Clinical Investigation, Stanford Cardiovascular Institute

Adrian Hernandez, MD, MHS

Director, Health Services and Outcomes Research
Duke Clinical Research Institute
Faculty Associate Director and Associate Professor of
Medicine, Cardiology
Duke University School of Medicine

George Hripcsak, MD, MS

Vivian Beaumont Allen Professor of Biomedical Informatics,
Columbia University
Chair, Department of Biomedical Informatics, Columbia
University
Director, Medical Informatics Services, NewYork-Presbyterian
Hospital/Columbia

Charles Jaffe, MD, PhD

Chief Executive Officer
Health Level Seven International

Jonathan Jarow, MD

Senior Medical Advisor, CDER
Food and Drug Administration

Harlan Krumholz, MD,

Harold H. Hines, Jr. Professor of Medicine (Cardiology) and
Professor in the Institute for Social and Policy Studies of
Investigative Medicine and of Public Health (Health Policy)
Yale School of Medicine

Rebecca Kush, PhD

President and CEO
Clinical Data Interchange Standards Consortium

Michael Levy

Deputy Vice President
Pharmaceutical Research and Manufacturers of America

David Madigan, PhD

Executive Vice President, Dean of Faculty of Arts and Sciences,
Professor of Statistics
Columbia University

Mark McClellan, MD, PhD

Former Commissioner, Food and Drug Administration
Director, Duke-Robert J. Margolis, MD Center for Health Policy
Duke University

Shawn Murphy, MD, PhD

Associate Director of the Lab of Computer Science, Associate
Professor of Neurology, Associate Professor of Biomedical
Informatics
Harvard Medical School and Massachusetts General Hospital

Peter Neumann, ScD

Professor of Medicine, Sackler School of Graduate Biomedical
Sciences
Tufts University

J. Marc Overhage, MD, PhD

Chief Health Informatics Officer
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Richard Platt, MD

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Head of the Department of Population Medicine
Harvard Pilgrim Healthcare

Russell Rothman, MD, MPP

Professor, Internal Medicine, Pediatrics and Health Policy
Vice President, Population Health Research
Director, Center for Health Services Research
Vanderbilt University Medical Center

Patrick Ryan, PhD

Senior Director and Head, Epidemiology Analytics
Janssen Research and Development

Richard Schilsky, MD

Senior Vice President and Chief Medical Officer
American Society of Clinical Oncology

Abby Sears

Chief Executive Officer
Oregon Health Information Network (OCHIN)

Joe V. Selby, MD, MPH

Executive Director
Patient-Centered Outcomes Research Institute

Andrew von Eschenbach, MD

Former Commissioner, Food and Drug Administration
President, Samaritan Health Initiatives, Inc.

Scott Wasserman, MD

Vice President, Global Development
Amgen

Marcus Wilson, PharmD

President
Healthcore, a Wholly-Owned Subsidiary of Anthem

It is important to note that while the interviewees provided important input to the development of the report, the findings and recommendations in this report were not specifically reviewed or endorsed by those interviewed.

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