



# Expanding the Use of Real-World Evidence in Regulatory and Value-Based Payment Decision-Making for Drugs and Biologics

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BIPARTISAN POLICY CENTER

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## DISCLAIMER

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# Letter from the Former FDA Commissioners

Exciting progress has been made in recent years in the discovery and development of new therapies and treatments, particularly for patients fighting diseases thought to be incurable just a generation ago.

Scientific breakthroughs coupled with a faster, more streamlined process for the development of novel drugs and biologics is accelerating the pace at which patients are receiving new, more effective treatments. But this acceleration is also enabling market entry based on biomarkers and surrogates rather than definitive information about risks and benefits in practice.

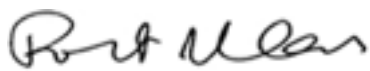
These advances are set against the backdrop of continually rising health care costs, declining life expectancy, and ongoing concerns about affordability and disparities in the U.S. health care system. Efforts to shift from volume-based to value-based payment for care delivery are showing promise and providing lessons that can inform new models of payment for medical products that can help address these concerns. Just as the life cycle of drug development is being modernized through the use of real-world data and real-world evidence, so too can new models of value-based payment benefit from data generated through care processes and by patients themselves. Real-world data and evidence can improve regulatory and payment decision-making. It can also provide generalizable knowledge to support clinician and patient decision-making.

We have already made significant progress in creating a framework for the use of real-world evidence in regulatory decision-making, but there is more work to do. This report examines both the progress so far and the barriers we must address if we are to meaningfully expand the role of real-world data and evidence to inform the discovery, development, and delivery of new therapies for patients, provide high-quality evidence about risks and benefits in practice, and inform which therapies are best for which patients.

The report's recommendations focus on clearing barriers to the access and use of real-world data to provide an evidence base for regulatory evaluation and value-based payment programs, expanding opportunities to use new data sources and approaches, and advancing new models of collaboration among payers, manufacturers, regulators, clinicians, and—most importantly—patients.

We are living in an age of remarkable scientific progress. We owe it to the patients we serve to support that progress by continually examining and improving our processes to deliver new, effective therapies to them as fast as is safely possible. We believe the recommendations in this report are important steps toward reaching that critical goal.

Sincerely,



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# Executive Summary

The amount of electronic health care data is increasing at unprecedented rates, due to the now widespread adoption of electronic health records (EHRs) and other technology in health care, as well as the significant increase in the number of patients that are now using technologies—such as wearables, biosensors, apps, and other digital health tools—to track their activities and health status and connect with the health system.

These real-world data sources provide the opportunity to improve the evidence base for the development of new drugs and biologics, regulatory evaluation by the Food and Drug Administration (FDA), and new value-based payment arrangements, which align pricing or payments with outcomes.

Real-world data and evidence have significant bipartisan support. Several provisions related to real-world evidence were contained in the 21st Century Cures Act passed and signed into law in December 2016, as well as the FDA Reauthorization Act of 2017 and other user fee legislation passed in 2017. The FDA has taken several steps to advance the generation and use of real-world evidence for regulatory decision-making, including the publication of the *Framework for FDA's Real-World Evidence Program* (FDA Framework) in December 2018.

While there are many opportunities to leverage these new data sources as real-world evidence to support regulatory efforts and new value-based payment arrangements for drugs and biologics, there are also barriers to their use. The recommendations below are expected to advance the generation and use of real-world evidence for regulatory evaluation and value-based payment decision-making.

## 1. ASSURING ADEQUATE FUNDING OF REAL-WORLD EVIDENCE ACTIVITIES

### 1.1 Fully Fund the FDA's FY2020 Budget Request for the Creation of a New Medical Data Enterprise to Advance the Use of Real-World Evidence

As it finalizes appropriations for FY2020, Congress should fully fund the FDA's \$60 million budget request for a Medical Data Enterprise to advance the use of real-world evidence to evaluate both effectiveness and safety of drugs, biologics, and devices.

## 2. IMPROVING REGULATORY CLARITY

### 2.1 Continue and Expand Upon Efforts to Improve Regulatory Clarity

The FDA should build on the recent momentum related to real-world evidence and rapidly develop and publish guidance—as required by the 21st Century Cures Act—regarding the circumstances under which sponsors and the FDA may rely on real-world evidence to help support the approval of a new indication for an existing drug, as well as to help support or satisfy post-approval study requirements. Such guidance should address key issues raised within the recently released FDA Framework. The guidance should be informed not only by the FDA Framework, but also by insights gained from pilot activities and robust processes for soliciting stakeholder and expert input.

## 3. IMPROVING ACCESS TO DATA

### 3.1 Adopt Electronic Health Information Export Provisions, as Proposed, in Updates to 2015 Edition Certification Criteria

The Office of the National Coordinator for Health Information Technology (ONC) should adopt, as proposed, a new 2015 Edition ONC Health Information Technology (IT) Certification criterion that requires health IT developers to enable all electronic health information to be exported—in a computable, electronic format, along with instructions to facilitate interpretation and use—for a patient or designee upon request. ONC should further clarify the ways in which data can be accessed by patients or their designees to support the use of patient data—while appropriately protecting privacy—for research.

### 3.2 Adopt API Provisions Contained in ONC Proposed Rule

ONC should adopt, as proposed, 2015 Edition ONC Health IT Certification criteria that would require health IT developers to support application programming interface (API)-enabled services for all data contained in the U.S. Core Data for Interoperability (USCDI) on a single patient and multiple

patients, using the Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR®) standard and related implementation specifications, so that information can be accessed, exchanged, and used without special effort. Such data should include all available data elements defined within the USCDI, whether structured or unstructured.

### **3.3 Collaborate on the Development and Use of HL7 FHIR® Implementation Guides to Support Regulatory and Value-Based Payment Real-World Evidence Needs Related to Medical Products**

The FDA, the Centers for Medicare and Medicaid Services (CMS), and ONC should collaborate with HL7, as well as other stakeholders, including payers, providers, academic and research institutions, and patient groups, to develop, test, and utilize HL7 FHIR® implementation guides to gain access to real-world data—while effectively protecting privacy—to support the evidence needs of both regulatory evaluation and value-based payment decision-making.

### **3.4 Facilitate Access to Medicare Data to Support the Real-World Evidence Needs of Regulatory Evaluation and Value-Based Payment of Medical Products**

CMS should explore ways to make Medicare beneficiary data available—in formats that help to meet the reliability and relevance requirements of evidence development—to support the real-world data needs of regulatory evaluation and value-based payment for medical products.

### **3.5 HHS Should Collaborate with Both Users and States to Accelerate Efforts to Make Standards-Based Mortality Information Available on a Timely Basis and at Reasonable Cost**

HHS should collaborate with users and states to develop and implement sustainable strategies to improve the availability, accuracy, timeliness, and cost of accessing mortality information for research and other population health improvement purposes. Such efforts should include the finalization and widespread adoption of mortality-related HL7 FHIR® standards among states and technology developers.

## **4. IMPROVING RELIABILITY AND RELEVANCE OF DATA**

### **4.1 Adopt the USCDI Standard in Updates to 2015 Edition Certification Criteria**

ONC should replace the Common Clinical Data Set (CCDS) and its references within the 2015 Edition of the ONC Health IT Certification requirements with the USCDI standard, as proposed, including new required data classes and elements related to patient demographics, clinical notes, and data provenance, increasing the minimum baseline of data classes that must be commonly available within certified health IT for interoperable exchange.

### **4.2 Align FDA Standards Requirements with the USCDI**

As the USCDI becomes the standard for health IT systems certified under the 2015 Edition, the FDA should consider aligning its standards and implementation requirements associated with real-world data and evidence that are derived from such systems, with the USCDI.

### **4.3 Adopt Real-World Testing of Interoperability as Condition and Maintenance of Certification Under 2015 Edition**

ONC should include, as proposed, provisions for real-world testing of interoperability of health IT systems as a Condition of Certification and for Maintenance of Certification in its updates to the 2015 Edition of the ONC Health IT Certification Program.

### **4.4 Include Patient Email Address and Specify that the U.S. Postal Service Standard be Used for Patient Address in the USCDI**

To improve patient matching, ONC should:

- Include the patient email address in the list of patient demographic-related data elements contained within the proposed USCDI Version 1 standard.
- Specify the use of the U.S. Postal Service standard in its requirements for an address contained within the proposed USCDI Version 1 standard.



## 5. LEVERAGING TECHNOLOGY TO GAIN INPUT DIRECTLY FROM PATIENTS

### 5.1 Develop Guidance to Accelerate the Use of Digital Tools for the Collection of Data Directly from Patients to Support the Entire Drug Development Life Cycle

The FDA should build upon both its considerable progress related to patient-focused drug development and its *Framework for the FDA's Real-World Evidence Program* to develop more detailed guidance on the use of digital tools to support the collection of data directly from patients—including mobile technologies, wearables, biosensors, and other digital health tools—to serve as real-world data and evidence across the medical product development life cycle.

## 6. EXPANDING EFFORTS TO LEVERAGE ARTIFICIAL INTELLIGENCE

### 6.1 Expand FDA Activities to Explore the Use of AI to Support Real-World Evidence Needs Across the Medical Product Development Life Cycle

The FDA should fully implement the artificial intelligence (AI), natural language processing, and machine learning actions contained in the *Sentinel Initiative Five-Year Strategy*. The FDA should also conduct and disseminate learnings from demonstration projects designed to assess the utility, feasibility, and replicability of applying AI and natural language processing tools to novel data sources to facilitate their usage in studies leveraging real-world evidence across the medical product development life cycle.

## 7. ACCELERATING PILOTS AND DEMONSTRATION PROJECTS FOR NEW DATA SOURCES AND ADDITIONAL MEDICAL PRODUCTS

### 7.1 Accelerate FDA Pilot Projects Focused on New Data Sources, Including EHRs, Registries, Wearables, and Other Mobile Technologies, as well as Additional Medical Products, including Biologics, Such as Cell Therapies

The FDA should expand upon its efforts to leverage new data sources, such as electronic health records (EHRs), registries, wearables, and other mobile technologies, through pilot projects, to explore their utility in supporting real-world evidence needs across the medical product development life cycle. The FDA should also support the development and launch of real-world evidence pilots that address the needs of not only single molecule drugs, but also biologics, including regenerative cell therapies.

### 7.2 Launch a CMS Demonstration Project Focused on Using Data from Multiple Sources to Measure Outcomes for Value-Based Payment Models for Drugs and Biologics

The CMS Innovation Center should develop and launch a demonstration project that explores how clinical, administrative, and patient-generated data from multiple sources can be used to generate evidence for outcomes or value-based payment models for high-cost drugs and biologics. The Innovation Center and its awardees should publish methods used, outcomes, and lessons learned to inform future value-based payment arrangements for drugs and biologics.

## 8. ASSURING PRIVACY AND CONFIDENTIALITY

### 8.1 Consider the Real-World Evidence Needs of Regulatory Evaluation and Value-Based Payment Decision-making in Privacy Policy

Public- and private-sector organizations engaged in the generation and use of real-world data and evidence—such as academic and research institutions, health systems, payers, regulators, technology companies, and patient organizations—should study, deliberate, and develop a set of privacy-related policy principles and recommendations to support the use of administrative, clinical, and patient-generated data across multiple settings for evidence generation for clinical research, regulatory evaluation, and value-based payment decision-making related to medical products. Such an effort should be convened by the federal government or a trusted, independent, non-profit organization.

## **8.2 Advance a Federal Data Privacy Framework That Creates Baseline Protections and Addresses Entities Handling Health Information That are Not Covered Under HIPAA**

Congress should pass bipartisan legislation that clarifies expectations for use and disclosures of health information among entities not covered under HIPAA. Congress should advance federal, baseline protections to improve consumer trust and certainty, which need not preempt existing state laws with more robust requirements.

## **9. ADVANCING INNOVATIVE, NEW MODELS OF DRUG DEVELOPMENT**

### **9.1 Continue and Accelerate Efforts to Advance Innovation in Drug Development, Leveraging Real-World Evidence**

The FDA should continue and accelerate its efforts to modernize and advance innovation in drug development, including innovative clinical trials that leverage real-world evidence drawn from EHRs, other clinical and administrative systems, mobile technologies, and other digital health tools, with the ultimate goal of reducing the cost and complexity of clinical trials.

The FDA should also continue with its plans to create a new Office of Drug Evaluation Science that will advance innovation in drug development, advance the science of prediction, and make it less expensive and less risky to create new drugs.

## **10. ADDRESSING REGULATORY BARRIERS**

### **10.1 Create New or Modify Existing Safe Harbors to Provide Regulatory Certainty Regarding Value-Based Payment Arrangements for Medical Products**

HHS should create new or modify existing safe harbors to provide clarity related to the use of value-based payment arrangements for medical products.

### **10.2 Expand Existing Safe Harbors to Enable Donation or Cost-Sharing of Software Supporting Real-World Evidence Needs**

HHS should expand upon existing safe harbors to enable donation or cost-sharing associated with software, hardware, and related direct training associated with the collection, normalization, curation, and submission of clinical, administrative, and patient-reported data associated with outcomes measurement to support both regulatory evaluation and value-based payment arrangements for medical products.

## **11. EXPANDING CMS WORKFORCE TO SUPPORT EVALUATION OF NEW EMERGING THERAPIES**

### **11.1 Increase Capacity and Expertise at CMS to Support Innovation in Payment and Access to Transformative Medical Products**

Congress should assure adequate capacity and both scientific and value-based payment expertise within CMS to support coverage determinations and the implementation of new payment models for drugs, biologics, and medical devices.

## **12. PROMOTING COOPERATION AND COLLABORATION**

### **12.1 Improve Collaboration Between the FDA and CMS on Evidence Generation and Development**

The FDA and CMS should collaborate on ways to generate evidence and improve its development for medical products, including the evaluation and transition of pilot collaborations into permanent partnership programs. Such collaboration will foster more efficient and comprehensive evidence development for potentially high-impact, high-cost medical products, in an environment where complex, new therapies are emerging rapidly, the amount of clinical and patient-generated data to support evaluation is increasing significantly, and the expertise in this new emerging area is scarce.





## **12.2 Advance Collaborative Models to Move Beyond Silos of Evidence Development**

Leaders representing payers, manufacturers, regulators, providers, and patients should advance collaboration and collective action on the generation and use of real-world evidence for both regulatory and value-based payment decision-making for drugs and biologics, drawing upon lessons, tools, and infrastructure of existing efforts.

This report presents an overview of how real-world evidence can support both value-based payment arrangements and regulatory evaluation, a summary of the opportunities and challenges associated with its use, and a more detailed description of policy recommendations.



## Introduction

The amount of electronic health care data is increasing at unprecedented rates, projected to exceed 2,314 exabytes—or one billion gigabytes—by 2020.<sup>1</sup> This rapid growth is due to a number of factors, including widespread adoption of electronic health records (EHRs) and other technology in health care, as well as the significant increase in adoption of digital health tools among individuals in the United States.

About 90 percent of non-federal acute care hospitals and physicians are now using EHRs.<sup>2,3</sup> While claims and other administrative data have been available for years, EHRs open the door to new types of clinical data never before available on such a scale, including diagnostic test results, vital signs, clinical notes, diagnoses, procedures, allergies, and problem lists.

Patients themselves are also generating data. Wearables, biosensors, and other technologies help people track their habits, activities, and health status. Increasingly, individuals are electronically accessing their health information, which resides in hospitals, physician offices, laboratories, health plans, and other health care organizations. The use of connected devices within the home, including remote patient monitoring, is also on the rise, especially among the chronically ill and the elderly. This improves care by giving patients the ability to connect with their clinicians on an ongoing basis, enabling monitoring of clinical status between clinic visits to catch issues early. Traditional medical devices, such as blood glucose monitors, are increasingly becoming connected, enabling use of the data to assess and improve outcomes. Registries are also an important source of real-world data and are widely used. Registries are organized systems that use observational study methods to collect uniform clinical and other data to evaluate specified outcomes for a population defined by a particular disease, condition, or usage of a drug, device, or other treatments.<sup>4,5</sup>

These real-world data sources provide the opportunity to improve the evidence base and modernize current methods for developing and evaluating medical products for regulatory and payment decision-making, including new outcomes or value-based models of payment for drugs and biologics.

The number of new therapies available to patients in need is growing at a considerable pace. New medical products, including small-molecule drugs and biological products—such as cell and gene therapies—are showing great promise for those with cancer, neurodegenerative diseases, and other diseases for which there is not yet a cure. The Food and Drug Administration (FDA) is making great strides in modernizing regulatory evaluation and approval processes by leveraging the use of digital data, patient-reported outcomes, and other drug development tools, to expand the use of expedited programs, explore new adaptive pathways, respond to more precision and personalized approaches to medicine, and implement rational



programs for post-marketing evaluation. Central to these advancements in innovation is the use of real-world data and evidence to support learning and decision-making across the medical product life cycle, including pre-market development and post-market use.

At the same time, given the increased focus on the affordability and value of prescription medicines, policymakers and payers have begun to explore applying value-based principles to prescription drugs and biologics, just as public- and private-sector payers have sought to shift from volume-based to value-based financial incentives for providers of care. The number of value-based payment arrangements among payers and manufacturers has increased significantly over the last several years.<sup>6,7,8</sup>

Real-world data—data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources—as well as real-world evidence—the clinical evidence about the usage and potential benefits or risks of a medical product derived from the analysis of real-world data—can and should significantly inform and improve both regulatory evaluation and innovative payment models based on value and outcomes.<sup>9</sup>

Real-world evidence has significant bipartisan support as evidenced by provisions contained in the 21st Century Cures Act and the User Fee Amendments passed in 2017. The FDA has also been a strong proponent of the use of real-world evidence. Former FDA Commissioner Scott Gottlieb has made several statements regarding the important role that real-world evidence plays in evidence development.<sup>10,11</sup> During a public event at the Bipartisan Policy Center on January 28, 2019, he stated that new streams of real-world data gathered from EHRs, lab systems, wearable devices, insurance claims, and even social media could provide important evidence on product safety and effectiveness in settings or populations that may be very different than the information gleaned from registration trials used for approval.<sup>12</sup> In his first all-hands meeting on April 15, 2019, Acting FDA Commissioner Ned Sharpless shared his enthusiasm for real-world evidence as a means to speed clinical trials, which began while he was director of the National Cancer Institute.<sup>13</sup> Principal Deputy Commissioner Amy Abernethy has also described real-world evidence as a key strategic priority for the FDA and has expressed interest in understanding how data collected during the routine care of patients, such as data stored in EHRs, and patient-generated data can add to the body of evidence to inform regulatory decisions and broaden clinical evidence generation so that study results are maximally applicable to real-world populations.<sup>14</sup>

This report explores the benefits and challenges of using real-world data and evidence to inform regulatory and value-based payment decision-making and the policy actions needed to accelerate their use.



## Using Real-World Evidence to Support Value-Based Payment

In 2017, the United States' national health expenditure was \$3.5 trillion, about 10 percent of which was for prescription drugs.<sup>15,16</sup> Over the next decade, the Centers for Medicare and Medicaid Services (CMS) projects that the spending for prescription drugs will be the fastest growing health category, consistently outpacing other health spending.<sup>17</sup>

The use of value-based payment arrangements has been a common theme across a number of policy proposals to improve the affordability of drugs, including those contained in the administration's *American Patients First Blueprint* and other private-sector proposals.<sup>18,19</sup> Drug affordability is also being explored on a bipartisan basis by several members of Congress.<sup>20,21,22,23,24,25,26</sup>

Value-based payment arrangements for medical products are intended to align pricing and/or payments to observed or expected value for individuals and populations.<sup>27</sup> Such arrangements come in many forms, including outcomes-based contracts, which link payment for medical products to their actual performance in a patient or population, or indication-based pricing, an evidence-based model in which the same drug is priced differently based on the indication for which it is being used.<sup>28</sup> Value-based insurance design can reduce out-of-pocket expenses for high-value drugs (and other medical services) that deliver significant health benefits.<sup>29</sup>

Value-based payment arrangements offer a number of benefits. For example, they offer payers the opportunity to address uncertainties about assumptions made relative to a product's performance within their payment arrangements. This is particularly important for drugs approved under accelerated pathways, where trials to gain marketing approval use biomarkers or surrogates rather than clinical outcomes over a relevant period of time, to define clinical effects and costs. Value-based payment arrangements also give manufacturers increased opportunities to demonstrate the value of their therapies, which can provide earlier market entry and penetration. For patients and other health system stakeholders, shifting toward a value-based payment system may help speed access to innovative therapies, better align payments with a product's true value, and provide critical evidence about whether the benefits and risks of a product match expectations.<sup>30</sup>

Interest in such arrangements among payers and manufacturers is on the rise. According to one recent study, 20 percent of payers have had in place at least one outcomes-based contract (defined as a contracting strategy that ties payment to the achievement of specific goals in a predetermined patient population and rewards good patient outcomes), with 86 percent having renewed at least one such arrangement in the last five years. Seventy-one percent of payers had interest in future outcomes-based contracting use.<sup>31</sup> At the same time, 33 percent of manufacturers have had at least one outcomes-based contract in place, with 80 percent having renewed at least one contract in the last five years; 63 percent of manufacturers had interest in future use.<sup>32</sup> In addition, a study published in 2019 indicates that value-based payment arrangements may be far more prevalent in the United States than previously estimated.<sup>33</sup>

Examples of recent value-based payment arrangements, include:

- Amgen's agreement with Cigna for Repatha, whereby the insurer got a rebate if patients did not experience reductions in LDL cholesterol levels comparable to those observed in the drug's pre-approval trials.<sup>34</sup>
- Amgen's agreement with Harvard Pilgrim for Repatha, whereby the manufacturer provided full reimbursement for the cost of the drug for patients who had a heart attack or stroke while taking the drug.<sup>35</sup>
- Novartis' agreements with Aetna and Cigna for Entresto. Aetna's payments were based on the drug replicating results from its clinical trials, including reductions in heart failure-related hospital admissions, as well as deaths. Cigna's payments to Novartis also depended on the proportion of patients admitted to the hospital for heart failure.<sup>36,37</sup>
- Pitney Bowes' initiative to reduce or eliminate cost-sharing for statins and clopidogrel.<sup>38</sup>
- Spark Therapeutics' agreement with Harvard Pilgrim for Luxturna, whereby payment amounts were determined by measuring sight improvements at 30- to 90-day intervals, as well as at the 30-month mark.<sup>39</sup>

State Medicaid programs are also employing value-based payment approaches. In June 2018, CMS approved Oklahoma's request to experiment with outcomes-based payment arrangements through Medicaid, allowing the state to negotiate supplemental rebates based on drug treatment outcomes.<sup>40</sup> In November 2018, CMS announced approval for similar flexibility within Michigan's Medicaid program.<sup>41</sup>

The FDA also recognizes that real-world evidence has the potential to make America's health care system more competitive and efficient as validated outcomes measures based on real-world data are incorporated into value-based payment contracts.<sup>42</sup>

Value-based payment arrangements generally rely on a mix of objective, measurable patient outcomes associated with product use, along with cost data. Historically, payers have had very little information beyond cost and utilization data from their own claims systems and the results of clinical trials—many of which do not measure meaningful long-term outcomes and resource use—to inform decision-making on payment for novel drugs and biologics.

A recent study indicated that the most common outcomes measures used in value-based payment arrangements include those related to laboratory results, medical encounters (such as hospitalization rates and length of stay), financial outcomes, and drug utilization.<sup>43</sup> Those participating in BPC roundtable discussions also indicated the desire to capture patient-reported outcomes, as well as other data, such as radiology results, diagnoses, and other clinical events, to assess outcomes. While most of these data now exist in electronic form, much of it is not easily accessible and it is rarely in structured or standards-based formats to support outcomes analyses.

Several studies have shown that challenges related to data collection and evidence development, and the inability to obtain accurate data or outcomes measures, are primary barriers to developing value-based payment arrangements.<sup>44,45,46</sup> Legal and regulatory barriers also exist, including uncertainty about the implications of federal anti-kickback statutes and Medicaid best price rules, which require that manufacturers offer Medicaid programs the lowest or "best price" based on what is available to other purchasers.<sup>47,48,49,50,51</sup>

Follow-up interviews with both payers and manufacturers in one study revealed that enhanced data sharing and analytic capabilities would result in not only a larger number of value-based payment arrangements, but also more sophisticated arrangements.<sup>52</sup> More than 90 percent of payers in another study identified simple and easily measurable outcomes as a critical element in successful outcomes-based contracting arrangements.<sup>53</sup>



## Using Real-World Evidence to Support Regulatory Evaluation

Clinical trials are the most expensive and time-consuming phase of the drug development process, and a confirmatory clinical trial is the final basis for the evaluation of whether a drug should be approved for a specific indication. Clinical trials can take as long as seven years and have cost \$1.5 billion of the more than \$2 billion spent on drug development.<sup>54,55</sup>

Researchers in the United States have conducted clinical trials for FDA submissions for regulatory approval in essentially the same way for more than 50 years. These clinical studies are largely based on a traditional model in which trials are randomized and often double-blinded, conducted within a research infrastructure that is largely parallel to routine clinical practice, and designed to control variability and maximize data quality. Such studies often involve a relatively homogeneous study population with the goal of attributing an outcome solely to the treatment, but the real world of patients is highly heterogeneous and unforeseen events—both positive and negative—can often occur when that treatment is used in real-world settings.

Because traditional, regulated, randomized controlled trials are often conducted with a narrowly defined group of patients, they may not reflect the realities that would be present if the drug were used in a real-world population of patients for whom the treatment was intended. Often missing from such trials are representative samples of patients with multiple comorbidities, concomitant use of the spectrum of other drugs, varying races and ethnicities, ages at both the low and high ends of the spectrum, and different practice settings. By augmenting traditional, randomized controlled trials among targeted, tightly controlled populations with data from a broader, more diverse group of patients in different practice settings, researchers can improve the generalizability of trials.<sup>56</sup>

Sponsors and researchers are increasingly able to move clinical studies based on the traditional, randomized approach into the actual clinic, embedding a randomized trial into routine clinical care. Often referred to as pragmatic clinical trials or large simple trials, these study designs allow for more diverse patient populations to be enrolled in studies within their own care settings, all while maintaining randomization (through patient, site, or cluster randomization). Early examples include the Salford Lung Study<sup>57</sup> and the ADAPTABLE study from the Patient-Centered Outcomes Research Institute's PCORnet (National Patient-Centered Clinical Research Network).<sup>58</sup>

The FDA recognizes that, while prospectively randomized, placebo-controlled clinical trials are often the most powerful tools for answering fundamental questions about the safety and efficacy of new medical products, greater efficiency is needed, as clinical trials are becoming more costly and complex to administer.<sup>59</sup> The FDA further recognizes that overly complex trials and unnecessary data collection can deter patient enrollment, exhaust investigators, and discourage the development of second and third-to-market innovations, meaning that first-in-class drugs enjoy monopolies for longer periods of time, thereby reducing competition that lowers prices. The FDA also recognizes that many of the new products that it is being asked to evaluate are not easily evaluated using these traditional approaches.<sup>60</sup>

The FDA is working with the Clinical Trials Transformative Initiative and the Medical Device Innovation Consortium to facilitate innovative trial designs and patient-centered endpoints for drugs and medical devices that can make clinical trials more efficient, and in some cases, more rigorous.<sup>61,62</sup> Many of these new approaches are made possible by new technologies and sources of data.<sup>63</sup>

The benefits of using real-world data and evidence to support clinical trials are well documented and include:

- Enabling more efficient and targeted recruitment of patients for clinical trials;<sup>64</sup>
- Expediting the generation of hypotheses to inform the design of clinical studies;<sup>65</sup>
- Enabling the identification of subpopulations with higher risk-benefit ratios to target development efforts;<sup>66</sup>
- Supporting the identification of drug development tools, such as biomarkers;<sup>67</sup>
- Helping to assess trial feasibility by examining the impact of planned inclusion/exclusion criteria within relevant populations;<sup>68</sup>
- Supporting the assembly of geographically distributed research cohorts (for example, in drug development for rare diseases or targeted therapeutics);<sup>69</sup> and
- Improving the efficiency of studies that assess clinical benefit and risk for drugs approved under the FDA's expedited programs.<sup>70</sup>

Real-world data and evidence are also necessary for the implementation of many novel development and approval pathways. As medicine becomes more personalized and drugs become targeted for smaller populations, traditional, large-scale, randomized controlled trials will become increasingly less feasible. Additional approaches will be needed to assure safety and efficacy and protect the public's health.

Over the last decade, an adaptive approval pathway (also referred to as adaptive licensing, progressive approval, or staged approval) has been proposed. In an adaptive approval process, data and evidence generated on a smaller, distinctively defined patient population allows regulatory approval and subsequent access to the therapy for that specific subpopulation. As data and evidence continue to accrue on additional or broader populations—either through randomized controlled trials, observational studies, or other study methods as deemed appropriate—the drug is additionally approved for use in those populations.<sup>71</sup> The opportunity to leverage real-world data and evidence to support such an approach would pair a focus on the entire drug life-cycle and close-monitoring techniques to augment randomized controlled trials conducted within the smaller populations. This approach is not unlike the European Medicine Agency's Adaptive Pathway Pilot Program.<sup>72</sup> Former FDA Commissioner Scott Gottlieb has, on multiple occasions, commented on the potential of an adaptive approval process in which a drug demonstrating clear positive clinical effect early in development could be granted market access given a real commitment to evidence generation post-approval.<sup>73,74</sup>

To date, the FDA has primarily used real-world data and real-world evidence to support its post-market safety surveillance efforts. In limited instances, the FDA has also used real-world evidence to evaluate effectiveness in product approvals. Historical examples include drugs approved for

HIV and use of fibrinolytic therapy for patients with acute myocardial infarction. More recently, the FDA has accepted real-world evidence to support the evaluation of efficacy in product approvals—using data from registries, natural history studies, and chart reviews—to establish a comparison arm in single-arm trials in oncology and rare diseases, because a parallel-review control arm would have been unethical or not feasible and because the effect size was expected to be large.<sup>75,76</sup>

While the use of real-world evidence to support FDA regulatory effectiveness determinations has been limited in the past, the FDA's implementation of the 21st Century Cures Act is expected to expand such use. Specifically, the Act requires the FDA to implement a program to evaluate the potential use of real-world evidence to support a new indication for an approved drug or for post-approval study requirements. It also requires the FDA to develop a framework for implementation. The FDA is expected to publish guidance that describes the circumstances under which sponsors and the FDA may rely on real-world evidence and the appropriate standards and methodologies for collection and analysis of real-world evidence submitted.<sup>77</sup> The FDA Reauthorization Act of 2017 also contains provisions related to real-world evidence.<sup>78</sup> Finally, the 21st Century Cures Act allows for the use of real-world evidence to support post-approval requirements for regenerative advanced therapies that are granted accelerated approval.<sup>79</sup>

In response to the 21st Century Cures Act, in December 2018 the FDA published the *Framework for FDA's Real-World Evidence Program* (FDA Framework). The FDA Framework outlines the structure the FDA intends to use to implement a multi-faceted program that involves demonstration projects, stakeholder engagement, internal processes to gain FDA input and promote shared learning and consistency in applying the Framework, and guidance documents to assist developers interested in using real-world evidence in support of FDA regulatory submissions. Importantly, the FDA Framework indicates that, in addition to supporting the approval of a new indication for a drug already approved under Section 505(c) of the Food and Drug Cosmetic Act or to help support or satisfy drug post-approval study requirements, the FDA also intends to apply the FDA Framework to biological products licensed under the Public Health Service Act.<sup>80</sup>

In response to the 2007 Food and Drug Administration Amendments Act, the FDA launched the Sentinel Initiative and the Sentinel System—an FDA-funded network of 18 data partners and collaborating institutions—to complement and support its post-market surveillance efforts. Fully implemented in 2016, the Sentinel System conducts queries and studies using primarily claims and pharmacy dispensing data. The recently published FDA report, *Sentinel System—Five-Year Strategy 2019-2023*, indicates the FDA's intent to invest in approaches for using EHR data in future years.<sup>81</sup>

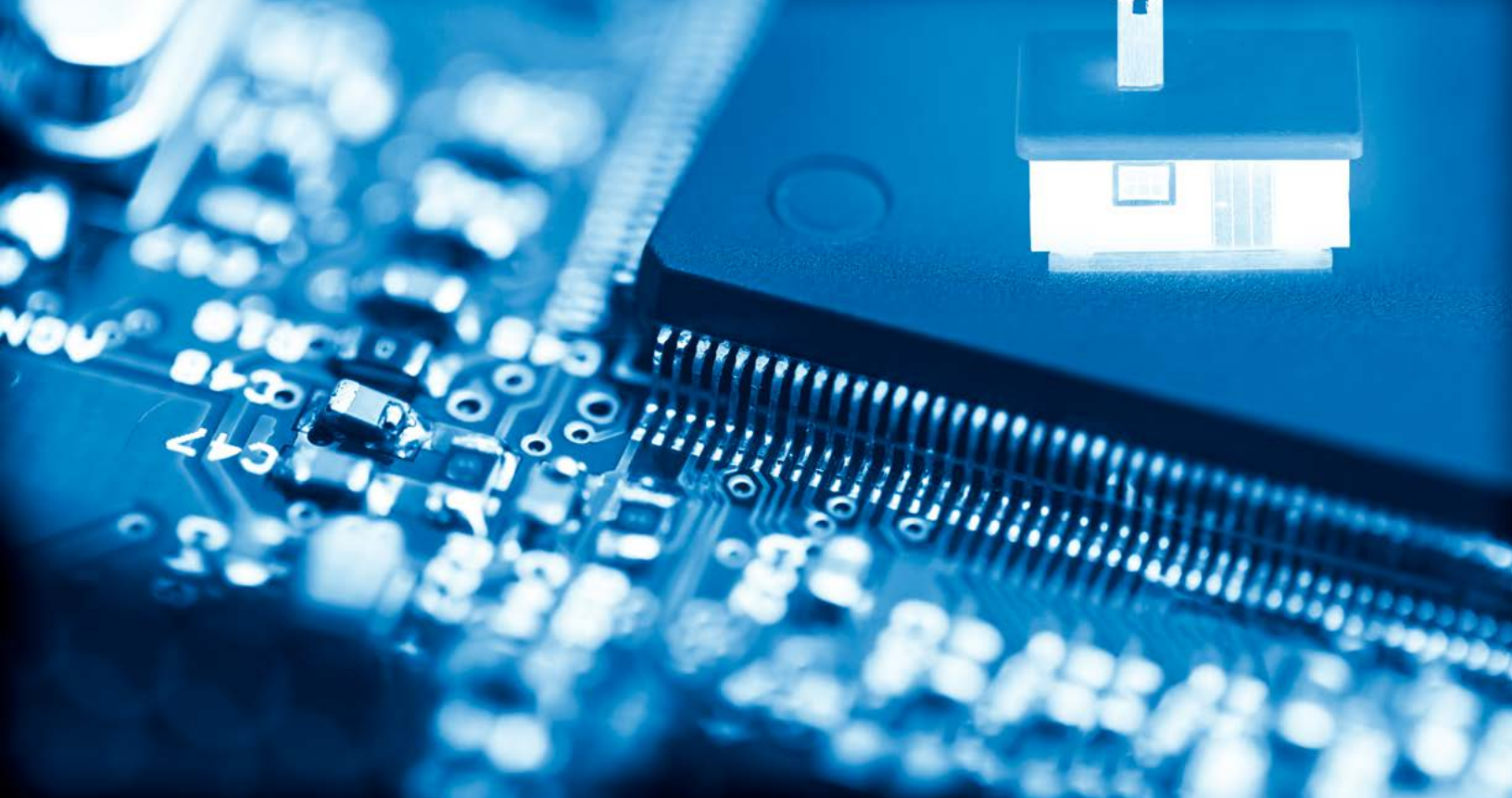
The FDA also recently launched the Biologics Effectiveness and Safety (BEST) Initiative within the Center for Biologics Evaluation and Research (CBER), which is designed to conduct safety and effectiveness studies of blood, advanced therapeutics, and vaccines. To date, BEST has been used to perform queries related to safety and regulatory questions such as estimating blood usage, identifying reasons for transfusions, and identifying transfusion-related adverse events and estimating their rates.<sup>82</sup> While there has been a considerable increase in the development of cell and gene therapies, CBER has not yet invested in real-world evidence pilots for these products.

Within the Center for Devices and Radiological Health (CDRH) and in collaboration with the National Evaluation System for health Technology (NEST), the FDA has relied on real-world evidence to approve new devices, expand the indications for marketed devices, and reduce the time and cost associated with device-makers meeting their post-market study requirements.<sup>83</sup>

Examples of the types of real-world data needed to evaluate drug safety and effectiveness in regulatory decision-making include medications, including dose, dose regimen, and route of administration; diagnoses; medical history; laboratory, radiology, and other diagnostic test results; patient-reported outcomes; and mortality rates. The sources of such data include EHRs used within provider settings, such as hospitals, physician offices, and clinics; laboratory, pharmacy, and radiology systems; administrative claims and billing systems; registries; vital record systems; and patient technologies, such as wearables, biosensors, remote monitoring devices, apps, and other digital health tools.

Similar to value-based payment arrangements, barriers to the use of real-world evidence for regulatory evaluation include limited access to data, the reliability and relevance of these data, as well as both the cost and lack of a data infrastructure to measure outcomes.<sup>84,85,86</sup> The lack of clarity around the circumstances under which real-world evidence can be used, as well as the standards and methodologies that will govern its usage, are also key barriers.<sup>87,88</sup> Additional barriers include the need for transparency and continuous improvement of methods and the need for data governance and assurance related to data security and privacy.<sup>89,90,91</sup>





## Policy Recommendations

Given the digitization of health care, there are several opportunities to leverage new data sources to support more comprehensive and timely evidence development and meet the needs of regulatory evaluation and value-based payment models. The amount of clinical data that now resides within physician offices, hospitals and health systems, and other care and service providers, as well as digital technologies, mobile devices, and biosensors to modernize capture of patient-reported outcomes, is significant. The use of artificial intelligence, natural language processing, and advanced data analytics capabilities, such as machine learning, can assist with gleanings greater insights from the vast amount of data that currently exists. However, several barriers stand in the way of generating and using real-world data and evidence for both regulatory and value-based payment decision-making.

A more detailed overview of barriers and opportunities, along with recommendations for further advancing the generation and use of real-world evidence for regulatory evaluation and value-based payment decision-making, is provided below.

### 1. ASSURING ADEQUATE FUNDING OF REAL-WORLD EVIDENCE ACTIVITIES

Advancing the generation and use of real-world evidence is a high priority for both Congress and the administration. The 21st Century Cures Act—passed on a nearly unanimous, bipartisan basis in December 2016—contained several provisions designed to advance the generation and use of real-world evidence.<sup>92</sup> The amount of new data now emerging to support the medical product development and evaluation process is significant, and the increase in new data curation and collection approaches, including natural language processing and machine learning, offer the opportunity to modernize regulatory processes and reduce the time and cost associated with bringing safe and effective treatments and cures to patients.

The FDA has taken several steps to advance the use of real-world evidence to evaluate the safety and effectiveness of medical products, including the engagement of stakeholders, the development of a framework, and the development of a five-year strategy for the Sentinel Initiative.

At the same time, there is still much that is left to do. To date, the Sentinel System has relied primarily on claims data to help evaluate post-market safety for drugs.<sup>93</sup> Expanding the role of real-world evidence to evaluate effectiveness—in accordance with the 21st Century Cures Act—will require linking to and using clinical data contained in EHRs and other clinical systems. To date, CDRH's real-world evidence activities associated with medical

devices through NEST have primarily relied on registries to evaluate safety and effectiveness, but face some challenges because they do not link to EHRs. Finally, more work is needed to fully realize real-world evidence capabilities for biologics through the BEST Initiative and other related activities.<sup>94</sup>

The FDA's fiscal year 2020 budget request contains \$60 million for a new "Medical Data Enterprise" to advance the use of real-world evidence to better inform patient care and provide more efficient, robust, and potentially lower-cost ways to develop clinical data that can inform product review and promote innovation. The \$60 million request supports all FDA centers, including those focused on human drugs (\$20 million), biologics (\$13 million), medical devices (\$23 million), and animal drugs (\$4 million).<sup>95</sup>

As outlined in the FY2020 budget request, the FDA believes that expanding its capacity to utilize real-world evidence to evaluate the safety and effectiveness of medical products will generate data that can be used to improve the efficiency of the regulatory process and reduce the burdens that drive up the time and cost required to bring innovative and life-saving products to the market. The FDA further believes that real-world evidence is integral to advancing public health, such as combatting the public health threats posed by increasing antimicrobial resistance.<sup>96</sup>

Congress should fully fund the FDA's FY2020 budget request of \$60 million for a new Medical Data Enterprise to advance the use of real-world evidence across the medical product development life cycle across all FDA centers.

## Recommendation 1.1

### Fully Fund the FDA's FY2020 Budget Request for the Creation of a New Medical Data Enterprise to Advance the Use of Real-World Evidence

As it finalizes appropriations for FY2020, Congress should fully fund the FDA's \$60 million budget request for a Medical Data Enterprise to advance the use of real-world evidence to evaluate both effectiveness and safety for drugs, biologics, and devices.

## 2. IMPROVING REGULATORY CLARITY

The 21st Century Cures Act requires that the FDA establish a draft framework for implementation of a real-world evidence program that addresses the following:

- The sources of real-world evidence, including ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcome research activities;
- The gaps in data collection activities;
- The standards and methodologies for collection and analysis of real-world evidence; and
- The priority areas, remaining challenges, and potential pilot opportunities that the program will address.<sup>97</sup>

In December 2018, the FDA released the *Framework for FDA's Real-World Evidence Program*, describing its general approach toward evaluating the potential use of real-world evidence to support changes to labeling about drug product effectiveness, adding a new population, or adding comparative effectiveness or safety information.<sup>98</sup>

In addition to describing the current use of real-world data for evidence generation and potential sources of real-world evidence, the FDA Framework describes a very general approach for how it will evaluate individual applications and guide its real-world evidence program. The FDA's approach contains three primary components:

- Whether the real-world data are fit for use;
- Whether the trial or study design used to generate real-world evidence can provide adequate scientific evidence to answer or help answer a regulatory question; and
- Whether the study conducted meets FDA regulatory requirements (such as for study monitoring and data collection).<sup>99</sup>



Neither detailed standards and methodologies for collection and analysis, nor potential pilot opportunities are described in the FDA Framework. Also, gaps in data collection activities are not described in detail. The FDA does describe areas where additional guidance is needed, including the following:

- How to assess the reliability and relevance of real-world data from medical claims and EHRs used to generate real-world evidence regarding drug product effectiveness, including registry data and international electronic health care data;
- Potential gaps in real-world data sources and how to address them;
- Considerations for designing clinical trials that include pragmatic design elements and that generate evidence of effectiveness for regulatory decisions;
- The potential use of real-world data to generate external control arms; and
- Observational study designs using real-world data, including whether and how these studies might provide real-world evidence to support product effectiveness in regulatory decision-making, along with reporting requirements for such studies.<sup>100</sup>

The 21st Century Cures Act requires the FDA to publish, by no later than December 2021, draft guidance that describes the circumstances under which sponsors and the FDA may rely on real-world evidence to help support the approval of a new indication for an existing drug, as well as to help support or satisfy post-approval study requirements.<sup>101</sup>

In July 2018, the FDA released the guidance titled *Use of Electronic Health Records in Clinical Investigations*, which includes recommendations for using EHR data as electronic source data in clinical investigations, including inspection, record-keeping, and record retention requirements.<sup>102</sup> The FDA Framework references this, and other guidances that have been previously released, indicating that such guidances will be reviewed to assess whether they adequately address key issues identified by the FDA Framework. The FDA does indicate in the FDA Framework that additional guidance will be necessary, presumably to fully carry out the provisions of the 21st Century Cures Act.

A list of other guidances referenced in the FDA Framework is provided below.

- FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Health Care Data*, published in 2013;<sup>103</sup>
- FDA guidance *Electronic Source Data in Clinical Investigations*, published in 2013;<sup>104</sup> and
- FDA guidance *Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers*, published in 2017.<sup>105</sup>

In the coming months, the FDA should maintain its momentum on real-world evidence and build on the significant progress it has made toward implementing provisions contained within the 21st Century Cures Act, through rapid implementation of the real-world evidence program and publication of much-needed guidance. Such guidance should reflect continued engagement of and solicitation of input from experts and stakeholders, as well as the results of pilot activities. Initial remarks by Acting FDA Commissioner Ned Sharpless at an all-hands meeting in April 2019 indicate his support for continuing to build upon progress made on real-world evidence to date.<sup>106</sup>

## **Recommendation 2.1**

### **Continue and Expand Upon Efforts to Improve Regulatory Clarity**

The FDA should build on the recent momentum related to real-world evidence and rapidly develop and publish guidance—as required by the 21st Century Cures Act—regarding the circumstances under which sponsors and the FDA may rely on real-world evidence to help support the approval of a new indication for an existing drug, as well as to help support or satisfy post-approval study requirements. Such guidance should address key issues raised within the recently released FDA Framework. The guidance should be informed not only by the FDA Framework, but also by insights gained from pilot activities and robust processes for soliciting stakeholder and expert input.

### 3. IMPROVING ACCESS TO DATA

As noted previously, one of the most commonly cited barriers to the use of real-world evidence to inform both regulatory evaluation and value-based payment arrangements is limited access to the real-world data that supports such evidence.

Examples of the types of data used for regulatory and value-based payment decision-making include medication information; laboratory, radiology, and other diagnostic results; diagnoses; hospitalizations; medical and vital status, including deaths; patient-reported outcomes; and other data types. Financial outcomes data are also necessary for value-based payment arrangements.

While such data are now largely in electronic form, many of the systems in which these data reside—such as those contained in physician offices, clinics, hospitals and health systems, laboratories, pharmacies, radiology centers, and health plans, as well as applications used by individuals—are not fully interoperable, making data access difficult and costly. Resistance to information sharing—also known as “information blocking”—among some providers and technology companies has also been identified as a key issue.<sup>107,108</sup>

HHS has made interoperability and information sharing a key priority, as evidenced by numerous regulatory actions and other activities. On March 4, 2019, both the Office of the National Coordinator for Health IT (ONC) and CMS released proposed rules related to interoperability and information sharing that are expected to improve and transform efforts to improve health and health care in the United States.<sup>109,110</sup> Key elements of such proposed rules that are expected to have a positive impact on the availability and reliability of real-world data for evidence development are detailed below.

#### Overview of ONC-Proposed Requirements for Health IT Developers

ONC’s recently released proposed rule, *21st Century Cures Act: Interoperability, Information Blocking, and the ONC Health IT Certification Program* (ONC Proposed Rule), implements several provisions of the 21st Century Cures Act and is designed to support seamless and secure access to, exchange of, and use of electronic health information.<sup>111</sup> The ONC Proposed Rule contains several provisions that are expected to improve access to data to support the generation and use of real-world evidence. For example, as a condition of and maintenance of ONC Health IT Certification, ONC proposes to require health IT developers to:

- Adopt a new 2015 Edition certification criterion that requires all electronic health information to be exported for a single patient upon request or all patients when a provider seeks to change health IT systems;
- Publish open, standards-based application programming interfaces (APIs)—including transparent information on how to access these APIs—and allow health information from their technology to be accessed, exchanged, and used without special effort, through the use of such APIs or successor technology or standards; and
- Provide assurances that they will not take any actions that constitute information blocking or any other actions that may inhibit the appropriate exchange, access, and use of electronic health information.<sup>112</sup>

#### Electronic Export Provisions

The 21st Century Cures Act requires that a patient’s electronic health information be accessible to that patient and the patient’s designees, in a manner that facilitates communication with the patient’s health care providers and other individuals, including researchers, consistent with the patient’s consent.<sup>113</sup> The electronic export provision contained in the ONC Proposed Rule is intended to provide patients and health IT users with a means to efficiently export the entire EHR for a single patient or all patients—upon a valid request—in a computable, electronic format, and facilitate the interpretation and use of the electronic health information by the recipient. The export function is also designed to support portability when a health care provider—such as a hospital, health system, or physician practice—chooses to transition or migrate information to another health IT system.<sup>114</sup>

BPC supports the electronic health information export provisions and encourages their adoption in the final rule. However, greater clarity is needed in the final rule regarding the ways in which data can be accessed by patients and for patient populations—with patient consent—to support research, in accordance with the provisions of the 21st Century Cures Act.



## Recommendation 3.1

### Adopt Electronic Health Information Export Provisions, as Proposed, in Updates to 2015 Edition Certification Criteria

ONC should adopt, as proposed, a new 2015 Edition ONC Health IT Certification criterion that requires health IT developers to enable all electronic health information to be exported—in a computable, electronic format, along with instructions to facilitate interpretation and use—for a patient or designee upon request.

ONC should further clarify the ways in which data can be accessed by patients or their designees to support the use of patient data—while appropriately protecting privacy—for research.

## Use of APIs to Facilitate Data Sharing

APIs are sets of commands, functions, protocols, and tools published by a software developer that enable other software developers to create programs and applications that interact with the software without needing to know its internal workings.<sup>115</sup>

The API provisions contained in the ONC Proposed Rule would require health IT developers to support API-enabled services for data on a single patient and multiple patients, using the HL7 Fast Healthcare Interoperability Resources (FHIR®) standard, along with a set of related implementation specifications. Health IT developers would need to provide API access and search capabilities for all data contained in the U.S. Core Data for Interoperability (USCDI), described in further detail below. Finally, health IT developers would need to make business and technical documentation publicly available and also comply with other rules designed to promote an open and competitive marketplace.<sup>116</sup>

Requiring health IT developers to publish APIs and allow health information from their technology to be accessed, exchanged, and used without special effort, while protecting privacy, will significantly accelerate the availability of real-world data to be used as real-world evidence. Also, individuals and their designees should be able to access data elements included in the USCDI regardless of whether they are in structured or unstructured formats.

## Recommendation 3.2

### Adopt API Provisions Contained in ONC Proposed Rule

ONC should adopt, as proposed, 2015 Edition ONC Health IT Certification criteria that would require health IT developers to support API-enabled services for all data contained in the USCDI on a single patient and multiple patients, using the HL7 FHIR® standard and related implementation specifications, so that information can be accessed, exchanged, and used without special effort. Such data should include all available data elements defined within the USCDI, whether structured or unstructured.

CMS also released a proposed rule that was published in the Federal Register on March 4, 2019. The rule proposes to require that Medicaid, the Children's Health Insurance Program (CHIP), Medicare Advantage plans, and Qualified Health Plans in the Federally-facilitated Exchanges provide enrollees with electronic access to medical claims and other health information electronically through open APIs using the same standards proposed by ONC—the HL7 FHIR® standard. Information proposed to be required includes adjudicated claims (including cost), encounters with capitated providers, provider remittances, enrollee cost-sharing, and clinical data, including laboratory results, when available.<sup>117</sup>

The Lower Health Care Costs Act of 2019—bipartisan legislation approved by the Senate Health, Education, Labor, and Pensions Committee on June 26, 2019—would require commercial health insurers to make similar information available to enrollees and beneficiaries, along with information about in-network practitioners and expected out-of-pocket costs.<sup>118</sup>

As is the case with adoption of open APIs among health IT developers and their clients, the ability of individuals to access, exchange, and use the health information contained within their health plans and other insurers, without special effort and through third-party apps and developers, has the potential to significantly expand the availability of data to support the real-world evidence needs of regulatory evaluation of and value-based payment for medical products.

Collaboration among regulators, payers, clinicians, patients, and other key stakeholders interested in advancing the use of real-world evidence for both regulatory and value-based payment decision-making is needed to explore and pursue strategies to leverage the transformational information-sharing efforts now underway with leadership by the administration and Congress.

## Collaboration on HL7 FHIR® Implementation Guides to Facilitate Information Sharing

The use of APIs has been a key component of the Department of Health and Human Services (HHS) strategy and private sector efforts to accelerate access to and mobility of information contained in EHRs.<sup>119,120</sup> Multiple organizations, including providers, developers, and standards organizations, have used the HL7 Argonaut Project or the HL7 DaVinci Project to develop HL7 FHIR® implementation guides to meet specific needs for various use cases.<sup>121,122</sup> An Argonaut Project implementation specification is referenced in the ONC Proposed Rule.<sup>123,124</sup>

For example, multiple payers are collaborating with providers, technology vendors, and ONC to accelerate adoption of HL7 FHIR® for production exchange of clinical information between providers and payers. Led by the P2 FHIR Taskforce and HL7 DaVinci Project, this project is “bridging” the payer-provider data divide by developing HL7 FHIR® standards and implementation guides, conducting reference implementations, and both piloting and deploying solutions for nine use cases that span quality measure collection, clinical data exchange, and pre-order (or prior authorization) burden reduction.<sup>125</sup>

Public and private sector payers, manufacturers, the FDA, and other key stakeholders should collaborate on a similar process to develop implementation guides and profiles based on HL7 FHIR® and other relevant standards to improve access to real-world data from multiple sources, including EHRs, to support regulatory evaluation and value-based payment arrangements for medical products. Adoption of HL7 FHIR® standards and implementation guides by other federal agencies for their own program requirements is referenced in the ONC Proposed Rule.<sup>126</sup>

### Recommendation 3.3

#### Collaborate on the Development and Use of HL7 FHIR® Implementation Guides to Support Regulatory and Value-Based Payment Real-World Evidence Needs Related to Medical Products

The FDA, CMS, and ONC should collaborate with HL7, as well as other stakeholders, including payers, providers, academic and research institutions, and patient groups, to develop, test, and utilize HL7 FHIR® implementation guides to gain access to real-world data—while effectively protecting privacy—to support the evidence needs of both regulatory evaluation and value-based payment decision-making.

## Access to Medicare Data

Access to Medicare data is important in that it will assure that outcomes for individuals 65 and older are effectively analyzed and addressed in medical product development, evaluation, and payment processes. Older adults frequently have several chronic health conditions which require multiple medications and prescription drug use has increased dramatically among older adults over the last several years.<sup>127</sup>

CMS currently makes available to authorized users—through access to APIs and other means—clinically relevant Medicare data. CMS makes beneficiary-level data available to researchers,<sup>128</sup> specifically as identifiable data files<sup>129</sup> and limited data sets.<sup>130</sup> Identifiable data files—which contain protected health information and/or personally identifiable information—are available to a limited set of stakeholders for research purposes. Data requests require a research protocol and a data-use agreement and are reviewed by the CMS Privacy Board. Access to limited data sets—which have less identifiable data—must relate to projects that could improve the U.S. health care delivery system. This requirement includes projects related to improving the quality of life for CMS beneficiaries or improving the administration of CMS programs, including payment-related projects and the creation of analytical reports. In addition, these research projects must contribute to generalizable knowledge.<sup>131</sup>

CMS also enables access to files by innovators who are employed by for-profit organizations or want to conduct research to create tools or products and intend to sell the tool or product or create analyses for organizational business needs.<sup>132</sup> The agency has established certain conditions under which innovator researchers may access CMS data, although such provisions do not support the private sector’s use of the data for drug development or payment models.



While researchers have had access to Medicare fee-for-service data for some time, as described above, in 2018 CMS announced plans to also make Medicare Advantage encounter data, including provider identifiers, diagnoses, and date and type of service, available to researchers.<sup>133</sup> In February 2019, CMS announced its intent to share Medicare Parts A, B, and D data—through HL7 FHIR®-based APIs—with accountable care organizations.<sup>134</sup>

The FDA Sentinel Initiative has been working to bring data from CMS into its system.<sup>135</sup> PCORnet has also made progress. A subset of PCORnet members recently conducted a CMS Linkage Pilot Project to develop, test, and evaluate processes for using Medicare claims data to supplement PCORnet data in pragmatic clinical trials, using the ADAPTABLE study as a test case. Lessons learned were documented in a white paper released in early 2019.<sup>136</sup>

Building on its considerable leadership in making health information available to support improvements in health and health care, CMS should explore ways to make Medicare beneficiary data more readily available—in formats that help to meet the reliability and relevance requirements of evidence development—to support the real-world data needs of regulatory evaluation and value-based payment.

### **Recommendation 3.4**

#### **Facilitate Access to Medicare Data to Support the Real-World Evidence Needs of Regulatory Evaluation and Value-Based Payment of Medical Products**

CMS should explore ways to make Medicare beneficiary data available—in formats that help to meet the reliability and relevance requirements of evidence development—to support the real-world data needs of regulatory evaluation and value-based payment for medical products.

### **Access to Vital Status Information**

For clinical studies associated with both regulatory evaluation and value-based payment decision-making, as well as other health improvement purposes, survival is a critical outcome measure. However, researchers have difficulty accessing high-quality mortality data in a timely, cost-effective manner. In the past, researchers have used the Death Master File to obtain vital status information, however, due to policy changes in 2011 that require the omission of protected state death records, this is no longer a useful resource.<sup>137</sup> The CDC National Center for Health Statistics (NCHS) makes available the National Death Index (Index), a centralized database of death record information compiled from state vital statistics offices, as a resource for epidemiological studies and other types of health and medical research. However, there is considerable delay between the date of death and inclusion in the Index, as well as administrative and cost burdens, all of which can make the use of this resource challenging.<sup>138</sup> There is a need for nationwide, sustainable, timely access to mortality information that is standards-based and available at reasonable cost. To help achieve these goals, NCHS has worked with HL7 to create a FHIR® standard for trial use for mortality reporting, but additional work is needed to test the standard, extend their scope, and prove their suitability for widespread adoption. HHS should collaborate with users of mortality data, state vital statistics offices, and other key stakeholders to assess the current state, including key challenges; identify high-priority mortality information needs; and both develop and drive the adoption of standards and practices that will improve the availability of death-related information.

### **Recommendation 3.5**

#### **HHS Should Collaborate with Both Users and States to Accelerate Efforts to Make Standards-Based Mortality Information Available on a Timely Basis and at Reasonable Cost**

HHS should collaborate with users and states to develop and implement sustainable strategies to improve the availability, accuracy, timeliness, and cost of accessing mortality information for research and other population health improvement purposes. Such efforts should include the finalization and widespread adoption of mortality-related HL7 FHIR® standards among states and technology developers.

## 4. IMPROVING RELIABILITY AND RELEVANCE OF DATA

In assessing fitness of real-world data for use in regulatory decisions, the FDA assesses both data reliability (data accrual and data quality control or data assurance) and the relevance of the underlying data.<sup>139</sup> Data provenance information supports traceability—another key requirement of the FDA. Finally, standardization of data is also necessary to support data analyses within and across multiple data sets.<sup>140,141</sup>

Examples of the types of data used for regulatory and value-based payment decision-making include medication information; laboratory, radiology, and other diagnostic results; diagnoses; clinical notes; hospitalizations; vital and medical status; patient-reported outcomes; and other data types.

While many data standards exist, and in some cases are required through federal regulation, much of the data contained within clinical and other systems are not currently standardized, resulting in significant labor and cost associated with normalization and other types of data curation. Artificial intelligence, natural language processing, and machine learning are being explored to support the translation of unstructured data into real-world evidence that can be used to support pre- and post-market studies.

Also, to a large extent, information regarding data provenance—which enables traceability of data back to its source—does not exist. Finally, matching an individual's data across disparate systems—which is required to effectively use real-world data for evidence development—can be difficult and labor-intensive, given the lack of standards for patient identification or matching, a challenge that has been also been recognized by ONC, CMS, and the FDA.<sup>142,143,144</sup>

### An Overview of ONC Proposed Rule Provisions Supporting Relevance and Reliability

The ONC Proposed Rule contains several provisions, summarized below, that will help to improve data relevance and reliability.

- Adoption of the USCDI to replace the Common Clinical Data Set (CCDS) and proposed establishment of a requirement that all certified health IT must support the USCDI, increasing the minimum baseline of data classes and data elements that must be commonly available for interoperable exchange;
- Requiring health IT developers to successfully test the real-world use of their technology for interoperability both as an initial condition of certification, as well as periodically through maintenance of certification;
- Requiring health IT developers to use the HL7 FHIR® standard for APIs to allow health information from their technology to be accessed, exchanged, and used without special effort; and
- Updating the electronic prescribing SCRIPT standard.<sup>145</sup>

### Leveraging the USCDI for Standardization of a Core Data Set

In the ONC Proposed Rule, the USCDI Version 1 is proposed as a standard, that—if adopted—would require health IT developers to update their certified health IT to support all data classes and elements included in the new standard. Standardization of the data classes and data elements included in the USCDI will assist with the standardization of data needed to support both regulatory evaluation and value-based payment decision-making, such as patient demographics, laboratory tests and results, medications, clinical notes, vital signs, problems, and procedures. New data classes and elements will also support data provenance needs, as well as patient matching.

New proposed USCDI data classes and elements relevant to the generation and use of real-world evidence that were not contained in the predecessor CCDS standard include:

- Provenance data, including author, author organization, and author time stamp, which is needed to improve traceability and the trustworthiness and reliability of data being exchanged;
- Additional patient demographic data, including address and phone number, which will improve patient data matching across systems; and
- Clinical notes for both inpatient and outpatient settings.





Data classes and data elements included in the proposed USCDI contained in the ONC Proposed Rule are summarized in Figure 1 below.

**Figure 1. USCDI, Version 1, ONC Proposed Rule**

Data Class	Data Element	
Assessment and Plan of Treatment		
Care Team Members		
Clinical Notes (NEW)	<ul style="list-style-type: none"> <li>• Consultation Note</li> <li>• Discharge Summary Note</li> <li>• History and Physical</li> <li>• Imaging Narrative</li> </ul>	<ul style="list-style-type: none"> <li>• Laboratory Report Narrative</li> <li>• Pathology Report Narrative</li> <li>• Procedure Note</li> <li>• Progress Note</li> </ul>
Goals	<ul style="list-style-type: none"> <li>• Patient Goals</li> </ul>	
Health Concerns		
Immunizations		
Patient Demographics	<ul style="list-style-type: none"> <li>• First Name</li> <li>• Last Name</li> <li>• Previous Name</li> <li>• Middle Name (including middle initial)</li> <li>• Suffix</li> <li>• Birth Sex</li> </ul>	<ul style="list-style-type: none"> <li>• Date of Birth</li> <li>• Race</li> <li>• Ethnicity</li> <li>• Preferred Language</li> <li>• Address (NEW)</li> <li>• Phone Number (NEW)</li> </ul>
Laboratory	<ul style="list-style-type: none"> <li>• Tests</li> <li>• Values/Results</li> </ul>	
Medications	<ul style="list-style-type: none"> <li>• Medications</li> <li>• Medication Allergies</li> </ul>	
Problems		
Procedures		
Provenance (NEW)	<ul style="list-style-type: none"> <li>• Author</li> <li>• Author Organization</li> <li>• Author Time Stamp</li> </ul>	
Smoking Status		
Unique Device Identifier(s) for a Patient's Implantable Device(S)		
Vital Signs	<ul style="list-style-type: none"> <li>• Diastolic Blood Pressure</li> <li>• Systolic Blood Pressure</li> <li>• Body Height</li> <li>• Body Weight</li> <li>• Heart Rate</li> <li>• Respiratory Rate</li> <li>• Body Temperature</li> </ul>	<ul style="list-style-type: none"> <li>• Pulse Oximetry</li> <li>• Inhaled Oxygen Concentration</li> <li>• Pediatric Vital Signs (NEW)                             <ul style="list-style-type: none"> <li>• BMI percentile per age and sex for youth 2-20</li> <li>• Weight for age per length and sex</li> <li>• Occipital-frontal circumference for children &gt; 3 years old</li> </ul> </li> </ul>

## Recommendation 4.1

### Adopt the USCDI Standard in Updates to 2015 Edition Certification Criteria

ONC should replace the CCDS and its references within the 2015 Edition of the ONC Health IT Certification requirements with the USCDI standard, as proposed, including new required data classes and elements related to patient demographics, clinical notes, and data provenance, increasing the minimum baseline of data classes that must be commonly available within certified health IT for interoperable exchange.

The FDA Framework indicates that the FDA will identify data standards and implementation considerations that apply to the FDA's proposed uses of real-world data and evidence, identify gaps that need to be addressed, and collaborate with stakeholders to adapt or develop standards and implementation strategies for real-world data and evidence solutions at the FDA. As the USCDI becomes the recognized standard for health IT, the FDA should work to align its data standards and implementation strategies with this standard.

## Recommendation 4.2

### Align FDA Standards Requirements with the USCDI

As USCDI becomes the standard for health IT systems certified under the 2015 Edition, the FDA should consider aligning its standards and implementation requirements associated with real-world data and evidence derived from such systems, with the USCDI.

## Real-World Testing of Interoperability

Health IT system interoperability is tested by ONC-accredited certifying bodies prior to granting ONC Health IT Certification. However, health IT systems are rarely installed off the shelf and are almost always customized to meet individual user needs. The 21st Century Cures Act requires health IT developers—as a condition of certification and maintenance of certification—to have successfully tested the real-world use of the technology for interoperability in the type of setting in which such technology would be marketed.<sup>146</sup> The ONC Proposed Rule defines real-world testing to mean that:

- The certified health IT continues to be compliant with certification criteria, including required technical standards and vocabulary code sets;
- The certified health IT is exchanging electronic health information in the care and practice settings for which it is intended for use; and
- Electronic health information is received by and used in the certified health IT.<sup>147</sup>

Implementation of real-world testing for interoperability both as an initial condition of certification and for maintenance of certification over time will help to assure data standards conformance both prior to and upon implementation of health IT systems, thereby improving the quality of data used for real-world evidence purposes.

## Recommendation 4.3

### Adopt Real-World Testing of Interoperability as Condition and Maintenance of Certification Under 2015 Edition

ONC should include, as proposed, provisions for real-world testing of interoperability of health IT systems as a Condition of Certification and for Maintenance of Certification in its updates to the 2015 Edition of the ONC Health IT Certification Program.

## Improving Patient Matching

The real-world data needed to support regulatory and value-based payment decision-making resides in multiple settings. Analysis of such data requires that records across multiple settings belonging to the same individual are matched. Patient record matching is ordinarily conducted by the application of algorithms based on demographic information, such as the patient's name, date of birth, sex, mother's maiden name, address, phone number, and in some cases, social security number.<sup>148</sup> Inaccurate, incomplete, or inconsistently formatted demographic information can pose challenges to accurate matching. Unfortunately, patient matching rates vary widely, with health care facilities failing to link records for the same patient up to half of the time.<sup>149</sup>



BPC convened multiple stakeholders to develop a set of recommendations for improving patient record matching, including widespread adoption of common standards for the minimum types of demographic data to be collected and the content and formats in which such data should be collected.<sup>150</sup> Similar recommendations have been made by other organizations, including the Pew Charitable Trusts.<sup>151</sup> In January 2019, the Government Accountability Office (GAO) released its report on patient matching as required by the 21st Century Cures Act. GAO's findings also highlighted the fact that implementing common standards for how certain demographic data should be formatted—such as names and addresses—could improve the consistency of data across providers and thus make it easier to match records.<sup>152</sup> Finally, BPC and the Healthcare Leadership Council reached similar conclusions, as outlined in the report *Advancing Interoperability, Information Sharing, and Data Access: Improving Health and Healthcare for Americans*, released in February 2019.<sup>153</sup>

The ONC Proposed Rule requires ONC-certified health IT to utilize common standards contained in the USCDI for the following patient demographic information which can assist with patient matching: first name, last name, previous name, middle name, suffix, birth sex, date of birth, race, ethnicity, preferred language, address, and phone number. Research conducted by the Pew Charitable Trusts indicates that use of the U.S. Postal Service Standard for the patient address could improve match rates—even further if combined with standardization of the last name.<sup>154</sup> Other patient demographic information, such as an email address—which is already contained in 54 percent of patient records, according to one study—could further improve matching rates.<sup>155</sup>

## Recommendation 4.4

### Include Patient Email Address and Specify that the U.S. Postal Service Standard be Used for Patient Address in the USCDI

To improve patient matching, ONC should:

- Include the patient email address in the list of patient demographic-related data elements contained within the proposed USCDI Version 1 standard.
- Specify the use of the U.S. Postal Service standard in its requirements for an address contained within the proposed USCDI Version 1 standard.

## 5. LEVERAGING TECHNOLOGY TO GAIN INPUT DIRECTLY FROM PATIENTS

Both public- and private-sector leaders are increasingly recognizing the importance of integrating patient perspectives in the design and conduct of clinical trials, regulatory decision-making, and the assessment of value, to ensure that medical products are relevant to and meet the needs of the end user—or patient.<sup>156,157,158,159</sup> Patient perspectives also play a critical role in improving health care.<sup>160</sup>

Patient engagement contributes to study design, selecting study outcomes, tailoring interventions to meet patients' needs and preferences, and enrolling participants.<sup>161</sup> Patient input comes in many forms, including patient preference information, patient experience data, and patient-reported outcomes. Patient preference information is defined by the FDA as an assessment of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions.<sup>162</sup> The 21st Century Cures Act called for the use of patient experience data to inform regulatory decision-making. This includes data intended to provide information about patients' experiences with a disease or condition. According to the Act, patient experience data can be interpreted as information that captures patients' experiences, perspectives, needs, and priorities related to, but not limited to: the symptoms of their condition and its natural history; the impact of the conditions on their functioning and quality of life; their experience with treatments; input on which outcomes are important to them; patient preferences for outcomes and treatments; and the relative importance of any issue as defined by patients.<sup>163</sup> Finally, a patient-reported outcome (PRO) is any report of a patient's health condition that comes directly from the patient about the status of the patient's health condition, without amendment or interpretation of the patient's response by a clinician or anyone else.<sup>164,165</sup> PROs typically include information about health-related quality of life, symptoms, function, satisfaction with care or symptoms, side effects, adherence to prescribed medications or other therapies, and satisfaction and perceived value of treatment.<sup>166,167,168</sup>

Challenges associated with gathering and integrating information from patients include cost, technology, and operational barriers associated with data collection, lack of expertise in designing and implementing patient-focused data collection methods, patient health literacy, patient fatigue or burden, and the lack of understanding of and the need for consistent standards and guidance documents for measuring and utilizing patient perspective information.<sup>169,170,171</sup>

The use of mobile technologies, wearables, biosensors, and other digital health tools can improve both the capture and reporting of information from patients, while also improving convenience and reducing burden. Digital health tools also offer other advantages, including those related to scale, cost-effectiveness, capture frequency, data volume, measurement objectivity, and capture of setting.<sup>172</sup>

There is significant interest at the FDA in using patient-generated information as real-world evidence to support the entire drug development life cycle. Across medical product centers, the FDA is exploring how it can use not only EHRs, but also apps and other mobile health technologies, to collect more reliable, continuous data on products' benefit and risk profiles in the pre- and post-market.<sup>173</sup> The FDA's work is in the early stages but the agency is already working on ways to leverage such technologies to facilitate a modernized ecosystem for innovation that can help the FDA better meet its mission of protecting and promoting the public's health.<sup>174</sup>

In 2009, the FDA released guidance on the use of PRO measures in medical product development to support labeling claims. In response to the 21st Century Cures Act and the FDA Reauthorization Act of 2017, the FDA is developing a series of four methodological patient-focused drug-development guidance documents to enhance the incorporation of the patient's voice in medical product development and regulatory decision-making. To date, the FDA has issued a draft guidance for collecting comprehensive and representative input.<sup>175</sup> It has also released discussion documents on methods for identifying what is important to the patient and selecting, developing, or modifying fit-for-purpose clinical outcomes assessments which—when final—will replace the 2009 guidance.<sup>176,177</sup> The FDA's discussion documents describe the benefits of capturing outcomes data electronically and address paper-electronic migration and equivalence, device validation, and minimal data-related regulatory considerations.<sup>178</sup>

In November 2018, the FDA introduced the MyStudies app, a new mobile technology to foster the collection of real-world data via patients' mobile devices to help inform regulatory decision-making. Developed by the FDA and private sector partners, and pilot-tested by Kaiser Permanente, the app gives researchers and developers access to open source code and technical documentation, so the app and patient data storage system can be reconfigured, customized, and branded by organizations conducting clinical research.<sup>179</sup> The FDA MyStudies App is designed to facilitate the input of real world data directly by patients, which can be linked to electronic health data supporting traditional clinical trials, pragmatic trials, and observational studies.<sup>180</sup>

In August 2018, the Agency for Healthcare Resources and Quality announced the Step Up App Challenge, which is designed to advance patient engagement technologies that collect PRO measures by encouraging teams to design, develop, and pilot user-friendly applications that simplify the process of collecting, interpreting, aggregating, and sharing PRO data related to physical function outcomes in the ambulatory care setting.<sup>181</sup>

The FDA has stated on multiple occasions that better capture of real world data—collected from digital health and other technologies—has the potential to make new drug development processes more efficient, improve safety, and reduce the cost of drug development. It has also stated that it recognizes that its work is in the early stages. The FDA Framework describes the agency's intent to explore the use of mobile technologies, electronic PRO tools, wearables, and biosensors to fill gaps in data collection.

## **Recommendation 5.1**

### **Develop Guidance to Accelerate the Use of Digital Tools for the Collection of Data Directly from Patients to Support the Entire Drug Development Life Cycle**

The FDA should build upon both its considerable progress related to patient-focused drug development and its *Framework for FDA's Real-World Evidence Program* to develop more detailed guidance on the use of digital tools to support the collection of data directly from patients—including mobile technologies, wearables, biosensors, and other digital health tools—to serve as real-world data and evidence across the medical product development life cycle.

## **6. EXPANDING EFFORTS TO EXPLORE THE USE OF ARTIFICIAL INTELLIGENCE**

The explosion in the amount of data available through new data sources offers significant, new opportunities in clinical research, regulatory evaluation, and decision-making about payment. Yet the data from many of these sources are largely unstructured, requiring new approaches for using these data for real-world evidence.



Data contained in EHRs and other clinical systems, such as imaging and laboratory systems, are increasingly standardized, due in large part to interoperability efforts led by the federal government. Nevertheless, the amount of non-standardized or unstructured data contained in these systems is still considerable. Other novel data sources, such as wearable devices, mobile technologies, and social media networks also contain unstructured data. The rich data from these sources can help researchers identify critical signals of clinical outcomes, including potentially new biomarkers, as well as post-market safety signals.<sup>182</sup>

In order to leverage these new, rapidly expanding data sources to measure outcomes and generate evidence, researchers may need to employ advanced analytical tools such as artificial intelligence (AI). AI is the ability of a computer to perform tasks commonly associated with human beings, such as the ability to reason, discover meaning, generalize, or learn from past experience.<sup>183</sup>

Natural language processing—a type of AI—aims to make human language accessible to machines and involves linking words, phrases, or terms listed within unstructured data to indicate a specific condition or event.<sup>184,185</sup> Natural language processing can be used to identify adverse events or other outcomes not routinely or consistently coded in EHRs that are frequently used in drug utilization, comparative effectiveness research, PRO, and other studies.<sup>186</sup> By systematically scanning open fields with text in EHRs or physician dictation notes, natural language processing can also facilitate the capture and analysis of additional information to confirm or contrast findings drawn from structured data fields or codes.<sup>187</sup>

Machine learning can also be applied to improve studies utilizing real-world evidence. Machine learning is the process by which a computer is able to improve its own performance by continuously incorporating new data into statistical models and tuning algorithms.<sup>188,189,190</sup> According to the FDA, one of the greatest benefits of AI and machine learning reside in their ability to learn from real-world use and experience, and their capability to improve performance.<sup>191</sup> One key advantage of machine learning is its ability to operate on numerous predictive features in datasets, including outliers, noise, and collinearities, without the stability and reliability concerns of traditional statistical modeling, enabling complex patterns and interactions to be identified.<sup>192</sup>

The FDA has demonstrated its recognition of the importance of AI in its real-world evidence activities through public statements as well its FY2020 budget request.<sup>193,194,195</sup> While the *Framework for the FDA's Real-World Evidence Program* does not discuss AI, natural language processing, or machine learning, the *Sentinel Initiative Five-Year Strategy* does indicate that in the next five years, the FDA will focus its Sentinel investments on innovations emerging from new data science disciplines, such as natural language processing and machine learning.<sup>196,197</sup> Specifically, the five-year strategy includes the establishment of standards for natural language processing to identify complex health outcomes defined by multiple data elements and establishment of best practices for other types of advanced analytics, such as machine learning.<sup>198</sup> The conduct of and dissemination of learnings from demonstration projects can also help advance the use of AI approaches to support the use of novel data sources as real-world evidence.

CMS has also demonstrated interest in exploring the use of AI in future payment and delivery models. For example, in March 2019, CMS announced the CMS AI Health Outcomes Challenge, through which CMS—in collaboration with the American Academy of Family Physicians and the Laura and John Arnold Foundation—will engage with innovators to harness AI solutions to predict health outcomes for potential use in CMS Innovation Center innovative payment and service delivery models.<sup>199</sup>

Further study and pilot or demonstration projects can help the FDA assess the utility of AI to support its mission. The FDA should continue to explore whether and how AI, natural language processing, and machine learning can be applied to support real-world evidence needs.

## **Recommendation 6.1**

### **Expand FDA Activities to Explore the Use of AI to Support Real-World Evidence Needs Across the Medical Product Development Life Cycle**

The FDA should fully implement the AI, natural language processing, and machine learning actions contained in the *Sentinel Initiative Five-Year Strategy*. The FDA should also conduct and disseminate learnings from demonstration projects designed to assess the utility, feasibility, and replicability of applying AI and natural language processing tools to novel data sources to facilitate their usage in studies leveraging real-world evidence across the medical product development life cycle.

## 7. ACCELERATING PILOTS AND DEMONSTRATION PROJECTS FOR NEW DATA SOURCES AND ADDITIONAL MEDICAL PRODUCTS

The amount of data available to support evidence development is growing exponentially, primarily driven by the now widespread adoption of EHRs among physicians, hospitals, and other health care providers, and the widespread use of mobile technologies, wearables, and other technologies among individuals. Registries can also serve as an important data source for evidence development for both regulatory evaluation and payment.

Pilots play a critical role in assessing the feasibility, challenges, and strategies needed to leverage these new data sources to generate evidence for regulatory and value-based payment decision-making.

### Real-World Evidence Pilots for Medical Product Development

Both Congress and the administration recognize the importance of pilots. The 21st Century Cures Act calls for the FDA to both develop and implement a framework for real-world evidence that contains—among other things—potential pilot opportunities that the FDA's real-world evidence program will address.<sup>200</sup> Performance goals for the Prescription Drug User Fee Act VI, which are referred to in Title 1 of the FDA Reauthorization Act, require that the FDA initiate—or fund by contract—appropriate activities, such as pilot studies or methodology development projects aimed at addressing key outstanding concerns and considerations in the use of real-world evidence for regulatory decision-making, by no later than the end of FY2019.<sup>201,202</sup>

The FDA has considerable experience with demonstration projects that draw from administrative and claims data to identify safety events. The Sentinel System—a key component of the FDA's post-market safety surveillance set of resources—contains information from more than 297 million members combined from 17 different data partnerships, which are derived primarily from national health insurers and managed care organizations.<sup>203,204</sup>

The *Sentinel System: Five-Year Strategy*, released in December 2018, calls for the conduct of specific real-world data-driven demonstration projects, the expansion of access to and use of EHRs, and the exploration of novel data sources, such as mobile health technologies, wearable devices, and registries, not only for safety purposes, but also for effectiveness questions.<sup>205</sup> The FDA Framework also references the importance of pilot projects that further the understanding of potential uses of real-world data and evidence, stating that the FDA will continue these efforts.<sup>206</sup>

One of the FDA's primary goals is to significantly expand the use of EHR data and explore the use of other novel data sources in its real-world activities.<sup>207</sup> The continuation and expansion of pilot projects that explore both access to and use of new data sources, such as EHRs, registries, mobile technologies, wearables, and other technologies, is critically important to expanding the evidence base across the medical product development life cycle. Such pilots should cover not only single molecule drugs, but also biologics such as regenerative cell therapies.

### Recommendation 7.1

#### **Accelerate FDA Pilot Projects Focused on New Data Sources, Including EHRs, Registries, Wearables, and Other Mobile Technologies, as well as Additional Medical Products, including Biologics, Such as Cell Therapies**

The FDA should expand upon its efforts to leverage new data sources, such as EHRs, registries, wearables, and other mobile technologies, through pilot projects, to explore their utility in supporting real-world evidence needs across the medical product development life cycle. The FDA should also support the development and launch of real-world evidence pilots that address the needs of not only single molecule drugs, but also biologics, including regenerative cell therapies.

### Real-World Evidence Demonstration Projects for Value-Based Payment Models

CMS has a long history of conducting demonstration projects to evaluate new approaches for improving quality and reducing spending. Under a statutory mandate and with an authorized annual budget of \$1 billion per year, the Center for Medicare and Medicaid Innovation (Innovation Center) tests innovative payment and service delivery models that have the potential to preserve or enhance the quality of care, and reduce Medicare, Medicaid, or CHIP spending.<sup>208</sup>

Paying for value is a central premise of the Innovation Center’s work. The Innovation Center is developing and testing models that complement HHS’ “four Ps” of driving toward value: patients as consumers, providers as accountable patient navigators, paying for outcomes, and preventing disease before it occurs.<sup>209,210</sup>

Increasing concerns about the affordability of drugs and biologics, combined with the considerable increase in the amount of data available to support evidence development, provide CMS with the opportunity to explore the use of these data sources to support decision-making regarding value-based payment models.

CMS’ recently released proposed rule contained a request for public comment on ways the Innovation Center might further promote interoperability among model participants and other health care providers as part of the design and testing of innovative payment and service delivery models.<sup>211</sup>

Launching a demonstration project to explore the use of clinical, administrative, and patient-generated data in assessing outcomes for value-based payment models for drugs and biologics is aligned with goals contained in the administration’s *American Patients First Blueprint*, which call for the advancement of value-based payment models that pay for outcomes and improve the affordability of drugs. The demonstration project also supports HHS’ goals related to advancing interoperability and electronic data exchange using open APIs to support patients, providers, payers, and researchers, and improve health care for all Americans.

## Recommendation 7.2

### Launch a CMS Demonstration Project Focused on Using Data from Multiple Sources to Measure Outcomes for Value-Based Payment Models for Drugs and Biologics

The CMS Innovation Center should develop and launch a demonstration project that explores how clinical, administrative, and patient-generated data from multiple sources can be used to generate evidence for outcomes or value-based payment models for high-cost drugs and biologics. The Innovation Center and its awardees should publish methods used, outcomes, and lessons learned to inform future value-based payment arrangements for drugs and biologics.

## 8. ASSURING PRIVACY AND CONFIDENTIALITY

Access to, linking of, and use of large amounts of real-world data drawn from clinical, administrative, and patient-generated sources for any effort, including for regulatory and value-based payment decision-making, requires considerable focus on assuring privacy and confidentiality and strong data governance.

As background, the primary laws governing the use of real-world data include the Health Insurance Portability and Accountability Act (HIPAA) and the Revised Common Rule. The HIPAA Privacy Rule prohibits covered entities and their business associates from unauthorized use or disclosure of personal health information (PHI) unless the individual provides written authorization. Authorization for the disclosure of PHI for research purposes must also identify a specific research study and must contain certain core elements and required statements.<sup>212</sup> The Privacy Rule permits the use of PHI for research as long as at least one of several rules are met, which include receipt of an informed consent; an Institutional Review Board (IRB) waiver of requirements for authorization; research involving only de-identified data; research using or disclosing a Limited Data Set; or various other exceptions.<sup>213</sup> The HIPAA Security Rule requires covered entities to implement physical, technical, and administrative safeguards to protect electronic PHI.<sup>214</sup>

The Revised Common Rule also contains federal requirements to protect the privacy and confidentiality of human subject research, with an exemption for the use or disclosure of PHI that is regulated by HIPAA as research, public health, or health care operations. Furthermore, the Revised Common Rule requires the use of a centralized IRB for multi-site research, with certain exceptions.<sup>215</sup>

In response to the 21st Century Cures Act, the HHS Office of Civil Rights released additional guidance on HIPAA and individual authorization of uses and disclosures of PHI for research.<sup>216</sup>

The considerable number of recent, large-scale privacy breaches—such as those related to Facebook and others—have led Congress to consider legislation designed to give individuals greater transparency, choice, and control over how their data is used.<sup>217,218,219</sup> In addition, the GAO has recommended that Congress consider developing comprehensive legislation on Internet privacy that would enhance consumer protections and provide flexibility to address a rapidly evolving Internet environment.<sup>220</sup> As part of its Regulatory Sprint to Coordinated Care, HHS has sought public input on how HIPAA Rules could be modified to further coordinated, value-based health care.<sup>221</sup>

Recent studies indicate a willingness among individuals and stakeholders to share data for research purposes. A survey of clinical trial participants indicated that 93 percent were very or somewhat likely to allow their own data to be shared with university scientists, while 82 percent were very likely or somewhat likely to share with scientists in for-profit companies.<sup>222</sup> Factors that influence the willingness of stakeholders to share data in multi-center effectiveness research studies include perceptions of the purpose, benefit, and value of the research.<sup>223</sup> A majority of clinical trial participants in one study did not express significant concerns about data sharing, although about one-third of respondents did raise the following concerns: that data sharing might make others less willing to enroll in clinical trials (37 percent), that data would be used for marketing purposes (34 percent), and that data might be stolen (30 percent).<sup>224</sup>

Real-world evidence efforts must assure compliance with applicable laws related to privacy and security and establish policies and principles for data sharing, as well as strong data governance. Multi-center initiatives, such as the Sentinel Initiative and PCORnet, have established policies and principles for data sharing.<sup>225,226</sup> Similar data governance methods will be needed in other efforts that leverage real-world data across multiple settings to support regulatory evaluation and value-based payment decision-making.

Key considerations for privacy and security based on the unique, real-world evidence needs of both regulatory evaluation and value-based payment decision-making should be brought to bear as both Congress and the administration advance policy in this area.

## **Recommendation 8.1**

### **Consider the Real-World Evidence Needs of Regulatory Evaluation and Value-Based Payment Decision-making in Privacy Policy**

Public- and private-sector organizations engaged in the generation and use of real-world data and evidence—such as academic and research institutions, health systems, payers, regulators, technology companies, and patient organizations—should study, deliberate, and develop a set of privacy-related policy principles and recommendations to support the use of administrative, clinical, and patient-generated data across multiple settings for evidence generation for clinical research, regulatory evaluation, and value-based payment decision-making related to medical products. Such an effort should be convened by the federal government or a trusted, independent, non-profit organization.

## **Advancing a Privacy Framework to Build Trust**

Many of the settings or organizations from which real-world data are derived—including health care providers, health plans, and clearinghouses—are covered entities or business associates under HIPAA. However, there are also an increasing number of companies that hold a wealth of health information that can be leveraged for real-world evidence—such as consumer technology companies, app developers, mobile health technology companies, manufacturers of wearables, and social media sites—that are not subject to existing privacy protections under HIPAA.

There are limited protections for data held by non-covered entities under current state and federal law. The Federal Trade Commission has the authority to enforce against unfair or deceptive acts or practices when a company fails to act in accordance with its stated privacy or security policy.<sup>227</sup> In 2016, HHS released a report identifying gaps that exist between HIPAA-regulated entities and those not regulated by HIPAA. The HHS report details significant challenges in safeguarding electronic health information as a result of these gaps, including individuals having a limited or incorrect understanding of when their data is protected by law and when it is not and inconsistent security standards that may pose a cybersecurity threat.<sup>228</sup>

Through rules recently proposed by ONC and CMS, HHS is advancing transformative new policies that will give patients greater access to data through open APIs, enabling individual health information to be downloaded into third-party applications, most of which are not covered under HIPAA.<sup>229,230</sup> These proposed rules are also expected to increase access to data for improvements in population health, including the generation of real-world evidence for regulatory and payment decision-making.





A data privacy framework for use of health information by non-HIPAA covered entities is needed to improve trust among individuals and health care organizations that have stewardship over health care data. Expectations of acceptable uses and disclosures of health information that are consistent across entities covered by HIPAA and entities that are not covered by HIPAA can help eliminate confusion and streamline research and other population improvement activities. National baseline data protections can help health care and technology organizations—many of which operate across state lines—as well as multi-center research networks, operate more effectively when sharing patient information. National baseline protections would not necessarily preempt state laws with stronger protections, such as those passed in California.<sup>231</sup> The Senate Committee on Commerce, Science, and Transportation is exploring policy principles for a federal data privacy framework that will provide consumers with more transparency, choice, and control over their data—key principles that are being embraced by several consumer technology companies and other stakeholders.<sup>232,233</sup>

## **Recommendation 8.2**

### **Advance a Federal Data Privacy Framework That Creates Baseline Protections and Addresses Entities Handling Health Information That are Not Covered Under HIPAA**

Congress should pass bipartisan legislation that clarifies expectations for use and disclosures of health information among entities not covered under HIPAA. Congress should advance federal, baseline protections to improve consumer trust and certainty, which need not preempt existing state laws with more robust requirements.

## **9. ADVANCING INNOVATIVE, NEW MODELS OF DRUG DEVELOPMENT**

The vast amount of clinical data now available to inform the science of drug development and evaluation, coupled with the widespread use of mobile technology among Americans, offer the opportunity to modernize and improve clinical studies and regulatory decision-making, based on data and science.

The FDA recognizes the need for new approaches that will improve the efficiency and reduce the complexity of clinical trials, citing the need to not only address the potential for declining patient enrollment and high costs, but also longer periods of monopoly that promote higher prices. The FDA also faces the challenge of regulating new areas of novel and emerging science, like gene therapy, targeted medicine, and digital health, where traditional approaches to product regulation may not be well suited for such products.<sup>234</sup> The FDA has several activities underway that are designed to develop and facilitate innovative, new trial designs.

On January 8, 2019, the FDA commissioner described plans to create a new office dedicated to advancing innovation in drug development, creating tools that will make it less expensive and less risky to create new drugs and advance the science of prediction. This new Office of Drug Evaluation Science—which is expected to launch in 2019—will also focus on improving and modernizing internal FDA approaches to help clinical reviewers make data-driven decisions.<sup>235</sup> The new FDA office should include in its plan the exploration of new methods of drug development that take into account rapidly emerging technologies and vast new data sources, such as adaptive approval pathways. The office should also be charged—in collaboration with FDA leadership—with integrating new innovative approaches across all FDA regulatory efforts.

The FDA should continue and accelerate its plans to advance innovative clinical trial designs to accommodate new therapies—such as those that are personalized and precision-based—and reduce the cost and complexity of medical product development.

## **Recommendation 9.1**

### **Continue and Accelerate Efforts to Advance Innovation in Drug Development, Leveraging Real-World Evidence**

The FDA should continue and accelerate its efforts to modernize and advance innovation in drug development, including innovative clinical trials that leverage real-world evidence drawn from EHRs, other clinical and administrative systems, mobile technologies, and other digital health tools, with the ultimate goal of reducing the cost and complexity of clinical trials. The FDA should also continue with its plans to create a new Office of Drug Evaluation Science that will advance innovation in drug development, advance the science of prediction, and make it less expensive and less risky to create new drugs.

## 10. ADDRESSING REGULATORY BARRIERS

Recent surveys of both payers and manufacturers indicate that some of the most significant barriers to value-based payment arrangements are legal and regulatory concerns, including concerns about potentially implicating anti-kickback statutes or uncertainty about how to structure the arrangements to ensure compliance with the law.<sup>236,237,238</sup>

### Overview of Anti-Kickback and Stark Laws

The federal anti-kickback statute provides criminal penalties for individuals or entities that knowingly and willfully offer, pay, solicit, or receive remuneration to induce or reward referral or business reimbursable under federal health care programs. It is designed to protect patients and federal health care programs from fraud and abuse.<sup>239</sup>

HHS was given the authority by Congress—through the Medicare and Medicaid Patient and Program Protection Act of 1987—to protect certain arrangements and payment practices under the anti-kickback statute through the establishment of safe harbors.<sup>240</sup> Several safe harbors have been added by the Office of the Inspector General (OIG) over the years, including those related to donation of EHRs, waivers for cost-sharing for emergency ambulance services, free or discounted transportation services, and various protections that will help reduce the cost of prescription drugs.<sup>241</sup>

HHS is currently reviewing safe harbors as part of its Regulatory Sprint to Coordinated Care—an effort led by HHS Deputy Secretary Eric Hargan designed to identify and address unnecessary government obstacles to coordinated care and transformation to a value-based health care system.<sup>242</sup> HHS released two requests for information related to the anti-kickback statute and the physician self-referral law (also known as the “Stark Law”). On August 27, 2018, the OIG issued a request for information to identify ways in which it might modify or add new safe harbors to the anti-kickback statute, and exceptions to the beneficiary inducements civil monetary penalty definition of “remuneration,” in order to foster arrangements that would promote care coordination and advance the delivery of value-based care, while also protecting against harms caused by fraud and abuse.<sup>243</sup> This followed the June 25, 2018 release of a request for information by CMS to identify how the Stark law might impede care coordination.<sup>244</sup>

### Regulatory Clarity Associated with Value-Based Payment Arrangements

There is significant uncertainty among manufacturers, payers, providers, and other stakeholders about how the anti-kickback statute applies to value-based payment arrangements in which remedies are provided when certain clinical or cost outcomes are not achieved. In the OIG Advisory Opinion 17-03, the OIG stated that its current safe harbor for warranties protects remedial actions by suppliers to address products that fail to meet bargained-for requirements.<sup>245</sup> At the same time, in its Spring 2018 semi-annual report to Congress, the OIG indicated that further study was required regarding a public proposal for a new safe harbor that would protect value-based warranties offered by manufacturers or suppliers that provide certain assurances about clinical and/or cost outcomes and appropriate remedies where such outcomes are not achieved. The report stated that questions about the application of the anti-kickback statute to such arrangements should be addressed on a case by case basis.<sup>246</sup> To address such uncertainties, the OIG should codify and clarify that existing safe harbor regulations can apply to value-based payment arrangements related to medical products, or—if appropriate—issue new safe harbor regulations for such arrangements.

#### Recommendation 10.1

##### Create New or Modify Existing Safe Harbors to Provide Regulatory Certainty Regarding Value-Based Payment Arrangements for Medical Products

HHS should create new or modify existing safe harbors to provide clarity related to the use of value-based payment arrangements for medical products.

### Safe Harbors to Facilitate Use of Technology for Information Sharing

As detailed in this report, the development of real-world evidence to measure outcomes—whether for regulatory evaluation or value-based payment arrangements—will require the collection, normalization, curation, and submission of vast amounts of data. In some cases, natural language processing or machine learning protocols will be applied. To support value-based payment arrangements and post-market surveillance requirements,



such outcomes monitoring may continue over several years. Those responsible for collecting the data at its source—such as physician practices, hospitals, or health systems—will likely need training and may need to install software to support data capture and analysis. Depending on how arrangements are structured, the provision of tools, resources, and services, or payment for submission of data, could fall under the definition of “remuneration” under the anti-kickback statute and/or trigger violations under the Stark Law.

Currently a safe harbor under the anti-kickback statute and an exception under the Stark Law exist related to the donation of interoperable EHR software and related direct training services.<sup>247,248</sup> The August 2018 HHS RFI on the anti-kickback statute also invited feedback from the public on an additional safe harbor related to cybersecurity-related items and services.<sup>249</sup> To support real-world evidence needs associated with regulatory evaluation and value-based payment arrangements for medical products, HHS should consider expanding the types of software and technologies contained in the safe harbor to include software and related training and equipment that support the collection of clinical, administrative, and patient-generated data; natural language processing, machine learning, and data analytics; and other functions required for ongoing outcomes measurement and analysis.

## **Recommendation 10.2**

### **Expand Existing Safe Harbors to Enable Donation or Cost-Sharing of Software Supporting Real-World Evidence Needs**

HHS should expand upon existing safe harbors to enable donation or cost-sharing associated with software, hardware, and related direct training associated with the collection, normalization, curation, and submission of clinical, administrative, and patient-reported data associated with outcomes measurement to support both regulatory evaluation and value-based payment arrangements for medical products.

## **11. EXPANDING CMS WORKFORCE TO SUPPORT EVALUATION OF NEW EMERGING THERAPIES**

In August 2017, CMS announced its intent to issue future guidance regarding how pharmaceutical manufacturers can engage in innovative payment arrangements, such as outcomes-based pricing for medicines in relation to clinical outcomes.<sup>250</sup> On February 15, 2019, CMS announced proposed Coverage with Evidence Development (CED) for FDA-approved CAR T-cell therapies<sup>251</sup> and on May 17, 2019, CMS announced a delay in the final National Coverage Determination for such therapies, indicating that a decision was forthcoming.<sup>252</sup> On May 2, 2019, CMS Administrator Seema Verma outlined CMS’ comprehensive strategy to foster innovation for transformative medical technologies, addressing issues such as coverage, coding, and payment.<sup>253</sup>

The number of CMS staff devoted to coverage and analysis is limited, with an estimated 30 staff focused on CMS determinations for all health care-related services and products, including drugs and biologics.<sup>254</sup> The evaluation of medical products—particularly new gene and cell-based therapies—as well as the development of new value-based payment arrangements, require specific, specialized expertise. Hiring of individuals with expertise in emerging therapies and value-based payment arrangements can be difficult given competition for talent, particularly from the private sector. Similar challenges have been faced by the FDA, many of which were addressed through provisions contained in the 21st Century Cures Act.<sup>255,256</sup>

Having both the capacity and expertise—including scientific and new outcomes-based payment expertise—will be extremely important as CMS continues its efforts to foster innovation and enhance access to new, transformative technologies.

## **Recommendation 11.1**

### **Increase Capacity and Expertise at CMS to Support Innovation in Payment and Access to Transformative Medical Products**

Congress should assure adequate capacity and both scientific and value-based payment expertise within CMS to support coverage determinations and the implementation of new payment models for drugs, biologics, and medical devices.

## 12. PROMOTING COOPERATION AND COLLABORATION

The growing focus on not only safety and efficacy, but also on value, and the significant infrastructure and related labor costs associated with conducting studies, highlights the need for greater cooperation and collaboration among those who regulate new therapies, those who pay for them, those who conduct clinical studies, and those that both use and develop technology and data systems where real-world data reside.

In particular, regulators and payers have many common needs when it comes to evidence development, but rarely collaborate on these activities, given their different areas of focus.

### Collaboration Between CMS and FDA

Greater collaboration between the FDA and CMS can foster more efficient total life-cycle evidence development for medical products. Significant time lags can occur between FDA approval and CMS coverage, given that patient populations covered by large national payers like CMS are often not well-represented within clinical studies conducted for regulatory evaluation. As a result, strong evidence that a medical product is “reasonable and necessary” within that population (per CMS’ statutory mandate) is substantially lacking. This has led to the use of tools such as CED to provisionally cover a product while additional evidence accrues.

On February 15, 2019, CMS proposed to cover—under CED—FDA-approved CAR T-cell therapy, which is a new form of cancer therapy that uses a patient’s own immune system to fight the disease. CAR T-cell therapies were some of the first therapies approved by the FDA under the Regenerative Medicine Advanced Therapy (RMAT) Program, authorized by the 21st Century Cures Act.<sup>257,258</sup> The proposed National Coverage Determination would require Medicare to cover the therapy nationwide when it is offered in a CMS-approved registry or clinical study, in which patients are monitored for at least two years post-treatment. Evidence from the registries or studies would help CMS identify the types of patients that benefit from CAR T-cell therapy, informing a future decision by the agency regarding the types of cases in which Medicare would cover the treatment with no registry or trial requirement.<sup>259</sup> CMS proposed to leverage the FDA’s requirements for post-approval studies for CAR-T to the fullest extent possible in reviewing studies for CMS approval.<sup>260</sup> There is considerable bipartisan support among members of the House and Senate for CMS to leverage existing registries that are already supporting FDA post-market study requirements, such as the Center for International Blood and Marrow Transplant Research Cellular Therapy Registry, which is working collaboratively with participating CAR T-cell patients in collecting long-term safety and efficacy data to fulfill requirements required by the FDA.<sup>261</sup>

Also, in the past decade, there have been proposals and pilot programs aimed at implementing a “parallel review” process to reduce both the potential evidentiary and time gaps between FDA approval and payer coverage. This involves the joint consultation of regulatory and payer bodies during the pivotal trial design phase so that medical product sponsors can gather relevant evidence to meet both FDA’s “safe and effective” and CMS’ “reasonable and necessary” mandates. While some proposals involve the joint review of the resultant evidence as both agencies weigh their ultimate decisions regarding approval and coverage, current FDA and CMS practice is to review such information separately in keeping with scientific best practice and regulatory mandates.

A parallel review program for medical devices does exist in the U.S. The FDA’s CDRH and CMS launched a pilot for parallel review of Class III medical devices in 2011, making the program permanent in 2016.<sup>262</sup> In a recent speech, CMS Administrator Seema Verma described the multitude of meetings whereby both CMS and FDA have worked together to provide coordinated regulatory and coverage advice to manufacturers of medical devices.<sup>263</sup> The European Union (EU) has also formalized a process for “parallel consultation” between drug manufacturers and two EU agencies—the European Medicines Agency and the European Network for Health Technology Assessment.<sup>264</sup> The FDA’s FY2020 budget request calls for strengthening the Parallel Review program related to medical devices to streamline Medicare coverage. CMS’ proposal strengthens the existing parallel review process to improve device manufacturer participation and increase transparency.<sup>265</sup>

Greater cooperation between the FDA and CMS is needed on evidence generation and use. This is especially true for any adaptive approval pathways that support approval of drugs that have been shown to be effective for smaller, more well-defined subpopulations.



## Recommendation 12.1

### Improve Collaboration Between the FDA and CMS on Evidence Generation and Development

The FDA and CMS should collaborate on ways to generate evidence and improve its development for medical products, including the evaluation and transition of pilot collaborations into permanent partnership programs. Such collaboration will foster more efficient and comprehensive evidence development for potentially high-impact, high-cost medical products, in an environment where complex, new therapies are emerging rapidly, the amount of clinical and patient-generated data to support evaluation is increasing significantly, and the expertise in this new emerging area is scarce.

### Collaboration to Support Evidence Generation

The convergence of rapidly emerging new therapies, the vast increase in the amount of data available across multiple settings to support evaluation, the growing focus on value, and the significant labor and costs associated with conducting even a single study, together are paving the way for a new collaborative paradigm for continuous and more comprehensive evidence development. Outdated, bifurcated models, where evidence is developed sequentially and in silos for regulators, payers, and both clinicians and patients to facilitate decision-making, are too expensive and neither effective nor efficient enough to meet the growing needs for timely evidence development. As real-world data and evidence are generated to support a growing number of needs, mechanisms will be needed for increasing the efficiency of data collection and development of evidence that are fit for a variety of purposes.

A new paradigm built around continuous and more timely evidence development will require greater collaboration among public and private sector payers, manufacturers, regulators, providers, and patients, to generate and facilitate the use of evidence needed to simultaneously inform regulatory evaluation, new value-based models of payment, and potentially other purposes.

There have been several collaborative efforts focused on different types of evidence development which offer key lessons and a number of resources and tools that can be leveraged to support broader adoption of collaborative models of evidence generation for both regulatory evaluation and payment. They include Observational Health Data Sciences and Informatics,<sup>266</sup> the Patient-Centered Outcomes Research Institute's PCORnet,<sup>267</sup> the People-Centered Research Foundation,<sup>268</sup> NEST, the Learning Health Community,<sup>269</sup> and the Sentinel System.<sup>270</sup>

Key principles and attributes for this new model for collaboration on evidence development—drawing on the lessons learned from existing efforts—include the following:

- **Patient-Centered.** Collaborative models should place the patient at the center.
- **Inclusive.** Models for collaboration should be open and inclusive. All organizations and individuals willing to give time, data, or funding, and who agree to abide by common principles, should be able to participate. Governance should include those who benefit from and contribute to evidence development, including representatives of patients, clinicians, hospitals and health systems, payers, industry, academic researchers, health IT and data-analytics companies, and regulators. Conflicts of interest should be made transparent and managed.
- **Distributed.** A distributed model that leverages a multitude of data sources or participants should be utilized. Mechanisms that enable analyses to be conducted locally at the data-source sites, as well as centrally, should be employed, while protecting patient privacy.
- **Common Standards.** Data participants should adopt common standards recognized by the federal government such as the USCDI. Encoding and relationships among concepts should be explicitly and formally specified so that—to the extent possible—queries can be rapidly executed at any time, without modification.
- **Transparency in Methods and Results.** Participants should commit to transparency regarding methods used (including source code), analysis results, and other evidence generated, so that they can be subject to peer review, replicated by others to increase confidence in results, and support learning in the field.
- **Privacy and Security.** Participants should adopt baseline principles and policies associated with privacy and security to build and maintain trust.
- **Sustainability.** Joint funding by the organizations that benefit from its existence, including—but not limited to—payers, manufacturers, researchers, and regulators can help assure sustainability.

Leaders representing public and private sector payers, manufacturers, regulators, providers, and patients should explore and advance models of collaboration to significantly increase and improve the evidence base for both regulatory and value-based payment decision-making for drugs and biologics. Lessons, experiences, tools, and infrastructure of existing efforts should be leveraged, when appropriate. The key principles and attributes described above can serve as a starting point for this effort.

## **Recommendation 12.2**

### **Advance Collaborative Models to Move Beyond Silos of Evidence Development**

Leaders representing payers, manufacturers, regulators, providers, and patients should advance collaboration and collective action on the generation and use of real-world evidence for both regulatory and value-based payment decision-making for drugs and biologics, drawing upon lessons, tools, and infrastructure of existing efforts.





## Conclusion

Real-world evidence generated from the application of appropriate research methods and analysis of data derived from clinical, claims, and patient-facing software and systems can play a significant role in improving and modernizing both the drug evaluation and approval process and new value-based payment arrangements in the United States. Progress has already been made by the FDA in establishing a framework for the use of real-world evidence for regulatory decision-making. Significant progress has also been made by ONC and CMS in advancing interoperability and use of common standards in systems, particularly through the development of recently proposed rules. Recent efforts by HHS to promote regulatory reforms can also play a key role in modernizing evidence development.

Regulatory and payment decision-making will be informed and improved by improving regulatory clarity; increasing support for real-world evidence activities; enabling access to and analysis of data; improving its reliability and relevance; expanding pilot and demonstration projects; clearing regulatory barriers; building capacity within federal agencies; and promoting collaboration among payers, regulators, and other key stakeholders around the generation and use of real-world evidence. These steps will ultimately help to accelerate the availability of safe, effective, and affordable medicines for patients in need.

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