Regulatory acceptable real-world effectiveness endpoints: How clarity can best be achieved in the United States

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REGULATORY ACCEPTABLE REAL-WORLD ENDPOINTS OF TREATMENT EFFECTIVENESS: HOW CLARITY CAN BEST BE ACHIEVED IN THE UNITED STATES

Background: The therapies many patients need do not exist today. Real-world evidence (RWE) can accelerate patient access to treatment. However, lack of clarity on regulatory acceptable real-world effectiveness endpoints can result in delayed or lost new therapy opportunities to bring new treatments to patients.

Research question: How can clarity on regulatory acceptable real-world effectiveness endpoints in the United States best be achieved?

Methods: A qualitative research study was conducted by interviewing expert informants from diverse stakeholder types to explore their perceptions of gaps, solutions, action needed, and determinants for achieving clarity. Themes were derived using an inductive coding approach, followed by an appraisal of the potential macro-level solutions using Bardach's criteria for policy analysis.

Results: Four macro-level solutions were identified: Food and Drug Administration (FDA) Advancing RWE Program, FDA report or dashboard for stakeholders to more easily locate FDA reviews and decisions about RWE, a tool to help stakeholders apply existing related FDA guidance, and FDA guidance on real-world effectiveness endpoints.

Plan for Change: Recommended actions for implementing the four solutions and potential evaluation measures were derived from interview themes and Expert Recommendations for Implementing Change. Of the four solutions, an immediate opportunity that FDA and non-FDA stakeholders could initiate is a tool to help stakeholders apply existing FDA guidance, precedent, and endpoint validation principles from the scientific literature.

Conclusion: Two solutions are already in progress to increase stakeholders experiences with RWE for regulatory decision making (e.g., FDA Advancing RWE Program and FDA report on

RWE submitted for regulatory review). Parallel implementation of other solutions is likely needed (e.g., developing a tool to help stakeholders navigate the existing guidance and precedents on real-world effectiveness endpoints), with regulatory guidance on real-world effectiveness endpoints to follow. Good engagement and transparency across the stakeholder communities are essential to make the most meaningful impact.

Lisa M Hess

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CHAPTER 1. INTRODUCTION

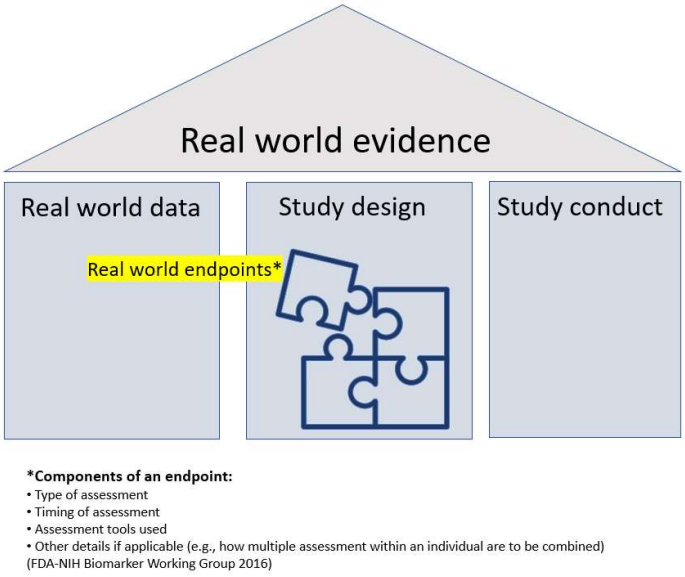
The therapies many patients need do not exist today. Real-world evidence (RWE) can accelerate patients' access to new therapies and is increasingly used to inform decision making among many stakeholders (e.g., regulatory agencies, payers, public health agencies, healthcare providers, etc.). RWE is clinical evidence about the use, benefits, and risks of a medical product derived from real-world data (RWD), such as electronic health records and claims collected in the routine provision of healthcare (FDA 2020a). For example, the United States (US) Food and Drug Administration (FDA) has used RWD to assess safety events in electronic databases (Sentinel n.d.) and to monitor and act on adverse effects of pharmaceutical products (e.g., Clarridge et al. 2021, Sansing-Foster et al. 2021). More recently, RWE has been used both to support approval and, in some cases, to reduce the time to approval of new pharmaceutical therapies by the FDA (Mahendraratnam et al. 2022, Purpura et al. 2022). For example, RWE was used as the primary evidence of effectiveness to accelerate FDA's approval of Zolgensma (onasemnogene abeparvovec-xioi) to treat young children with a specific type of spinal muscular atrophy (SMA); the RWE from natural history data of infants with SMA was used as a control in the single-arm phase 3 study of Zolgensma to demonstrate substantial improvements in survival at 14 months of age and the proportion of subjects able to sit independently for ≥ 30 seconds by 18 months of age (FDA 2019). In another example, the FDA used RWE as the basis of its decision to grant a new drug approval to Prograf (tacrolimus) for the prevention of lung transplant rejection. Prograf had previously been approved for the prophylaxis of organ rejection in patients receiving other types of organ transplants based on evidence from randomized controlled trials. RWE on Prograf use from the United States Scientific Registry of Transplant Recipients was used to demonstrate the dramatic survival improvement in real-world patients receiving Prograf off label (outside the Prograf's FDA-approved uses) for the prevention of lung transplant rejection when compared

with the documented natural history of patients with a transplanted lung and no or minimal immunosuppressive therapy (FDA 2021a).

A foundational building block of RWE is the real-world endpoint, which bridges real-world data (RWD) and study design to generate evidence about the effectiveness and/or safety of therapies (Figure 1). The focus, or scope, of the research question in this dissertation is on real-world endpoints that measure treatment effectiveness. Real-world effectiveness endpoints were chosen as the focus given their growing importance in regulatory decision making and unmet needs for clarity on regulatory acceptability (e.g., lack of specific regulatory guidance or framework). While regulatory agencies like the FDA have used RWE to support safety surveillance efforts for over a decade (Platt et al. 2011), the use of RWE for regulatory decision making on the effectiveness of therapies is emerging (21st Century Cures Act, 2016; Purpura et al. 2022). Regulatory policy on acceptable real-world effectiveness endpoints does not yet exist in the US or globally and represents an important and timely need in global public health (Duke Margolis 2020, Beyrer et al. 2022). Lack of clarity on regulatory acceptable real-world effectiveness endpoints can result in delayed or lost new therapy opportunities to bring new treatments to patients. Greater clarity on regulatory acceptable real-world effectiveness endpoints will help secure and expedite the discovery and development of treatment for patients who need advances in care.

Figure 1

Real-world endpoints bridge real-world data and study design in developing real-world evidence



Note: Adapted from *Framework for FDA's real-world evidence program* (FDA 2018).

1.1. Definition of real-world effectiveness endpoints

An endpoint is "a precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question" (FDA-NIH Biomarker Working Group 2021). Effectiveness endpoints describe whether an intervention (e.g., treatment) results in a positive clinically meaningful effect (i.e., a positive effect on how an individual feels, functions, or survives) (FDA-NIH Biomarker Working Group 2021).

Real-world endpoints are derived from RWD. RWD are "the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources" (FDA 2020a). Those sources include but are not limited to healthcare administrative data (e.g., claims), patient health record data, and disease or medication registries. Health outcomes research translates RWD to RWE about diseases and the therapies used to treat patients. RWE is "the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD" (FDA 2020a). Thus, a real-world effectiveness endpoint is a precisely

defined variable derived from RWD that describes whether an intervention results in a positive clinical outcome. Components of a real-world effectiveness endpoint include the type of assessment (e.g., mean change in HbA1c, overall survival, tumor response), the timing of the assessment (e.g., at 26 weeks, during the line of therapy, etc.), assessment tools used (e.g., these codes or approach on the dataset), and possibly other details such as the analysis approach (e.g., how to combine multiple assessments within an individual, proportion of events exceeding a threshold, etc.) (Figure 2).

Figure 2

Roadmap for selecting a feasible and relevant endpoint as illustrated by an example

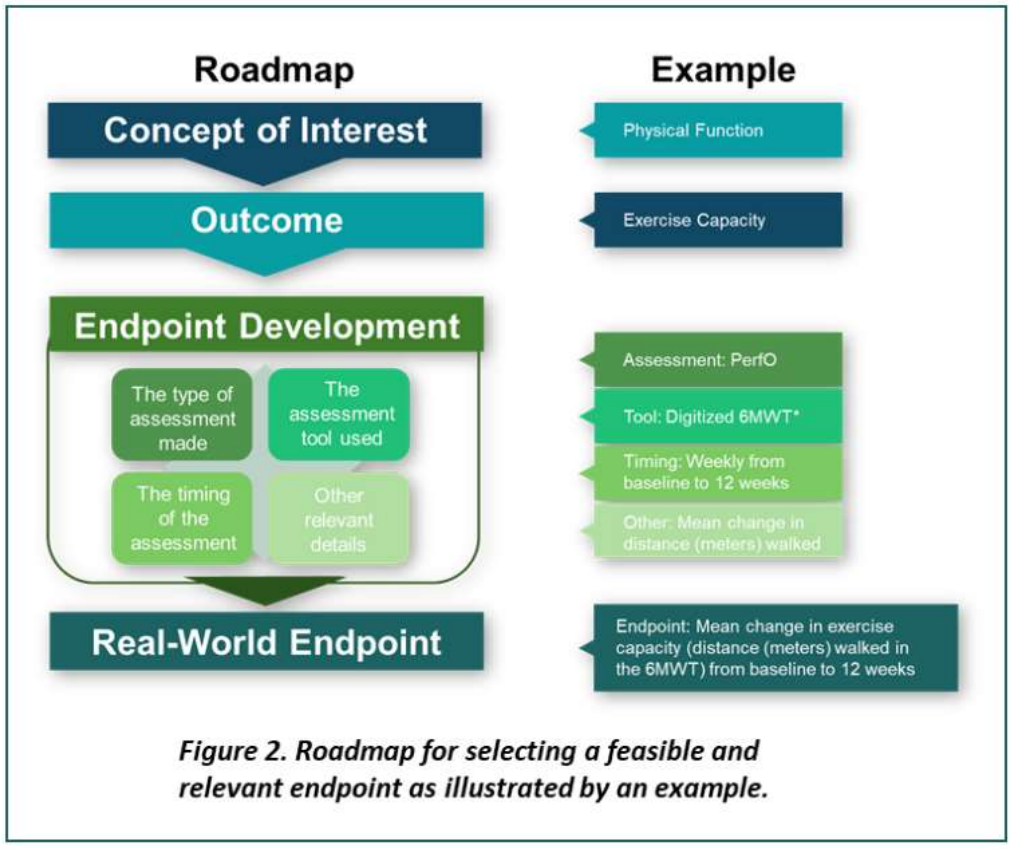


Figure 2. Roadmap for selecting a feasible and relevant endpoint as illustrated by an example.

Note: From *A Roadmap for Developing Study Endpoints in Real-World Settings* by Duke Margolis Center for Health Policy, 2020. Copyright 2020 by the Duke Margolis Center for Health Policy. Reprinted with permission.

Real-world effectiveness endpoints are important because the credibility and value of RWE are either supported or undermined by the endpoints used (Levenson 2020, Beyrer et al. 2022). An endpoint with undesirable properties (e.g, low positive predictive value) may have a detrimental effect on the study (e.g., leading to uninterpretable results or a wrong decision based on faulty evidence). Examples of real-world endpoints that measure treatment effectiveness include, but are not limited to, the following:

- Quarterly changes in HbA1c as measured by lab values in EMR data (Nunes et al. 2017)
- Overall survival or 1-year survival rate as measured by a mortality algorithm applied in claims data (Chamberlain et al. 2021, Shah et al. 2021, Khorana et al. 2021)
- Tumor overall response rate during a line of therapy as measured by clinician assessment recorded in EMR data (Ma et al. 2021, Torres et al. 2022).

By law (Applications for FDA approval to market a new drug, 1985), the substantial evidence used to support claims of effectiveness for new drugs approved by the FDA must contain adequate and well controlled investigations or studies. The endpoints used in these studies must meet the following characteristics:

- Adequate measures are taken to minimize bias
- The methods of assessment of subjects' response are well-defined and reliable
- Analysis of the results of the study adequate to assess the effects of the drug that includes assessing, among other things, the comparability of test and control groups with respect to pertinent variables. (Applications for FDA approval to market a new drug, 1985).

The details on meeting these statutory requirements are better defined for clinical trial endpoints, while defining regulatory acceptable real-world endpoints is relatively new territory.

1.2. The public health impact of achieving clarity on regulatory acceptable real-world effectiveness endpoints

As RWE is increasingly used to support regulatory decision making, a lack of clarity on regulatory acceptable real-world endpoints poses a growing risk of delaying or losing new therapy opportunities for patients. For example, companies can decide to de-prioritize or discontinue development of a therapy in the absence of regulatory guidance (e.g., if therapy development is considered too risky from a regulatory perspective), or companies may take significantly longer to generate the evidence needed to support a regulatory decision and thereby delay important therapy to patients (Silverman 2011, Forum on Neuroscience and Nervous System Disorders 2014, Sutter 2015, Kawai et al. 2018, Richardson et al. 2018, Weidman & Belsky 2020, Sharma 2021a). Ambiguity on acceptable real-world effectiveness endpoints also poses a challenge to the FDA and other regulators when reviewing novel real-world endpoints for the purpose of informing their decisions, such as whether to approve a new therapy or changes in the use of one that is already approved. As regulators make these decisions, they consider other treatments for the same disease ("indication") and their effectiveness. They may reflect on the evidence for each of these treatments to understand or determine the meaningfulness of the clinical evidence for the new therapy they are being asked to approve. For example, regulators may review the evidence from another medication with the same mechanism of action for treating the same disease to understand whether the treatment effect for the new therapy is consistent and predictable (FDA 2023a) This assessment will be difficult if the endpoints that measure treatment effectiveness are different across the studies or when no commonly accepted standard endpoint exists (Duke Margolis 2020).

A recent example illustrates the regulatory risks with respect to real-world effectiveness endpoints. A drug manufacturer sought FDA's approval for its cancer therapy, tafasitamab-cxix in relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The FDA stated that the company had not appropriately validated the real-world response endpoint. The real-world

endpoint (overall response rate within 6 months of first documented treatment) included tumor scan data collected from available patient medical records. The tumor scan data were collected for patients not on the new experimental therapy (patients who had received other available systemic cancer therapies as part of routine care) to build an external control arm for the single-arm clinical study of the experimental therapy. The FDA stated that an inadequate validation approach for the real-world endpoint was a key reason for determining that the provided RWE was not relevant for its decision making on the new cancer therapy. Interrater agreement was used as the validation approach to evaluate agreement between an independent review committee assessment of the patient charts and investigator-assessed response; however, the FDA requested an evaluation of concordance of the response endpoint between the real-world control arm and the trial to evaluate the impact of differences in data elicitation between clinical trials and clinical practice (i.e., estimate differences in outcome ascertainment between the clinical trial data and real-world data) (FDA 2020b, FDA 2020c). A concordance analysis could have provided evidentiary support for the comparability of test and control groups on the real-world response endpoint but was not included in the FDA submission. This is not the only recent example in which FDA reviewers deemed the real-world endpoint validation to be inadequate (Sutter 2020, Purpura et al. 2022).

1.3. Current gaps in clarity on regulatory acceptable real-world effectiveness endpoints

Gaps in clarity on regulatory acceptable real-world effectiveness endpoints were identified in a prior targeted literature review on RWE algorithms (Beyrer et al. 2022). The literature review synthesized the published guidance and perspectives from key decision makers, including regulatory and payer organizations: US FDA, European Medicines Agency (EMA), International Conference on Harmonisation (ICH), National Quality Forum (NQF), National Committee for Quality Assurance, Agency for Healthcare Research and Quality (AHRQ), and Patient-Centered Outcomes Research Institute (PCORI). Key themes and sub-themes of the

recommendations were abstracted. The gaps, or areas of ambiguity with respect to regulatory acceptable real-world effectiveness endpoints, were as follows:

a. *Acceptable approaches to validating real-world effectiveness endpoints for different contexts of use.* The type of validation or evidence necessary for evaluating an endpoint's suitability for a particular context of use may not be obvious today, as there are examples of different expert interpretations about the relevant validation approach for different contexts of use, including real-world external control arm scenarios (FDA 2020b, FDA 2020c).

b. *The level of evidence (i.e., the quantitative or qualitative evidentiary support) needed to demonstrate the validity, or fit for purpose, of the real-world effectiveness endpoint for different contexts of use.* The recent FDA draft guidance on real-world data for assessing electronic health records and medical claims data to support regulatory decision-making for drug and biological products (FDA 2021b) mentions these concepts; however, it does not describe the level of certainty needed for the various contexts of use nor does it provide criteria for evaluating whether the validation evidence is sufficient to meet the level of certainty needed. A framework that addresses both quantitative and qualitative aspects is needed.

c. *The evidence needed to demonstrate an acceptable level of transportability of the real-world endpoint across different RWD sources.* It is not always possible to validate real-world endpoints in the same data source in which they will be applied. In those situations, other RWD sources are sometimes used to conduct the endpoint validation study. Factors such as the type of RWD source, country or region, the type of healthcare system in which the RWD were generated, and more may affect whether the endpoint is transportable (i.e., able to be adopted or adapted in a different RWD source). The validation data source (in which the real-world endpoint was validated) and the target data source (in which the real-world endpoint will be used) should be assessed but the

level of evidence needed to demonstrate an acceptable level of transportability could be clarified.

d. The role patient relevance or patient centricity should play, if any, in contributing to the evidence.

e. The role should health equity play, if any, in contributing to the evidence.

In summary, the literature review identified important areas of ambiguity on acceptable real-world endpoints that need to be addressed. Additional research on stakeholder perspectives may provide new or deeper insights on needs for achieving greater clarity on regulatory acceptable real-world endpoints.

1.4. Implementation needs for clarity on regulatory acceptable real-world endpoints

Establishing a suitable implementation strategy is important to achieve regulatory clarity on real-world endpoints. Specifically, there is a need to identify the actions that will achieve clarity on regulatory acceptable real-world effectiveness endpoints. Solutions to address these real-world endpoint needs should be developed and implemented in collaboration with stakeholders.

1.5. Urgency to identify and implement solutions now

RWE can accelerate the development and delivery of new therapies to patients and is increasingly used to inform decision making by the US Food and Drug Administration (FDA) primarily due to important policy efforts to promote the use of RWE in regulatory decision making (21st Century Cures Act, 2016; FDA Reauthorization Act, 2017). These policies created meaningful impacts for expanding the use of RWE to expand patient access to new therapies to treat cancers and other serious health needs. For example, in the last 2.5 years, 65% of FDA-approved drugs had applications that included RWE on therapy effectiveness (Purpura et al. 2022).

The need for clarity on regulatory acceptable real-world effectiveness endpoints is timely. Some traditional clinical trials may be unethical or infeasible to conduct, such as trials in rare disease populations or research on the long-term effectiveness of a quickly growing number of novel cell and gene therapies. At the same time, the availability of RWD to answer many of these questions is also growing, which can accelerate the development of and expand patients' access to new treatments.

The need for regulatory clarity on acceptable real-world endpoints also has timely relevance outside the US. Regulators worldwide are currently addressing related issues. For example, in 2020, the Japan Pharmaceuticals and Medical Devices Agency (PMDA) issued new guidance on validating RWE algorithms for the purpose of safety studies (PMDA 2020). More recently, the major international regulatory policy organization (the International Conference on Harmonisation [ICH]) announced its intent to begin developing guidance on planning and designing pharmacoepidemiological studies that utilize real-world data for safety assessment of a medicine (Sharma 2021b). It can be expected that real-world endpoints will be addressed in some way in the international (ICH) guidance in the future.

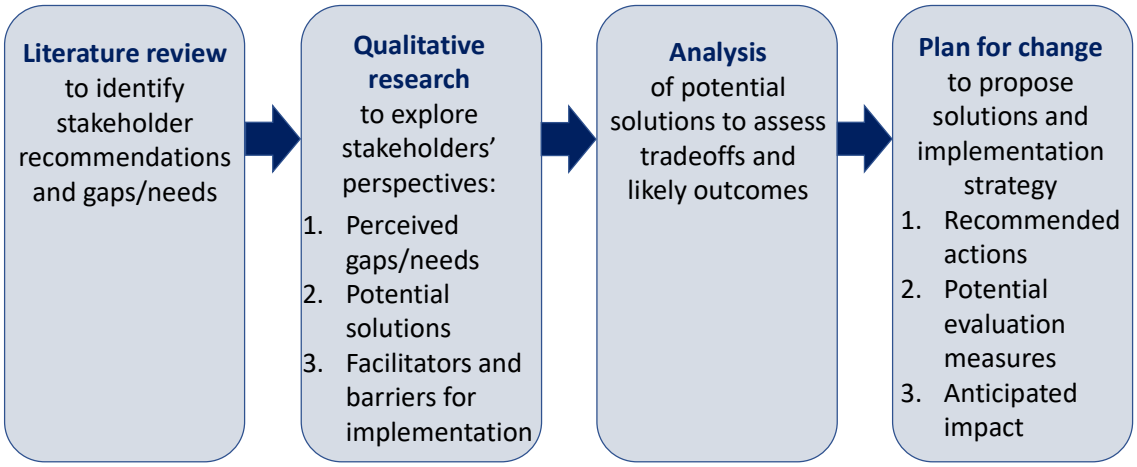
1.6. Purpose and scope of the research

In summary, there is awareness of the importance and timeliness of RWE for informing the development and regulation of medicines for many stakeholders. However, how best to achieve regulatory clarity on acceptable real-world endpoints, which could include specific policies that need to be advanced and the mechanisms to advance them, has not yet been formulated and conveyed. The purpose of this research is to answer the question of how best to achieve clarity on regulatory acceptable real-world effectiveness endpoints in the US. The US was chosen as a single country to help narrow the answer to a feasible scope for the dissertation. While the need is global, different countries have different regulatory environments that will influence these answers. In some cases, answers relevant in country may be adopted or adapted more globally. Therefore, this question will be addressed by exploring stakeholders' perceptions of gaps,

potential solutions and implementation, and determinants (i.e., enablers and barriers) for achieving regulatory clarity in the US. Answers to questions about gaps, potential solutions, and implementation needs will inform the optimal solutions for achieving regulatory clarity on real-world endpoints in the US, as shown in the process map in Figure 3.

Figure 3

Roadmap for developing the plan for change



CHAPTER 2. CONCEPTUAL FRAMEWORKS

The stakeholders' perspectives, coupled with conceptual frameworks for RWE and implementation, will be used to develop a plan for change that recommends solutions and actions for achieving clarity. Two types of conceptual frameworks are applied in this dissertation:

1. Content framework (what should be addressed in future RWE solutions), and
2. Implementation framework (how best to implement solutions).

2.1. Content framework

The content of any proposed regulatory activities related to RWE in the US should adhere to the FDA RWE framework (FDA 2018) and consider other related published FDA guidance. The conceptual model describes assessing the fitness of RWD for use in regulatory decisions. In the FDA RWE framework, both data relevancy and reliability need to be assessed before concluding whether a real-world effectiveness endpoint is fit for purpose (i.e., the level of validation is sufficient to support its context of use; FDA-NIH Biomarker Working Group 2021). Relevancy addresses whether the needed data are present for the research question; reliability addresses data accrual and data quality control (data assurance), including whether the codes (or data variables) and other components of the real-world endpoint adequately represent the underlying medical concepts they are intended to represent (FDA 2018). This framework is important in building content of any future solution for achieving clarity on regulatory acceptable real-world effectiveness endpoints because it is the underlying conceptual model for FDA to develop guidance on RWE topics.

2.2. Implementation framework

While there are many relevant implementation frameworks that could be applied, the plan for change used the Expert Recommendations for Implementing Change (ERIC) (Powell et al. 2015). ERIC is a list of implementation approaches compiled from implementation experts, using a modified Delphi process to generate consensus on implementation strategies and their

definitions (Powell et al. 2015). ERIC was developed in the context of health services research for implementing evidence-based healthcare interventions, but the strategies defined by ERIC are relevant in the context of regulatory science as well. ERIC strategies are reviewed against the themes derived from informant interviews to develop recommendations for specific implementation actions in the plan for change.

CHAPTER 3. METHODS

A qualitative research study was conducted. The following subsections describe the research question and methods for the study.

3.1. Research question

The research question is how can clarity on regulatory acceptable real-world effectiveness endpoints in the United States best be achieved? The qualitative research addressed this question by providing the inputs for building a plan for change that stakeholders could act on to achieve greater clarity on regulatory acceptable real-world effectiveness endpoints.

3.2. Participant eligibility

Experts likely to be knowledgeable about the research topic were eligible to participate in interviews. These could be experts in RWE, RWE algorithm or endpoint validation, related regulatory policy, and/or clinical measurement science (e.g., clinical outcome assessment). Efforts were made to identify diverse the stakeholder types recruited (Figure 4), particularly to ensure views from FDA or former FDA representatives. Expertise was judged by the author, the committee members, the author's professional colleagues, and/or the research participants (referred to as expert "informants" in the dissertation) in some cases.

Figure 4

Stakeholder wheel for identifying informants

3.3. Institutional review board review and consent to be interviewed

The dissertation proposal was submitted to the Indiana University (IU) institutional review board (IRB). The proposal received an exemption determination from the IRB. Informants received a study information sheet (Appendix 3) prior to being interviewed and were asked at the beginning of each interview for consent to be interviewed.

3.4. Identification and recruitment of informants

Informants were identified through the scientific literature and conference presentations (publishing related articles or public presentations) and professional connections, including those of the author, committee members, the author's professional colleagues, and other informants (a snowball sampling technique). The recruitment procedures for the study are described in Appendix 4. Participants were recruited through email or LinkedIn messages after IRB review and exemption. Appendix 5 describes confidentiality and privacy procedures for the study.

3.5. Methods for interviewing and recording

Interviews took place between February and April 2023 with representatives of all stakeholder types and a goal of no less than 15 interviews unless saturation achieved earlier. Interviews lasted approximately one hour and were conducted using the author's IU Zoom account. With the verbal consent of informants, interviews were recorded for all but one interview. For the first interview, Zoom did not permit recording (user technical error), and informant responses were handwritten and typed. Interview scripts were transcribed and stored on a secure server in the IU cloud (OneDrive). Interview transcripts were anonymized by removing the informant's name and genericizing the informants' titles/position (i.e., replacing a specific title with a more generic description such as "research director" or "executive"). Additionally, the names of the informant's current workplace and prior workplace history were genericized. Throughout this document, quotes are attributed to individuals in an anonymized manner. However, it was not possible to genericize the name of the regulator stakeholder type, as FDA is the sole regulator for medical products in the US. Additionally, the majority of informants who shared FDA related perspectives are former (not current) FDA employees and noted as such.

3.6. Data collection

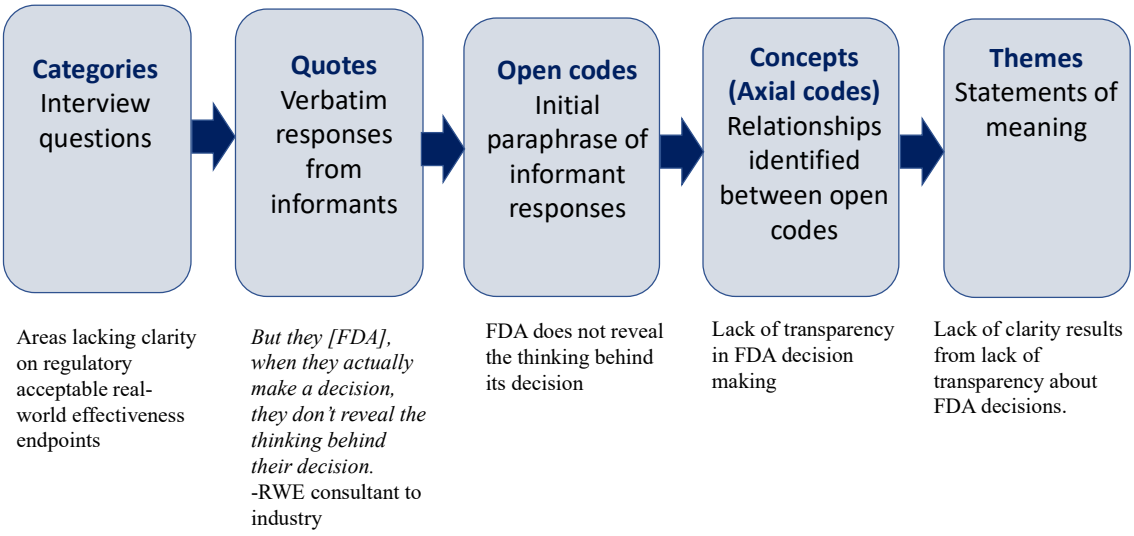
Data collection focused on obtaining perspectives from diverse types of stakeholders. The main interview questions, or topics, included informants' perceived gaps in clarity on regulatory acceptable real-world effectiveness endpoints and potential solutions. Informants were also asked to suggest actions and stakeholders to engage and to describe implementation determinants (i.e., enablers and barriers for implementing proposed solutions). For informants who were not experts in RWE or real-world effectiveness endpoints but had expertise in analogous areas (e.g., clinical outcome assessments), the interview questions focused on how regulatory or stakeholder clarity has been achieved in those areas and the lessons learned. A semi-structured interview guide (Appendix 1 and Appendix 2) was used to conduct online interviews.

3.7. Analysis plan

The analysis was primarily qualitative in nature. For qualitative data, key themes were derived from stakeholder interviews and/or public commentary using the thematic analysis methods of Braun and Clarke (2006). Because the purpose of the qualitative research was to glean new perspectives and ideas from key informants, an inductive coding process was used. The coding process begins with the interview questions, which are the pre-defined "categories" for creating codes and themes. A simple example is described here and illustrated in Figure 5. The example category (interview question) is "Areas lacking clarity on regulatory acceptable real-world effectiveness endpoints." For each category, quotes from interviews are reviewed to create the initial codes, or "open" codes (Williams and Moser 2019). Open code are paraphrased ideas or comments expressed by the informants, using as much of the informants' own language as possible ('in vivo' coding). Qualitative data analysis software (NVivo version 14) was used for open coding. In this example, the open code is "FDA does not reveal the thinking behind its decision." Open codes were then reviewed to derive concepts, or "axial" codes (Williams and Moser 2019). Concepts describe relationships between the open codes (e.g., these open codes are all about "lack of transparency in FDA decision making"). From these concepts, themes (statements of meaning) were derived. The theme derived in this example was "Lack of clarity results from lack of transparency about FDA decisions."

Figure 5

Approach to inductive coding of interviews



Coding of the interview data was done solely by the author. Rigor and trustworthiness of the qualitative research was established using the following strategies: reflexive memos, member checking in cases where the interview transcript seemed unclear, negative case analysis, peer examination by the committee members, and maintaining an audit trail (Anney 2014).

Quantitative data (e.g., participant characteristics or questions that assigned a rating or 'yes/no' response) were analyzed using Microsoft Excel and reported with descriptive summary statistics (counts and percentages for categorical data).

The solutions proposed by informants were analyzed using Bardach's criteria for policy analysis (Bardach 2009). Bardach's criteria were used to assess the tradeoffs and likely outcomes of the potential solutions proposed by informants to identify which solutions would be relevant to include in a plan for change:

- How feasible is the solution (e.g., in terms of complexity, constraints, and costs)?
- What is the desirability and acceptability from the perspective of different stakeholders (e.g., Who incurs the costs? How cost-effective is the solution?)?

- What are precedents, if any?
- What are considerations with respect to timing?
- What compromises are needed?
- What uncertainties exist?
- What is the likely outcome?

After analyzing the potential solutions using Bardach's criteria, those solutions considered relevant to implement were added to the plan for change. The plan for change describes the solutions (i.e., the technical/scientific content) informed by the literature review (Beyrer et al. 2023) and interviews. For each solution, the plan for change recommends implementation actions, which were also derived from insights from the research. Implementation actions were reviewed against the ERIC implementation strategies to ensure that as many as possible potentially relevant implementation strategies were considered and included. Thus, recommended actions are derived from multiple sources (literature review, qualitative research, and ERIC strategies). Finally, potential evaluation measures were proposed for each solution for the purpose of evaluating both implementation outcomes and the final outcome (i.e., whether the solution created clarity on regulatory acceptable real-world effectiveness endpoints).

CHAPTER 4. RESULTS

The following subsections describe results of the qualitative research.

4.1. Informant recruitment

The informant recruitment strategy is described in Section 3.4. In some cases, a professional colleague or committee member emailed the potential informant directly to inquire about his or her interest in being interviewed on this topic. Most of the potential informants who were contacted (19 of 21) agreed to be interviewed (Table 2). The majority (14 of 19, 74%) were identified by the author or committee, while three (16%) were identified by professional colleagues and two (11%) by other informants. All informants were located in the United States. The study information sheet (Appendix 3) was emailed to all informants.

Table 1

Informant recruitment

Current stakeholder type[a]	**Invited N(%)**	**Interviewed N(%)**
TOTAL	21(100)	19[b](100)
Drug and device manufacturers	8(38)	7(37)
Real-world data and analytics companies	5(24)	4(21)
Experts in analogous fields (e.g., endpoints from clinical outcome assessments or digital healthcare)	2(10)	2(11)
Academic organization, hospital or healthcare organization	2 (10)	2(11)
Patients (e.g., advocacy)	2(10)	2(11)
FDA	1(5)	1(5)
US government policy and industry legal counsel	1(5)	1(5)

Note. FDA = Food and Drug Administration, N = number of informants

[a] Current stakeholder type represents employment at the time of interview.

[b] Two informants who accepted the invitation were unable to be interviewed, initially due to scheduling conflicts and later not responsive to further contact. One informant (a digital healthcare expert) delegated the interview to someone else in the company with RWE regulatory policy expertise.

4.2. Informant characteristics

Informants represented diverse current and former stakeholder perspectives, with deep expertise in RWE, RWE algorithm or endpoint validation, RWE policy, and membership in many different related scientific and professional societies (Table 3). Additional areas of related expertise described by informants included the following: clinical outcome assessment (COA), digital healthcare devices and measurement, diagnostic tests, safety real-world endpoints, regulatory innovation, patient registries, and patient-centric study design.

Table 2

Description of informant characteristics

Characteristics	**N (%)**
Number of informants	19(100)
Current and former stakeholder types represented[a]	
Drug and device manufacturers	9(47)
FDA	7(36)
Academic organization	5(26)
Real-world data and analytics companies	5(26)
Hospital or healthcare organization	4(21)
Experts in analogous fields	3(16)
Payer organization	2(11)
Government funded scientific research organization	2(11)
Policy organization	2(11)

US government policy and industry legal counsel	1(5)
Job description[a]	
Managerial	11(58)
Consultant	6(32)
Research	5(26)
Strategy or policy leader	4(21)
Project manager	1(5)
Sex[b]	
Female	9(47)
Male	10(53)
Years working in this field	
1-5	2(11)
6-10	4(21)
11-15	3(16)
16-20	1(5)
21-25	3(16)
>25	6(32)
Experience with RWE (low, medium, medium-high, or high)	
Low	0
Medium	1(5)
Medium-high[c]	2(11)
High	16(84)
Experience with real-world endpoint validation or RWE algorithm validation (low, medium, medium-high, or high)	
Low	4(21)

Medium[d]	5(26)
Medium-high[c]	1(5)
High[e]	9(47)
Experience with policy (e.g., FDA policy) related to RWE (low, medium, medium-high, or high)	
Low	1(5)
Medium	3(16)
Medium-high[c]	4(21)
High[f]	11(58)
Professional organizations or affiliations you belong to related to this topic (RWE, real-world endpoints, policy, etc.)[a,g]	
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	7(37)
International Society for Pharmacoepidemiology (ISPE)	5(26)
American Society of Clinical Oncology (ASCO)	4(21)
Drug Information Association (DIA)	4(21)
Duke Margolis	4(21)
American Medical Informatics Association (AMIA)	2(11)
International Association for the Study of Lung Cancer (IASLC)	2(11)
International Society for Quality of Life Research (ISOQOL)	2(11)

Note. FDA = Food and Drug Administration, N = number of informants, RWE = real-world evidence

[a] Percentages are derived by dividing the category (numerator) by the total number of informants (denominator); they do not sum since each informant can contribute to (may represent) multiple categories.

[b] Sex was not self-reported by informants.

[c] Response options presented to informants were low, medium, or high, but some informants requested that their expertise be considered 'medium-high.'

[d] One informant was asked but did not give a self-report, so medium was assigned based on informant's statements about validating other types of endpoints but not real-world endpoints.

[e] One informant stated 'high' in the context of COA (clinical outcome assessments)

[f] One informant stated 'high' in the context of COA (clinical outcome assessments), and one informant was not asked this question but 'high' was assigned since the informant's career is dedicated to RWE policy and has been influencing RWE policy for more than a decade.

[g] Informants reported professional affiliations (not employment) when responding to this question. Additional professional affiliations reported by a single informant were as follows: Academy of Managed Care Pharmacy (AMCP), American Association for Cancer Research (AACR), American Medical Association (AMA), American Public Health Association (APHA), APASL-ACLF Research Consortium (AARC), Biotechnology Innovation Organization (BIO), California Life Sciences, Critical Path Institute PRO Consortium, Digital Medicine Society (DiME), European Federation of Pharmaceutical Industries (EFPIA), Evidence Mobilization Action Collaborative, FDA Sentinel, Food and Drug Law Institute (FDLI), Friends of Cancer Research, Health Technology Assessment International, National Academy of Medicine, None, Patient-centered Outcomes Research Institute (PCORI), Pharmaceutical Research and Manufacturers of America (PhRMA), Reagan-Udall Foundation for the FDA, Real-world Evidence (RWE) Alliance, Society for Epidemiologic Research (SER), Society for Medical Decision Making (formerly), and Transcelerate.

4.3. Informants' perspectives about the meaning of clarity on regulatory acceptability

In the first interview question, informants were asked what clarity on regulatory acceptability means to them. These themes were identified:

- Clarity means written expectations.
- Clarity is knowledge about expectations and evidence.
- Clarity is a feeling of confidence or certainty.

4.3.1. Clarity means written expectations

Informants described clarity as written expectations and gave examples of frameworks, case studies, and guidance. Frameworks include a written roadmap for evidence generation,

presentation, and assessment. Guidance encompasses a description of the studies and level of evidence needed to demonstrate that an endpoint can be used to make a decision. Case studies refers to the accumulation of examples, or precedents, that describe FDA actions (e.g., approval or rejection of RWD/RWE in a new drug application).

4.3.2. Clarity is knowledge about expectations and evidence

Informants described clarity as knowledge of FDA's expectations as to what it will or will not accept as well as knowledge of the underlying RWD. Knowledge of FDA expectations includes knowing how to operationalize those expectations and knowing where FDA is flexible (e.g., working with data that are less than ideal). Informants expressed timing as a consideration, as a desire to know FDA's expectations prior to submitting the evidence for FDA's review. Informants described knowledge of the RWD as important for clarity on regulatory acceptability, including data provenance (i.e., the origins and handling of data), variable definitions, and the methods for translating data into RWE.

4.3.3. Clarity is a feeling of confidence or certainty

Informants described clarity as confidence or certainty that regulators would use the RWE to inform their decision:

> I would say having enough confidence for the FDA or other global regulators to utilize this type of information, to inform decisions in front of them…. I don't think it needs to replace or be the sole source of information but that they have confidence that it is adding value and providing useful information to inform their decisions. (Patient advocacy organization executive leader)

Another term used was "predictability." Similarly, some informants expressed the subjective (or sometimes impossible) nature of clarity because the full rationale behind the FDA's decision may not be known. These desires for certainty were acknowledged by other informants who expressed their views that clarity is not "like a cookbook" (i.e., a uniform prescription that

will work in all circumstances and across FDA divisions) because acceptability is dependent upon context, including context of the evidence, the decision, and the sociology of organizations (e.g., different expectations across FDA review divisions):

> I think that the asks around clarity and certainty are inconsistent with the reality of human beings and sociology, even within an organization. (Real-world data and analytics company executive and former FDA representative)

In summary, the informants' views about clarity on regulatory acceptability can be thought of as having both aspects of objectivity (e.g., written expectations) and subjectivity (e.g., feelings of certainty). Themes are related in some cases. For example, having written expectations may ultimately contribute to knowledge about expectations and a feeling of confidence or certainty. However, if written expectations do not result in knowledge of those expectations or feelings of confidence or certainty, then these could be considered unrelated themes.

A full list of informant responses (quotes) for this question (Supplementary Table 1) and other interview questions is presented in Appendix 6.

4.4. Informants' perspectives on whether there is sufficient clarity on regulatory acceptable real-world effectiveness endpoints

When asked whether there is sufficient clarity on regulatory acceptable real-world effectiveness endpoints, the majority of informants (n=13 of 19, 68%) replied no (Table 5). Of remaining informant responses (n=6), one felt there is clarity, three felt there are some areas of clarity as well as lack of clarity, one expressed there are some areas of clarity with respect to clinical outcome assessments (COA) but was unsure about real-world effectiveness endpoints, and one did not know (Table 5). A qualitative assessment of areas of clarity or barriers to clarity as described by informants is described in Sections 4.5 and 4.6, respectively.

4.5. Informants' perspectives on areas of clarity on regulatory acceptable real-world effectiveness endpoints

Informants were asked where they saw clarity today on regulatory acceptable real-world effectiveness endpoints. These themes were identified:

- Clarity is in science.
- Clarity is in FDA communications and interactions.
- Clarity has been created through stakeholder engagement and consensus.

4.5.1. Clarity is in science

Informants described clarity they observe today in scientific frameworks or textbooks. According to one informant, "the principles are pretty universal." Another informant described measurement principles repeated across textbooks on test validity (e.g., a reference standard, inclusion of cases and controls to identify sensitivity in addition to positive predictive value, and a sufficient sample to measure accuracy). One informant who was a drug and device manufacturer research director specializing in clinical outcome assessments (COAs) stated that the measurement principles for COAs have evolved to an emphasis on modern validity theory (an argument-based approach to evaluating fit for purpose in a context of use).

4.5.2. Clarity is in FDA communications and interactions

Informants described finding clarity in FDA communications and interactions. These include publications, with one informant suggesting that the FDA Oncology Center of Excellence (OCE) has published articles on real-world effectiveness endpoints and another pointing to presentations and public comments from FDA representatives about preferable endpoints. Proprietary FDA-sponsor interactions are another mechanism for obtaining clarity today. Laws, such as amendments in 1962 to the Food Drug and Cosmetic Act to require substantial evidence of effectiveness, in addition to safety, are another mechanism that historically gave clarity. However, one informant described related FDA policies as leading to "codified habit" or an

expectation of two randomized controlled trials for demonstrating efficacy of medical products. FDA guidance documents, which are often written in response to the enactment of new laws, were cited as another way to get clarity on regulatory acceptable real-world effectiveness endpoints. Four FDA draft guidance documents were cited by one informant (a former FDA representative):

1. Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products (FDA 2021b)
2. Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry (FDA 2021c)
3. Data Standards for Drug and Biological Product Submissions Containing Real-World Data (FDA 2021d)
4. Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (FDA 2021e)

However, other informants suggested clarity comes from other FDA guidance documents on surrogate or biomarker endpoints and safety real-world endpoints as well as in therapeutic area guidance documents. Looking to regulatory or legal precedent (i.e., past examples) was also cited as a way for stakeholders to find clarity today. Regulatory precedent and FDA communications suggested to some informants that certain real-world endpoints (i.e., perceived objective measures that are easy to obtain from real-world data sources) are more likely to be regulatory acceptable today.

4.5.3. Clarity has been created through stakeholder engagement and consensus

Informants saw areas of clarity on regulatory acceptable real-world effectiveness endpoints in scientific community engagement and consensus on the high-level principles for appraising real-world data, as reflected in pilot projects, largely between the academic community and FDA (e.g., Project DUPLICATE, Wang et al. 2023) or in related tools such as the Transcelerate real-world data audit readiness considerations document (Transcelerate 2022) and frameworks developed by

the HMA (Heads of Medicines Agencies) and EMA (European Medicines Agency) Big Data Steering Group (HMA EMA 2022). An expert in COA shared that the COA scientific community's strong engagement in developing the latest FDA draft guidance on COA and patient-focused drug development has helped to create predictability for the stakeholder community:

> You can't write a guidance specific enough to be across the board. So, the longer we've worked within- because even though it's [patient-focused drug development guidance] a draft guidance, we've been along for the ride, and so it's not really a surprise. (Drug and device manufacturer research director specializing in clinical outcome assessments)

A full listing of informant responses is available in Supplementary Table 2.

4.6. Informants' perspectives on areas lacking clarity on regulatory acceptable real-world effectiveness endpoints

Informants were asked what areas are lacking clarity today on regulatory acceptable real-world effectiveness endpoints. These themes were identified:

- Lack of clarity results from lack of transparency about FDA decisions.
- Lack of FDA education and consistency on RWD/RWE leads to lack of clarity.
- Lack of stakeholder experience submitting RWE for demonstrating treatment effectiveness leads to lack of clarity.
- Lack of written clarity from FDA leads to clack of clarity for stakeholders.
- Complexity of validating real-world effectiveness endpoints contributes to lack of clarity.

4.6.1. Lack of clarity results from lack of transparency about FDA decisions

The inability to easily find examples from FDA reviews, or precedent, was given as an area where clarity is lacking today on regulatory acceptable real-world effectiveness endpoints. Informants described specific aspects of the current environment that contribute to their inability to easily find the FDA precedent (Supplementary Table 3):

- FDA-sponsor interactions are proprietary, so it is challenging for all stakeholders to be aware of important information they need about the endpoints from those interactions.
- Finding instances where real-world data are reviewed by FDA is challenging.

Even when the examples can be identified (e.g., on FDA' web site), the absence of clear communication about what 'good' looks like and what the deficiencies are was stated as a reason why clarity is lacking. This includes not knowing what good documentation of acceptable endpoints looks like for FDA (i.e., what would the dossier for real-world endpoint validation look like? where would the dossier show up in the submission?). In addition, the absence of FDA-recommended solutions for resolving deficiencies creates gaps in clarity:

> They [FDA] don't say anything other than this is the problem; we're not going to use it. It's not like these variables don't have enough completeness for us to make a valid inference. Maybe you should consider going back and trying to have some follow up with these patients to capture more complete information. Then we would consider using the data. (Real-world data and analytics company director)

Finally, in another example of lack of transparency, one former FDA reviewer expressed frustration that FDA individuals are not named as authors or acknowledged on policies they help to write.

4.6.2. Lack of FDA education and consistency on RWD/RWE leads to lack of clarity

A lack of education and consistency of FDA reviewers was given as another reason for lacking clarity. With some exceptions (e.g., the Oncology Center of Excellence), even reviewers with epidemiology, statistics, or similar background may not be familiar enough with real-world effectiveness endpoints, particularly since methods are novel and evolving as the real-world data and technology continue to evolve. FDA reviewer and division inconsistency (e.g., different interpretation within FDA) combined with a lack of knowledge and skepticism about RWD and RWE were areas that informants felt contributed to lack of clarity. Informants expressed that

some of the perceived inconsistency may be driven by case-by-case differences but could be arbitrary sometimes:

> In fact, you could take an algorithm that FDA has used to make a regulatory decision and use it, and the other people at FDA might say, 'Nah, I don't want to use that one. I don't believe it. I want to use a different one.' So, it's all case specific. (Real-world data and analytics company executive and former FDA scientist)

4.6.3. Lack of stakeholder experience submitting RWE for demonstrating treatment effectiveness leads to lack of clarity

Similarly, some sponsors lack sufficient experience submitting real-world endpoints and real-world data to FDA, particularly for the purpose of demonstrating treatment effectiveness. Lack of experience results in mere "hypothetical ideas" about regulatory acceptability of real-world effectiveness endpoints, according to one informant. Lack of experience (or attempts to submit RWE for demonstrating treatment effectiveness) may be a result of having few prior examples or precedents where FDA has accepted real-world effectiveness endpoints and leads to lack of validation for some endpoints:

> The availability of these kinds of datasets, the availability of complete enough information from real-world settings to start to mimic the clinical trial is a relatively new phenomenon. The development of the appropriate scientific methods to make sense of that is an evolving phenomenon, And the development of meaningful endpoints within that is also a new phenomenon… So, in fact, the reason it feels like we don't have clarity is because we're still knocking those things into place. (Real-world data and analytics company executive and former FDA representative)

4.6.4. Lack of written clarity from FDA leads to clack of clarity for stakeholders

Informants pointed out there is no single FDA guidance that focuses on real-world endpoints. Informants also felt that some of the concepts that are generally relevant to endpoint acceptability

in other guidance documents need to be made more specific to be useful for stakeholders. Informants identified the following as areas relevant to real-world effectiveness endpoints that lack clarity in current guidance:

- The specific issues or challenges with respect to regulatory acceptability and the solutions
- Factors that confer reasonable likelihood of success
- How best to engage early with FDA, and knowing who at FDA reviews real-world endpoint validation
- Approaches to assessing fit for purpose, which includes addressing the following questions raised by informants:
    - What needs to be appraised?
    - How to appraise it?
    - How much of the data does one need to validate?
    - Does the approach need to change for different RWD sources?
    - Can a previously accepted endpoint be re-used and expected to be regulatory acceptable?
    - Is there a list of items that need to be routinely appraised? And if so, how much weight should one put on demonstrating that each item is sufficient or not a threat to validity?
    - How best to apply fit-for-purpose RWD frameworks?
    - What are real-world data curation best practices?
    - Ideal data are often described in guidance, but where are the flexibilities?
    - What are the appropriate methods to deal with missing data?
    - How best to handle measures that are collected at different frequencies in the real world versus in clinical trials?
- Methods to demonstrate validity

    - What does validation mean?
    - What are methods to demonstrate the validity of the endpoint? What are methods when there is no gold standard? How best to demonstrate validity of less objective or well-defined endpoints?
    - What are methods to demonstrate the validity and reliability of treatment effect estimates?
    - What does an unbiased assessment look like to the regulator?
    - How to handle selection bias and confounding by indication?
    - What evidence is needed when this topic intersects other topics like digital health measurement?
- Guidance for specific types of real-world endpoints or situations (e.g., for which therapeutic areas are these relevant and which not?)
- Whether and what individual-level data, if any, should be submitted with the validation evidence.

In summary, these gaps may be inter-related, as lack of experiences or education could lead to lack of written clarity (e.g., guidance documents).

4.6.5. Complexity of validating real-world effectiveness endpoints contributes to lack of clarity

Other reasons for lacking clarity include complexity of validating real-world effectiveness endpoints. Elements of complexity include the fragmented RWD sources, varying performance (e.g., data completeness, patient follow-up, etc.) for a given datapoint across RWD sources, and the diverse approaches that could be used to validate real-world endpoints:

> I hear a lot of questions about the endpoint, particularly in oncology because there's so many ways… to shave it, that you head is spinning. (Real-world data and analytics company executive and former FDA representative)

4.7. Informants' perspectives on the priority of achieving clarity on regulatory acceptable real-world effectiveness endpoints

When asked where this topic (achieving clarity on regulatory acceptable real-world endpoints) ranked in perception of priorities relative to other RWE regulatory related needs, the majority of informants (13 of 19, 68%) rated it as a high priority (Supplementary Table 4). "In the critical path" and "a top 3 priority" were some of informants' expressions about the importance of advancing clarity. For comments where priority was ranked as high by the informant, the following themes were identified:

- Lack of clarity creates drug development obstacles.
- Lack of clarity diminishes opportunities to understand outcomes most important to patients.
- Even the experts are challenged to provide answers.

4.7.1. Lack of clarity creates drug development obstacles

Some informants expressed that lack of clarity creates drug development obstacles on critical study development aspects such as RWE feasibility and calculating statistical power. The lack of clarity today, according to one informant, and hesitation by FDA to a priori define an RWD outcome as acceptable results in "hesitation for the community":

> The topic of regulatory acceptance of real-world endpoints ranks very high. Uncertainty around what a regulator will accept regarding a real-world endpoint creates hesitation for the community. This leads to discussion of what is good enough for endpoint definitions and questions of whether the endpoint has been "validated." Sometimes "validated" means each endpoint was reviewed by a clinician, sometimes it means a validated algorithm was used with a known level of precision. In my experience in safety studies, FDA is hesitant to a priori define a RWD outcome definition as acceptable. (Real-world data and analytics company executive and former FDA scientist)

One informant described the need for sponsors to be able to get clarity about the regulatory pathway to understand regulatory acceptability of a specific endpoint in a specific context. Another informant described the significant global impact, beyond FDA, considering that FDA may be a good place to begin but that stakeholders avoid drug development obstacles (benefit) the most by being able to use a validated endpoint globally ("in a streamlined way"). Other informants described clarity as important to incentivize investment in the use of RWD/RWE for informing regulatory decisions:

> I've been answering a little bit, perhaps cavalierly saying, I don't think there should be progress on clarity for the outcomes, and I am not putting myself in the part in the position of the pharmaceutical company, which, of course, anybody wants clarity before they spend to try to convince somebody on something, as you want to know if that would convince them. So I think there is tremendous value for that. (Real-world data and analytic company executive leader)

4.7.2. Lack of clarity diminishes opportunities to understand outcomes most important to patients

Some informants described the lack of clarity as diminishing opportunities to understand outcomes most important to patients. One informant contrasted a real-world endpoint that measures the number of emergency room (ER) visits per month with a pediatric asthma clinical trial endpoint that measures forced expiratory volume in 1 minute, stating that the real-world endpoint would better represent an outcome that matter more to patients and caregivers (e.g., fewer visits to the ER):

> But if you ask parents, and you ask ER [emergency room] physicians, what really matters, it's like I want to keep my kid out of the emergency room. I would like to go to the emergency room 4 times fewer this month, thank you very much. And if this drug, if you know that this drug changes that, that matters to me as a parent. It matters to me as a

> patient. Not FEV [forced expiratory volume]. I don't care about that. Wouldn't it be great if a new drug approval could have that in the labeling? But you can't get that unless you've done the real-world evidence, and that's truly a real-world evidence study, and it hinges on that effectiveness endpoint, not the randomization question, not the other variables that were in your analysis as control or predictor variables that were measured in the real-world evidence study, not the study design. It's that endpoint is relevant to people, and they want to know about that and that's where FDA- so that's why I think it's the most important. (Drug and device manufacturer research senior executive)

Another informant cited examples in Parkinsons Disease and Duchenne muscular dystrophy as patient-centric outcomes (i.e., those most relevant for patients) that are likely to be derived from imperfect real-world measurements.

4.7.3. Even the experts are challenged to provide answers

Informants expressed that achieving clarity on regulatory acceptable real-world effectiveness endpoints was a high priority because they saw pilot projects and similar efforts by FDA to make progress on this topic and regulatory acceptability of RWE more generally. One informant described having similar struggles getting clarity on regulatory acceptability in an analogous measurement field (digital healthcare measurement) as a reason for rating this topic as important. For example, the issue of how to develop and validate a regulatory acceptable endpoint in the absence of a reference (gold) standard is an unanswered question for both real-world effectiveness endpoints and digital endpoints. Another informant described how even FDA is trying to acquire experience through its Advancing RWE pilot program to provide greater clarity:

> They're [FDA] going to see, and they probably going to update their guidance at some point based upon a few years of this FDA RWE pilot program… this Advancing RWE. I don't know. Maybe that's what's needed, like. Okay, so let's get some experience under our belt, and maybe we can be more definitive in the future. Maybe I should just give

them the benefit of the doubt that that's their plan, but I think this is important to establish clarity. I really do. How does it fit with respect to other things that are going on in this area? I don't know. It seems very important. It almost is in the critical path. (Drug and device manufacturer director)

Of the six informants who did not rate this topic as high priority, three felt the priority for achieving clarity is medium, or in the middle of other regulatory needs. Reasons given were that randomized controlled trials are still the gold standard for FDA decision-making, a perception that RWD often do not capture the relevant effectiveness or patient experience endpoints, that there are competing RWD/RWE needs such as evaluation of RWD fit for purpose and other aspects of RWE study design, and that there are other emerging opportunities for accelerating drug development such as decentralized trials. One informant, a director and research scientist at an academic healthcare organization, said this topic was not important today for the informant's organization, as it does not currently develop real-world evidence for submission and decision-making by FDA. For one informant, this question was missed during the interview and emailed after the interview, with no follow-up response received. For one informant, this question was missed during the interview; unforeseen circumstances prevented further direct follow-up on this question but the informant later (after the interview period) expressed interest in a related project.

4.8. Solutions recommended by informants

When asked for solutions for achieving clarity on regulatory acceptable real-world endpoints, informants proposed many solutions with the following themes:

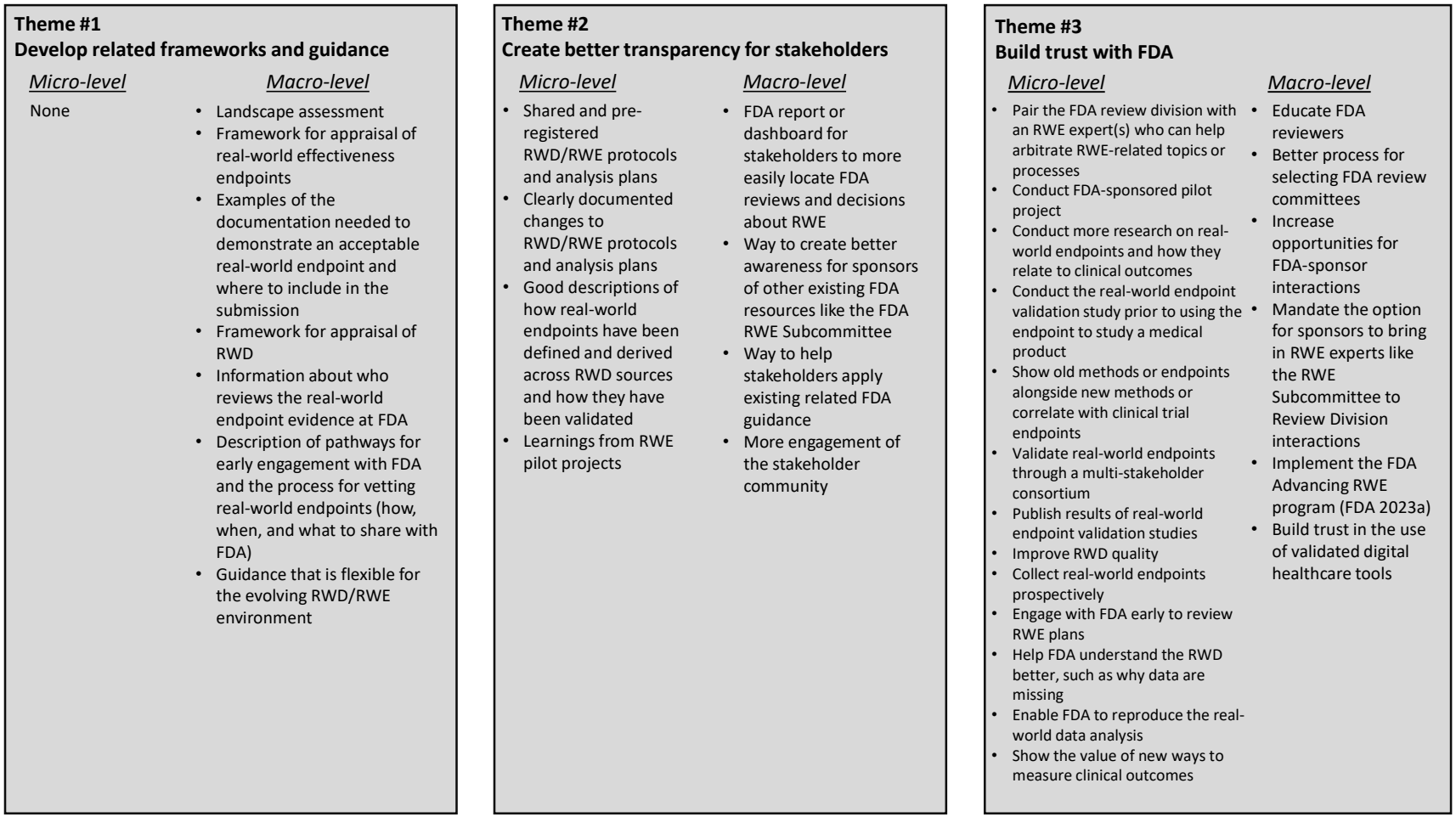
- Develop related frameworks and guidance.
- Create better transparency for stakeholders.
- Build trust with FDA.

Within each of these themes are many individual micro-level and macro-level solutions proposed by informants (Figure 6). Micro-level solutions are those that advance clarity within the context

of a single company's drug development program, and in a specific RWD source, or for a specific real-world effectiveness endpoint. Macro-level solutions are those that impact many stakeholders across the broader RWD/RWE and regulatory environment.

Figure 6

Micro- and macro-level solutions proposed by informants



4.8.1. Develop related frameworks and guidance

Informants proposed a real-world effectiveness endpoint framework and addressing related gaps in regulatory guidance that include the following:

- A landscape assessment to outline the relevant principles
- A framework for appraising real-world effectiveness endpoints that could include the following:
    - the ESTIMAND framework (ICH 2019)
    - a common terminology
    - the contexts of use for real-world endpoints
    - how to appraise or demonstrate fit for purpose
    - which variables need documented evidence of validity and reliability
    - acceptable methods to deal with bias
    - how to appraise chart abstraction when there is no external gold standard
    - how to appraise the combination of machine learning abstraction of data and manual verification
- Information about who reviews the real-world endpoint evidence at FDA
- Examples of the documentation needed to demonstrate an acceptable real-world endpoint in the submission
- Description of the pathways for early engagement with FDA and the process for vetting real-world endpoints (how, when, and what to share with FDA)
- Information about how to denote where RWE is present in the submission
- Flexibility for updates as real-world data and measurement methods evolve

A former FDA reviewer considered the ESTIMAND framework as a useful starting point for a framework on real-world effectiveness endpoints with practical examples that stakeholders who are not strong methodologists could readily understand:

> I think a framework is the way… the ESTIMAND framework sort of came to be during my time at FDA… a lot of people have done a lot of work to make it more accessible to everybody who really felt that this is a way that we should be thinking about endpoints. So, ok, we read the guidance. It's very technical. It's very difficult. But we love what it's trying to ultimately do, so we're going to break it apart and break it down and show examples of how to do it and walk through really practical examples so that someone who isn't a methodologist can follow along too. I think the same thing here would be great. (Patient advocacy research director and former FDA reviewer)

Informants also proposed that a RWD quality framework be developed, with alignment among real-world data providers and other stakeholders, that would include how best to describe real-world data sources and quality. Some informants acknowledged existing frameworks or tools by the HMA (Heads of Medicines Agencies) and EMA (European Medicines Agency) Big Data Steering Group (HMA EMA 2022), ICH (International Conference on Harmonization) real-world data quality reflection paper (ICH 2023), and Transcelerate RWD audit readiness tool (Transcelerate 2022).

4.8.2. Create better transparency for stakeholders

Creating better transparency for stakeholders was proposed in terms of developing a better way for stakeholders to easily locate FDA reviews and decisions about RWE, making sponsors more aware of other existing FDA resources like the FDA RWE Subcommittee, and helping stakeholders apply existing related FDA guidance. To make finding FDA reviews and decisions about RWE easier, informants suggested that FDA should develop a way for stakeholders to easily locate information about FDA reviewers' comments and decisions about RWE submitted by sponsors (e.g., a report or dashboard) and maintain the content. One informant described a new requirement in the Prescription Drug User Fee Act VII (PDUFA VII) for FDA to aggregate the information and publish a report by June 30, 2024:

> They [FDA] are supposed to aggregate information about how many submissions they got containing real-world evidence and then what happened, like how it was used. So, I think that would be helpful. We tried to do it as an industry anonymously, like BIO collected a lot of information, but I think the unvarnished information from the regulator is going to be more useful. (Drug and device manufacturer leader and former FDA representative)

The report or dashboard would ideally provide sufficient details to be meaningfully informative to stakeholders. Sufficient details included which real-world endpoints have been reviewed, whether FDA accepted them and why or why not, and what solutions FDA proposed to the sponsor, if any, to support evaluating or developing a fit for purpose real-world endpoint (e.g., any additional evidence FDA recommended that the sponsor provide):

> …if it [the FDA-issued RWE report required under PDUFA VII] comes out like a checklist where they [FDA] say, 'Yeah, we received 50 applications, and 30 of them were rejected,' and like they stopped there, that won't be that helpful. It will give us ammunition to complain but- or look you really don't want to use real-world evidence, but it won't give anything meaningful. So, I feel like they have to at least give a little bit of insight into decision making. So, maybe all 30 were not useful because 50% of the data was missing. I think they have to tell us why they made the decisions that they made, not just the numbers or information that doesn't provide insights. (Drug and device manufacturer leader and former FDA representative)

Subsequently, stakeholders should review the real-life examples of FDA reviews of RWE and real-world endpoints (i.e., precedents).

Helping stakeholders apply existing FDA guidance was described as a near-term solution, as there are various FDA guidance documents on other types of endpoints and even more guidance documents that speak to considerations for validating RWD and generating RWE:

> You know it does strike me that for whatever reason people don't use the guidance that's available that they could extrapolate or make a bridge from, and so maybe if we could continue to make those links for people and show them how existing guidance applies or existing approaches apply, I think that would go a long way. I've never totally understood why people don't view it that way, and you know I'll tell you we've had meetings with FDA recently where we've asked for regulatory certainty or clarity or more guidance on certain topics, and they'll tell us this is best practices for research 101. So that doesn't put researchers in a good light if we're not understanding that there are best practices for research that apply to any clinical data that you're going to use, not just RCT data. So maybe it would be helpful to continue to get some like level setting on the expectation for best practices, for research, transparency, developing protocols, reporting. Maybe that is the best way to get value if people are trying to validate or justify real-world endpoints. To the extent that we can leverage what we already know for other types of outcome assessments, I think that would be really helpful. (Drug and device manufacturer leader and former FDA representative)

Additional areas where informants felt that FDA or other stakeholders could create clarity through greater transparency are the following:

- More engagement of the stakeholder community
- Shared and pre-registered RWD/RWE protocols and analysis plans
- Clearly documented changes to RWD/RWE protocols and analysis plans
- Good descriptions of how real-world endpoints have been defined and derived across RWD sources and how they have been validated
- Learnings from RWE pilot projects

4.8.3. Build trust with FDA

Informants expressed the importance of building trust with FDA, including their confidence in RWE generally, to obtain clarity on acceptable real-world effectiveness endpoints. Specific solutions described by informants to help build trust with FDA were the following:

- Educate FDA reviewers by increasing reviewers' experiences with RWE and having FDA's RWE experts peer review sponsor submissions and coach other division reviewers (a "see one, do one" model).
- Pair FDA review divisions with RWE experts, such as individuals in the FDA Office of Medical Policy, who can help arbitrate RWE-related topics or processes.
- Design a better process for selecting FDA review committees.
- Conduct FDA-sponsored pilot projects (e.g., methods to address bias).
- Conduct more research on real-world endpoints and how they relate to clinical outcomes.
- Conduct pilot projects as concrete experiments versus hypotheticals.
- Conduct the real-world endpoint validation study prior to using the endpoint to study a medical product.
- Show old methods or endpoints alongside new methods or correlate with clinical trial endpoints.
- Validate real-world endpoints through a multi-stakeholder consortium.
- Publish results of real-world endpoint validation studies.
- Improve RWD quality (e.g., by implementing a learning healthcare system in the US and at the point of care through minimum core data standards).
- Collect real-world endpoints prospectively.
- Engage with FDA early to review RWE plans.
- Help FDA understand the RWD better, such as why data are missing.
- Enable FDA to reproduce the real-world data analysis.

- Increase opportunities for FDA-sponsor interactions.
- Mandate the option for sponsors to bring in RWE experts like the RWE Subcommittee to Review Division interactions.
- Implement the FDA Advancing RWE Program (FDA 2023b).
- Show the value of new ways to measure clinical outcomes.
- Build trust in the use of validated digital healthcare tools.

Themes of building trust and creating transparency are interrelated. As one RWE consultant to industry stated, transparency is essential to building FDA trust:

> The more you are transparent with them [FDA], and they think you have nothing to hide, that you're trying to be as completely transparent as possible, the more than likely to trust you because at the end of the day, trust is a value judgment. (RWE consultant to industry)

A full listing of informant responses is available in Supplementary Table 5.

4.9. Actions recommended by informants

When asked what actions are needed to achieve the solutions, informants described specific actions that fall under these themes:

- Incentivize stakeholders.
- Remove barriers.
- Accelerate stakeholder efforts versus give it time.

4.9.1. Incentivize stakeholders

Informants described providing incentives and similar enabling actions that could help achieve clarity on regulatory acceptable real-world effectiveness endpoints. One suggested action was to align evidentiary standards for regulators and payers to help de-risk and incentivize development of real-world endpoints that meet the requirements of multiple decision makers. Similarly, informants proposed providing incentives for advancing novel methods, including FDA financial support for projects that aim to advance this space. An analogous COA example

was shared, in which FDA grant funds were used to develop core outcome sets for COA. Another enabling action was to form and work through a community. Examples included creating a multi-stakeholder consortium for validating endpoints and having the community (e.g., professional societies) develop best practices before FDA develops guidance or other policy. Finally, legislative incentives, or rather mandates, were suggested, such as advocating for Congressional action. Examples of past congressional policy efforts were shared, including the 21st Century Cures Act (21st Century Cures Act, 2016), the Prescription Drug User Fee Act (PDUFA) authorization in 2022, and the Food and Drug Omnibus Reform Act (FDORA 2022) that required FDA to communicate expectations and invest in efforts to advance the use of RWE for regulatory decision making. A future opportunity described was the next PDUFA authorization in 2027, during which industry stakeholders could seek FDA policy on clearer processes for RWE interactions, including getting clarity on real-world endpoint(s) that would be acceptable for the regulatory decision. One informant stated that multiple related policies may need to be implemented in parallel.

4.9.2. Remove barriers

Informants described how removing barriers, such as reducing heavy FDA workloads, would allow FDA reviewers to learn more about RWE and participate in pilot projects. Assuring RWD providers of confidentiality of information between sponsors and FDA was another action proposed to address a perceived barrier of intellectual property and reputation concerns among RWD companies.

4.9.3. Accelerate stakeholder efforts versus give it time

Finally, conflicting concepts were expressed about whether stakeholders should accelerate their efforts or wait. One informant expressed the importance of patience and giving the environment time to evolve:

> I don't know if there's anything more that needs to be done. Maybe we just need to be patient. I don't know. It moves slowly. (Drug and device manufacturer director)

However, another informant expressed a need for speed:

> We need to be moving faster to it. It [real-world data] has got so many benefits. It's how we get to a real learning health care system where actually we've got a healthcare system that learns. All the technology's there… The health sector and drug sectors are behind other sectors like finance and retail and other things, and we just- we're behind. We don't know why, but it's just time for this to happen. (Drug and device manufacturer research executive)

Increasing the opportunities for real-time interactions between sponsors and FDA was suggested as a way to accelerate achieving solutions. A full listing of informant responses is available in Supplementary Table 6.

4.10. Informants' recommendation on stakeholders to involve in developing solutions

When asked about which stakeholders to involve in developing solutions, many different stakeholders and diverse expertise were described by informants. Informants often named stakeholders but did not describe their roles, possibly assuming the interviewer was already expert on the general roles that these stakeholders play with respect to regulatory decisions. The following stakeholders were named and, when available, a description of the role as suggested by informants is provided:

- Academic experts: provide methodologic, analytic, and clinical expertise; may serve as special part-time FDA employees to help develop guidance and provide training to FDA and other stakeholders
- Clinical experts
- Congress: providing legislative course correction for the regulatory environment

- FDA and other regulatory authorities: aggregate information on real-world uses and publish the information under the PDUFA user fee commitments; lead stakeholder discussions about regulatory acceptable RWD/RWE; sponsor pilot projects
- Healthcare providers: improve stakeholders' understanding about why and how specific real-world datapoints are collected; enable changes in the types of RWD collected in healthcare settings
- Industry associations
- Journal editors
- Legal experts
- Patient groups: serve as an unbiased facilitator of pilot projects; host multistakeholder meetings and conferences; provide perspectives on which endpoints are most relevant to patients
- Payer organizations: provide perspectives on payers' evidentiary needs for enabling access to medical products
- Professional societies: issue best practices, reporting guidelines, and templates
- Real-world data and analytics organizations: align on RWD quality definitions and practices; prioritize the same metrics as FDA
- Regulatory experts: interact and negotiate between FDA and industry on the evidentiary needs for regulatory decisions on individual products
- Scientific experts
- Drug and device manufacturers (sponsors)
- Stephan Lanes: provide scientific expertise on validation studies

A full listing of informant responses is available in Supplementary Table 7.

4.11. Good ways to engage stakeholders recommended by informants

When asked for good ways to engage the stakeholders, informants described these themes:

- Choose a recognized facilitator.
- Identify the value and implications for each stakeholder.
- Engage the full stakeholder community, especially FDA.

4.11.1. Choose a recognized facilitator

Informants described the importance of recognized facilitators to engage the stakeholders. FDA or patient nonprofit organizations (e.g., Critical Path Institute) were named as recognized facilitators. Nonprofits, particularly those with a policy outreach team, were suggested as well positioned to facilitate the development of solutions because of their purpose of helping patients access treatments and because of their connections to FDA and payers but absent financial incentives for marketing a particular product:

> I feel like groups that don't have that vested interest are able to bring together stakeholders from different drug companies who don't like to play together too much just on their own. Some are better than others. Then you can bring them together, and then we also have connections with FDA and payers to bring them to the table… and you can have these conversations about doing pilot projects or writing policy. So, I think that the nonprofits are well positioned to this kind of work. (Patient advocacy research director and former FDA reviewer)

4.11.2. Communicate the value and impact for each stakeholder

Informants described identifying and communicating the value and impact, or implications, such as anticipating FDA concerns about the real-world endpoint for each FDA therapeutic division and communicating to various stakeholders how the proposal will impact them (e.g., accelerate medication to patients, save time and money, advance the science, etc.).

One informant felt that FDA may not understand the impact of its communications on industry, as some FDA "blanket policies" and ambiguous feedback left industry scientists spending hours together trying to clarify FDA's meaning but without knowing how to reach out to FDA to get clarity. One informant expressed that anticipating FDA's priorities before engaging the agency would help increase the probability of success:

> Where I think things are successful is when FDA is bought in and excited, and I think there are a lot of people at FDA now that are working on RWE a lot, and I think the more people internally at FDA that are working on it, the more excitement there is internally, the more the agency is going to be behind, making these decisions and providing clarity on when's it going to be acceptable or not. (US government policy and industry legal counsel and former FDA representative)

Understanding the therapeutic area context at FDA and keeping science and evidence at the forefront of interactions were described as ways to speak to FDA values. One informant shared that FDA's new Advancing RWE Program (FDA 2023b), designed to offer sponsors additional opportunities to interact with FDA on topics like regulatory acceptability of proposed RWE and real-world endpoints, is a signal that the FDA does perceive the value of providing greater clarity. Another informant expressed concerns that a perceived lack of value by any of the stakeholders could lead to gaps in the RWE lifecycle, from the collection of RWD through its analysis and its use for regulatory decision making.

4.11.3. Engage the full stakeholder community, especially FDA

Some informants expressed the importance of engaging FDA along with the rest of the stakeholder community and, ideally, having FDA initiate the efforts. One informant gave an example of an effort by the Digital Medicine Society (DiMe) that had inclusion of all stakeholders except FDA:

> They include all stakeholders… They're just broad in their thinking, but it's still not endorsed by FDA. And when it's not endorsed and you're not guaranteed FDA collaboration, then it's like, well, I'm glad we have these standards…. (Drug and device manufacturer research director specializing in clinical outcome assessments)

The example of lack of FDA representation in the DiMe's effort was contrasted with an effort that did include FDA (a good research practice report developed by an ISPOR task force):

> But the beauty of it is we do have FDA on the [ISPOR] task force, and even though they can't speak for the entire agency, that is representative of the current thinking, the current expectations, and it influences that as well. (Drug and device manufacturer research director specializing in clinical outcome assessments)

One informant expressed the importance of bringing together the entire stakeholder community (e.g., FDA, drug and device manufacturers, payers, researchers, etc.) to engage the patient community but was unsure about the right mechanism for doing this:

> I think that if the community would come together, then… and I say community meaning, okay, the pharma, the payer, the researchers, we're going to do this and agree that let's not compete about who developed this and whose idea gets the IP [intellectual property], then they could find the patient community. Now, how to do it? I don't know. (Regulatory advisor to industry)

A full listing of informant responses is available in Supplementary Table 8.

4.12. Enablers (facilitators) of action described by informants

When asked what would help enable (or facilitate) solutions, many ideas were suggested by informants. The themes derived from informants' responses are as follows:

- Incentives for stakeholders will lead to action.
- Organizational structure and culture can help optimize the probability of success.

- Procedural improvements can accelerate solutions.
- Prior knowledge and experience facilitate solutions.
- Mechanisms that reduce legal risks enable collaboration.
- Favorable circumstances help achieve solutions.

4.12.1. Incentives for stakeholders will lead to action

Informants described incentives needed for stakeholders to act. Financial support was suggested as an enabler for pilot projects. Support could come from FDA broad agency announcements (BAAs) and Centers of Excellence in Regulatory Science and Innovation (CERSI) funding and through industry sponsors. Congressional action and legislation, such as the Prescription Drug User Fee Act (PDUFA) reauthorization cycles were described as enablers for RWE needs. One informant (US government policy and industry legal counsel and former FDA representative) recommended identifying the key members of Congress who have historically handled certain policy issues and engaging them through PhRMA (Pharmaceutical Research and Manufacturers of America) and patient groups. Informants described improved RWD quality as an enabler of achieving clarity on regulatory acceptability of real-world effectiveness endpoints. To enable improved RWD quality, healthcare providers need incentives to capture the RWD reliably. One informant described a healthcare system's value-based arrangements and quality metrics, tied to revenue, as an incentive for improving RWD quality:

> I do think that's a big incentive for some of these integrated health systems that are really interested in improving on quality metrics, which their revenue is tied to. And if they've got value-based arrangements, they certainly are. So, I think on the health system level there is an incentive to adopt this kind of platform within their EHR is because they can use that information to inform, not only clinical decision making, but kind of C-suite executive level decision making on how to improve on quality metrics within their system. So, I think there's a health system incentive there to get more standardized, to get

more interoperable, especially as you think about some of these large integrated health systems. (Digital healthcare and policy expert)

4.12.2. Supportive organizational structures and cultures can help optimize the probability of success

Informants described the importance of organizational structure and culture to optimize success. One informant shared that a matrixed organizational structure at FDA, such as having a center of excellence that supports different review divisions, has helped achieve clarity on regulatory acceptability for COA. By reporting up to the same FDA division, COA experts can share and hone their expertise, while championing the appropriate use of COA within individual review divisions. Another organizational enabler described by informants was inclusion of the patient perspectives and patient representatives to persuade Congress to act.

Organizational and stakeholder community culture was described an important to optimizing the success of related pilot projects. Good facilitators, or individuals who can connect people and technical needs, were described as instrumental in the success of pilot projects. According to one informant, good facilitators are individuals who are motivated and able to facilitate interaction between different organizations or areas of expertise across the lifecycle of a project. Additionally, project coordinators are important to help ensure continual progress throughout the project. Transparent and inclusive culture, including leaders that both listen and clearly communicate priority needs, was described as essential for incentivizing pre-competitive collaborations:

> Pre-competitive collaborations usually have a longer timeline before any return on that investment is realized, and organizations may have competing priorities, so to be able to identify those areas that are the problems that are ripe for solving, and those problems that will have meaningful impact if they are solved, I think, is important. And trying to understand that and articulate it upfront. You know some of these things, or just they

> ideally aren't just like 'wouldn't it be nice if'. (Patient advocacy organization executive leader)

One example of identifying and clearly communicating priority RWE needs was shared—FDA RWE experts in the Office of Medical Policy identify and communicate the RWE areas that warrant FDA investment. FDA has been transparent and inclusive in another area (patient-focused drug development, PFDD), according to one informant. Transparency is enabled by co-authorship of the PFDD guidance documents, as FDA hosted workshops with the stakeholder community and offered opportunities for feedback in many different venues including professional conferences. Inclusivity in developing the PFDD guidance documents was enabled by FDA's efforts to invite multiple types of stakeholders to participate on conference panels with FDA. Another cultural enabler of community is each stakeholder's perception of value of community efforts. Informants described the importance of stakeholders viewing community efforts (e.g., pilot projects) as a valuable investment of time and resources. Informants described FDA perceiving value when the effort aligns with ensuring public health and meeting statutory requirements and fits within FDA's capacity constraints. Value for industry was described by one informant (drug and device manufacturer director) as getting the right answer for patients and "furnishing evidence that will influence a [regulatory] decision in the right way, not just a 'yes' answer." The importance of emphasizing for FDA the value of incremental innovation was expressed by one informant:

> What I could say is, if I were the FDA, you learn by experience, and you take baby steps as opposed to big leaps. (RWE consultant to industry)

A learning mindset was described as an enabler of collaboration and teamwork for communities, including a willingness to test to learn, take risks, get unexpected results, and learn things that may be unpopular or undesirable. Finally, an expert in COA (clinical outcomes

assessment) described the COA scientific community and questioned whether an analogous community exists for measurement in RWD/RWE.

4.12.3. Procedural improvements can accelerate solutions

Informants described procedural enablers for accelerating solutions. Procedures that accelerate solutions, but could be improved, are existing mechanisms for FDA interdisciplinary review and more real-time FDA-sponsor interactions. According to one informant, a mechanism for FDA interdisciplinary reviewer exists but it is unclear whether reviewers are consistently using it to seek advice from experts in measurement science, for example, or how well it is working. Creating mechanisms for more real-time FDA and sponsor interaction was described as important to sustain momentum within the stakeholder community by one informant:

> But PRO consortium, like the beauty of that is that it's an ongoing forum with a workshop every year with a lot of FDA involvement. And so it's just a continued conversation because you can't just have the conversation and close the door if it's going to build on itself. (Drug and device manufacturer research director specializing in clinical outcome assessments)

4.12.4. Prior knowledge and experience facilitate solutions

Informants described the power of prior knowledge and experience to facilitate solutions. For example, FDA's prior experience with specific real-world endpoints creates regulatory comfort and trust for some real-world endpoints, which helps to promote clarity on regulatory acceptability of those endpoints. Conducting a landscape assessment to gather prior knowledge (e.g., experiences and examples) and understanding the various RWD sources (e.g., how the same real-world endpoint performs across data sources) were described as enablers. Another enabler identified by informants is time to build experience:

> Some of this, I think, is just going to take time. And I've kind of come across that after just watching the way things play out. It just takes a while for new ideas to kind of trickle down. (Drug and device manufacturer research executive)

4.12.5. Mechanisms that reduce legal risks enable collaboration

Informants described diverse mechanisms for reducing legal risk to help enable collaboration. One example shared was to require joint financial investment in solutions so that intellectual property and access rights can be shared (e.g., to collaborate on development of registries). Another example was to use alternative mechanisms such as registries for collecting health data that pose legal risks if they were to be captured in the EHR (e.g., data collected from wearable devices outside of a research protocol). Another informant suggested creating a mechanism that would make it legally acceptable for FDA to rely on prior evidence that demonstrated the acceptability of the endpoint submitted by a drug or device manufacturer (Sponsor 1) for reviewing a new application(s) submitted by another manufacturer (Sponsor 2). An enabler of stakeholder collaboration for developing new regulations or guidance documents is assuring sufficient flexibility in the policies, such that FDA retains flexibility for case-by-case regulatory judgments as needed and for policy to evolve as RWD and technology evolve.

4.12.6. Favorable real-world data circumstances help achieve solutions

Favorable RWD circumstances were also described as enablers for achieving clarity on regulatory acceptable real-world effectiveness endpoints. Informants described favorable circumstances in terms of the therapeutic areas that are more likely to have readily available (captured in existing RWD sources) real-world effectiveness endpoints and clear needs for using them, such as oncology and rare diseases.

A full listing of informant responses is available in Supplementary Table 9.

4.13. Barriers to action described by informants

When asked to describe barriers to developing solutions, informants shared many ideas. The themes derived from informants' responses are sometimes the inverse of themes about enablers, or facilitators. Barriers described were as follows:

- Lack of right incentives for stakeholders restrains action.
- Organizational structure and culture can inhibit action.
- Lack of knowledge and experience limits achieving solutions.
- Legal risks disincentivize collaboration.
- Complexity of real-world data and science impedes progress.
- Costs can deter developing optimal solutions.

4.13.1. Lack of right incentives for stakeholders restrains action

Informants described how the lack of right incentives restrains stakeholder actions. Examples of lacking the right incentives were systems of motivation and reward that are misaligned with achieving goals that are collective (e.g., interdisciplinary and/or multi-stakeholder) or goals with longer term impact, versus siloed or short-term impact wins. Money was described as a lack of right incentives for community efforts on RWE pilot or demonstration projects, as more lucrative contracts with sponsors may pull RWD companies away from voluntary or less well funded multi-stakeholder initiatives. One disincentive may be a concern about unfairness at being the first to develop the evidence package to validate the real-world endpoint, as subsequent sponsors could benefit from another company's initial investment, without having to contribute or invest themselves. According to informants, the US healthcare system lacks the right incentives to invest in RWD, including data collection infrastructure and standards. One informant described the US healthcare system's fragmented nature as contributing to the lack of right incentives to improve healthcare data collection and contrasted this with right incentives in Europe (i.e., government mandates). A lack of incentive for the US Congress amid many other competing

priorities was described as resulting in a lack of prioritization of RWE and relevant policy solutions:

> I think some of the challenges have been there are other more pressing issues that are getting Congress's attention these days and same with FDA… there's just so many things that FDA is responding to that the use of real-world evidence, I don't know that it's been as high up on the priority radar of late for FDA. So, that's a barrier and elevating that as an issue and getting people who are really talking about the Inflation Reduction Act and the threats on accelerated approval, and all of those things are taking over and taking attention off of this, I think, to some extent. (Drug and device manufacturer research senior executive)

4.13.2. Organizational structure and culture can inhibit action

Informants described certain organizational structures and cultures as inhibiting action. Organizational structure at FDA and the lack of community involvement coupled with the lack of transparency are considered barriers to achieving clarity. These barriers (lack of community involvement and lack of transparency) often co-occur in informants' responses. Examples described by informants include FDA organizational structures that stifle the flow of information, such as top-down flow (or lack of flow) of information and the many different therapeutic area review divisions and disparate priorities of FDA. An executive at a real-world data and analytics company expressed that FDA "does not speak with one voice" while another informant perceived a sometimes arbitrary nature in FDA disparate perspectives:

> FDA is staffed by folk who don't trust real-world data. The decision makers or staff, that staff doesn't really trust real-world data… In fact, you could take an algorithm that FDA has used to make a regulatory decision and use it, and the other people at FDA might say, 'Nah, I don't want to use that one. I don't believe it. I want to use a different one.' So, it's

all case specific. (Real-world data and analytics company executive and former FDA scientist)

Additional examples of the absence of community involvement and lack of transparency were described such as FDA drafting regulatory guidance behind closed doors, a lack of clarity about whether and when stakeholders will receive a response when providing feedback on FDA draft guidance, and FDA not including non-academia stakeholders in FDA-funded pilot projects.

Examples of organizational culture barriers were general risk aversion of both FDA and industry and FDA's skepticism that RWD/RWE might "undermine the gold standard of approval." One informat (a real-world data and analytics company executive and former FDA scientist) described some FDA reviewers as overly conservative, needing perfect information to make decisions. FDA's risk aversion was described by a former FDA representative as FDA's intent to preserve "all flexibility it possibly can until the last moment, so that it has all options on the table." Another informant, a former FDA scientist, perceived that FDA is unable or unwilling to state whether a real-world endpoint is acceptable or not before the study is conducted. A wait-and-see approach was described, with FDA waiting to see the study's results and magnitude of treatment effect before deciding whether the endpoint is (was) appropriate. Several informants commented that FDA's risk aversion has been exacerbated by bad actors who erode trust (e.g., sponsors who do not fulfill post-marketing requirements). The organizational cultures of Congress, FDA, and some nonprofits were sometimes described as being slow to change or make progress. One possible reason given for FDA being slow to change is heavy workload. An example shared of FDA being slow to change is its "codified habit" of requiring two randomized controlled trials to demonstrate substantial evidence of effectiveness of new medical products, when this solution may not always make sense. Another informant described the bureaucratic processes to develop a final guidance document taking years. However, one informant expressed that a slow process may be appropriate in some cases:

> In the regulated space with these regulators, like FDA, changing the way of thinking and doing business is a slow process, and that's the nature of this regulator, and there are reasons why that's not necessarily all a bad thing. There's good and bad with that. (US government policy and industry legal counsel and former FDA representative)

Organizational cultures of the pharmaceutical industry and US healthcare system were also sometimes described as barriers. For the pharmaceutical industry, competitive cultures were described as a barrier to forming a multi-stakeholder community and collaborating between organizations to achieve clarity. Formality was described an organizational cultural trait among drug and device manufacturers in terms of the importance or seriousness they give to their interactions with FDA; manufacturers may not feel comfortable permitting other organizations, even close partners (e.g., RWD company), to participate in their interactions with FDA. A gap and need for healthcare systems to foster a culture of research using RWD was perceived as a barrier by an expert in digital healthcare policy:

> I think it [improved healthcare data collection in health records] takes a bent towards the culture of research and a real clear tie between, Hey, we're already generating a ton of data on our patients that we can leverage in a way that'll help us improve clinical decision making and inform a learning kind of healthcare system, at least internally kind of going forward. So, I think it'll be that culture shift as well there. (Digital healthcare and policy expert)

4.13.3. Lack of knowledge and experience limits achieving solutions

Some informants felt that lack of knowledge and experience limited solutions. Informants described FDA's variable expertise on RWE, with only a few divisions perceived as having deep expertise. Lack of experience with real-world endpoints makes it difficult for FDA to make it clear for other stakeholders what information and level of evidence are needed:

> For what it's worth, the guidance seems to come out, and it surprises. I have colleagues, old colleagues from FDA who I trust fully of understanding real-world data, deep deep expertise, and I know that they were not involved in writing guidance about the real-world data. So, there is a lack of expertise. (Real-world data and analytics company executive and former FDA scientist)

Informants described a lack of consistent industry experiences also limiting solutions: "because if somebody doesn't know how to do something, they're less likely to do it" (Drug and device manufacturer research director specializing in clinical outcome assessments). The absence of a framework on regulatory acceptable real-world effectiveness endpoints was described as limiting clarity on the appropriate use and validation of real-world endpoints and exacerbating the cost of validating real-world endpoints (e.g., because industry uncertainty may lead to going above and beyond what is really needed to validate the endpoint):

> No one knows what they're really supposed to do, so we all do the most we can imagine doing. (Real-world data and analytics company executive and former FDA scientist)

4.13.4. Legal risks disincentivize collaboration

Informants described legal risks that disincentivize collaboration on achieving solutions. Legal risks or considerations described were intellectual property issues with respect to real-world endpoints and EHRs. Different perspectives about intellectual property of real-world endpoints were shared. Some informants described the proprietary aspects of real-world endpoints (e.g., artificial intelligence or data mining algorithms), while one informant, a drug and device manufacturer research director specializing in COA, stated, "Our proprietary advantages are drug, not our ruler. Nobody wants their methods to be their advantage. You want to have the best treatment." The proprietary nature of EHRs was described as further contributing to lack of interoperability, an impediment to collaboration using RWD. Another barrier of EHRs described is the legal risk of having certain types of patient information attached to the EHR. One example

shared was that of a patient transferring digital data that could reveal atrial fibrillation from his wearable device to the EHR. If the patient's physician is unaware that those data have been uploaded by the patient, s/he may not act on the information (and it may be unclear what responsibility the physician has to review all the data a patient may upload). Finally, one informant (US government policy and industry legal counsel and former FDA representative) stated that there are no unmanageable legal barriers to the proposed solution of FDA implementing an RWE or real-world endpoints dashboard, although FDA would need to navigate the disclosure regulations in the CFR.

4.13.5. Complexity of real-world data and science impedes progress

Informants described the complexity of RWD and science as a barrier to progress. The complexity of RWD includes difficulty accessing certain data (e.g., direct access to patient charts), increasingly large datasets with lots of noise requiring novel natural language processing (NLP) and artificial intelligence (AI) methods that FDA does not trust, worries about certain companies being perceived as having inferior RWD, gaps in hardware available to analyze large datasets, EHR interoperability challenges, inconsistency across providers when collecting the same datapoints in EHRs, and uncertainty about how to best to handle missing data. Additional aspects of complexity related to RWD or evolving measurement science with respect to real-world endpoints were described by informants as follows:

- Context of use, which affects certainty or confidence for making a decision based on the real-world endpoint
- The need to consider many different scenarios for the endpoint and how it might be used
- Many approaches to validate a real-world endpoint
- Many factors that need to be appraised when validating (e.g., real-world coding practice changes, such as International Classification of Diseases, Ninth Revision (ICD-9) to

Tenth Revision (ICD-10), and varying performance of the endpoint by disease, such as for different types of cancers)

- Many different ways of collecting and measuring an outcome across RWD sources
- Continual evolution of data, technology, and medicine
- Different expectations from different stakeholders
- Different types of expertise required
- Many RWD companies that would need to convene to set standards
- The need to balance learning about how real-world endpoints perform across RWD sources while protecting the reputation of RWD organizations (not a "bake-off between the different data sources")
- Coordination of many interdependent moving parts on pilot projects
- Managing divergent personalities and working styles during pilot projects
- Different models for developing FDA guidance
- Difficulty interpreting results of pilot projects
- Difficulty finding a good real-world comparator to demonstrate treatment effects
- Lack of focus (trying to tackle everything) that creates complexity in some pilot projects
- RWD formats (e.g., implementing Clinical Data Interchange Standards Consortium [CDISC] standards)

4.13.6. Costs can deter developing optimal solutions

Cost barriers were described as a barrier to solutions in terms of industry's reluctance to invest in validating a given real-world endpoint or invest in the precompetitive efforts needed to achieve longer term impact:

> Pre-competitive collaborations usually have a longer timeline before any return on that investment is realized, and organizations may have competing priorities. (Patient advocacy organization executive leader)

A full listing of informant responses is available in Supplementary Table 10.

4.14. Examples of similar efforts to achieve regulatory clarity on similar RWE or other topics described by informants

When asked to describe examples of similar efforts to achieve clarity on other RWE topics or regulatory topics, informants shared examples of similar efforts to achieve clarity on regulatory acceptability of measurement tools including clinical outcome assessments (COA) and digital healthcare measures, manufacturing purity metrics, surrogate clinical trial endpoints such as response rate and progression-free survival in oncology clinical trials, emerging biomarkers such as ctDNA (circulating tumor DNA), and real-world safety endpoints (Supplementary Table 11). Concepts shared by informants in previous interview questions were often repeated. The themes are as follows:

- Communities help achieve clarity.
- FDA guidance helps achieve clarity, but clarity is not always popular.
- Pilot projects and tools do not always create clarity.
- Policy can help create clarity on FDA legal and procedural topics.
- Scientific clarity may be attained by relating the unknown to the known.
- Perceived urgency can compel action to create clarity.

4.14.1. Communities help achieve clarity

Informants described the benefit of collaborating within multi-stakeholder communities and forums. Examples included Critical Path Innovation Meetings (CPIMs), Getting Better Together and other PRO or eCOA communities, Duke Margolis Center for Health Policy, ISPOR, the National Academies, and partnerships with IQVIA. The informants expressed that these communities enable more open cross-stakeholder communication and collaboration on scientific and regulatory questions, such as how to validate COA instruments, develop good research

practices and standards, publish, and otherwise determine how best to make progress that benefits the entire community versus a single company.

4.14.2. FDA guidance helps achieve clarity, but clarity is not always popular

Informants expressed the importance, and in some cases, the desire for written clarity like that provided by FDA guidance documents, but in at least one case, the clarity was not popular, as it was perceived not to reflect the community's voice but rather a single person at FDA:

> …I don't know how much you follow the PFDD guidances, but certainly they haven't always been popular. Even though different voices get listened to, perhaps they feel not listened to because at the end of the day, a decision has to be made. And yeah, it's a tough one… FDA guidances tend to be written mostly by the FDA with listening to- but there's always strong voices at the agency, so when someone leaves you'll see a shift in priorities, or shift in thinking, if you will, because one person has got the pulse and the power and sway, and can argue for their case fairly well, and that those things can shift and change. (Patient advocacy research director and former FDA reviewer)

For one former FDA reviewer, publishing FDA guidance (FDA 2013) led to greater clarity on regulatory acceptable RWE for safety studies and helped avoid requests to FDA for clarification.

4.14.3. Pilot project and tools do not always create clarity

No informants identified an example of real-world effectiveness endpoint pilot projects or validation of a real-world endpoint that had been done within a multistakeholder pre-competitive forum (in any of the interview questions), with the exception of the Friends of Cancer Research pilot projects on oncology real-world endpoints. However, one informant doubted whether Friends of Cancer Research pilot projects would be described as "validation" by FDA. Examples of multistakeholder efforts to validate other types of endpoints were shared, such as FDA partnering with multiple stakeholders to establish pathological complete response (pCR) as

a surrogate endpoint in clinical trials and FDA Sentinel validation of safety real-world endpoints. According to informants, efforts like these can help the endpoints gain greater trust and acceptability with FDA but may not help if FDA is not involved:

> I haven't seen any demonstration projects where, front and center, it was clear to me what did FDA want to do? How did it influence them? How do they change things? Maybe I'd even say the first round of the pilots too because I feel like the pilots were- they were proposed, and they had their own machinery, and then people said, Okay, well, we're going to make one of those the pilot, but then it—I didn't see FDA involved in it. So, I don't know if it'll change. (Drug and device manufacturer research executive)

Similarly, tools were described as sometimes beneficial and sometimes not for achieving greater clarity. One informant described an example of a successful tool (HARPER protocol template), which is likely to be more widely adopted as EMA (European Medicines Agency) begins to require its use for certain types of post-marketing studies. Another informant described an effort outside the United States to catalog information about real-world healthcare data sources (EU EHDEN, European Health Data Evidence Network), without commenting on how beneficial the catalog is for the RWE community. However, one informant expressed skepticism that tools will be adopted because people may not want them. Two examples shared were Agency for Healthcare Quality and Research (AHRQ) efforts to build a uniform endpoints framework in the early 2000s and a search tool for clinicaltrials.gov, neither of which were well adopted by others, according to the informant:

> …it was a thankless job, and it really didn't go anywhere because people didn't want it. They were stuck with what they had. There was no reason to use the framework. It's not clear we would have been better off with it… Outcome measures framework is what they called it… but it fizzled. It was like arm to arm, as far as I understood it, fizzled, and we also made an extension to clinical trials.gov for registries, and that pretty much has-

> nobody uses it. It doesn't search well. It was promoted heavily, but not widely adopted or used. (Real-world data and analytic company executive leader)

4.14.4. Policy can help create clarity on FDA legal and procedural topics

One informant described how policy can help create clarity on legal and procedural topics related to FDA's reviews. An example shared was the role of the 21st Century Cures Act (2016) in creating a process for qualification of biomarkers. This process was designed to help multiple sponsors navigate the intellectual property challenges for using or referring to the same evidence package for validation of the biomarker or endpoint (avoiding the need to re-create the validation evidence package). However, this pathway has not been widely adopted by stakeholders. Another example shared is the Medical Device User Fee Act (MDUFA) giving sponsors the ability to request other FDA specialized technical or scientific experts (e.g., the Digital Health Center of Excellence within the Center for Devices and Radiological Health) to consult or help arbitrate the FDA review division's review of medical devices.

4.14.5. Scientific clarity may be attained by relating the unknown to the known

Informants described how scientific clarity may be attained by relating the unknown to the known. For example, research frameworks for patient-reported outcomes influenced one informant's efforts to develop and validate real-world effectiveness endpoints. Another informant thought that FDA achieves clarity, or at least comfort, with new proposals when it can relate the proposal to something known (e.g., a familiar RWD source):

> I think it [FDA Sentinel] did [help FDA get comfortable with RWE for safety studies] because I think a lot then it got a much more familiarity within the agency. It made sponsors much more comfortable to propose things because—and I know, and I remember advocating for this within the company to say, Look, we're talking about using Healthcore data [rebranded in March 2023 as Carelon Research]. Same data FDA is looking at. We're not talking about something that's… [Interviewer: Something they've

not seen?] Right. And so, I think the same will help a lot. (Drug and device manufacturer research executive)

4.14.6. Perceived urgency can compel action to create clarity

Informants expressed perceived urgency as a key enabler of actions, such as validation efforts to accelerate clinical trials of cancer investigational therapies or to investigate potential safety risks of products already used by patients in routine care. One informant described surrogate endpoints for oncology drug development as an example of how FDA's perceived urgency led to it doing some of the work to help validate those surrogate endpoints:

> Those [progression and pathological complete response endpoints] are surrogate endpoints where FDA actually did the work in some cases to help validate those surrogate endpoints by confirming that the surrogate endpoints were reflective of the ultimate clinical endpoint, and the thing was is the reason they did that is because they were forced to do it because people started living longer with cancer, and you can't power every trial for overall survival. So, they had to say, like, okay, Well, are we going to make this trial last 15 years? What else can we use? And so that's where PFS [progression-free survival] and pCR [pathological complete response] came from, so it was a necessity…. (Real-world data and analytics company director)

4.15. Anticipated impact of achieving clarity on regulatory acceptable real-world effectiveness endpoints described by informants

When asked to describe the impact of achieving clarity on regulatory acceptable real-world effectiveness endpoints, informants repeated some concepts shared in previous interview questions, such as accelerating patients' access to treatments and increased incentives, investment, and confidence in RWD/RWE. These themes were derived from informants' responses:

- Clarity will lead to better healthcare decisions for patients.

- Clarity will help accelerate patient access to treatment and minimize patient burden in clinical trials.
- Clarity will reduce time, costs, waste, and frustration in developing new treatments.
- Clarity will help improve RWD and empower a learning health system.

4.15.1. Clarity will lead to better healthcare decisions for patients

Better healthcare decisions for patients could result from clarity on regulatory acceptable real-world effectiveness endpoints. Informants described how better healthcare decisions may result from evidence that better reflects real-world healthcare practice and endpoints that matter to patients (patient-centric endpoints) and is more generalizable than clinical trial data to the patients who receive therapy in routine care. RWE and real-world endpoints could contribute to an improved understanding of benefits and risks, including off-label treatment outcomes, leading to better treatment decisions for patients.

4.15.2. Clarity will help accelerate patient access to treatment and minimize patient burden in clinical trials

Accelerating patient access to therapy and minimizing patient burden was described in terms of expediting clinical research and development timelines using RWE. An example is increasing patients' access to promising experimental treatments in clinical trials, by building real-world external or hybrid control arms. This RWE use case is only possible if acceptable real-world effectiveness endpoints can be identified. One informant described improved research efficiency, which could be the result of requiring fewer in-trial patient procedures and relying instead on available RWD for the patient. Informants described how these impacts would have further downstream impacts of encouraging patients to enroll in clinical trials, a challenge for clinical investigators, and prioritizing RCTs for situations in which they are truly needed to answer questions. One informant, a professor and research scientist in epidemiology, acknowledged that expedited drug development is a potential benefit but expressed skepticism

that patients would directly notice the difference. This informant felt that if the research and evidence supporting the product's effectiveness and safety are of sufficient quality (regardless of the methods or approach used to generate the evidence), the impact as perceived by patients would be small. Another informant felt that more global alignment across multiple stakeholders on acceptable real-world endpoints could also help accelerate patient access to treatment; reducing the variability in regulatory (and payer) requirements could focus clinical research efforts (again, research efficiency) and expedite global approvals and access to treatments. Finally, greater clarity could translate to greater confidence in the acceptability of real-world effectiveness endpoints to encourage more holistic and cross-therapeutic use of RWE for regulatory decision making, which has been predominantly focused on oncology and rare disease products to date:

> [If we] Did nothing? I just think it's going to be more canaries in the coal mine or bespoke longer and more painfully. The sooner we have clarity on some of this, the more we can have holistic use of RWE consistently cross-therapeutic areas benefiting patients with all sorts of diseases and conditions. It will just be a longer, more painful journey to that if we—the sooner we get clarity, the better. (US government policy and industry legal counsel and former FDA representative)

4.15.3. Clarity will reduce time, costs, waste, and frustration in developing new treatments

Reduction of time, costs, waste, and frustration in the development of new treatments was a benefit described by informants. This theme is also closely related to accelerating patient access to treatment and minimizing patient burden but also addresses costs savings, waste, and frustration of the non-patient stakeholders. For example, clarity can help sponsors more easily being able to identify or develop acceptable versus unacceptable real-world effectiveness endpoints (before the study is conducted). The improved ability to designate an endpoint as regulatory acceptable a priori (before conducting the study in real-world data) instead of post hoc

(waiting to review study results to decide whether the endpoint was fit for purpose) would save stakeholders time and money and help reduce waste and frustration during clinical development.

Clarity can help sponsors right-size validation efforts (instead of "just doing absolutely everything") and eliminate unnecessary expensive validation activities, such as double data entry or dual data abstraction by clinicians for some cases. Informants expressed that time, money, waste, and frustration may be reduced through aligned evidentiary needs across regulators and other decision makers (e.g., payers such as CMS). Greater clarity leads to time and money savings when it opens opportunities for existing RWD sources to generate evidence where other research approaches pose significant challenges or are not feasible (e.g., enrollment in some post-marketing pregnancy registries). Finally, RWD/RWE demonstration projects like the Friends of Cancer Research pilots help provide stakeholders with clarity on how real-world effectiveness endpoints perform across different RWD sources to support improved decision making with respect to the appropriate uses of RWD.

4.15.4. Clarity will help improve RWD and empower a learning health system

Informants described how clarity would increase stakeholder confidence ("de-risk") to invest in improving the collection and quality of RWD and help advance a learning health system in the US. A learning health system is one in which routinely collected healthcare data can be used to inform more than patient-level decisions but also population-level decisions for regulators like FDA. Another informant suggested that upstream solutions for incentivizing improved RWD are needed before clarity on endpoints can have a significant impact.

A full listing of informant responses is available in Supplementary Table 12.

4.16. Additional perspectives shared by informants

When asked in the final interview question for any additional perspectives to share on regulatory acceptable real-world effectiveness endpoints, informants shared ideas on the following themes:

- Context of use influences the validation needed to demonstrate fit-for-purpose real-world endpoints.
- Stakeholders should focus on patient-centric endpoints.
- Stakeholders should put science first and adapt the regulatory system accordingly.
- Stakeholders need to right-size their expectations of RWD/RWE.
- The solutions for achieving clarity are inter-dependent.
- Stakeholders may consider alternative approaches to RWD/RWE or regulatory approval.

4.16.1. Context of use influences the validation needed to demonstrate fit for purpose real-world endpoints

Informants gave examples of how context of use influences the validation needed to demonstrate that a real-world endpoint is fit for purpose. One informant contrasted the differing level of validation that decision makers will likely expect for safety versus real-world effectiveness endpoints, suggesting a lower level of validation may be expected for use cases that relate to real-world safety endpoints:

> I think safety signals carry a different level of validation- whether it is cause enough to be an indicator that there is potential risk at hand, so probably would not be held to the same standards to be validated as an efficacy endpoint would. (Patient advocacy organization executive leader)

Context of use was also described as necessitating tradeoffs in levels of validation, both in terms of performance measure (e.g., sensitivity versus specificity) and of the effort or thoroughness of data abstraction and adjudication needed. Informants described different situations needing different validation approaches. Examples of different external validity approaches were shared, such as comparing the endpoint with a gold standard (e.g., for validating a real-world overall survival endpoint) and evaluating the endpoint to determine whether it correlates with or predicts downstream events (e.g., for validating a real-world tumor response endpoint), an approach

similar to surrogate biomarker validation. One informant contrasted an FDA audit of RWD (e.g., traceability from results to source data) with endpoint validation (defined by the informant as "abstraction protocols to define that variable").

4.16.2. Stakeholders should focus on patient-centric endpoints

One informant felt that the endpoints that matter to patients are often highly functional and overlooked. An example patient-centric endpoint shared is the ability to engage in hobbies (e.g., play a musical instrument), which was important to a patient who was wheelchair-bound but able to play guitar after having a neuromodulating medical device implanted in his brain. This informant expressed anger at effectiveness endpoints that prioritized healthcare providers over patients:

> …a big focus is the patient-centered endpoints. Maybe that's the phrase everybody's using. But I think we lose track of that. We've seen more presentations, or somebody was telling me about our presentation. They saw that that was all about saving the doctors time. Oh, it's about using what do you call it when it has a multi-drugs in one tablet drug combinations. He was talking about using combination products… It was lively discussion. But the topic was fixed dose combination pills for whatever condition and patients, saying that combination doesn't work for me. I need more of this and less of that. It needs to be tweaked. It needs to be individualized, and I can't do that with your product. And the response was, But this- it's better. My combination is better because it saves time for physicians. They actually said that at the podium! (Real-world data and analytic company executive leader)

Note that the perceived importance of patient-centric endpoints was expressed by informants in an earlier interview question too, when describing the priority of achieving clarity on regulatory acceptable real-world effectiveness endpoints for another interview question (see Section 4.7).

4.16.3. Stakeholders should put science first and adapt the regulatory system accordingly

One informant expressed the importance of putting science first and adapting the regulatory system accordingly. This informant saw parallels with the history of COA regulations in the US. According to the informant, an underlying scientific framework (modern validity theory) was still evolving even after FDA published its initial guidance on patient-reported outcomes (FDA 2009). FDA's guidance had to later evolve with the maturation of measurement science, which led to FDA updating the COA guidance by more recently publishing a series of patient-focused drug development draft guidance documents (FDA 2023c).

4.16.4. Stakeholders need to right-size their expectations of RWD/RWE

The need to right-size expectations of RWD/RWE was expressed by informants. Right-sized expectations include recognizing that some RWD may never be fit for making certain types of regulatory decisions. The theme of needing to right-size expectations of RWD/RWE was also embedded in an informant's recommendation that FDA find appropriate ways to interpret RWE in which the treatment effect may be relatively small but is similar in magnitude to that observed in clinical trials. In a related comment or idea, another informant reminded that even clinical trials have lots of subjectivity. Informants often gave recommendations about right-sizing expectations that relate more broadly to RWD/RWE overall but not specifically to real-world effectiveness endpoints. For example, one informant expressed a view or expectation that the main value of RWD for accelerating drug development and patient access with RWE is through existing RWD (i.e., using RWD previously collected in routine care) versus prospectively collecting RWD. One informant cautioned that many RWE submissions to FDA may not be used for decision making and that the actual number is likely far less than some publications state. The informant (a real-world data and analytics company executive and former FDA scientist) said that this perception came from firsthand experiences on behalf of various sponsor companies to submit RWD to FDA, in which the RWD/RWE rarely provided the primary evidence of effectiveness in the application.

4.16.5. The solutions for achieving clarity are inter-dependent

Another theme in this final interview question is that solutions to achieving clarity are likely to be inter-dependent:

> They [potential solutions] are all very closely intertwined and interrelated, so it's hard to disentangle the effect of one alone. (Professor and research scientist in epidemiology)

A similar concept about needing to implement multiple solutions in parallel was expressed by a different informant in an earlier interview question, when describing the actions needed to achieving clarity on regulatory acceptable real-world effectiveness endpoints (see Section 4.9).

4.16.6. Stakeholders may consider alternative approaches to RWD/RWE or regulatory approval

Informants suggested alternative approaches to RWD/RWE and/or regulatory approval. One informant recommended alternative approaches to obtaining RWD on patients (e.g., using patient contacts to obtain follow-up data on patients). Another informant recommended considering alternative paradigms for new drug approvals, in which progressive FDA approvals incorporate RWE. Another informant described the need for novel approaches that better disentangle benefits from risks in rare populations or subgroups. Finally, an informant suggested considering whether alternative approaches for evaluating surrogate endpoints may be needed, giving an example of a surrogate endpoint that effectively measured the biomarker (blood pressure) but had an unanticipated relationship with the clinical outcome (mortality):

> …theoretically lowering your blood pressure should increase your life expectancy because we know that blood pressure adds on to a whole bunch of other things and increases cardiovascular mortality. But then there long came some drugs that lowered blood pressure. But guess what? They increased mortality. So now, if you asked anybody, is the scientific underpinning for these presumptions that these are good surrogate endpoints, good ones they would say, yes. What happened here? Well, it turned out that these drugs had other effects aside from affecting the surrogate endpoint, which

> overcompensated for their good effects. So, is a surrogate endpoint good enough? That's a question we're going to be facing, more and more. And I don't know the answer to that. (RWE consultant to industry)

A full listing of informant responses is available in Supplementary Table 13.

4.17. Analysis of solutions proposed by informants using Bardach policy criteria

Building a plan for change requires not only describing the potential solutions, but also understanding the tradeoffs and projecting the outcomes (Bardach 2009). While many individual solutions were proposed by informants during interviews, some solutions related to RWD/RWE more generally but only indirectly related to real-world endpoints. These solutions were not analyzed or included in the plan for change. Instead, this plan for change focused on those solutions that most directly relate to clarifying regulatory acceptability of real-world effectiveness endpoints. Furthermore, this plan focuses on macro-level solutions (solutions that impact many stakeholders and the broader RWE and regulatory environment), while recognizing that progress on micro-level solutions is also essential to achieving impact. The following potential solutions meet both criteria (i.e., macro-level solutions that relate directly to achieving clarity on regulatory acceptably real-world effectiveness endpoints):

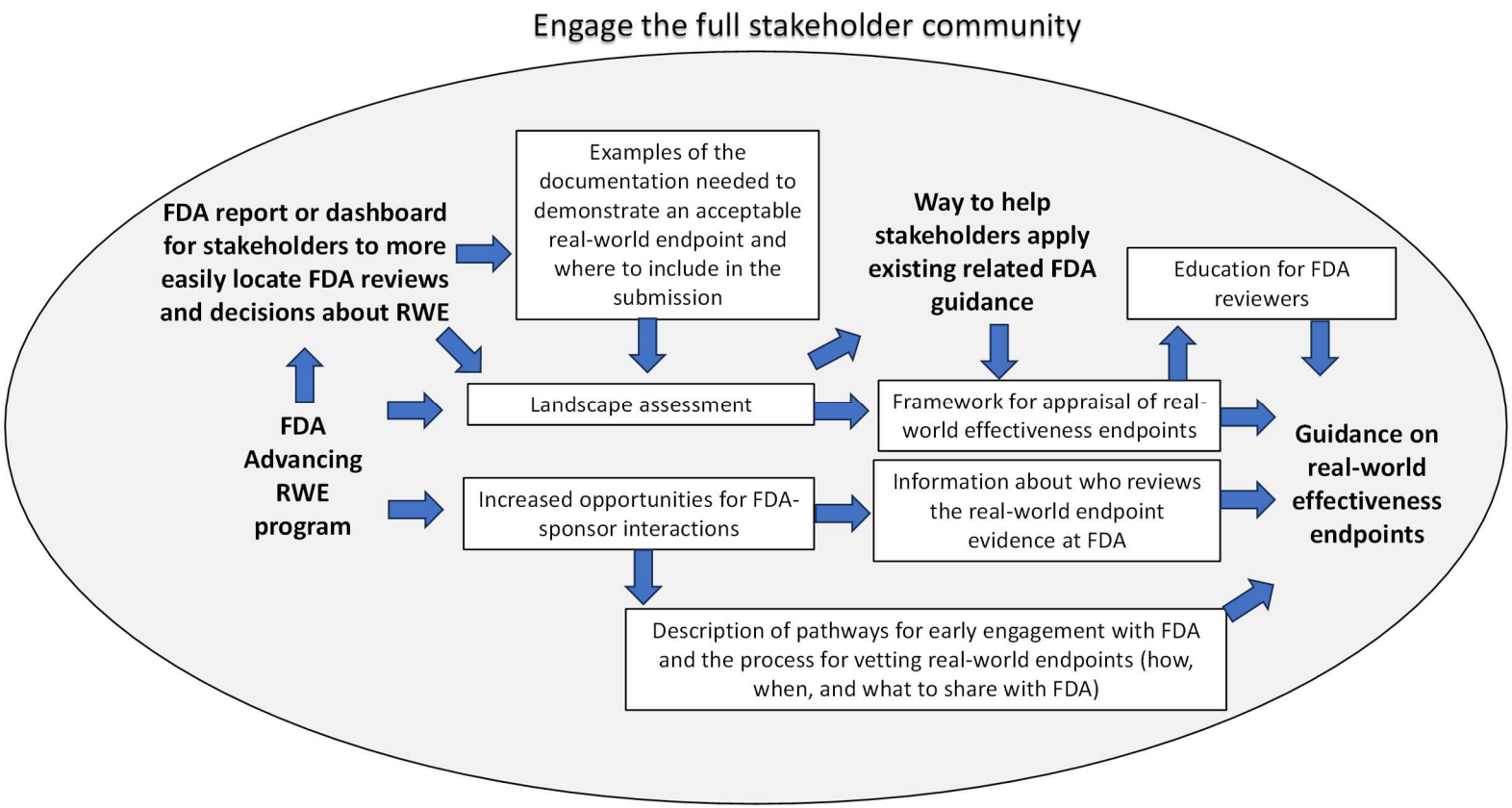
- Landscape assessment
- Framework for appraisal of real-world effectiveness endpoints
- Examples of the documentation needed to demonstrate an acceptable real-world endpoint and where to include in the submission
- Information about who reviews the real-world endpoint evidence at FDA
- Description of pathways for early engagement with FDA and the process for vetting real-world endpoints (how, when, and what to share with FDA)
- Guidance on real-world effectiveness endpoints (that is flexible for the evolving RWD/RWE environment)

- FDA report or dashboard for stakeholders to more easily locate FDA reviews and decisions about RWE
- Ways to help stakeholders apply existing related FDA guidance
- More engagement of the stakeholder community
- Increased opportunities for FDA-sponsor interactions
- FDA Advancing RWE Program

The potential solutions are shown in Figure 7, which illustrates how the solutions may be viewed as interrelated, with some are precursor steps or intermediaries that lead to other solutions. By depicting relationships between the potential solutions this way, some potential solutions (bolded in Figure 7) more clearly stand out as main solutions that may be essential for initiating others and create the written expectations and transparency that stakeholders said represents clarity to them. For example, implementing FDA's Advancing RWE Program will lead to increased opportunities for FDA-sponsor interactions. FDA's Advancing RWE Program will also lead to increased experiences with RWE examples that FDA will publicly share through reports or dashboards (FDA 2023b). Together, these solutions lead to a potential (debatably) final solution describing the regulatory expectations in writing—guidance on real-world effectiveness endpoints. Although additional solutions may be needed even if/after FDA guidance were to be published, the proposals from informants seem to end with guidance as the most final, conclusive solution. Engaging the full stakeholder community is an enabler described by informants that should be implemented to achieve all solutions.

Figure 7

Flow diagram of potential macro-level solutions to achieving clarity on regulatory acceptable real-world effectiveness endpoints



Thus, a list could be consolidated as four main potential macro-level solutions (those highlighted in bold text in Figure 7):

1. FDA Advancing RWE Program
2. FDA report or dashboard for stakeholders to more easily locate FDA reviews and decisions about RWE
3. Ways to help stakeholders apply existing related FDA guidance
4. Guidance on real-world effectiveness endpoints

These four potential solutions are evaluated using the criteria proposed by Bardach.

4.17.1. Analysis of Solution 1: FDA Advancing RWE Program

The FDA Advancing RWE Program should be considered a relevant solution to help achieve clarity on regulatory acceptable real-world effectiveness endpoints. The goal of the program is to "improve the quality and acceptability of RWE-based approaches in support of new intended labeling claims, including approval of new indications of approved medical products or to satisfy post-approval study requirements" (FDA 2023b).

4.16.1.1. Feasibility

The feasibility of implementing the program is rated as high. The program is already in progress, with sponsors submitting applications for FDA review twice yearly through 2027 (FDA 2023b).

4.16.1.2. Desirability and acceptability

The desirability and acceptability of the program is rated as high. Several drug and device manufacturer informants described this program during interviews, including mentions that they were planning to submit a proposal to the program. The program enables an expressed desire by informants for increased opportunities for FDA-sponsor interactions. Many stakeholders are likely to benefit besides the sponsor submitting the proposal, as FDA will publicly disclose its insights on regulatory acceptability of the accepted proposals. Furthermore, the accepted proposals will contribute to and increase the number of available real-life examples (precedents)

and FDA's experience. This solution may have broad stakeholder impact for achieving greater clarity on regulatory acceptable RWE, including real-world effectiveness endpoints.

4.16.1.3. Precedents

Informants did not identify precedents or past examples that seemed directly analogous to the FDA Advancing RWE Program. However, a similar concurrent FDA program is the Complex Innovative Trial Design (CID) meeting program. Like the Advancing RWE Program, the CID program offers selected sponsors and proposals additional FDA interactions and advice, with the caveat that some study details will be included as public case studies. The case studies may be presented by FDA (e.g., in a guidance or public workshop) for the purpose of advancing novel clinical trial designs (FDA 2023g).

4.16.1.4. Timing

The program initiated in 2023 and will continue through 2027 (FDA 2023b).

4.16.1.5. Compromises

A key compromise for sponsors who choose to submit a proposal to the program is that FDA will make some details public. Sponsors typically prefer to keep drug development details and interactions with FDA as proprietary information (competitive advantage). Some informants felt that real-world endpoints and other measurement tools should not be considered proprietary, however.

4.16.1.6. Uncertainties

The related questions, or areas of uncertainty, with respect to the FDA Advancing RWE Program are as follows:

- When and how will the case studies and important insights from the program be made publicly available? The program web site (FDSA 2023b) describes the possibility that case studies could inform guidance or a public workshop. The PDUFA VII authorization in 2022 requires updates or new draft RWE guidance based on experience with the program: "By no later than December 31, 2026,

experience gained with the Advancing RWE Program, as well as CDER's and CBER's RWE Program in general, will be used to update existing RWE-related guidance documents or generate new draft guidance, as appropriate" (FDA 2023d). However, the timing and mechanism of public disclosures of case studies are unknown.

- What level of insight will be shared with stakeholders on acceptability of real-world effectiveness endpoints? Endpoints are on the list of details that may be publicly disclosed. However, the level of information or insights that may be shared with respect to real-world effectiveness endpoints is unknown.

4.17.2. Analysis of Solution 2: FDA report or dashboard for stakeholders to more easily locate FDA reviews and decisions about RWE

An FDA report or dashboard to help stakeholders more easily locate FDA reviews and decisions is considered a relevant solution if it provides the details that informants described as important to them. These details include FDA reviewers' comments with insights on aspects of the RWE (or real-world effectiveness endpoint) considered unacceptable by FDA as well as any proposals to resolve the issues. However, if the report is implemented as described in PDUFA VII, it may be minimally effective for achieving clarity on regulatory acceptably real-world effectiveness endpoints. The language in the PDUFA VII commitment letter (FDA 2022) suggests that the report will contain aggregated and anonymized information and may miss the insights recommended by informants:

> By no later than June 30, 2024, FDA will report aggregate and anonymized information, on at least an annual basis and based on available sources (e.g., information provided by review divisions), describing RWE submissions to CDER and CBER. The reports will describe application type (e.g., primary focus on safety or effectiveness), data sources used (e.g., medical claims, electronic health records, registries, digital health

technologies), study design employed (e.g., randomized trial, externally controlled trial, observational study), and regulatory request (e.g., new indication, population, dosing information, post-approval study requirement for a marketed product). This reporting will include but not be limited to protocols emerging from the Advancing RWE Program. (FDA 2022).

4.16.2.1. Feasibility

The feasibility of an FDA report or dashboard that helps stakeholders more easily locate FDA's RWE reviews and decisions is rated as high. A critical enabler is a current legislative mandate in the Prescription Drug User Fee Act (PDUFA) VII authorization (FDA 2022). Potential barriers to successful implementation as described by informants are FDA workload and legal risks (anonymizing the sponsors):

> A barrier might be that they [FDA] have to respect confidentiality, so it's going to be challenging for them to give too much- too many details for products that weren't approved. They'll have to aggregate the information. So that could be a barrier to information sharing. (Drug and device manufacturer leader and former FDA representative)

However, these barriers were considered likely surmountable:

> I do think there's a level of detail they [FDA] could share that's not proprietary, but they would have to make sure that under their regulations, they can't even say or summarize or enough data if it can be the mosaic effect, if you could piece it together, and like, figure out who you're talking about. So, dashboard challenges are that FDA would have to navigate its own confidentiality rules. I think they're called the disclosure regulations in Part 20 of the C-F… Code of Federal regulations. That's how it's all governed. (US government policy and industry legal counsel and former FDA representative)

4.16.2.2. Desirability and acceptability

Desirability and acceptability for stakeholders is rated as high for reports or dashboards that provide good transparency on RWE examples and meaningfully describe regulatory acceptability and FDA proposals, if any, to improve the RWD/RWE submitted by the sponsor. However, desirability and acceptability are rated low for reports or dashboards that provide counts only and do not meaningfully inform stakeholders:

> …if it [the FDA-issued RWE report required under PDUFA VII] comes out like a checklist where they [FDA] say, 'Yeah, we received 50 applications, and 30 of them were rejected,' and like they stopped there, that won't be that helpful. It will give us ammunition to complain but, or look you really don't want to use real-world evidence, but it won't give anything meaningful. So, I feel like they have to at least give a little bit of insight into decision making. So, maybe all 30 were not useful because 50% of the data was missing. I think they have to tell us why they made the decisions that they made, not just the numbers or information that doesn't provide insights. (Drug and device manufacturer leader and former FDA representative)

4.16.2.3. Precedents

Precedents for the FDA's RWE report or dashboard include the qualification of endpoints (qualified drug development tools) report (FDA 2023f).

> I think of what I'll call public qualification of endpoints [these are 'qualified drug development tools'], and this was something that Cures [Act] spent a lot of time doing right around biomarkers and drug development tools, creating a process which FDA has not used that much to qualify endpoints…. (US government policy and industry legal counsel and former FDA representative)

An FDA report on qualified drug development tools (DDTs) provides quantitative metrics (counts of submissions and approvals) but little other context or interpretation (FDA

2021f), similar to the PDUFA VII description of FDA's report. However, FDA has a searchable dashboard of DDTs, including validated COA instruments that includes some FDA context or interpretation by linking to FDA reviews and responses on individual DDTs: https://force-dsc.my.site.com/ddt/s/. FDA also has a COA compendium that includes clinical outcome measurement tools that have been used to inform medical product labels, whether a qualified DDT or not, that lists prior products, indications, and FDA approval dates: https://www.fda.gov/drugs/development-resources/clinical-outcome-assessment-compendium. These latter examples (a report or dashboard linking to specific FDA reviews) are more aligned with the desired solution for RWE and real-world effectiveness endpoints described by informants.

4.16.2.4. Timing

The deadline for the FDA report required under PDUFA VII is June 30, 2024 (FDA 2022). Although an RWE report or dashboard with the desired information described by informants (beyond the PDUFA VII requirement) could be developed at any time, whether and what legislative action will be needed to initiate this effort will be clear after the PDUFA VII require report is published.

4.16.2.5. Compromises

The main compromise for developing the FDA report or dashboard will be the tradeoff between providing some aggregate metrics versus the additional qualitative insights from FDA that stakeholders desire.

4.16.2.6. Uncertainties

The related questions, or areas of uncertainty, with respect to the FDA report or dashboard are as follows:

- What utility will stakeholders find in an anonymized report? Will the details be too generic to be meaningfully inform and clarify regulatory acceptability?

- Will the report or dashboard include examples of applications that were rejected by FDA? Failed examples are likely to be as much or possibly more helpful than successful examples. However, details on rejected applications are not publicly disclosed.

4.17.3. Analysis of Solution 3: Ways to help stakeholders apply existing related FDA guidance

Ways to help stakeholders apply existing related FDA guidance is considered a relevant solution. One informant, a real-world data and analytics company executive and former FDA representative, proposed a ways to help stakeholders apply existing related FDA guidance that may be somewhat effective for achieving clarity on regulatory acceptably real-world effectiveness endpoints:

> …so maybe if we could continue to make those links for people and show them how existing guidance applies or existing approaches apply, I think that would go a long way… So maybe it would be helpful to continue to get some like level setting on the expectation for best practices, for research, transparency, developing protocols, reporting. Maybe that is the best way to get value if people are trying to validate or justify real-world endpoints. To the extent that we can leverage what we already know for other types of outcome assessments, I think that would be really helpful. (Drug and device manufacturer leader and former FDA representative)

Potential formats could include a peer-reviewed publication, conference presentation, a webinar series, a research tool, and others. These are not mutually exclusive formats. For example, a research tool could be published in a peer-reviewed publication and also presented at conference or in a webinar.

4.17.3.1. Feasibility

The feasibility of developing ways to help stakeholders apply existing FDA guidance is rated as medium. Developing this solution does not require Congressional action or pose any known legal risks. However, it likely requires financial support and time to build. Some

informants expressed organizational barriers for investing in pre-competitive partnerships (e.g., multistakeholder collaboration to develop a research tool), which are not "quick wins" or sometimes even obvious wins. However, the financial support and time needed are not intractable barriers if the anticipated impact can be clearly communicated:

> Pre-competitive collaborations usually have a longer timeline before any return on that investment is realized, and organizations may have competing priorities, so to be able to identify those areas that are the problems that are ripe for solving, and those problems that will have meaningful impact if they are solved, I think, is important. And trying to understand that and articulate it upfront. You know some of these things, or just they ideally aren't just like 'wouldn't it be nice if'. (Patient advocacy organization executive leader)

The scientific complexity of real-world endpoint validation was another barrier or concern described by informants but not likely to be insurmountable.

4.17.3.2. Desirability and acceptability

Desirability and acceptability for stakeholders is rated as high. In addition to this solution being recommended by a former FDA representative, other informants also described potential FDA interest in related types of pilot or demonstration projects on real-world effectiveness endpoints:

> They [FDA] have multiple projects going on, but I thought they were doing one maybe even with Reagan Udall [Foundation] on endpoints development, so they must see it as valuable. (Drug and device manufacturer leader and former FDA representative)

FDA's web site also describes OCE [FDA Oncology Center of Excellence] interest in pilots on real-world effectiveness endpoints to support regulatory decisions for oncology products:

> OCE [FDA Oncology Center of Excellence] is also interested in research to define and validate real world endpoints that can be collected from Electronic Health Records (EHR) and how real-world endpoints perform relative to traditional endpoints used in clinical trials to support regulatory approval oncology products, such as Overall Response Rate, Progression Free Survival, and Overall Survival. Collecting traditional oncology endpoints is labor-intensive and normally only performed in the context of a clinical trial, so it is unclear whether data collected during the course of clinical care will provide comparable information. (FDA 2023e)

There are currently multiple ongoing FDA demonstration projects related to specific real-world effectiveness endpoints for cancer and other types of drug development programs, including respiratory disease, rheumatoid arthritis, and multiple sclerosis (FDA 2023h). Furthermore, this solution addresses a critical need of stakeholders to know the regulatory acceptability of the endpoint before conducting the study, which was described as a gap today:

> In my experience in safety studies, FDA is hesitant to a priori define a RWD outcome definition as acceptable. (Real-world data and analytics company executive and former FDA scientist)

This solution also conforms to proposals by informants for multi-stakeholder persistent engagement in this space and building of community. This type of solution may represent the most straightforward way to educate a wide variety of stakeholders and to level-set on the currently known generalizable principles. Furthermore, this solution may be a preferable one in stakeholders' risk averse cultures, as it represents a flexible start that can be adapted (e.g., for making revisions, for adopting, etc.) as regulatory precedents accumulate and the RWD environment evolves:

> We need to systematically deconstruct accumulating examples of RWE for regulatory decision making, keeping in mind that it will keep changing as the technical

> underpinnings improve. (Real-world data and analytics company executive and former FDA representative)

Finally, a tool can represent greater pragmatic simplicity for stakeholders, depending on how it is constructed (e.g., a list of appraisal questions). Greater simplicity may translate to an increased likelihood to act compared with a published literature review or standalone framework.

4.17.3.3. Precedents

Precedents for developing this type of solution can be found in the Algorithm CErtaInty Tool (ACE-IT). The ACE-IT was not described by stakeholders in interviews but is a recent analogous tool that helps stakeholders apply existing regulatory guidance to appraise whether a real-world safety endpoint is fit for purpose for a particular context of use (Singh 2023). The development of the ACE-IT aligned with informants' recommendations for successful multi-stakeholder collaboration to develop solutions; the ACE-IT was co-authored and reviewed by broader stakeholder community, including representatives from FDA. It was informed by a landscape assessment, consolidated the scientific principles, and provided education for FDA and other stakeholders.

This precedent and another described by one informant (AHRQ uniform endpoints framework in the early 2000s) show that early alignment and agreement on the priority and anticipated impact of the tool is important for a successful outcome:

> I once worked on a project for AHRQ, the Agency for Health Care Research and Quality on trying to come up with a uniform endpoint framework, I think, is what it was called, and it was a thankless job, and it really didn't go anywhere because people didn't want it. They were stuck with what they had. There was no reason to use the framework. It's not clear we would have been better off with it… Outcome measures framework is what they called it… but it fizzled. It was like arm to arm, as far as I understood it, fizzled…. (Real-world data and analytic company executive leader)

4.17.3.4. Timing

Development of this solution could begin anytime and would ideally finish prior to or in parallel with development of potential future guidance on real-world effectiveness endpoints, if such guidance is ever proposed.

4.17.3.5. Compromises

The main compromise with this solution versus a policy solution, for example, is the non-binding nature. Stakeholders are not required to use tools, publications, or similar in their interpretation of acceptable real-world effectiveness endpoints or make their decisions using the tool. Because this type of solution is non-binding, or at least less binding than regulatory guidance or policy, it does not carry the same weight with stakeholders nor represent a full solution to the lack of clarity on regulatory acceptability. Some uncertainty is likely to persist.

4.17.3.6. Uncertainties

The relevant remaining questions include the following:

- Who will invest? Some stakeholders may not value incremental innovation (learning by "baby steps versus big leaps" as described by one informant), which this solution would represent.
- Who are the likely champions at FDA? Some FDA staff (e.g., in the Office of Medical Policy and the Oncology Center of Excellence) have online or publicly commented on real-world effectiveness endpoints and related needs. However, informants stated that FDA does not speak with one voice and that having FDA champions in different therapeutic area review divisions will be important for success.

4.17.4. Analysis of Solution 4: Guidance on real-world effectiveness endpoints

Regulatory guidance on real-world effectiveness endpoints is not considered relevant today. While regulatory guidance generally does or should help stakeholders to achieve clarity on regulatory acceptability, guidance on real-world effectiveness endpoints is considered currently

premature. One informant expressed that attempting this solution today is likely to result in conservative FDA guidance that lacks sufficient (real) clarity and with limited opportunities for future improvement:

> …you're going to get an answer that is as conservative as it needs to be because people are being asked to come up with something that's applicable in such a broad number of settings, and it's just completely bland, and then it becomes hard to move off. (Real-world data and analytics company executive and former FDA representative)

4.17.4.1. Feasibility

The feasibility of developing a guidance document on real-world effectiveness endpoints is rated as low in the short-term (next 1-3 years) but higher in the longer term (next 4-6 years). Some informants expressed skepticism that FDA would be able to draft meaningful, relevant guidance today, as expressed by one informant: "Like we want something, but FDA doesn't know what to say about it" (Regulatory advisor to industry). FDA workload was also considered a potential barrier, although one solution could be for FDA to contract special employees (e.g., top academics) to help develop guidance, similar to what FDA has done to author the PFDD guidance series. This solution would likely require a Congressional action (legislation) to prompt FDA to draft guidance, but an informant (US government policy and industry legal counsel and former FDA representative) perceived this as not a top priority for Congress today.

4.17.4.2. Desirability and acceptability

Desirability and acceptability for stakeholders is rated as low in the short term for stakeholders but possibly higher in the longer term. One consideration is that Congressional action to develop a legislative mandate for guidance could be negatively perceived by some stakeholders (e.g., FDA) as punitive and undesirable. This solution may be premature and therefore, also undesirable for other stakeholders. For example, informants described FDA and other stakeholders needing additional experiences with real-world effectiveness endpoints for

regulatory decision making. One program to enable these additional experiences is the FDA Advancing RWE Program, which initiated recently (2023) and will continue through 2027 (FDA 2023b). In addition, precursor efforts (some now in progress) are still needed to achieve greater clarity on regulatory acceptable RWD and related frameworks, as described informants. If attempted today, the resulting guidance would likely not deliver the clarity that stakeholders need.

4.17.4.3. Precedents

Given the absence of a real-world effectiveness endpoints community today (or at least an important question posed by informants as to whether one exists), a poor outcome for guidance may be anticipated. Informants perceived a poor outcome for FDA guidance in cases where engagement with the full scientific community was absent. For example, multiple informants described the RWE draft guidance documents issued in 2021 as a precedent with a poor outcome. The draft guidance documents were described as rushed ("barely beat[ing] the legislative deadline" and "written really quickly"), overly conservative ("went after here is what ideal data look like"), premature (e.g., "vague and overarching," "not very definitive," and "surprising"), and possibly lacking involvement from the right expert authors.

Another precedent of issuing FDA guidance that had a similarly poor outcome was the FDA Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (FDA 2009). According to one informant, the guidance was developed behind "closed doors" and perceived as "this is what we [FDA authors of the guidance] decided with the 4 brains that be in the field. It's just no ownership. There's no uptake." In contrast, transparency and good collaboration with the measurement community contributed to one informant's perception that the PFDD guidance series (FDA 2023c) has been successful.

4.17.4.4. Timing

Desirable timing for guidance on real-world effectiveness endpoints may be after the next round of PDUFA (Prescription Drug User Fee Act) authorization in 2027, assuming that clarity on real-world effectiveness endpoints is a priority for Congressional action at that time. This

timing coincides with the final submission deadlines for the FDA Advancing RWE Program (2023-2027). The PDUFA VII authorization in 2022 required updates or new draft RWE guidance based on experience with the program: "By no later than December 31, 2026, experience gained with the Advancing RWE Program, as well as CDER's and CBER's RWE Program in general, will be used to update existing RWE-related guidance documents or generate new draft guidance, as appropriate" (FDA 2023d). Clarity on regulatory acceptable real-world effectiveness endpoints could be among the topics included in future guidance.

4.17.4.5. Compromises

The main compromise is giving the environment time to evolve to a point where meaningful guidance can be developed. While some informants expressed the importance of accelerating action toward solutions, the right factors need to be in place before guidance will do more harm than good. These factors include regulatory RWD frameworks, more experience with RWE submissions to FDA (and FDA's Advancing RWE Program), and other precursor solutions shown in Figure 7.

4.17.4.6. Uncertainties

Important areas of uncertainty remaining with respect to regulatory guidance are as follows:

- Who will invest in precursor activities needed to do this successfully (e.g., landscape assessment, forming a scientific community)?
- Will guidance on real-world effectiveness endpoint be a priority for Congress and FDA in 2027 (next re-authorization of PDUFA)?
- How should FDA guidance incorporate clarity on real-world effectiveness endpoints? For example, should FDA publish a single guidance that attempts to address general considerations and/or as part of existing or future multiple guidance documents that describe therapeutic area or other RWE considerations?
- How can regulatory guidance keep up with the pace of evolving technology?

CHAPTER 5. PLAN FOR CHANGE

The plan for change will recommend actions and describe potential measures for evaluating outcomes of each of the four solutions:

1. FDA Advancing RWE Program
2. FDA report or dashboard for stakeholders to more easily locate FDA reviews and decisions about RWE
3. Ways to help stakeholders apply existing related FDA guidance
4. Guidance on real-world effectiveness endpoints

5.1. Recommended Actions

Recommended actions for implementing solutions are presented separately for non-FDA and FDA stakeholders with the understanding or premise that FDA will initiate and facilitate developing and implementing the solutions. However, some actions could be re-assigned to non-FDA stakeholders as needed. The recommended actions are outlined below.

Recommended non-FDA stakeholder actions:

- Read and evaluate the report/tool/guidance to identify changes (e.g., content, format) that would provide meaningful insights.
- Conduct a formative evaluation (e.g., as done in the informant interviews). This type of evaluation could be repeated locally within individual stakeholder organizations to assess readiness, identify barriers and enablers, and tailor strategies.
- Champion the solutions within professional organizations and the workplace.
- Engage colleagues to contribute ideas, seeking diverse expertise and perspectives.
- Collate stakeholders' suggestions and submit these to FDA through stakeholder communities or workgroups (e.g., PhRMA, ISPOR, BIO, etc.).
- Advocate for changes needed, including through legislation if needed (e.g., in the next round of PDUFA authorization).

- Incentivize FDA to provide insights that stakeholders find most valuable.

Recommended FDA actions:

- Engage across the full stakeholder community, seeking diverse expertise and perspectives.
- Identify advisory boards and workgroups through trusted facilitators (e.g., Reagan Udall Foundation for the FDA).
- Develop memorandums of understanding and other types of contractual arrangements needed for stakeholders to collaborate on solutions.
- Ask stakeholders to identify what insights and format would be most beneficial and provide information on those topics. Some may be topics that informants recommended during interviews, and there may be additional topics of importance to the full stakeholder community.
- Consider good ways to engage stakeholders (e.g., hosting workshops to inform direction and to develop and review the solution).
- Provide stakeholders with a roadmap and timeline, showing where stakeholder input will be sought and incorporated.
- Secure resources needed for implementation (e.g., funding from FDA or industry, additional funds through PDUFA, etc.).
- Create a mechanism to keep the content as current as possible, given the quickly evolving RWD/RWE environment.
- Build a strategic communication plan and use multiple channels of communication to create broad awareness of insights. Examples include scientific publications, information posted on FDA's web site, conference panel presentation, webinars, social media, and the use of stakeholder champions to promote learnings within their own organizations.

- Provide educational webinars and conference presentations. Invite non-FDA stakeholders involved to be part of a conference panel with FDA where other stakeholders can ask questions.
- Address known barriers such as heavy FDA workload (e.g., by hiring special employees or contractors to support development), disclosure regulations in the CFR, and other potential challenges (e.g., organizational, technical, or legal issues) that may not have been described by informants.

Some solutions have additional recommended actions that are tailored to that solution. The recommended tailored actions as well as recommended content for each solution are described in further detail in the following subsections.

5.1.1. FDA Advancing RWE Program

Although the FDA Advancing RWE Program is currently underway, stakeholders should implement the recommended actions (see Section 5.1) to advocate for greater clarity on regulatory acceptable real-world effectiveness endpoints.

5.1.1.1. Recommended content: Insights on real-world effectiveness endpoints

FDA representatives implementing the Advancing RWE Program should provide insights not only on the RWE broadly, but also insights on the real-world effectiveness endpoints specifically. The topics to be addressed should be those that matter to stakeholders. These topics could include these described by informants during interviews or identified during the literature review (Beyrer et al. 2023):

- Description of real-world effectiveness endpoints that FDA has reviewed, the clinical and regulatory context of use for the endpoint, decisions made regarding regulatory acceptability of the endpoint, the rationale for the decision, and any proposals or attempts made to resolve the problems identified in its review.

- Examples and recommendations on the evidence and documentation needed to demonstrate an acceptable real-world endpoint.
- Examples and recommendations for appraising the validation of chart abstraction or other real-world data validation in situations where there is no external gold standard.
- Examples and recommendations for appraising the combination of machine learning abstraction of data and manual verification.
- The types of evidence needed to demonstrate an acceptable level of generalizability of the real-world endpoint across different RWD sources.
- The role patient-centricity should play, if any, in evaluating the fit for purpose of real-world effectiveness endpoints.
- The role health disparities or health equity should play, if any, in developing the evidence to evaluate the fit for purpose of real-world effectiveness endpoints.

Additionally, insights should be communicated according to the following principles:

- Include all RWE use cases, including those from rejected applications and the FDA Advancing RWE Program.
- Seek to provide the most information possible, without disclosing proprietary information or violating confidentiality agreements.
- Synthesize and consolidate the scientific and regulatory principles.
- Describe how the context of use for the real-world effectiveness endpoint affects regulatory acceptability, citing relevant guidance and/or precedents.

5.1.2. FDA report or dashboard for stakeholders to more easily locate FDA reviews and decisions about RWE

The FDA report on RWE to be developed by FDA under the PDUFA VII requirement may need to add content that informants said they need. Based on the language in PDUFA VII, the report is likely to be a static (one-time) reporting of aggregate and anonymized metrics about

RWE submitted to FDA, due to be published by FDA no later than June 30, 2024. Stakeholders should evaluate FDA's RWE report to be developed under the PDUFA VII commitment and determine whether additional information is needed to meaningfully address their needs. The recommended actions described in Section 5.1 should be implemented if there are deficits in clarity on regulatory acceptability of the real-world endpoints reviewed by FDA.

5.1.2.1. Recommended content: Insights on real-world effectiveness endpoints

The insights should be communicated according to the following principles:

- Include insights from reviews of real-world effectiveness endpoints, including real-world effectiveness endpoints FDA has reviewed, the clinical and regulatory context of use for the endpoints, decisions made regarding regulatory acceptability, and rationale.
- Include all RWE use cases, including those from rejected applications and the FDA Advancing RWE Program.
- Describe any proposals or attempts made to resolve the problems identified in its reviews.
- Seek to provide the most information possible, without disclosing proprietary information or violating confidentiality agreements.
- Synthesize and consolidate the scientific and regulatory principles.
- Consider the context of use aspects for using the real-world effectiveness endpoint to identify the specific considerations for regulatory acceptability, citing relevant guidance and/or precedents.

5.1.3. Ways to help stakeholders apply existing related FDA guidance

The solution is envisioned here as a research tool (versus a standalone conference panel or presentation, for example) given its pragmatic simplicity (e.g., as a list of appraisal questions) and potentially preferred format for stakeholders, some of whom emphasized the importance of having clarity in writing. Putting ideas in writing (e.g., tool) can also help stakeholders co-navigate the complexity of this topic and align on how to apply existing related FDA guidance.

The tool should connect the multiple existing related guidance documents and regulatory precedents described by informants and possibly any other relevant guidance from FDA not described by informants. The tool should support stakeholders in their understanding and ability to interpret and apply the guidance to specific real-world situations that they encounter when appraising the regulatory acceptability of a real-world effectiveness endpoint. An example or model for this is the ACE-IT that appraises the fit for purpose, or likely regulatory acceptability, of RWE algorithms for safety outcomes (Singh et al. 2023). Such a tool could lead to a future real-world effectiveness endpoints framework and guidance that describes regulatory acceptable real-world effectiveness endpoints.

Ideally, FDA would lead development of the tool, but if not, other stakeholders could initiate action while engaging FDA representatives in tool development and implementation. FDA engagement in developing the tool is critical for the tool to achieve the most value in terms of stakeholder adoption and informing potential future guidance.

5.1.3.1. Recommended content: Tool for applying existing guidance

The content for the tool should be developed according to the following principles:

- Conduct a landscape assessment, including a review of related guidance documents from FDA or other agencies and existing real-world examples or precedents. The landscape assessment should be informed by insights from FDA reviews of real-world effectiveness endpoints, including real-world effectiveness endpoints FDA has reviewed, the clinical and regulatory context of use for the endpoints, decisions made regarding regulatory acceptability, and rationale. FDA precedents help to illustrate the real-world application of existing guidance and are likely to shed even more light on interpreting the existing guidance. Precedents may add even more current insights on FDA's perspectives not yet captured in guidance (i.e., additional clarity not yet available in any FDA guidance).
- Consider whether to expand the purpose of the tool to address guidance from other non-FDA agencies (e.g., payers such as CMS). Given the potential impact of the tool for

developing future guidance, stakeholders may consider whether any non-FDA guidance offers insights for achieving greater clarity in future guidance.

- Include a concrete vignette(s). Describe a specific real-world endpoint (preferably ones for which FDA reviews are already available) and contextual details relevant to the decision(s), as was done in a previous tool (Singh et al. 2023). Regulatory acceptability, or certainty, depends on myriad factors (Cocoros et al. 2021, FDA 2023c). Avoid hypotheticals and address the context of use in which the real-world endpoint is used.
- Synthesize and consolidate the scientific and regulatory principles.
- Consider the context of use aspects for using the real-world effectiveness endpoint to identify the specific considerations for regulatory acceptability, citing relevant guidance and/or precedents.
- Develop a framework for appraising the regulatory acceptability of real-world effectiveness endpoints. The FDA RWE framework (FDA 2018), ESTIMAND framework (ICH 2019), and any accepted RWD quality frameworks are important inputs. The framework should include a description of the relevant approaches and scientific principles for demonstrating fit for purpose for different contexts of use.

5.1.4. Guidance on real-world effectiveness endpoints

Guidance on real-world effectiveness endpoints, although premature today, is a solution that stakeholders should consider promoting in the next round of PDUFA authorization in 2027. An important precursor need is an accepted RWD framework, as real-world effectiveness endpoints are a bridge between the RWD and RWE. Other precursors are shown in Figure 7, such as more examples of RWE (successes and failures) for informing regulatory decisions (e.g., FDA's Advancing RWE Program) and a landscape assessment of existing guidances and precedents.

5.1.4.1. Recommended content: Guidance on real-world effectiveness endpoints

Based on interviews and the literature review (Beyrer et al. 2023), guidance should be developed as follows:

- Build on a scientific framework.
- Describe the criteria for regulatory acceptability.
- Provide insights on topics that matter to stakeholders.

5.4.1.1.1. Build on a scientific framework

Guidance should build on a scientific framework for appraising the regulatory acceptability of real-world effectiveness endpoints. The FDA RWE framework (FDA 2018), ESTIMAND framework (ICH 2019), and accepted RWD quality framework are important inputs. The real-world effectiveness endpoints framework should be informed by a landscape assessment that includes a review of related guidance documents from FDA or other agencies and existing real-world examples or precedents and synthesize the scientific and regulatory principles. The framework should include a description of the relevant approaches and scientific principles for demonstrating fit for purpose for different contexts of use.

5.4.1.1.2. Describe the criteria for regulatory acceptability

The guidance should describe the criteria for regulatory acceptability of the real-world effectiveness endpoint. Specifically, guidance should address how context of use influences its regulatory acceptability, citing any other relevant guidance or precedents. Where possible, the guidance should describe the level of certainty needed for the various contexts of use and the criteria FDA will use to evaluate whether the validation evidence is sufficient to meet the level of certainty needed, including quantitative and qualitative considerations as applicable. The guidance should not (only) describe ideal data, but also describe where FDA is flexible (e.g., working with data that are less than ideal, which is almost always the case with RWD). Specific case examples (successes and failures) should be included where possible and without disclosing

proprietary information or violating confidentiality agreements. The examples serve to illustrate principles of regulatory acceptability and potential ways to resolve the problems (i.e., problems with the endpoint or the supporting evidence that demonstrates the endpoint's fit for purpose reviewed by FDA).

5.4.1.1.3. Provide insights on topics that matter to stakeholders

Guidance should provide insights on topics that matter to stakeholders. These topics could include those described by informants during interviews or were identified during the literature review (Beyrer et al. 2023), such as the following:

- Description of real-world effectiveness endpoints that FDA has reviewed, the clinical and regulatory context of use for the endpoint, decisions made regarding regulatory acceptability of the endpoint, the rationale for the decision, and any proposals or attempts made to resolve the problems identified in its review.
- Examples and recommendations on the evidence and documentation needed to demonstrate an acceptable real-world endpoint.
- Examples and recommendations for appraising the validation of chart abstraction or other real-world data validation in situations where there is no external gold standard.
- Examples and recommendations for appraising the combination of machine learning abstraction of data and manual verification.
- The types of evidence needed to demonstrate an acceptable level of generalizability of the real-world endpoint across different RWD sources.
- The role patient-centricity should play, if any, in evaluating the fit for purpose of real-world effectiveness endpoints.
- The role health disparities or health equity should play, if any, in developing the evidence to evaluate the fit for purpose of real-world effectiveness endpoints.
- Recommendations for operationalizing the guidance.

The choice of topics to address in guidance should also be informed by the stakeholder community at the time when the guidance is initiated (i.e., in case new important topics emerge). The guidance should be written in a way that is flexible for the evolving RWD/RWE environment, which continues to quickly evolve, to prevent the guidance from becoming quickly outdated.

5.2. Potential evaluation measures

Evaluation measures are described as "potential" and not "recommended" measures because stakeholders should co-develop and align on meaningful measures to achieve collective impact (Kania and Kramer 2011). Evaluation measures may be viewed as formative or summative:

- Formative: the intent is to identify how to improve on the solution, for example, in terms of content, format, or implementation.
- Summative: the intent is to conclusively evaluate the impact of solutions on how effectively they contribute to clarity on regulatory acceptability of real-world effectiveness endpoints (Chen 2015).

The outcomes to be evaluated may be the final public health and regulatory impact (i.e., achieving clarity on regulatory acceptability on real-world effectiveness endpoints) or implementation outcomes, such as adoption or acceptability (satisfaction) of solutions (Proctor et al. 2011) or awareness (PROSCI n.d.). The data to inform performance measures should be sought from broad, diverse stakeholder types. Results should be stratified by stakeholder type or other relevant characteristics (e.g., education background, job role, level of experience with RWE, etc.) to identify patterns indicating potential gaps. One potential challenge in the interpretation of evaluation measures is the intersectionality or interdependence of solutions. For example, if the FDA report or dashboard described here were to be published at the same time the

FDA Advancing RWE Program completes, it would be difficult perhaps to attribute clarity exclusively to either solution or weigh each solution's impact on achieving clarity.

5.2.1. FDA Advancing RWE Program

Potential measures for evaluation include measures of awareness and satisfaction:

- Awareness: Number of views of publication(s), attendance at conferences and webinars, views/shares/comments in social media, number and types of stakeholder organizations sharing the tool within their organizations
- Satisfaction: Stakeholders' perceived value of the program for achieving clarity on regulatory acceptability of real-world effectiveness endpoints (e.g., from survey data), sentiment in social media

5.2.2. FDA report or dashboard for stakeholders to more easily locate FDA reviews and decisions about RWE

Potential measures for evaluation include measures of FDA report or dashboard adoption and satisfaction:

1. Adoption: use of the report or dashboard based on counts of online views
2. Stakeholder satisfaction (e.g., from survey data) on the following:
    - Level of insights on regulatory acceptability on real-world effectiveness endpoints
    - Ease of locating insights from FDA reviews and decisions about real-world effectiveness endpoints
    - Timeliness of content

5.2.3. Ways to help stakeholders apply existing related FDA guidance

Potential measures for evaluation include measures of tool awareness, adoption, and satisfaction:

- Awareness: Number of views of publication(s), attendance at conferences and webinars, views/shares/comments in social media, number and types of stakeholder organizations sharing the tool within their organizations
- Adoption: Number of individual users and types of stakeholders who say they use or reference the tool (e.g., from survey data)
- Satisfaction: Perceived value of the tool for achieving clarity on regulatory acceptability of real-world effectiveness endpoints (e.g., from survey data), sentiment in social media

5.2.4. Guidance on real-world effectiveness endpoints

Potential measures for evaluation include the following process and stakeholder satisfaction measures:

- The number and types of stakeholder comments on draft guidance **received** by FDA
- The number and types of stakeholder comments on draft guidance **addressed** by FDA
- Stakeholder satisfaction (e.g., from survey data) on the perceived value of the guidance for achieving clarity on regulatory acceptability of real-world effectiveness endpoints

5.3. The stakeholders and recommendations on how to engage them

A key enabler of solutions is engaging the full stakeholder community. The involvement of diverse stakeholders should also help to promote transparency and trust in solutions among FDA and other stakeholders, which were described as important considerations by the informants. The following stakeholder types should be included in developing the solutions:

- FDA representatives, and ideally including reviewers from multiple therapeutic area divisions
- Drug and device manufacturers who generate and submit RWE to seek FDA approval related to their medical products

- RWD organizations and healthcare providers who provide the underlying RWD and provide context about improving the collection of quality RWD
- Patient communities and advocacy groups who can help inform on meaningful endpoints for developing new therapies
- Measurement experts, including from academic organizations and from other analogous stakeholders from the fields of COA, digital health, and safety pharmacoepidemiology
- Payer organizations (e.g., Centers for Medicare and Medicaid services, private health plans, National Committee for Quality Assurance) to help better align evidentiary standards so that real-world endpoints can address multiple decision-making needs and to potentially incentivize improved collection of quality RWD.

One informant expressed skepticism that a true measurement community (a scientific community dedicated to real-world effectiveness endpoints) exists today. Engaging across diverse types of stakeholders for building solutions is one way to help build this type of learning collaboration and community.

Informants' recommendations for good ways to engage were to choose a recognized facilitator and communicate the value and impact for each stakeholder. Informants also emphasized the importance of FDA engagement for implementing these types of solutions and ideally, leading the development of solutions. Recognized facilitators should be trusted and effective connectors of people and ideas (i.e., individuals who are motivated and able to facilitate interaction between different organizations or areas of expertise). An example recognized facilitator in this space is the Reagan Udall Foundation for the FDA that helps advance FDA's mission and innovative regulatory science in the US. Other potential facilitators include professional societies, such as ISPOR or ISPE, or possibly a patient organization.

Cultivating a learning mindset among stakeholders will also be critical. Some ambiguity is to be expected; some issues may have no clear answers and diverse perspectives are likely to result

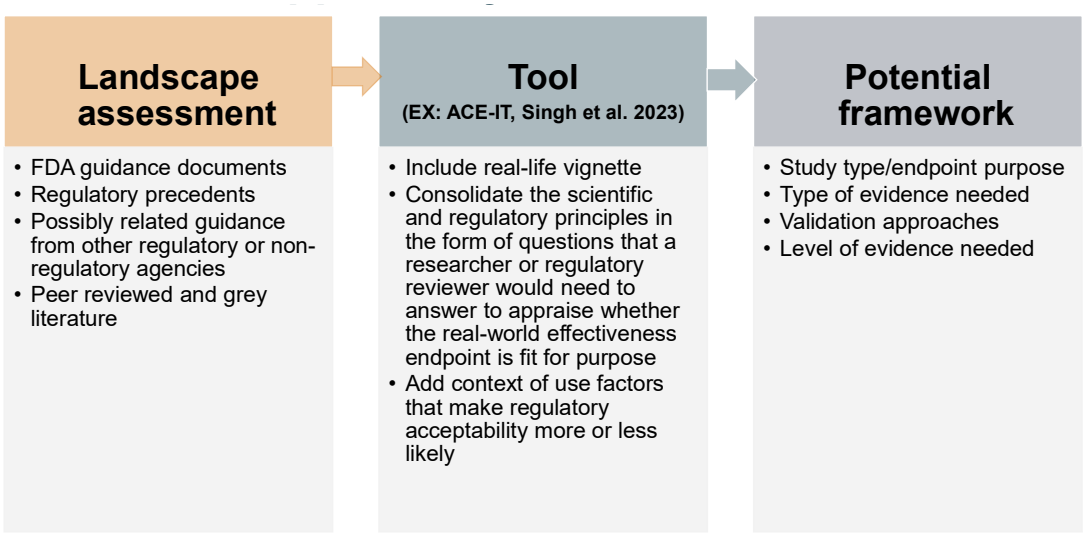
in different ideas about how to develop or implement solutions. Stakeholders who are persistent to see the process through to the end are also essential; as one informant described: “you have to play the long game in the regulatory space because regulatory precedent isn’t a quick win.”

5.4. Discussion

The solutions in the plan for change are not discrete or singular but very interrelated. As one informant stated, multiple policies or solutions (e.g., micro- and macro-level) may be needed in parallel. Two solutions (FDA Advancing RWE Program and FDA RWE report or dashboard) are already in progress. A tool to help stakeholders apply existing FDA guidance is the next opportunity to initiate a solution. An example of the tool is shown in Figure 8. The tool may be informed by a landscape assessment (input) and potential framework (output) that could contribute to a future regulatory guidance on real-world effectiveness endpoints.

Figure 8

Illustration of the potential tool, informed by a landscape assessment and contributing to a future framework for appraising regulatory acceptability of real-world effectiveness endpoints



No legislative mandate is needed to implement this solution. While FDA would ideally lead the development of this type of tool, other stakeholders could initiate and facilitate the process and engage FDA contributors. Although it is not yet clear who will invest, funding, time, and expertise could be provided by multiple stakeholder organizations who have a vested interest in achieving clarity on regulatory acceptable RWE and real-world effectiveness endpoints. The recommended actions for FDA stakeholders in this plan for change could be transferred to non-FDA stakeholders to develop the tool. Key resources for developing this type of tool include experts with pharmacoepidemiologic, statistical, clinical, and regulatory science expertise as well as funding and time for researchers to conduct the landscape assessment, develop the tool, and (ideally) construct a related framework for future regulatory guidance. Stakeholders described in Section 5.3 should comprise a public-private partnership workgroup(s), reviewer group, and/or advisory board. Section 5.3 describes the need for a trusted and committed facilitator. Ideally, a pilot evaluation of the tool would be conducted to understand the tool's relevance and reliability

for appraising real-world effectiveness endpoints beyond the vignette and adapting to make it more broadly generalizable, if needed.

Implementation strategies for all four main macro-level solutions are discussed in the context of ERIC strategies in the following subsections, followed by a discussion of the strengths and limitations of the research and plan for change and the global public health impact.

5.4.1. Implementation strategies

The list of relevant ERIC implementation strategies and how they align with informants' recommended actions for the four solutions is shown Table 3. Some ERIC strategies were not considered relevant for implementing the four solutions, based on the author's judgment and considering the input from informants. Therefore, only the relevant ERIC strategies are shown with the corresponding recommended actions described in Section 5.1.

Table 3

Recommended actions derived from the Expert Recommendations for Implementing Change (ERIC) strategies and informant interviews

Related ERIC strategies	Recommended actions
Access new funding	• Secure resources needed for implementation. • Address known barriers such as heavy FDA workload (e.g., by hiring special employees or contractors to support development), disclosure regulations in the CFR, and other potential challenges (e.g., organizational, technical, or legal issues) that may not have been described by informants.
Alter incentive/allowance structures	• Incentivize FDA to provide insights that stakeholders find most valuable. • Address known barriers such as heavy FDA workload (e.g., by hiring special employees or contractors to support development), disclosure regulations in the CFR, and other potential challenges (e.g., organizational, technical, or legal issues) that may not have been described by informants.
Assess for readiness and identify barriers and facilitators	Conduct a formative evaluation (e.g., as done in the informant interviews). This type of evaluation could be repeated locally within individual stakeholder organizations to assess readiness, identify barriers and enablers, and tailor strategies.
Build a coalition	• Engage across the full stakeholder community, seeking diverse expertise and perspectives. • Engage colleagues to contribute ideas, seeking diverse expertise and perspectives.

Related ERIC strategies	Recommended actions
	• Consider good ways to engage stakeholders (e.g., hosting workshops to inform direction and to develop and review the solution). • Provide stakeholders with a roadmap and timeline, showing where stakeholder input will be sought and incorporated. • Collate stakeholders' suggestions and submit these to FDA.
Conduct educational meetings	Provide educational webinars and conference presentations. Invite non-FDA stakeholders involved to be part of a conference panel with FDA where other stakeholders can ask questions.
Conduct educational outreach visits	Champion the solution within professional organizations and the workplace.
Conduct local needs assessment	Conduct a formative evaluation (e.g., as done in the informant interviews). This type of evaluation could be repeated locally within individual stakeholder organizations to assess readiness, identify barriers and enablers, and tailor strategies.
Conduct ongoing training	• Build a strategic communication plan and use multiple channels of communication to create broad awareness of insights. • Create a mechanism to keep the content as current as possible, given the quickly evolving RWD/RWE environment.
Create a learning collaborative	• Engage across the full stakeholder community, seeking diverse expertise and perspectives. • Engage colleagues to contribute ideas, seeking diverse expertise and perspectives. • Consider good ways to engage stakeholders (e.g., hosting workshops to inform direction and to develop and review the solution).

Related ERIC strategies	Recommended actions
	• Provide stakeholders with a roadmap and timeline, showing where stakeholder input will be sought and incorporated. • Collate stakeholders' suggestions and submit these to FDA.
Develop academic partnerships	• Engage across the full stakeholder community, seeking diverse expertise and perspectives. • Engage colleagues to contribute ideas, seeking diverse expertise and perspectives.
Develop educational materials	Provide educational webinars and conference presentations. Invite non-FDA stakeholders involved to be part of a conference panel with FDA where other stakeholders can ask questions.
Distribute educational materials	Provide educational webinars and conference presentations. Invite non-FDA stakeholders involved to be part of a conference panel with FDA where other stakeholders can ask questions.
Fund and contract for the clinical innovation	• Secure resources needed for implementation. • Address known barriers such as heavy FDA workload (e.g., by hiring special employees or contractors to support development), disclosure regulations in the CFR, and other potential challenges (e.g., organizational, technical, or legal issues) that may not have been described by informants.
Identify and prepare champions	Champion the solution within professional organizations and the workplace.
Identify early adopters	Champion the solution within professional organizations and the workplace.

Related ERIC strategies	Recommended actions
Inform local opinion leaders	Champion the solution within professional organizations and the workplace.
Involve executive boards	Engage across the full stakeholder community, seeking diverse expertise and perspectives.
Involve patients/consumers and family members	Engage across the full stakeholder community, seeking diverse expertise and perspectives.
Mandate change	• Advocate for changes needed (e.g., legislative action if needed). • Address known barriers such as heavy FDA workload (e.g., by hiring special employees or contractors to support development), disclosure regulations in the CFR, and other potential challenges (e.g., organizational, technical, or legal issues) that may not have been described by informants.
Obtain formal commitments	Develop memorandums of understanding and other types of contractual arrangements needed for stakeholders to collaborate on solutions.
Prepare patients/consumers to be active participants	Engage across the full stakeholder community, seeking diverse expertise and perspectives.
Promote network weaving	• Engage across the full stakeholder community, seeking diverse expertise and perspectives. • Engage colleagues to contribute ideas, seeking diverse expertise and perspectives. • Consider good ways to engage stakeholders (e.g., hosting workshops to inform direction and to develop and review the solution). • Provide stakeholders with a roadmap and timeline, showing where stakeholder input will be sought and incorporated.

Related ERIC strategies	Recommended actions
	• Collate stakeholders' suggestions and submit these to FDA.
Stage implementation scale up	Stage the development of solutions, starting with the FDA Advancing RWE Program and FDA report on RWE, followed by the tool to help stakeholders apply existing guidance. These may be followed by new legislation to promote guidance on real-world effectiveness endpoints, if desired by stakeholders in preparation for PDUFA VIII in 2027 (Figure 7).
Tailor strategies	Conduct a formative evaluation (e.g., as done in the informant interviews). This type of evaluation could be repeated locally within individual stakeholder organizations to assess readiness, identify barriers and enablers, and tailor strategies.
Use advisory boards and workgroups	Identify advisory boards and workgroups through trusted facilitators (e.g., Reagan Udall Foundation for the FDA).
Work with educational institutions	• Engage across the full stakeholder community, seeking diverse expertise and perspectives. • Engage colleagues to contribute ideas, seeking diverse expertise and perspectives.

Note. CFR = Code of Federal Regulations, ERIC = Expert Recommendations for Implementing Change, FDA = Food and Drug Administration, PDUFA = Prescription Drug User Fee Act

If stakeholders were to invest in the proposed solutions, more detailed tactical plans that describe activities, resources, timing, and governance for building the solutions would need to be developed. For all solutions, implementation is a critical component since achieving clarity among stakeholders is dependent on their awareness, desire, and ability to understand and apply measurement science and regulatory policies and precedent. Simply publishing or presenting at a conference may be insufficient for generating broad awareness and application.

It is also important to recognize that awareness of solutions by a single individual or FDA division does not constitute awareness for the full organization. To increase awareness broadly, Powell and colleagues (2015) proposed steps such as identifying and preparing champions within stakeholder groups and informing local opinion leaders and executive boards. Multiple channels of communication are likely needed and proposed in this plan for change. For clinical outcome assessment (COA), an analogous implementation challenge was addressed in PDUFA VII by requiring FDA to conduct internal training and consultations across review divisions as well as external targeted outreach including presentations, sessions, and other resources (FDA 2022). Similarly, the next round of PDUFA authorization in 2027 could include a similar provision for real-world effectiveness endpoints. Future implementation could be guided, and implementation outcomes measured, using frameworks like those of the PROSCI ADKAR model of individual change (PROSCI n.d.) and Proctor and colleagues (2011).

5.4.2. Strengths and limitations of the research and plan for change

An important strength of the research and plan for change is the deep and diverse expertise of the informants. Informants' diverse areas of measurement expertise and stakeholder perspectives provided rich details and analogous historic examples, current environmental factors, potential solutions, and likely enablers and barriers, all of which were significant inputs for building the plan for change and helped make important connections needed to optimize solutions. However, there were fewer stakeholders currently affiliated with an academic organization, hospital or healthcare organization, patient organization, or current FDA employees. Another related limitation is potential selection bias in recruiting informants. Informants were identified based on their expertise on real-world effectiveness endpoints or other types of endpoints used in clinical development of therapies. Because of their specialized expertise, informants may be more likely to rate this topic as a top priority than would other RWE and regulatory stakeholders who do not have similar expertise in measurement science. Regardless, it

is noteworthy that informants who were former FDA reviewers and other FDA representatives described areas that lack clarity and suggested solutions.

Another limitation is the author's own judgment or experience that may have contributed to unconscious bias when interpreting results. The author is an employee of one stakeholder type (drug and device manufacturer) and has previously helped develop a similar solution to the tool proposed in the dissertation (Singh et al. 2023). Reflexivity was applied throughout the research process through negative case analysis as themes were constructed and memos examining personal reactions during the coding process. To the extent possible, the interview questions were written to avoid assumptions about what clarity means or the importance of achieving clarity on regulatory acceptable real-world effectiveness endpoints for others. Informants were asked to describe their own perspectives on all topics. Their answers did not always align with the author's perspectives but were incorporated in the themes. Dual coding of interviews could possibly have enhanced reflexivity and trustworthiness of themes but was not feasible in the dissertation.

A potential criticism or limitation of solutions in the plan for change is that they may ultimately do little to remove hurdles for using real-world effectiveness endpoints in regulatory decisions. Examples of hurdles shared by informants were post hoc decisions about acceptability and ambiguous or unfit expectations about the requisite magnitude of real-world treatment effects. Another example shared was that some RWD simply are not fit to inform some decisions. Finally, there may be skepticism about how effective any of the macro-level solutions proposed will be. One informant expressed skepticism that clarity would improve until RWD quality improves:

> I don't know how much is really going to change, even if we have more examples and more clarity on endpoints, and I say that only because I think we've got to go a little bit upstream to data collection and improve data collection and have incentives for better

> data collection or have a more realistic understanding where it's appropriate to use real-world evidence. (Drug and device manufacturer leader and former FDA representative)

Still, the proposed solutions represent important first steps and align with comments from informants who expressed the importance of considering the value of incremental innovation and maintaining a clear focus (not trying to do too much) when building a solution. Given the growing impact of RWE for FDA decision making for all stakeholders, waiting is not an option, in the author's opinion. In fact, until greater clarity on regulatory acceptable real-world endpoints is achieved, stakeholders may be averse to invest in solutions that go even farther upstream to improve data collection and quality of RWD. Stakeholders may prefer greater clarity on what is regulatory acceptable to help provide a compass or direction as to what investments are most important to make in the RWD.

Finally, none of the informants specifically mentioned the new FDA Rare Disease Endpoint Advancement (RDEA) Pilot Program, which was initiated in the Food and Drug Omnibus Reform Act (FDORA 2022). The goal of this program is to increase the opportunities for sponsors to interact with FDA to develop efficacy endpoints for drug development for rare diseases. The author participated in an FDA seminar to introduce the program in 2023 and inquired whether real-world endpoints would be considered within the scope of this program; no reply was received, and the examples shared during the seminar were exclusively from the clinical trial setting. However, at least one use of RWE is described in the Omnibus Act—RWE to support the validation of efficacy endpoints. The RDEA program was not included in the proposed plan for change, but stakeholders could additionally watch this space and the FDA workshops, three of which are required to occur no later than September 30, 2026.

5.4.3. Anticipated global public health impact

While this plan is tailored to the US regulatory environment, the need is global. Across geographies, the scientific underpinnings are likely to be similar, but differences in the regulatory

policy pathways and actions needed should be considered. This plan for change could be further customized for other countries by following a formative evaluation process (i.e., conducting an assessment for readiness and identifying potential solutions, barriers, and enablers) like the approach used here. Alternatively, new tools or guidance built for the US could subsequently be incorporated globally through organizations like ICH. Many past regulatory efforts in medical product development started in a single geography and were later adopted or adapted by regulators in other regions.

Achieving greater clarity is likely to have significant public health impact for medical treatments for patients. Clarity on real-world effectiveness endpoints could help accelerate patient access to therapy and minimize patient burden in clinical trials. Examples include fewer patients needed on placebo arms in clinical trials (by using real-world control arms with acceptable real-world effectiveness endpoints), allowing more patients to receive promising experimental treatments instead. An example of minimizing patients' burden in clinical trials is fewer required clinical trial procedures by using patients' RWD. Minimizing patients' burdens may encourage more patients to enroll in clinical trials and prioritization of clinical trial procedures for situations where they are truly needed to answer the research question. Furthermore, clinical research efforts to develop new treatments could be streamlined and global treatment access accelerated, if the evidentiary standards were more clear and globally aligned. Achieving greater clarity is likely to reduce not only time, but also cost, waste, and frustration in clinical research. For example, both time and cost savings could be realized by better recognition of how to identify an acceptable endpoint early (before the study is conducted) and right-sized endpoint validation efforts. Clarity would help increase stakeholder confidence to invest in improving RWD quality across therapeutic areas and help empower a learning health system. Clarity could lead to improved collection and quality of healthcare data in routine treatment of patients such that real-world data can inform more than patient-level decisions but also population-level decisions that regulators like FDA must make. Clarity can help inform better health decisions, for example, by

supplementing evidence generated in RCTs with RWE, which is more generalizable and reflective of real-world healthcare practice. Evidence could be more easily be generated in patient populations who are difficult to study within clinical trials, including evidence on patient-centric endpoints (i.e., real-world endpoints that are more meaningful to patients, caregivers, and providers than clinical trial endpoints). This evidence could be more easily leveraged within product labels to improve healthcare providers' understanding of real-world benefits and risks of treatment, including off-label treatment outcomes. Finally, clarity could help promote more holistic and cross-therapeutic use of RWE, beyond oncology and rare diseases.

Finally, although the impact of achieving greater clarity was often expressed by informants in terms of benefits, the strategic details matter. An undesirable outcome could result from a solution that is misaligned with stakeholder needs (e.g., FDA reports on RWE use that do not provide the information stakeholders need) and/or badly timed (e.g., premature regulatory policy that is overly conservative and difficult to adapt).

5.5. Conclusions

In conclusion, the recommended plan for change to create clarity on regulatory acceptable real-world effectiveness endpoints comprises several solutions. While some solutions are already in progress to increase the number of stakeholders experiences with RWE for regulatory decision making (e.g., FDA Advancing RWE Program and FDA report on RWE for regulatory review), it is unclear what insights on regulatory acceptable real-world effectiveness endpoints will be easily gleaned from these. Stakeholders should consider what areas lack clarity, beyond the areas already identified through the literature review and informant interviews, and advocate for information from FDA on these topics. Parallel implementation of other solutions is likely needed (e.g., a tool to help stakeholders navigate the existing guidance and precedents on real-world effectiveness endpoints), with a regulatory guidance on real-world effectiveness endpoints to possibly follow. Good engagement and transparency across the stakeholder

community or communities, both in developing the individual solutions and also showing how solutions relate to one another, are essential to make the most meaningful impact.

The use of RWE to support regulatory decisions is likely to increase over time. The current lack of clarity on regulatory acceptable real-world endpoints poses a growing risk of delayed or lost new therapy opportunities. As one informant expressed, “I think that if we continue to drag our feet here development timelines will continue to be what they are.” However, the status quo is unacceptable. Changes in today’s environment demand a response. Some of these environmental changes include a quickly evolving RWD and technology landscape, a growing number of accountable care organizations (ACOs) and learning health system needs, increasing development of cell and gene therapies that require long-term (e.g., 15 years) evidence of effectiveness and safety from RWD, and shortened timelines to recoup drug development investments with the passing of the US Inflation Reduction Act (IRA 2022). Central to all these environmental factors, and most importantly, are patients waiting to access treatments they need.

REFERENCES

21st Century Cures Act, 42, Pub. L. No. 114-255, 201 Stat. (2016). https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf

Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.126 (1985). https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-D/section-314.126

Anney, V.N. (2014). Ensuring the quality of findings of qualitative research: looking at trustworthiness criteria. *Journal of Emerging Research Trends in Education Research and Policy Studies 5*(2), 272-281.

Bardach, E. (2009). *A practical guide for policy analysis: The eightfold path to more effective problem solving, fourth edition*. CQ Press College.

Beyrer, J., Abedtash, H., Hornbuckle, K., & Murray, J. F. (2022). A review of stakeholder recommendations for defining fit-for-purpose real-world evidence algorithms. *Journal of comparative effectiveness research, 11*(7), 499–511. https://doi.org/10.2217/cer-2022-0006.

Braun, V. and Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology, 3*(2), 77-101.

Campbell, U., Kim, S., Toh, D., Kent, S., Brown, J., & Rodriguez-Watson, C. (2022, Aug 28). Session 4: What do real world data validation best practices look like? Operationalizing guidance for real-world studies intended for decision-making., 38th annual ICPE conference. [Symposia and Workshops]. 38th ICPE (annual conference of the International Society for Pharmacoepidemiology 2022), Copenhagen, Denmark. https://pharmacoepi.org/pub/?id=A15839AD-B6E4-D28E-1C20-FA5A5B1D2B50

Chamberlain, C. X., Faust, E., Goldschmidt, D., Webster, N., Boscoe, A. N., Macaulay, D., & Peters, M. L. (2021). Burden of illness for patients with cholangiocarcinoma in the

United States: a retrospective claims analysis. *Journal of gastrointestinal oncology, 12*(2), 658–668. https://doi.org/10.21037/jgo-20-544

Chen, H.T. (2015). *Practical program evaluation: Theory-driven evaluation and the integrated evaluation perspective* (2nd ed). Sage Publications.

Clarridge, K., Chin, S., Eworuke, E., & Seymour, S. (2021). A boxed warning for Montelukast: The FDA perspective. *The journal of allergy and clinical immunology. In practice*, 9(7), 2638–2641. https://doi.org/10.1016/j.jaip.2021.02.057

Cocoros, N. M., Arlett, P., Dreyer, N. A., Ishiguro, C., Iyasu, S., Sturkenboom, M., Zhou, W., & Toh, S. (2021). The Certainty Framework for assessing real-world data in studies of medical product safety and effectiveness. *Clinical pharmacology and therapeutics, 109*(5), 1189–1196. https://doi.org/10.1002/cpt.2045

Collins, J. (2001). Good to great. Random House Business Books.

Duke Margolis Center for Health Policy. (2018, October 1). *Characterizing RWD quality and relevancy for regulatory purposes*. https://healthpolicy.duke.edu/sites/default/files/2020-03/characterizing_rwd.pdf

Duke Margolis Center for Health Policy. (2020, August 28). *A roadmap for developing study endpoints in real-world settings*. https://healthpolicy.duke.edu/sites/default/files/2020-08/Real-World%20Endpoints.pdf

FDA Reauthorization Act of 2017, Pub. L. No. 115-52, 131 Stat. 1005 (2017). https://www.congress.gov/115/plaws/publ52/PLAW-115publ52.pdf

[FDA] United States Food and Drug Administration. (2013). Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets. https://www.fda.gov/media/79922/download

[FDA] United States Food and Drug Administration. (2018, December). Framework for FDA's real-world evidence program. https://www.fda.gov/media/120060/download

[FDA] United States Food and Drug Administration. (2009). Patient-reported outcome measures: use in medical product development to support labeling claims. https://www.fda.gov/media/77832/download

[FDA] United States Food and Drug Administration. (May 23, 2019). BLA clinical review memorandum for Zolgensma for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene. https://www.fda.gov/media/128116/download

[FDA] United States Food and Drug Administration. (2020a). *Real-world evidence*. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

[FDA] United States Food and Drug Administration. (2020b). Center for Drug Evaluation and Research application number:761163orig1s000: other review(s). *Division of Epidemiology I (DEPI-I) review of the final report of a real-world evidence for efficacy study (MOR208C206)*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761163Orig1s000OtherR.pdf

[FDA] United States Food and Drug Administration. (2020c). Center for Drug Evaluation and Research application number: 761163orig1s000: Multi-discipline review. *BLA multi-disciplinary review and evaluation BLA 761163 Monjuvi (tafasitamab-cxix)*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761163Orig1s000MultidisciplineR.pdf

[FDA] (2021a, July 16). Center for Drug Evaluation and Research application number: 50708s053, 50709s045, 210115s005. Approval package for Prograf capsules, injection, oral suspension for the prevention of rejection in lung transplantation. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/050708Orig1s053;%20050709Orig1s045;%20210115Orig1s005.pdf

[FDA] United States Food and Drug Administration. (2021b). Real-world data: Assessing electronic health records and medical claims data to support regulatory decision-making for drug and biological products. https://www.fda.gov/media/152503/download

[FDA] United States Food and Drug Administration. (2021c). Real-world data: assessing registries to support regulatory decision-making for drug and biological products guidance for industry. https://www.fda.gov/media/154449/download

[FDA] United States Food and Drug Administration. (2021d). Data standards for drug and biological product submissions containing real-world data. https://www.fda.gov/media/153341/download

[FDA] United States Food and Drug Administration. (2021e). Digital health technologies for remote data acquisition in clinical investigations. https://www.fda.gov/media/155022/download

[FDA] United States Food and Drug Administration. (2021f). 21st Century Cures Act report regarding the qualification process under Section 507 of the Federal Food, Drug, and Cosmetic Act. https://www.fda.gov/media/155003/download?attachment

[FDA] United States Food and Drug Administration. (2023a). Demonstrating substantial evidence of effectiveness based on one adequate and well-controlled clinical investigation and confirmatory evidence. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-based-one-adequate-and-well-controlled-clinical

[FDA] United States Food and Drug Administration. (2023b). Advancing real-world evidence program. https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program

[FDA] United States Food and Drug Administration. (2023c). FDA patient-focused drug development guidance series for enhancing the incorporation of the patient's voice in medical product development and regulatory decision making.

https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

[FDA] United States Food and Drug Administration. (2023d). PDUFA VII commitment letter. https://www.fda.gov/media/151712/download?attachment

[FDA] United States Food and Drug Administration. (2023e). OCE scientific collaborative. https://www.fda.gov/about-fda/oncology-center-excellence/oce-scientific-collaborative

[FDA] United States Food and Drug Administration. (2023f). Drug development tool (DDT) qualification programs. https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs

[FDA] United States Food and Drug Administration. (2023g). Complex innovative trial design meeting program. https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

[FDA] United States Food and Drug Administration. (2023h). RWD and RWE-focused demonstration projects. https://www.fda.gov/science-research/real-world-evidence/rwd-and-rwe-focused-demonstration-projects

FDA-NIH Biomarker Working Group. (2021, Jan 25). *BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]*. Silver Spring (MD): Food and Drug Administration (US); 2016-. *Glossary*. 2016 Jan 28 [Updated 2021 Jan 25]. https://www.ncbi.nlm.nih.gov/books/NBK338448/ Co-published by National Institutes of Health (US), Bethesda (MD).

[FDORA] Food and Drug Omnibus Reform Act of 2022 in Consolidated Appropriations Act, Pub. L. No. 117-328 (2022). https://www.congress.gov/117/plaws/publ328/PLAW-117publ328.pdf

Forum on Neuroscience and Nervous System Disorders; Board on Health Sciences Policy; Institute of Medicine. (2014, Feb 6). *Drug development challenges.* In *Improving and accelerating therapeutic development for nervous system disorders: workshop summary*.

Washington (DC): National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK195047/

[HMA EMA] Heads of Medicines Agencies and European Medicines Agency Big Data Steering Group. (2022, Sept 30). Data quality framework for EU medicines regulation. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/data-quality-framework-eu-medicines-regulation_en.pdf

[ICH] International Conference on Harmonisation. (2019, Nov 20). Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1). https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

[ICH] International Conference on Harmonisation. (2023, June 30). ICH Reflection paper on proposed international harmonisation of real-world evidence terminology and convergence of general principles regarding planning and reporting of studies using real-world data, with a focus on effectiveness of medicines. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-reflection-paper-proposed-international-harmonisation-real-world-evidence-terminology_en.pdf

[IRA] Inflation Reduction Act of 2022. Pub. L. No. 117-169 (2022). https://www.congress.gov/117/plaws/publ169/PLAW-117publ169.pdf

Kania J. and Kramer M. (2011). Collective impact. *Stanford Social Innovation Review 9*(4): 36–41. https://doi.org/ 10.48558/5900-kn19

Kawai, A., Goto, T., Shibata, T., Tani, K., Mizutani, S., Nishikawa, A.,...Ueda, R. (2018). Current state of therapeutic development for rare cancers in Japan, and proposals for improvement. *Cancer science, 109*(5), 1731–1737. https://doi.org/10.1111/cas.13568

Khorana, A. A., Kuderer, N. M., McCrae, K., Milentijevic, D., Germain, G., Laliberté, F., MacKnight, S. D., Lefebvre, P., Lyman, G. H., & Streiff, M. B. (2021). Healthcare costs

of patients with cancer stratified by Khorana score risk levels. *Journal of medical economics, 24*(1), 866–873. https://doi.org/10.1080/13696998.2021.1948681

Levenson M. S. (2020). Regulatory-grade clinical trial design using real-world data. *Clinical trials (London, England), 17*(4), 377–382. https://doi.org/10.1177/1740774520905576

Ma, X., Bellomo, L., Magee, K., Bennette, C. S., Tymejczyk, O., Samant, M., Tucker, M., Nussbaum, N., Bowser, B. E., Kraut, J. S., & Bourla, A. B. (2021). Characterization of a real-world response variable and comparison with RECIST-based response rates from clinical trials in advanced NSCLC. *Advances in therapy, 38*(4), 1843–1859. https://doi.org/10.1007/s12325-021-01659-0.

Mahendraratnam, N., Mercon, K., Gill, M., Benzing, L., & McClellan, M. B. (2022). Understanding use of real-world data and real-world evidence to support regulatory decisions on medical product effectiveness. *Clinical pharmacology and therapeutics, 111*(1), 150–154. https://doi.org/10.1002/cpt.2272

Nunes, A. P., Loughlin, A. M., Qiao, Q., Ezzy, S. M., Yochum, L., Clifford, C. R., Gately, R. V., Dore, D. D., & Seeger, J. D. (2017). Tolerability and effectiveness of Exenatide once weekly relative to basal insulin among Type 2 diabetes patients of different races in routine care. *Diabetes therapy : research, treatment and education of diabetes and related disorders, 8*(6), 1349–1364. https://doi.org/10.1007/s13300-017-0314-z

Pettit, S. D., Silberman, P., Hassmiller Lich, K., Kirch, R. A., Lipshultz, S. E., Teal, R., & Basch, E. (2019). Stakeholder perspectives on addressing adverse events from adjuvant cancer therapy: A qualitative study. *Cancer, 125*(24), 4471–4480. https://doi.org/10.1002/cncr.32448

Platt, R., Carnahan, R. M., Brown, J. S., Chrischilles, E., Curtis, L. H., Hennessy, S.,…Weiner, M. G. (2012). The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. *Pharmacoepidemiology and drug safety, 21 Suppl 1*, 1–8. https://doi.org/10.1002/pds.2343

[PMDA] Japan Pharmaceuticals and Medical Devices Agency. (2020). *Formulation of "basic concepts for validating outcome definitions used in post-marketing database surveillance"*. https://www.pmda.go.jp/files/000235927.pdf

Powell, B. J., Waltz, T. J., Chinman, M. J., Damschroder, L. J., Smith, J. L., Matthieu, M. M., Proctor, E. K., & Kirchner, J. E. (2015). A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. *Implementation science : IS, 10,* 21. https://doi.org/10.1186/s13012-015-0209-1

Proctor, E., Silmere, H., Raghavan, R., Hovmand, P., Aarons, G., Bunger, A., Griffey, R., & Hensley, M. (2011). Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Administration and policy in mental health, 38*(2), 65–76. https://doi.org/10.1007/s10488-010-0319-7

PROSCI. (n.d.). The Prosci ADKAR Model: a goal-oriented change management model to guide individual and organizational change. https://www.cmcpartnership.com/hubfs/ADKAR%20eBook/1_ADKAR-Model-overview-eBook.pdf

Purpura, C. A., Garry, E. M., Honig, N., Case, A., & Rassen, J. A. (2022). The role of real-world evidence in FDA-approved new drug and biologics license applications. *Clinical pharmacology and therapeutics, 111*(1), 135–144. https://doi.org/10.1002/cpt.2474

Richardson, E., Daniel, G., Joy, D. R., Kweder, S. L., Maloney, D. M., Raggio, M. J., & Jarow, J. P. (2018). Regional Approaches to expedited drug development and review: Can regulatory harmonization improve outcomes?. *Therapeutic innovation & regulatory science, 52*(6), 793–798. https://doi.org/10.1177/2168479018764664

RWE Alliance. (2021, May 19). *Leading real-world data and analytics organizations form industry coalition to advance policies to support regulatory use of real-world evidence*. https://rwealliance.org/2021/05/19/leading-real-world-data-and-analytics-organizations-

form-industry-coalition-to-advance-policies-to-support-regulatory-use-of-real-world-evidence/

Sansing-Foster, V., Haug, N., Mosholder, A., Cocoros, N. M., Bradley, M., Ma, Y.,…Eworuke, E. (2021). Risk of Psychiatric Adverse Events Among Montelukast Users. *The journal of allergy and clinical immunology. In practice, 9*(1), 385–393.e12. https://doi.org/10.1016/j.jaip.2020.07.052

Sentinel. (n.d.). *About the Food and Drug Administration (FDA) Sentinel Initiative*. https://www.sentinelinitiative.org/about

Shah, R., Corman, S., Shah, A., Kebede, N., & Nwankwo, C. (2021). Phase-specific and lifetime economic burden of cervical cancer and endometrial cancer in a commercially insured United States population. *Journal of medical economics, 24*(1), 1221–1230. https://doi.org/10.1080/13696998.2021.1996958

Sharma, V. (2021a, August 26). *Real-world data: 'Don't Take Your Foot Off The Gas.'* https://pink.pharmaintelligence.informa.com/PS144852/Real-World-Data-Dont-Take-Your-Foot-Off-The-Gas

Sharma, V. (2021b, June 15). *ICH plans new guideline on pharmacoepidemiological studies using RWD*. https://pink.pharmaintelligence.informa.com/PS144483/ICH-Plans-New-Guideline-On-Pharmacoepidemiological-Studies-Using-RWD

Silverman, B. (2011, June 1). *Siren song of lupus has left a legacy of failed trials*. https://pink.pharmaintelligence.informa.com/PS004770/Siren-Song-Of-Lupus-Has-Left-A-Legacy-Of-Failed-Trials

Singh, S., Beyrer, J., Zhou, X., Swerdel, J., Harvey, R. A., Hornbuckle, K.,…Rodriguez-Watson, C. (2023). Development and evaluation of the Algorithm CErtaInty Tool (ACE-IT) to assess electronic medical record and claims-based algorithms' fit for purpose for safety outcomes. *Drug safety*, 46(1), 87–97. https://doi.org/10.1007/s40264-022-01254-4

Sutter, S. (2015, September 22). *Patient engagement needs 'regulatory guardrails' to encourage firms, advocates say*. https://pink.pharmaintelligence.informa.com/PS078940/Patient-Engagement-Needs-Regulatory-Guardrails-To-Encourage-Firms-Advocates-Say

Sutter, S. (2020, August 17). *Real-world evidence: Epizyme's epithelioid sarcoma natural history study falls flat at US FDA*. https://pink.pharmaintelligence.informa.com/PS142109/Real-World-Evidence-Epizymes-Epithelioid-Sarcoma-Natural-History-Study-Falls-Flat-At-US-FDA

Torres, A. Z., Nussbaum, N. C., Parrinello, C. M., Bourla, A. B., Bowser, B. E., Wagner, S.,…Miksad, R. A. (2022). Analysis of a real-world progression variable and related endpoints for patients with five different cancer types. *Advances in therapy, 39*(6), 2831–2849.

Transcelerate. (2022). RWD audit readiness considerations – Draft for public review December 2022. https://www.transceleratebiopharmainc.com/wp-content/uploads/2022/12/RWD-Audit-Readiness-Considerations-Document.pdf

Wang, S. V., Schneeweiss, S., RCT-DUPLICATE Initiative, Franklin, J. M., Desai, R. J., Feldman, W.,…Quinto, K. (2023). Emulation of randomized clinical trials with nonrandomized database analyses: Results of 32 clinical trials. *JAMA*, 329(16), 1376–1385. https://doi.org/10.1001/jama.2023.4221

Weidman J.R. & Belsky K. (2020, February 13). *Estimating the probability of regulatory registration success*. https://www.raps.org/news-and-articles/news-articles/2020/2/estimating-the-probability-of-regulatory-registrat

Williams, M. & Moser, T. (2019). The art of coding and thematic exploration in qualitative research. *International Management Review, 15*(1), 45-55.

APPENDIX 1. PRIMARY INTERVIEW GUIDE

Informant:

Date:

Start time:

End time:

Key interview questions:

1. *Gaps in US regulatory clarity on acceptable real-world endpoints*
2. *Plan for change (actions and implementation)*
3. *Determinants (facilitators and barriers) of the plan for change*

Questions may be omitted when the informant does not have the expertise to answer the question.

1. Opening statements

Thank you for agreeing to be interviewed. Did you have any questions about the purpose of the interview today or the information sheet I sent earlier? Do I have your consent to be interviewed?

To get started, may I collect a few characteristics from you?

Characteristics	
Stakeholder type	• Drug and device manufacturers • Real-world data and analytics companies • Prescribers • Patients • Congress • FDA

	• Experts in analogous field (*e.g.*, clinical outcome assessment, digital healthcare data, etc)
Position/title	Record title
Description of what you do in this role	Record description
Sex or gender	Record description
Years working in RWE and/or policy	Record number
Experience with real-world evidence (RWE)	• Low • Medium • High
Describe your experience with RWE (*e.g.*, generating RWE, reviewing RWE to inform decisions)	Record description
Experience with real-world endpoint validation or RWE algorithm validation	• Low • Medium • High
Describe your experience with real-world endpoint or RWE algorithm validation (*e.g.*, conducting validation studies, reviewing and applying the findings of validation studies to research you are conducting or reviewing)	Record description
Experience with policy (*e.g.*, FDA policy) related to RWE	• Low • Medium • High

Describe your experience with policy related to RWE? (*e.g.*, drafting policy, informing or influencing policy)	Record description
Professional organizations or affiliations you belong to related to this topic	Record organizations/affiliations
Describe your experience with other topics that you think may be relevant to this discussion (*e.g.*, clinical outcome assessments, digital healthcare data, etc)	Record description

Thank you very much. In addition to fulfilling the dissertation requirement, I am genuinely interested in understanding how others think about regulatory acceptable real-world endpoints. My focus is primarily on the United States regulatory environment (FDA) and real-world endpoints of effectiveness, which I define as measures of a medical product's effectiveness applied to real-world data, that is, data collected in a routine healthcare setting (think claims and EMR data for example). For example, quarterly changes in HbA1c using lab values in EMR data.
Do you have any questions about this definition of real-world effectiveness endpoints?
I am interested in hearing your views on safety or other types of endpoints as well. There are no wrong answers. My purpose is simply to understand how you view these topics.
I am going to go off video now in order to take notes and not distract your train of thought. Feel free to leave your video on or off as you prefer.

2. Regulatory clarity and perceived gaps

A. What does regulatory clarity mean to you?

B. Do we have regulatory clarity on real-world effectiveness endpoints in the US?

If yes, just to confirm, you feel that there is clear direction on what makes a real-world endpoint of effectiveness acceptable to FDA?

C. Where do you see regulatory clarity on acceptable real-world effectiveness endpoints?

D. Where do you think we are lacking regulatory clarity on acceptable real-world effectiveness endpoints?

Prompts: Do you think we have regulatory clarity in the US on these questions…

- What are acceptable approaches to validating real-world endpoints for different use cases (*e.g.*, external control arms, natural history study, etc.)?

  Examples of acceptable approaches could include criterion validity, comparing with an external benchmark/group, clinical or predictive validity, concordance/correlation (*e.g.*, comparability of real-world endpoint between clinical trial and ECA patient groups), inter-rater agreement, measuring data completeness, face validity (SME agreement and/or stakeholder alignment), etc.
- What are acceptable thresholds for the evidentiary support to demonstrate that a real-world endpoint is fit for purpose (either quantitative or qualitative; for example, what PPV is acceptable)?
- How to demonstrate an acceptable level of generalizability of the real-world endpoint across different RWD sources?
- What role health equity should play, if any, in determining whether a real-world endpoint is acceptable?
- What role patient relevance or meaningfulness should play, if any, in determining whether a real-world endpoint is acceptable?

E. You described X, Y, and Z gaps. How would you prioritize those gaps in terms of importance? Which is the most important gap? Why? What could be the consequence or result of not addressing this gap?

F. Where does this overall topic (US regulatory clarity on acceptable real-world effectiveness endpoints) rank in your perception of priorities relative to other RWE regulatory

related needs? For example, if regulatory clarity of acceptable real-world endpoints in the US is not achieved, what problem or impact does that make?

3. **Plan for change**

G. You said the top gap(s) was X. What solutions do you think would address this gap?

Prompts: scientific demonstration projects, legislation from Congress, FDA guidance document, tools on the FDA web site, additional communication mechanisms with FDA, something else

H. How would you prioritize these solutions (which is the most important)? Why? What would be the outcomes or consequences of implementing this solution?

I. What actions are needed to achieve this solution?

Prompts: we need Congress or FDA to do X, life sciences organizations to do Y, real-world data companies to do Z

J. Who are the stakeholders and what are their roles?

K. What are good ways to engage these stakeholder(s)?

4. Determinants

L. You said the top solution(s) was X. What would help to facilitate or enable this solution? What assumptions would need to be true to achieve this solution and ensure a successful outcome?

M. Do you see any barriers or risks to this solution? What could prevent the solution or a successful outcome with this solution? If yes, what are they?

Prompt: Is timing an important consideration? Why or why not?

N. Can you think of any similar efforts in the past to achieve regulatory clarity on similar RWE or other topics?

Follow-up questions: Which past efforts were successful, or which failed? Why?

5. Ending questions

O. If regulatory clarity on real-world effectiveness endpoints were achieved, what do you think would be the impact on the various stakeholders?

P. Are there any other important perspectives you would like to share about a real-world endpoints policy?

1. Ending comment

Thank you for your time and sharing your perspectives and expertise with me. With your permission, I may follow up later to check whether I have interpreted your comments correctly or if anything seemed unclear in the interview. Would you like to be invited to view the dissertation defense and/or read the results of this research when they are presented?

APPENDIX 2. ALTERNATIVE INTERVIEW GUIDE

For informants who are not RWE subject matter experts but have expertise in analogous fields (e.g., clinical outcome assessment, digital healthcare data, etc)

Informant:

Date:

Start time:

End time:

Key interview questions:

1. *Plan for change (actions and implementation)*
2. *Determinants (facilitators and barriers) of the plan for change*

Questions may be omitted when the informant does not have the expertise to answer the question.

1. Opening statements

Thank you for agreeing to be interviewed. Did you have any questions about the purpose of the interview today or the information sheet I sent earlier? Do I have your consent to be interviewed?

To get started, may I collect a few characteristics from you?

Characteristics	
Stakeholder type	• Drug and device manufacturers • Real-world data and analytics companies • Prescribers • Patients • Congress • FDA

	• Experts in analogous field (*e.g.*, clinical outcome assessment, digital healthcare data, etc)
Position/title	Record title
Description of what you do in this role	Record description
Sex or gender	Record description
Years working in RWE and/or policy	Record number
Experience with real-world evidence (RWE)	• Low • Medium • High
Describe your experience with RWE (*e.g.*, generating RWE, reviewing RWE to inform decisions)	Record description
Experience with real-world endpoint validation or RWE algorithm validation	• Low • Medium • High
Describe your experience with real-world endpoint or RWE algorithm validation (*e.g.*, conducting validation studies, reviewing and applying the findings of validation studies to research you are conducting or reviewing)	Record description
Experience with policy (*e.g.*, FDA policy) related to RWE	• Low • Medium • High

Describe your experience with policy related to RWE? (*e.g.*, drafting policy, informing or influencing policy)	Record description
Professional organizations or affiliations you belong to related to this topic	Record organizations/affiliations
Describe your experience with other topics that you think may be relevant to this discussion (*e.g.*, clinical outcome assessments, digital healthcare data, etc)	Record description

Thank you very much. In addition to fulfilling the dissertation requirement, I am interested in hearing your views about topic X [topic of expertise] and how learnings from this topic may help with a similar topic of how best to achieve regulatory clarity on acceptable real-world endpoints in the US. There are no wrong answers. My purpose is simply to understand how you view these topics.

I am going to go off video now in order to take notes and not distract your train of thought. Feel free to leave your video on or off as you prefer.

2. Regulatory clarity and perceived gaps

A. What does regulatory clarity mean to you?

B. Do we have regulatory clarity on topic X in the US?

C. Where do you see regulatory clarity on topic X?

D. Where do you think we are lacking regulatory clarity on topic X?

Prompts: Do you think we have regulatory clarity in the US on…

- What are acceptable approaches to validating X for different use cases (*e.g.*, external control arms, natural history study, etc.)

  Examples of acceptable approaches could include criterion validity, comparing with an external benchmark/group, clinical or predictive validity, concordance/correlation (*e.g.*,

comparability of real-world endpoint between clinical trial and ECA patient groups), inter-rater agreement, measuring data completeness, face validity (SME agreement and/or stakeholder alignment), etc.

- What are acceptable thresholds for the evidentiary support to demonstrate that X is fit for purpose (either quantitative or qualitative; for example, what PPV is acceptable)?
- How to demonstrate an acceptable level of generalizability of X across different data sources?
- What role health equity should play, if any, in determining whether X is acceptable?
- What role patient relevance or meaningfulness should play, if any, in determining whether X is acceptable?

E. You described X, Y, and Z gaps. How would you prioritize those gaps in terms of importance? Which is the most important gap? Why? What could be the consequence or result of not addressing this gap?

~~F. Where does this topic (US regulatory clarity on acceptable real-world effectiveness endpoints) rank in your perception of priorities relative to achieving regulatory clarity on other RWE topics? For example, if these gaps were not addressed, what problem or impact does that make?~~

3. **Plan for change**

G. You said the top gap(s) was X. What solutions do you think would address this gap?

Prompts: scientific demonstration projects, legislation from Congress, FDA guidance document, tools on the FDA web site, additional communication mechanisms with FDA, something else

H. How would you prioritize these solutions (which is the most important)? Why? What would be the outcomes or consequences of implementing this solution?

I. What actions are needed to achieve this solution?

Prompts: we need Congress or FDA to do X, life sciences organizations to do Y, real-world data companies to do Z

J. Who are the stakeholders and what are their roles?

K. What are good ways to engage these stakeholder(s)?

4. Determinants

L. You said the top solution(s) was X. What would help to facilitate or enable this solution? What assumptions would need to be true to achieve this solution and ensure a successful outcome?

M. Do you see any barriers or risks to this solution? What could prevent the solution or a successful outcome with this solution? If yes, what are they?

Prompt: Is timing an important consideration? Why or why not?

N. Can you think of any similar efforts in the past to achieve regulatory clarity on similar RWE or other topics?

Follow-up questions: Which past efforts were successful, or which failed? Why?

5. Ending questions

O. If regulatory clarity on X topic were achieved, what do you think would be the impact on the various stakeholders?

P. Are there any other important perspectives you would like to share about topic X?

2. Ending comment

Thank you for your time and sharing your perspectives and expertise with me. With your permission, I may follow up later to check whether I have interpreted your comments correctly or if anything seemed unclear in the interview. Would you like to be invited to

view the dissertation defense and/or read the results of this research when they are presented?

APPENDIX 3. PARTICIPANT INFORMATION SHEET

Participant Information Sheet for interviews on achieving regulatory clarity on acceptable real-world effectiveness endpoints in the United States (US)*

*adapted from Nyanchoka L, et al. BMJ Open 2020;10:e039932. doi: 10.1136/bmjopen-2020-039932

You are invited to take part in this interview on achieving regulatory clarity on acceptable real-world effectiveness endpoints in the US. Before you decide whether to participate, you should understand why the interview is being conducted and what it will involve. Please take your time to read the following information carefully and feel free to ask if you need more information or if there is anything that you do not understand.

What is the purpose of the interview?

This interview aims to explore perspectives on current gaps, potential solutions, and how to implement those solutions. The interviewer is researching this topic as part of her dissertation in the Indiana University Doctorate of Public Health (DrPH) program and chose this topic because she is genuinely interested in understanding others' perspectives on real-world endpoints. She routinely deals with real-world endpoints in her research career as a real-world evidence (RWE) scientist at a pharmaceutical company. She recognizes that other experts in this area may have unique perspectives based on their backgrounds or other career experiences. Therefore, there may be diverse views about this topic.

Why have I been chosen to take part?

You have been asked to take part because of you were identified as someone with expertise and/or interest in this topic.

Do I have to be interviewed?

It is your decision whether or not you agree to be interviewed. If you decide to be interviewed, you will be asked to verbally consent. If you agree to be interviewed but then change your mind, you are free to do so at any time without giving a reason.

What will happen if I am interviewed?

You will be asked to take part in an interview with a researcher, Julie Beyrer, about your views on real-world endpoints. The interviews will last approximately 60 minutes or for as long as you would like to talk about your views. With your permission, the interview will be audio recorded. You can stop the interview at any time, and you do not have to answer a particular question if you do not want to.

Where will the interview take place?

The interview will take place over the Internet or phone at a date and time that is convenient for you.

Are there any risks in being interviewed?

If you feel uncomfortable, you can stop the interview at any time, without giving a reason.

Are there any benefits in being interviewed?

You will be helping the interviewer to learn from your views on real-world endpoints, which may ultimately contribute to advancing US regulatory clarity on acceptable real-world endpoints of effectiveness. You may also learn new things about your own perspectives as you reflect and share. You will help the interviewer in conducting research in support of her dissertation.

Will my participation be kept confidential?

The information you provide will be kept strictly confidential. The interviewer will transcribe the recorded interview and remove identifying details such as names of individuals from the transcripts. Quotes from the interviews may be included in the dissertation, but the interviewer will ensure that the quote does not reveal your identity. The interviewer is the only person who will be able to attribute your interview transcript to you individually. Nobody else will know that the views in the interview transcript are yours.

Upon completion of the interviewer's DrPH degree requirements and any final disclosure(s), the research data, the anonymised interview transcript, and related notes will be deleted.

What will happen to the results of the study?

After the interview, the interviewer will analyze key themes from interviews. Themes from the interviews will be described in the dissertation and dissertation defense (presentation) and possibly in a disclosure(s), such as a conference or journal publication(s).

What will happen if I want to stop taking part?

If you decide at any point that you no longer wish to be interviewed, then you can withdraw without giving a reason. You can also request that your data be destroyed.

What if I am unhappy or if there is a problem?

If you are unhappy or if there is a problem, please let the interviewer know:

Julie Beyrer, Indiana University (beyrerj@iu.edu).

Who is funding the interview?

This interview is not funded.

Who is doing the interview?

The interviews will be conducted by Julie Beyrer, a student in the Indiana University DrPH program.

How can I find out more?

You can get in touch with Julie Beyrer, who will be happy to answer any questions you might have:

Julie Beyrer, Indiana University (beyrerj@iu.edu).

Thank you for taking the time to read this document.

This information sheet is for you to keep.

APPENDIX 4. RECRUITMENT PROCEDURES

Interviewees will be recruited using the following methods: 1. Purposive direct sampling (professional judgment, including professional contacts of the PI and dissertation committee members), and 2. snowball technique (will ask informants to recommend other informants to interview).

Potential interviewees will be recruited by email. The recruitment email will include the following text: *You are invited to take part in this interview on achieving regulatory clarity on acceptable real-world effectiveness endpoints in the United States. This interview aims to explore perspectives on current gaps on this topic, potential solutions, and how to implement those solutions. Julie Beyrer will be conducting the interview. Julie is researching this topic as part of her dissertation in the Indiana University Doctorate of Public Health (DrPH) program and chose this topic because she is genuinely interested in understanding others' perspectives on real-world endpoints. She also routinely deals with real-world endpoints in her research career as a real-world evidence (RWE) scientist at a pharmaceutical company. She recognizes that other experts in this area may have unique perspectives based on their backgrounds or other career experiences. Therefore, there may be diverse views about this topic. You have been asked to take part because of you were identified as someone with expertise and/or interest in this topic.*

The interviews will last approximately 60 minutes or for as long as you would like to talk about your views. The interview will take place over the Internet or phone at a date and time that is convenient for you. With your permission, the interview will be audio recorded. You can stop the interview at any time, and you do not have to answer a particular question if you do not want to. The information you provide will be kept strictly confidential and results of the interviews will be anonymized so that no information is attributable to individual interviewees. After the interview, Julie will analyze key themes from interviews. Themes from the interviews will be described in her dissertation and dissertation defense (presentation) and possibly in a disclosure(s), such as a conference or journal publication(s).

APPENDIX 5. PRIVACY AND CONFIDENTIALITY PROCEDURES

Personal identifiable information from technical experts (name, organization, contact information, areas of expertise) and their perspectives on the research topic are being collected in interviews. No healthcare information is being collected. Zoom interviews will be recorded and stored on the student's IU OneDrive account. Transcripts from the Zoom recordings will be reviewed and input into a qualitative data analysis (QDAS) tool for thematic analysis of the interviews using the student's IU account on a laptop with encryption software provided by IU. No written/paper records containing identifiable data will be generated.

APPENDIX 6 LISTING OF INFORMANT RESPONSES (QUOTES)

Supplementary Table 1

Interview results: What does clarity on regulatory acceptability mean to you?

Themes	**Concepts**	**Quotes**
Clarity means written expectations.	Having a framework for evidence generation, presentation, and assessment	*I feel like a lot of the concern centers around bias. What bias have we potentially introduced because we've stepped away from this RCT and how have we controlled for it, and do we think that that's a reasonable way for controlling it? And I think if you can provide kind of a roadmap for how you're doing that… and I wonder if it's something a bit like with the ESTIMAND framework that you use that… so that each drug company does it exactly the same way… So for me, having some sort of framework around presenting it would be really helpful to get to clarity.* - Patient advocacy research director and former FDA reviewer … *Operational frameworks that help sponsors present the data and helps reviewers. Regulatory guidance- how do you operationalize it?* - FDA representative
	Having sufficient FDA guidance	*I think when people talk about clarity in this context, they want to know would a regulator trust it for decision making and maybe information about how they could show that an endpoint was*

		valid. So kind of do they have enough guidance, or do they know what studies they have to do, what level of evidence that they need to show that an endpoint can be used to make a decision. - Drug and device manufacturer leader and former FDA representative
	Seeing case studies (examples/ precedents)	*We can see what they have done by things they have approved or not approved that give us clues how they are thinking about real-world data and real-world evidence, but clarity only really comes through accumulation of case studies. So, the more we see exactly what the FDA does, the more we are clear about what they're doing.* -RWE consultant to industry
Clarity is knowledge about expectations and evidence.	Knowing the expectations for FDA acceptability	*To me it means that regulated entities can have an expectation and an understanding on the front end for their planning as to what FDA is going to accept or not accept. Basically predictability is what they're after.* - US government policy and industry legal counsel and former FDA representative
	Understanding the real-world data	*One of the things I learned at FDA is people really, really value not only showing your work, but being transparent, like we did this work, and what we realized is in 4% of individuals, it just doesn't work. So, then we ran a sensitivity analysis with and without the 4% of individuals… that kind of transparency has huge value.*

		- Real-world data and analytics company executive and former FDA representative …. *It's really transparency of data- who is in it, what the variables mean, clear data provenance, better understanding of exposure variables, and how they are defined.* - FDA representative … *So, you can think about it more, okay, do I just have this clarity because FDA told me? Or do I actually understand how it was collected in all these different sources and are there differences?* -Regulatory advisor to industry
	Understanding where there are flexibilities	*I think that when 21st Century Cures passed and the FDA was required to issue guidance on real-world evidence, it took them a long time to do it and they barely beat the legislative deadline. The reason that it took so long is because they went after here's what ideal data looks like. So, I think that regulatory clarity is a little bit more of an understanding of where there's flexibilities and where those can be used.* - Real-world data and analytic company director

Clarity is a feeling of confidence or certainty.	Having confidence or certainty	*I would say having enough confidence for the FDA or other global regulators to utilize this type of information, to inform decisions in front of them…. I don't think it needs to replace or be the sole source of information but that they have confidence that it is adding value and providing useful information to inform their decisions.* - Patient advocacy organization executive leader
	Is impossible or subjective	*I don't think you- I don't think you get regulatory clarity. You get a decision, but you don't know why or necessarily you don't have the whole story.* - Real-world data and analytic company executive leader
	Is not a cookbook	*I think from a sponsor's perspective, they want the regulators to say yes, no, this is good, this is bad. From a regulator perspective, they can't say yes, no, because it depends. They can provide general guard guardrails, but it's going to be on a case-by-case basis.* - Professor and research scientist in epidemiology … *I realize they're very reluctant to make it be like a cookbook, and say, if you do A we'll say yes, if you do B we'll say no. But clarity, I would say it's clarity on expectations.* - Drug and device manufacturer research executive

		… *Things are different by therapeutic area, not just because the diseases are different, but the review divisions are different. And it's different also between CDER [Center for Drug Evaluation and Research] and CBER [Center for Biologics Evaluation and Research], and it's different also, based on regulatory pathway. So, I tell you that because the other part of this is that what people want when you sort of ask around this concept of regulatory clarity is for things to be uniform as well. It is so not… I tell you that because I think that the asks around clarity and certainty are inconsistent with the reality of human beings and sociology, even within an organization.* - Real-world data and analytics company executive and former FDA representative

Note. FDA = United States Food and Drug Administration, RWE = real-world evidence

Supplementary Table 2

Interview results: Where do you see clarity on regulatory acceptable real-world effectiveness endpoints?

Themes	**Concepts**	**Quotes**
Clarity is in science	Scientific framework	*The principles are pretty universal.* - Professor and research scientist in epidemiology … *Not sure… I think we are clear on how to validate a real-world endpoint.* - FDA representative … [comments on clarity on clinical outcome assessments]: *There's some [clarity]- like we've gone to it's clear that it's based on this modern validity theory, kind of an argument-based look at threats to validity and then demonstration of how the instrument is fit for purpose in the context of use, and I think that's very clear.* - Drug and device manufacturer research director specializing in clinical outcome assessments
	Scientific textbook	*There is a book I reference on test validity. Not just one way but definitely a lot there- the books say a lot of the same things. What messages are repeated? 1. A need to identify a reference*

		standard. 2. Ensure that you include cases and controls/negatives to identify not only PPV [positive predictive value] but also sensitivity. 3. Need a good enough sample to create measures of accuracy. - FDA representative
Clarity is in FDA communications and interactions	FDA public communications and interactions	*There's papers in the literature… it does give some insight into some thinking and the FDA, I know oncology, has published a few articles discussing some of these issues. So, I think there's some clarity there from those documents.* - Patient advocacy research director and former FDA reviewer … *They [FDA] do make a lot of presentations at public meetings and they have revealed preferences.* - RWE consultant to industry … *I think last year at the… conference that FDA was presenting, what was very telling was that even Rob Temple [at FDA] made a comment that he starts seeing a pattern that based on certain endpoints he believes real-world data can work with certain endpoints, certain diseases.* - Regulatory advisor to industry

	FDA-sponsor interactions	*I think the only way they [sponsors] are going to find out is to ask. And like regulators, especially FDA, keep on saying, Come in early, discuss often. Early engagement. Over and over again. Come in with questions, we can head you off.* - Professor and research scientist in epidemiology … *Clarity is part of an ongoing conversation, I would say, between sponsors and the FDA, both in proprietary meetings they have in developing a drug and in the scientific world, and it emerges over time.* - RWE consultant to industry … *Anybody wants clarity before they spend money to try to convince somebody on something, as you want to know if that would convince them. So, I think there's tremendous value for that, but that's a pre-agreement on what those endpoints should be… FDA offers an avenue to do that and if you can't get buy-in from them before you do it, you save a lot of money.* - Real-world data and analytic company executive leader
	Guidance	*Four guidances tell us the pathway:*

		1. *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products* 2. *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry* 3. *Data Standards for Drug and Biological Product Submissions Containing Real-World Data* 4. *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* *Data quality matters. Linkage and monitoring things across time matters. Thoughtful science matters. Building in digital sensors and digital measures matter.* - Real-world data and analytics company executive and former FDA representative … *FDA has put out guidance documents around things like validating surrogate endpoints and again, clinical measures. And I think that's something that could be leveraged and thinking about what a validation framework would need to look like for real-world endpoints.* - Patient advocacy organization executive leader …

		I know that they've put out some guidance documents, and there's a white paper and stuff like that, and I feel like they have been pretty straightforward and clear on the areas of concern that they have and the challenges that they see in terms of using real-world evidence. So, I feel like they've been very open and straightforward with respect to that. - Drug and device manufacturer research senior executive … *I think they [regulators] provide some clear principles about validation studies. They want to know what the performance characteristics are. They want to know clearly where things are sourced from, and is there selection bias, like the source of the data… They just want these people to be clear about what the potentials are and where it's coming from and lay it out and based on that, they can make a determination of whether it's acceptable in this case or not.* - Professor and research scientist in epidemiology
	Examples or precedent	*We have clues about what makes a trustworthy endpoint or trustworthy outcome assessment. I think sometimes we kind of behave as if that doesn't apply…In general, I think you can kind of look to the principles of any other endpoint and kind of understand what's expected… I guess if you look at summary basis of approvals in the US so we can see how regulators have reviewed different endpoints. That could be helpful.*

		- Drug and device manufacturer leader and former FDA representative ... *Maybe they're some examples of endpoint by endpoint of what it takes, but in general.* - Regulatory advisor to industry … *I think we know that some endpoints are more objective than others, and I think that's clear that the regulators prefer those…* - Drug and device manufacturer leader and former FDA representative … *What was very telling was that even Rob Temple [at FDA] made a comment that he starts seeing a pattern that based on certain endpoints, he believes real-world data can work with certain endpoints, certain diseases. I think, as an example, he really brought MI [myocardial infarction] and its outcomes. You would die or not die. So, I think we're starting to see this pattern that if you're relying on effectiveness on a very clear-cut endpoint, and then, of course, are you sure that you've collected the data without a bias, that you know you're not missing some of the outcomes for a selected group of patients, but that you're really collecting it? I think that we're at least seeing some patterns of what could be acceptable.*

		- Regulatory advisor to industry … *...perhaps sponsors should focus for now on endpoints that are more objective in nature (e.g., measures of hypertension and blood glucose) and have a higher probability of regulatory acceptability.* - Real-world data and analytics company executive and former FDA representative … *It's interesting to me as I talk through this, some of the features of real -world endpoints that have clarity is when also the effect size is large ...you can tolerate blunt where we understand the real-world comparator. That might be one of the ways that we know around real-world endpoints, when we've been able to see that the real-world endpoint performs comparatively to a clinical trial.* - Real-world data and analytics company executive and former FDA representative
	Law	*The two randomized control trials was really sort of, it came out of essentially habit, and… the need to build more confidence… we kind of developed habit of how to get to safety and effectiveness in line with the FD&C [Food, Drug, and Cosmetic Act]. That's why I sort of*

		described DESI [Drug Efficacy Study Implementation] as this kind of codification activity, but it was basically codified habit. It felt like it gave great clarity, didn't it? - Real-world data and analytics company executive and former FDA representative
Clarity has been created through stakeholder engagement and consensus	Community consensus	[on what makes regulatory grade fit-for-purpose data]: *At the highest level when you go to 50,000 feet, I think there's general agreement. But when you get down into the weeds, how people apply that or would apply that differs.* - RWE consultant to industry
	Community engagement	[commenting on clarity within the clinical outcome assessment community]: *You can't write a guidance specific enough to be across the board. So, the longer we've worked within- because even though it's a draft guidance, we've been along for the ride, and so it's not really a surprise.* - Drug and device manufacturer research director specializing in clinical outcome assessments
	Pilot projects	*So, Friends of Cancer Research did a…study, I guess you'd call it…* *FDA was involved in that, like around this. So, I think that those people are looking towards that as a source of information, because FDA can't do that kind of study itself, like not in a position to, but it doesn't mean that there's guidance.*

		- Patient advocacy research director and former FDA reviewer … *And then the other parts of the pathway show up in the essentially pilot programs and studies that have been done and that FDA has been advancing either within FDA or I'm going to call FDA curious examples… where FDA is essentially… replicating all the randomized trials, leveraging real-world data and seeing what was and was not possible, teaches you a ton of how they're thinking about how they want to understand endpoints, performing the projects being pushed forward by Friends of Cancer Research, Reagan Udall Foundation, together with FDA, tells you a ton about what FDA is curious about, where they're curious. What they're doing is trying to push forward methodological development to better clarify the path, but they have spelled out for us with incredible care what matters here.* - Real-world data and analytics company executive and former FDA representative
	RWD tools	*Well, you have to step back from the endpoint and ask whether the data source is regulatory acceptable… but how do you decide whether a data set is of adequate quality and fit for purpose for the question that is in front of the FDA? And there have been frameworks that have been recently released, one by the HMA [HMA = Heads of Medicines Agencies] EMA [EMA = European Medicines Agency] big data task force for EU [European Union] regulation, which is*

		very extensive. There was one just recently, an auditing criteria that was released by Transcelerate and there are other many, many articles have opined about what makes good quality real-world data… Duke Margolis had a white paper out in 2019 which just talked about the many dimensions you can do on quality checks. A lot of conversation going about it right now. I wouldn't say that there is any clarity about what represents a good quality data source. We know data sources that have been accepted for particular decisions. - RWE consultant to industry … *No, I think there is a lot of clarity. I don't know if you looked at the Transcelerate audit tool… but what that is it's drug sponsors, saying these are the questions FDA is going to ask us about our data that we're using. Let's answer them before we go to FDA. Let's look at our data and assess them based on this tool to know if we even should consider taking it to FDA. Or if we're just wasting our time.* - Real-world data and analytics company director

Note. FDA = Food and Drug Administration, RWE = real-world evidence

Supplementary Table 3

Interview results: Where do you think we are lacking clarity on regulatory acceptable real-world effectiveness endpoints?

Themes	**Concepts**	**Quotes**
Lack of clarity results from lack of transparency about FDA decisions	Cannot find the FDA examples or precedents easily	*I think, more summary basis of reviews that have, like a very thorough description of how the FDA considered the real-world data because in the past they're not super transparent about it, right? And also you didn't necessarily know that they used real-world data unless there was a press release. So, you have to like just take a shot in the dark every time an approval was posted, and go in there and see if there was real[-world] data.* - Real-world data and analytics company director … *What we probably don't have, and I guess we could use, are just kind of a repository of examples that have been acceptable in the past. I don't know that we have like just one place where can go and find that, and I'm hoping that we do over the next couple of years.* - Drug and device manufacturer leader and former FDA representative
	Lack of transparency in	*They [FDA] don't say anything other than this is the problem, we're not going to use it. It's not like these variables don't have enough completeness for us to make a valid inference. Maybe*

	FDA decision making	*you should consider going back and trying to have some follow up with these patients to capture more complete information. Then we would consider using the data.* - Real-world data and analytics company director … *They [FDA] haven't been clear on… they sort of have adopted this like, what does 'good' look like- we'll let you know when we see it. And so companies and sponsors and people doing these studies have to hope and pray, I think, a little bit that whatever they're doing is the right approach and that it will be acceptable from FDA because FDA generally is like you submit the submit the plans to us, and then we'll tell you if that's good versus being proactive and spelling out sort of what they would determine to be acceptable versus not.* - Drug and device manufacturer research senior executive … *But they [FDA], when they actually make a decision, they don't reveal the thinking behind their decision.* - RWE consultant to industry
Lack of FDA education and	Lack of education for FDA reviewers	*It's a learning curve. It's disseminating policy but really having more conversation with review divisions about how they would assess the guidance. They might not be as well versed in new*

consistency on RWD/RWE leads to lack of clarity		*methods. OMP [Office of Medical Policy] might be privy to this. An exception at FDA is OCE [Oncology Center of Excellence]. They are both the reviewer and the policy division. A gap is disconnect with reviewers.* - FDA representative … *Regulators aren't perfect, and they aren't the generators always of the best science, and that's fine, but they aren't always ready to be an educated consumer of the best science either, and their training isn't what we need it to be. And we've seen in the COA world how that creates issues because if you submit evidence that you know is robust, but the reviewer is used to seeing something else, and isn't experienced enough to review it kind of independently with a critical eye, they're kind of used to a checklist, they come back with feedback that is either wrong or off the mark, which leads to a lot of churn, and eventually I think we get to a good place.* - Drug and device manufacturer research director specializing in clinical outcome assessments … *…The ones who don't work with real-world data haven't considered all these nuances about epidemiology studies or these data sources, and I'm sure regulators are in the same boat. So, I think it's really helpful for everyone to see what the benefits are, the pros and cons, and I think*

		FDA finds it valuable because they continue to do projects, demonstration projects. They were involved with the Friends of Cancer Research. I think they're doing- it's on their website- they're doing some project themselves with data vendors. They have multiple projects going on, but I thought they were doing one maybe even with Reagan Udall [Foundation] on endpoints development, so they must see it as valuable. - Drug and device manufacturer leader and former FDA representative
	FDA reviewer and division inconsistency	*The review committees are not necessarily the FDA, and they don't speak with one voice, and they've never seen real-world data, and they're skeptical.* - Real-world data and analytic company executive leader … *In fact, you could take an algorithm that FDA has used to make a regulatory decision and use it, and the other people at FDA might say nah, I don't want to use that one. I don't believe it. I want to use a different one. So, it's all case specific.* - Real-world data and analytics company executive and former FDA scientist …

		That's the kind of thing that will happen on a case-by-case basis. I doubt we will ever get to the point where FDA will say what endpoints are okay or not. It would always be, the burden will always be on the company, in the case one way or the other. - Drug and device manufacturer senior executive and former FDA reviewer
Lack of stakeholder experience submitting RWE for demonstrating treatment effectiveness leads to lack of clarity	Few sponsors have enough experience submitting these endpoints/data to FDA	*I would say that the whole FDA regulatory requirements is, I would call it it's a small circle that has their own unique requirement, unique tools, unique trainings…* - Director and research scientist at an academic healthcare organization … *I think that's because RCTs have so much longer history. We never had this kind of RWE that we could submit. So, I think we just don't have enough history, and pharma companies are notoriously cautious.* - Real-world data and analytic company executive leader … *And what are the, from a regulatory point of view, what studies, evidence you have to present that you would reliably be able to define these endpoints each time you're going on with this study and collecting these outcomes for patients? I don't know that there is a well defined process endpoint by endpoint. There's some hypothetical ideas.*

		- Regulatory advisor to industry
	Not enough examples or precedent of FDA accepting these endpoints	*That's precedent basically, when we can see with clarity how FDA approached the use of real-world data, when we can see with clarity that they evaluated it. Here's the considerations that were taken into account. And here was the decision that was made… there's only a few cases of those with FDA, because not many real-world data sets are used as something we call substantial evidence. They're generally considered supportive or FDA just disregards them completely. So, generally speaking, in a review package, we don't see a lot of, here's how we did this. This is how this happened. Sponsors or the data providers were inspected, done, and there's only a couple of instances of that.* - Real-world data and analytics company director … *The availability of these kinds of datasets, the availability of complete enough information from real-world settings to start to mimic the clinical trial is a relatively new phenomenon. The development of the appropriate scientific methods to make sense of that is an evolving phenomenon. And the development of meaningful endpoints within that is also a new phenomenon. So, in fact, the science is relatively new, and the methods are evolving, and there's not the thousands of documents that lawyers can look through to codify a shorthand that creates*

		this… So, in fact, the reason it feels like we don't have clarity is because we're still knocking those things into place. - Real-world data and analytics company executive and former FDA representative
	Some of the endpoints have not been validated	*I think it's probably due to perhaps a lack of validation of some of the measures. Aside from perhaps safety endpoints, safety signals.* - Patient advocacy organization executive leader
Lack of written clarity from FDA leads to lack of clarity for stakeholders	Lack of clear guidance	*There's really no guidance on how to validate them [real-world effectiveness endpoints] at this point. So, and it again, it goes back to this, the chicken and the egg. How much of these examples of the validation FDA wants to see before they can say, this is the way to do it?* - Regulatory advisor to industry … *I led the review of the EHR and claims guidance for our team with a partner of mine at X [anonymized organization name]. And validation threw us really for a loop. We don't know what that means… I don't feel that the FDA guidance today is as explicit, maybe, as it needs to be on that specific point.* - Drug and device manufacturer director

		… *I think most of the general principles should be there in there, which may be why they're criticized sometimes for being a little bit vague, but I mean these are general pharmacoepi or epi principles about the potential sources of bias, so just be clear about what they could be. Allow the regulators to make an assessment of how severe those potential sources of bias would be in this particular use case relative to any potential, impact, signs, or similarities, conditions, or whatever. It all has to be weighed in together, which makes it very hard to say yes, no crystal clear each time beforehand, not knowing the context.* - Professor and research scientist in epidemiology … *The guidance and stuff that they sent out is to help, but obviously it's not specific enough for each use case, which is why, and I think the pathway for early engagement has not been clear right now, it's not clear right now, but they're trying to build more clear pathways for early engagement in which you will then get that clarity at the outset before you go embark and spend resources on doing a study that you know already is not going to fly or maybe re-direct the resources that you are using to address that particular question. So I think they are working on it. When that clarity on what would be regulatory acceptable or not come down, I'm not sure,*

		because the specifics aren't going to be in the guidance. Specifics are going to be when you come to that early engagement. - Professor and research scientist in epidemiology … *Some of these [FDA guidance documents on RWE] have been written really quickly. That is true, for better or worse. I don't know, because, as I said, they're vague.* - Patient advocacy research director and former FDA reviewer … *I think that when 21st Century Cures passed and the FDA was required to issue guidance on real-world evidence, it took them a long time to do it and they barely beat the legislative deadline. The reason that it took so long is because they went after here's what ideal data looks like. So, I think that regulatory clarity is a little bit more of an understanding of where there's flexibilities and where those can be used.* - Real-world data and analytic company director … *There's also this question of validation, which is, you know, there are different ways to do the validation. A lot of, in the claims data world, a lot of the validation studies are: pull a couple of*

		people, pull a handful of people who look like in the claims data that they had the event of interest or the health outcome of interest, and then pull a bunch of medical charts, either electronic or paper based, and verify if that patient actually had the event. And then you come up with like specificity, sensitivity of that definition,… that's the methodology that FDA has endorsed for like safety events and the Sentinel system, but I think that there is a lack of clarity on that in sort of more traditional regulatory decision making. - Drug and device manufacturer research senior executive … *What you need to validate- can it be a sample?* - FDA representative … *The whole concept of what it takes to validate an endpoint is-I don't think, that it is clear, and maybe they're some examples of on an endpoint-by-endpoint of what it takes, but in general. So that's one issue. The other one is, you think about endpoints- so your first, you collect the outcome, and then you turn it into the the endpoint. I don't think that there is clarity of how the outcomes have to be ascertained in order to change them into reliable endpoints. And we don't even have the clarity probably of how these outcomes are ascertained, and all these different*

		Linux that feed the data together, the variability of how the outcomes are ascertained. So, firstly, at least in my experience, how do you go from an outcome to the endpoint? How did you do this one? - Regulatory advisor to industry … *It sometimes depends on the endpoints… We all know, for example, what time to treatment discontinuation in oncology means. But okay, if we are going to take 4 or 5 different hospitals, are they actually measuring the same thing in the same way because it was the day that collected? It was their day of when the treatment started versus when it ended. How did they decide the day it ended? Is it always the last dose you see that the drug was administered, or was there something else? So, I don't know that there is this this way of saying you should use this, and then you should do these types of studies to confirm it. If you're using 5 different data sources, do you have to come up with this way? That in all these, from these 5 different data sources, you're getting something. That's what I'm saying. I don't think we have this idea, or even guidance, of how to do this.* - Regulatory advisor to industry …

		And so the issue with regulators right now is, how do you validate those endpoints and prove to us that that is an actual endpoint that's reflective of the clinical outcome? I mean, I think what you will hear from the data industry-and this is a repeated position- but there's questions: how do you validate an endpoint where there's no gold standard reference? Everybody says that. - Real-world data and analytics company director … *So, what am I supposed to do? Right? In some scenarios, it might be a weight went up. I don't know. Do I have to go to the medical record and check that the weight in the EHR is the weight that was scribbled in the nurse's note? That there's no transcription errors?* - Real-world data and analytics company executive and former FDA scientist … *I think we like clarity on how FDA wants us to deal with assessments that they're comfortable in a trial they are done, like blood draws because they're done on a certain schedule, and they're done randomly. And so people are confident in them. But in the real world, they're not always done as much, they're not done, they're done for different reasons. And so, I haven't seen a lot of clarity around how do they want to deal with that…. Will acceptability of real-world endpoints mean you have to do some kind of naturalistic study? So, it's kind of like it's*

		observational, but there's a schedule of assessment. So, I haven't heard much about how to deal with that bias, and this bias of just how, I guess you could call it a form of confounding by indication. - Drug and device manufacturer research executive … *I think that the industry take on the group of guidances that's been released in the last few months is that they they're conflicting, and that they're unclear in some places. So, I think that FDA can work to improve the clarity of those guidances and then further support clarity in evidence generation, either using RWE as supplemental evidence right for approval of secondary endpoints… I think approaches to addressing data missingness, approaches to assessing fitness for purpose- I think things like that are still missing in the RWE space, and coming down from the agency, I think, would provide a lot more clarity without being unnecessarily concrete.* - Digital healthcare and policy expert … *I think that the broad FDA guidances, series on real-world evidence- it's hard for those documents because they're intended to be not division specific, to sort of get into the weeds of*

		for oncology trial, you might use these things for a cardiovascular study, you might want to do these. They don't tend to do that. And then nobody's really happy, I feel, because they didn't get clear answers. - Patient advocacy research director and former FDA reviewer … *I don't want to get to into the weeds around COA, but we used to have a pretty clear, for better or worse, sense of a dossier of what an evidence package looks like. And now we've shifted to more of like an evidence package approach with these topics that we know reviewers will look for and they only need- certain aspects of validity only need to be addressed if it's a threat to the- or an obvious threat. But it's not clear how they expect to see that. Do we have to demonstrate that it's not a threat to validity that we need to address? Does it come in a package form? I mean, just things like if I look at it and say, well, obviously there's no test-retest reliability issue because it's clear, are they going to have the same judgment? And what do I need to show them so that we're on the same page, and I don't need to generate more prospective data saying so.* - Drug and device manufacturer research director specializing in clinical outcome assessments …

		Really basic questions of what is the source data? If it's part of a clinical trial, how does it get put into the trial master file and what gets put in there? Is it the cleaned transcript, or is it the original? We can't have the original because it might identify all that stuff. So, that does cause a bit of an issue because if somebody doesn't know how to do something, they're less likely to do it. It's a real barrier to getting approval to actually doing interviews within trials because nobody knows. Nobody wants to handle the data the wrong way. And so, it's like, Well, we're just not going to do it, which is not ideal. - Drug and device manufacturer research director specializing in clinical outcome assessments … *Even the methods to analyze the data- so we have, like these volumes of longitudinal data, and then what we end up doing is distilling it into what we could have collected with a palm pilot, right? Because we don't know how to take advantage of all the other data. All we know is that it must be better because it's more, but we don't know how or why, or how to take advantage of it. And so the cutting edge methods are really good from an academic perspective, but the regulatory comfort always comes second because public safety needs comfort. You can't just- one cutting edge method isn't going to cut it, and so we just aren't- we're there scientifically, but we're not there from a public health safety perspective. The science, yes, we trust it, but are*

		we going to bet our parents' lives on it? No, not yet. You know, we're not quite that comfortable, and that's the FDA's job. And so we're trying to get there I think. - Drug and device manufacturer research director specializing in clinical outcome assessments … [Interviewer: *So I think I hear you say even amongst the lack of clarity, the top issue would be just an understanding of what endpoints would be acceptable.*] *Yeah. Yeah. What goalposts do people feel like are reasonable likelihood of success with FDA that it's worth the time and investment. And frankly, the central diverted attention to RWE versus traditional evidence. No one wants a complete response letter because they took a risk.* - US government policy and industry legal counsel and former FDA representative
Complexity of validating real-world effectiveness endpoints contributed to lack of clarity	Performance differs by real-world data source	*Our RWD systems are not developed to follow a patient. They are designed to follow a plan or provider, whatever they see. If I gave blood 3 weeks ago, then do a drive-through COVID test, then feel worse and go to the ER, where do we identify the positive assay? Also, that I received vaccine at CVS? A lot of what we know about the pandemic came initially from health systems in Israel and South Africa. Why? Their universal health systems or 2 big health insurers. [This is] 90% of our problem.* - FDA representative

	So many aspects (complex) to validating real-world endpoints	*I hear a lot of questions about the endpoint, particularly in oncology because there's so many ways… to shave it, that your head is spinning.* - Real-world data and analytic company executive leader

Note. FDA = Food and Drug Administration, RWE = real-world evidence

Supplementary Table 4

Interview results: Where does this topic (US regulatory clarity on acceptable real-world endpoints) rank in your perception of priorities relative to other regulatory needs related to real-world evidence?

Rating	Themes	Concept	Quotes
High	Lack of clarity creates drug development obstacles	Creates hesitation for the community	*The topic of regulatory acceptance of real-world endpoints ranks very high. Uncertainty around what a regulator will accept regarding a real-world endpoint creates hesitation for the community. This leads to discussion of what is good enough for endpoint definitions and questions of whether the endpoint has been "validated." Sometimes "validated" means each endpoint was reviewed by a clinician, sometimes it means a validated algorithm was used with a known level of precision. In my experience in safety studies, FDA is hesitant to a priori define a RWD outcome definition as acceptable.* - Real-world data and analytics company executive and former FDA scientist
		Increases drug development and clinical	*RWE is gaining increasing importance in complementing traditional clinical trial data to support regulatory approvals and post-marketing assessments. The topic of regulatory clarity on acceptable real-world endpoints is critical within the broader discussions surrounding RWE in drug development and regulatory decision-making. It is imperative to*

		study challenges	*establish clear guidelines and standards for the appropriate use of real-world endpoints to ensure the reliability, validity, and consistency of the evidence generated from such sources. Without such clarity, critical aspects like calculating the study's statistical power may become challenging, impacting the feasibility of RWE studies.* - Drug and device manufacturer senior executive and former FDA reviewer … *I've been answering a little bit, perhaps cavalierly saying, I don't think there should be progress on clarity for the outcomes, and I am not putting myself in the part in the position of pharmaceutical company, which, of course, anybody wants clarity before they spend money to try to convince somebody on something, as you want to know if that would convince them. So I think there's tremendous value for that.* - Real-world data and analytic company executive leader
		A primary need for drug development	*I would say it's a top 3 priority because at the end of the day if FDA is not going to accept an RWE endpoint, it doesn't matter some of the subset, secondary policy issues around that data or how the data was procured or what access rights does FDA have to audit it. Like those kind of secondary policy issues all become mute if ultimately sponsors don't have the confidence to put the put the data forward in the first place.*

			- US government policy and industry legal counsel and former FDA representative … *I think it's pretty high because if I step back, and if the reason that we want, meaning we, the reason that some people believe real-world evidence should be in place of sometimes clinical trial data or pivotal evidence is because everybody agrees clinical development's got to be shorter. Things have to be shorter, and so I think that naturally leads us to we wouldn't be in as good a place if agencies say, Fine, you could send us real data claims, EHRs, but it's got- We need to see the same endpoints that go for you know, 5 years, 3 years. I feel like a conversation quickly gets to, Well, what are the endpoints relevant in that data? And they're going to be the effectiveness real-world endpoints. So yeah, I feel like it's pretty- it's pretty primary or prominent.* - Drug and device manufacturer research executive … *I actually think it's low priority, and it's ironic that I put it as low priority, because I feel like I'm sort of the person who started a ton of the work around describing regulatory grade and everything else. I think the reason I'm giving it low priority is because I, what I think is low priority is clarity on the endpoint, and <u>what I think is high priority is clarity on how to</u>*

			get to an approvable endpoint in a specific context [text underlined to clarify the high priority- versus low priority- need identified by the informant]. Now, what does one need to do to get from here to there? And I think that what you want clarity on is the pathway to get from here to there. And what I worry about, this is my last point, is that the risk of demanding a clear pathway in 2023 is that you get such a conservative answer that it's hard for regulators to move off of that. I've been quite vocal. Don't back regulators into a corner because you might not like the corner. And what I always get back is, Well, but I need to understand what I can and cannot do. And there is huge amount of risk in that because if nobody gives me the understanding what I can and cannot do, I might get it wrong. True. However, if you then say, well, I want to know at all times what I can do, you're going to get an answer that is as conservative as it needs to be because people are being asked to come up with something that's applicable in such a broad number of settings, and it's just completely bland, and then it becomes hard to move off. So, I think what you really want is what's the pathway to get there and give me enough flexibility in the pathway that, as the methods improve, I can accommodate for improving methods. - Real-world data and analytics company executive and former FDA representative …

			The only other layer I would put on is the global nature of RWE. I think for RWE to be successful in the long haul, some of these packages are going to have to be able to be used for multiple regulators, and not sort of asking for different things, and I think I would—I don't want to make your dissertation scope change. Obviously, it's not my role. But your question is a global question in my mind… I think FDA is the right place to start, but maybe it's a footnote, or because ultimately the Holy Grail here, whatever analogy you want to use, is you could have an RWE package for a validated endpoint and you sort of are able to use that globally in a very streamlined way that will open up new therapies for patients more quickly, and that's a good thing. That's a good policy outcome. - US government policy and industry legal counsel and former FDA representative
	Lack of clarity diminishes opportunities to understand outcomes most	Real-world endpoints may be more patient-centric than clinical trial endpoints	*I think it's the most important. I'm not just saying that because you picked it. But I- in my whole argument for why real-world evidence might be something that FDA should consider, my argument is always because randomized clinical trials traditionally don't have as endpoints things that really matter to the real world, like patients and payers and other things… it's always been my perfect example for pediatric asthma. If you're asking if you have a child who has asthma and it gets really bad, and they have to go to the emergency room, the clinical trial would measure forced expiratory volume in 1 minute. That's the*

	important to patients		*clinical endpoint. But if you ask parents, and you ask ER [emergency room] physicians, what really matters, it's like I want to keep my kid out of the emergency room. I would like to go to the emergency room 4 times fewer this month, thank you very much. And if this drug, if you know that this drug changes that, that matters to me as a parent. It matters to me as a patient. Not FEV [forced expiratory volume]. I don't care about that. Wouldn't it be great if a new drug approval could have that in the labeling? But you can't get that unless you've done the real-world evidence, and that's truly a real-world evidence study, and it hinges on that effectiveness endpoint, not the randomization question, not the other variables that were in your analysis as control or predictor variables that were measured in the real-world evidence study, not the study design. It's that endpoint is relevant to people, and they want to know about that and that's where FDA- so that's why I think it's the most important.* - Drug and device manufacturer research senior executive … *The big debate now with real-world evidence is data quality and fit for purpose, and I don't know it seems like splitting hairs when people are making the difference- putting data quality first, but I think fit for purpose has to go first, because otherwise, why bother*

			looking at any data… Yeah, I wasn't pushing for clarity, because first time pushing for relevance. I mean, imagine you have Parkinsons. You can't get out of a chair. You can't move. You can't, whatever. I'm not exactly sure what those panel of symptoms are, but I know they're debilitating, and I want to evaluate them, and they're going to be imperfect evaluations. It's just a question of how imperfect! But if it's Duchennes multiple dystrophy, any of those kinds of serious conditions, there might be really meaningful changes in endpoints that we don't know about yet that we'll discover, and we'll learn. So, I think endpoints should be evaluated for what they are. - Real-world data and analytic company executive leader … *How you get to understand which measures are most relevant. The Reagan Udall Foundation did something with FDA on developing patient-centered study design and endpoints for substance use disorders… abstinence is an endpoint, but patients are not saying it's the most important endpoint. Endpoints that matter—being able to work.* - FDA representative …

			If you were responsible for the clinical development of Jakafi with Incyte, I think you had great clarity. That's a PRO [patient-reported outcome], like incredibly practical real-world endpoint. - Real-world data and analytics company executive and former FDA representative
	Even the experts are challenged to provide answers	Experts trying to figure it out still	*I'm struggling with this issue, too. I need to spend more time on it. But my time is so limited. I would love to dig into some of these things… The digital health technologies- we're having the same exact discussions about how do you validate digital endpoints? It's the same thing. And what if there's no gold standard? …So, I'm trying to figure out some of these things, too. And I'm trying to work with our clinical outcome assessment team to figure out, okay, we had to have had a situation before when we're validating something with no gold standard. What did we do?* - Drug and device manufacturer leader and former FDA representative … *I think FDA finds it valuable because they continue to do [real-world endpoint pilot] projects, demonstration projects, and they were involved with the Friends of Cancer Research. I think they're doing- it's on their website- they're doing some project themselves with data vendors. They have multiple projects going on, but I thought they were doing one*

			maybe even with Reagan Udall [Foundation] on endpoints development. So, they must see it as valuable. - Drug and device manufacturer leader and former FDA representative … *… I think it's important… my fear in this whole thing and maybe this is what they've done in terms of a hedge, at least from the US FDA perspective and maybe this is even their strategy, they've put out some guidance. They've established a pilot program, and they're going to experiment. They're going to see, and they probably going to update their guidance at some point based upon a few years of this FDA RWE pilot program… this Advancing RWE. I don't know. Maybe that's what's needed, like. Okay, so let's get some experience under our belt, and maybe we can be more definitive in the future. Maybe I should just give them the benefit of the doubt that that's their plan, but I think this is important to establish clarity. I really do. How does it fit with respect to other things that are going on in this area? I don't know. It seems very important. It almost is in the critical path.* - Drug and device manufacturer director
Medium	N/A	RCTs are gold standard still.	*Probably a few years ago it was higher. It probably was, if you think like 1 to 10, it probably it- because it's so much hype that it was probably like somewhere about 7, 8. I*

		RWD do not capture patient experience. RWD fit-for-purpose is a broader, more important need. Other opportunities are emerging to accelerate drug development.	*think now it's in the middle. That's how I would say, you know 5, 6 now if you put it in a scale of one to 10. I think there is this feeling of we need better data, so it's not the regulators. We have to fix the data. There's only little we can push so that's one. Two, there's a technology and then the whole idea of well, is it real-world data or is it maybe the decentralized trial that is more important? Maybe using the mobile technologies, the digital technologies. So, I think some of these elements are pushing the real-world data up and down. And then even this concept of building all the virtual controls, so do we just skip over the real-world data for regulatory and can we eventually think of virtual controls? And what would that take? And should we be working towards that and using the real-world data just what it was, for the safety follow-up or some other evidence for payers. So, I don't know, but that's why I think it's not as high as it was just after the Twenty-first Century Cures [Act] and the 2016 or 20… PDUFA [Prescription Drug User Fee Act], where it was like really high pressure for FDA to generate guidance and everything. They put their guidance, and they're like, Okay, now you people have to get better data. We've done our job.* - Regulatory advisor to industry …

			I think, that in general there is a sort of larger question about what's fit for purpose, not necessarily just focused on endpoints, and so fit for purpose is going to just depend on all of the key parameters, including population, the eligibility criteria, the exposure, the outcomes, the potential confounders, and so that I think you need to sort of consider within the context of a particular question, whether a particular data source or sources are fit for purpose, and I think that is more important than focusing on just one component. And design. Yeah, do they fit together? Because that's how you determine whether it's a fit-for-purpose study. - Professor and research scientist in epidemiology … *I'd say it's in the middle. I mean, there's a reason that we have RCTs [randomized controlled trials]. They are the gold standard if it is ethically- and you know there are some ethics challenges around doing some of them because the way we changed sort of the paradigm of doing Phase 1 and 2 a little bit that you might end up finding that a randomized Phase 3 trial is difficult to do, and in high unmet need. But if it's ethical and feasible then I- the RCT still is the gold standard and gives us the best evidence. It's not perfect, that's true, but it does give us the ability to get rid of some of the confounders*

			because of the randomization. So, I don't think it's that- I think that some people get kind of hung up on it. Oh, it's going to replace the RCT. No. I don't think that at all. I think we have to learn how to supplement that in places where it's appropriate to do so. That's why I would put it as a medium for effectiveness. I do think there's a lot of value for, say, potentially for safety, though. In oncology, you're not getting any patient experience data right now. Claims doesn't have it. The EHR [electronic health record] is a mess. Good luck. Registries, same problems. Where are you getting patient experience data from?... I know PROs [patient-reported outcomes] are not being used for safety right now, but you know there's a lot of talk about tolerability, and how to better understand tolerability from that perspective, but if you move to relying on just real-world data, you'll miss that from my perspective, and that is a huge loss for patients. - Patient advocacy research director and former FDA reviewer
Low[a]	N/A	Not relevant to work my organization does	Not applicable

Unknown[a]	N/A	[No response received]	Not applicable

Note. FDA = Food and Drug Administration, N = number of informants, N/A = not applicable (where responses were considered too disparate derive a theme), RWE = real-world evidence

a One informant, a director and research scientist at an academic healthcare organization, said this topic was not important today for the informant's organization today, as it does not currently develop real-world evidence for submission and decision-making by FDA. For one informant, this question was missed during the interview and emailed after the interview, with no follow-up response received. For one informant, this question was missed during the interview but unforeseen circumstances prevented follow up on this question.

Supplementary Table 5

Interview results: What solutions do you think would address this gap?

Themes	**Concepts**	**Quotes**
Develop related frameworks and guidance	FDA develop guidance or other clarifications	*So, what they might do is put out some considerations… sometimes they publish guidance on how to do a trial design or how to measure efficacy or whatever, but they also do guidance that is much more high level, and so they could do a guidance that is considerations for validation of real-world endpoints.* - Real-world data and analytics company director … *I think FDA still needs to articulate what validation would need to look like [for real-world effectiveness endpoints]. They have at least like from the CtDNA standpoint, for example, they've articulated what types of meta-analyses would need to be performed in order to validate a potential surrogate endpoint.* - Patient advocacy organization executive leader …

		I think a framework is the way… the ESTIMAND framework sort of came to be during my time at FDA… a lot of people have done a lot of work to make it more accessible to everybody who really felt that this is a way that we should be thinking about endpoints. So, ok, we read the guidance. It's very technical. It's very difficult. But we love what it's trying to ultimately do, so we're going to break it apart and break it down and show examples of how to do it and walk through really practical examples so that someone who isn't a methodologist can follow along too. I think the same thing here would be great. - Patient advocacy research director and former FDA reviewer … *They [FDA] can go further than they do now. I almost think of like a grid, or like a table that articulates some of the instances when and types of real-world evidence endpoints would be deemed regulatory grade and useful for FDA. Maybe it's a couple of different tables… I think it's like first and foremost, when are you… answering the question and maybe in a table or in scenarios having some more information around when would real-world effectiveness endpoints be useful to answer particular regulatory questions? And what types of regulatory questions are those? And then once*

		you get past the idea of conceptually these kinds of real-world effectiveness endpoints would be useful in these kinds of cases and for these kinds of regulatory decisions, then the question is okay, that was assuming these were the best endpoints ever. Now, now we're in the real world. What would regulatory grade look like? How would we know that that particular dataset, or that particular study design resulted in quote unquote regulatory grade endpoints? - Drug and device manufacturer research senior executive … *You could imagine a world where FDA has much clearer policies around coming to alignment and working with sponsors on an RWE study. FDA talks in the guidance a lot about the need to meet early with FDA and the need to do this, but I think they could have more granular processes about how to do that, and when to do it, and what kind of feedback they would be giving…* - US government policy and industry legal counsel and former FDA representative
	Develop an RWD quality framework	[About an RWD quality framework] *These are the questions FDA is going to ask us about our data that we're using. Let's answer them before we go to FDA. Let's look at our data and assess them based on this tool to know if we even should consider taking it*

		to FDA or if we're just wasting our time… this is going to have sponsors who are the clients of our organization and data service providers, they're going to be asking data providers, Can you do this? Can you do this? Can you do this? And the more they say, No, the less people are going to pay. And when people start losing money because they're not doing what regulators want to see, that will change… and so if the money is going to dry up because you're not paying enough attention to data quality, then you're going to pay more attention to data quality. - Real-world data and analytics company director … *It would be helpful if they [data providers] also kind of align on best practices amongst themselves and share those because until they do, I find it a little bit challenging for regulators to use information if it's like comparing apples and oranges across these different studies… I guess professional societies like ISPOR [International Society for Pharmacoeconomics and Outcomes Research], and they do issue best practices. They have issued reporting guidelines and templates. I think those things are helpful.* - Drug and device manufacturer leader and former FDA representative …

		I think we can go as far as possible in boosting and defining, describing the data quality of data that we collect as part of routine care, and of course, of data that we collect in real-life settings. - Digital healthcare and policy expert
Create better transparency for stakeholders	Stakeholders review examples or precedents	*Perhaps trying to gain insight into other sponsors' programs to understand specific methodologies and how they were applied into those alternative use cases.* - Patient advocacy organization executive leader … *I don't know how much detail they [FDA] should provide, but presumably you'd have to justify the endpoint on some level in your submission, and it would be really helpful to find- to have that information. FDA has a pilot program on real-world evidence now, and they're going to select, you know, a handful of applicants every year. In that, part of the deal is if you get accepted to that program they can publicly share learnings, and I think endpoint validation is in there as one of the things they can share.* - Drug and device manufacturer leader and former FDA representative

	FDA make it easy for stakeholders to view examples or precedent (e.g., dashboard)	*They [FDA] are supposed to aggregate information about how many submissions they got containing real-world evidence and then what happened, like how it was used. So, I think that would be helpful. We tried to do it as an industry anonymously, like BIO collected a lot of information, but I think the unvarnished information from the regulator is going to be more useful.* - Drug and device manufacturer leader and former FDA representative … *They [FDA] are not very definitive in their guidances. So, I don't know, I mean, maybe they don't want to be pinned down… What we can do better, I think, is try to extract and then verify with them what are the principles? So, like say you- we were sending in Flatiron data and you get the response, well, this isn't right, and we don't like this. Why? To get the why there, the meaning. Okay, there's a principle. They don't like this, they're not going to like this scenario in any case.* - Drug and device manufacturer research executive … *FDA to create an RWE dashboard that… shows you all the endpoints accepted… That's one policy solution… FDA could be more public about endpoints that the agency has*

		decided are acceptable. It could be through a dashboard. I mean, I think they have to do that already with the Cures [Act] broader qualification program, but you could think about a dashboard that's RWE-specific that FDA really highlights where they have and where they haven't… found it acceptable and why. Are there ways to make it acceptable, or is it really an area that's not worth the goal? - US government policy and industry legal counsel and former FDA representative
	Help stakeholders be able to apply the various existing related guidances	*You know it does strike me that for whatever reason people don't use the guidance that's available that they could extrapolate or make a bridge from, and so maybe if we could continue to make those links for people and show them how existing guidance applies or existing approaches apply, I think that would go a long way. I've never totally understood why people don't view it that way, and you know I'll tell you we've had meetings with FDA recently where we've asked for regulatory certainty or clarity or more guidance on certain topics, and they'll tell us this is best practices for research 101. So that doesn't put researchers in a good light if we're not understanding that there are best practices for research that apply to any clinical data that you're going to use, not just RCT data. So maybe it would be helpful to continue to get some like level setting on the expectation for best practices, for research, transparency, developing*

		protocols, reporting. Maybe that is the best way to get value if people are trying to validate or justify real-world endpoints. To the extent that we can leverage what we already know for other types of outcome assessments, I think that would be really helpful. - Drug and device manufacturer leader and former FDA representative … *FDA guidance is always a starting point, though right now I think those are somewhat vague and overarching.* - Patient advocacy organization executive leader
	Create better awareness for sponsors about the FDA RWE Subcommittee	*We need a better system to let sponsors know this resource [the FDA RWE Subcommittee] is available.* - FDA representative
	Stakeholders create transparency	*I think it does require the collaboration of all the partners in a space where it's transparent. So, it can't be within an individual, IND or NDA because that doesn't come to light until 6 years from now. So, I don't know if it's FDA funded like they're*

		doing with the core outcome… so they have those core outcome sets for clinical outcome assessments, and the FDA has funded it with grant money. I think that that's really helpful because it eliminates some of the risk. It assumes some of the financial risk or at least shares it, and then it forces whomever's doing it to be public about it because you're working with that FDA, and that's just a requirement. - Drug and device manufacturer research director specializing in clinical outcome assessments … *Something you could think about with respect to the Friends of Cancer Research paper on endpoints- getting companies together or getting vendors together to talk about how to define endpoints and then to compare them and see if you're measuring the same things. It's really important, so there could be more transparency on how endpoints are defined and derived, especially where there's an algorithm involved.* - Drug and device manufacturer leader and former FDA representative *…* *Hopefully our collaborative efforts will create venues where these discussions happen transparently across various different stakeholders in non-products specific manners*

		that hopefully will allow those types of results and challenges that were encountered or opportunities to leverage this type of data can then be applied to other scenarios with greater clarity about how perhaps those studies could be conducted… there needs to be more research and application of these types of measures to understand how they relate to the actual clinical outcomes that are being observed. - Patient advocacy organization executive leader … *You want to have good data, good data, quality, good understanding of the provenance, the curation, the chain, all those things so you understand what you have and don't mischaracterize it. Then you should be trying to make an actual experiment out of it where you can extract epidemiologic information, something you can compare between these data sets.* - Real-world data and analytic company executive leader
Build trust with FDA	Build trust with FDA	*The more you are transparent with them [FDA], and they think you have nothing to hide, that you're trying to be as completely transparent as possible, the more than likely to trust you because at the end of the day, trust is a value judgment.* - RWE consultant to industry

		… *The community is trying, and so, when you see these initiatives like REPLICATE and DUPLICATE that Shirley Wang is doing at Harvard, I mean, those are all intended… the target audience for all of that stuff is the FDA reviewer… So all of those approaches, all those initiatives are intended totally to convince the reviewers.* - Real-world data and analytics company executive and former FDA scientist … *Well, that clarity comes from… so the FDA has a pilot program… where sponsors can agree to meet with them early and talk about how they're going to use real-world data. So, this is the way the FDA is going to do data gathering to see about what are the strengths and weaknesses they see with real-world data, and they'll learn from that. And as they learn from that… as the literature expands, as the datasets improve, which they are improving, as regulatory bodies have more experience in using real-world data in decision making, they'll come to a consensus, and eventually will release more clarity about what they think are criteria.* - RWE consultant to industry …

		I think it will take leveraging data from various different stakeholders in a concerted fashion in order to achieve success sooner than if every organization were trying to do it on their own, and I hope that we help catalyze that process. - Patient advocacy organization executive leader … *I think bringing the regulator along in terms of education is important as we think about how we're going to increase the use of this type of information in human decision making at the agency…Folks at the FDA are some of the smartest people in the in the whole world and some of the most mission driven… but they are still making more or less subjective decisions based on clinical evidence and scientific evidence on a risk-benefit framework. There's more than the data that goes into this, and we certainly need to account for that in how we're thinking about composite evidence packages that include real-world evidence. So, I think it is kind of bringing the regulator along from the beginning, showing them the value of access to this type of data, despite its sometimes messiness, and showing that it can be used safely and appropriately in situations where you know it's a fit for purpose measurement and is appropriate one-to-*

		one with our research question. I think that there's a subjective piece here. There's a teaching piece. - Digital healthcare and policy expert … *I would really love to see more just… I do think there should be more of these kinds of things where the companies that are pulling this data together, whether it be claims data or EHR data, they are coming together to show the value of it under hypothetical circumstances. Where there's no risk per se of it being for a treatment that you're trying to get to market, like we're really trying to poke the boundaries of it. Where can we go so very wrong? We've seen examples where people have been very wrong when they've had population level, even population level data from registries. What are some of these things that we need to be really really aware of that we could be let astray with this data? And I feel like having some more case examples where the boundaries are really pushed are really valuable. Do these companies know? Do they like want to participate in these sorts of things?* - Patient advocacy research director and former FDA reviewer …

		I think there's a space for the community broadly, this is going to mostly be pharma mining checks, to do validation studies, publish them, and then argue that we did a 300-person validation study for this outcome, it worked, this space, it's published, that's what I'm using…So that's pretty good. It's published. And I'm going to use that one. So, if the community went and started to publish, then they'd have an argument. - Real-world data and analytics company executive and former FDA scientist … *I think it does start with initiatives, therapeutic area specific initiatives like MCode, that can identify a clinically relevant set of data elements that are already captured within our health systems as part of routine care. I think that MCode, in particular, has applications across therapeutic contexts, but because of the way we deliver care, and because I think on a decision-making basis, all of our tools need to be fit for purpose. Our data collection instruments need to be fit for purpose. It may need to start therapeutic area specific and expand outwards. I think that piloting that in large scale big effect studies where safety is already well established and showing that we can do that at scale across multiple health systems in an interoperable way is the natural*

		extension of that kind of improvement in data collection, improved trust, improved evidence based for regulatory decision making. - Digital healthcare and policy expert … *I think it's critical to be able to sort of put these datasets to push them to the test. Where do they break? Where do they go wrong? I think some more [use cases]. There are no human lives at stake- we already have information; the drug is already approved… I think that the lesson sort of learned piece of it- there's not enough of that there in the regulatory setting.* - Patient advocacy research director and former FDA reviewer … *I think if you have a software solution that might be a medical device, and you're meeting with the review division and CDRH [Center for Devices and Radiological Health], I think MDUFA [Medical Device User Fee Amendments] might mandate that a sponsor has the option to bring in someone from the CDRH digital health center of excellence into the meetings. You'd want to verify that, but you could think about things on the drug side where there is an RWE subcommittee. And there's the Office of*

		Medical Policy, and could they be empowered more to be kind of an arbiter of RWE with different divisions from a process perspective? - US government policy and industry legal counsel and former FDA representative … *If you want to say to FDA, Look, we believe that this real-world performance status endpoint is reliable because we just think that the way clinical care is delivered is people come back every month to get their scans. And [if] I was a reviewer, I would say, yeah, you're full of it because nobody comes back every month to get your scans. But if you were to show me the data that says, you know what, we took 1,000 individuals with breast cancer, here's the pattern to which they get their scans, the outliers are 4% on either side, and we know that as long as people get their scans within plus or minus 10 days, it doesn't change the outcomes. You've actually completely shown me how I can actually trust the output. So, that's the kind of thing that I think we have the sort of responsibility to get right when we're talking about leveraging real-world data is understanding the shifting sands of clinical care, understanding what gets people anxious about why information may or not may not be reliable, and then understanding what needs to be modeled to provide that provide confidence.*

		- Real-world data and analytics company executive and former FDA representative … *In oncology, how we moved from this old tumor assessment, like the ECOG and others to RECIST, it took us 4 or 5 years. So first you have this independent committee who came up with all this data that RECIST and unidimensional measures versus the bidimensional measures are actually just as good and better and more accurate and everything in these analyses. And then I remember for years we had to collect both for the FDA. And first, our primary analysis had to be on these old methods, even if the old methods did not make sense because everybody was using something else. So, you thought RECIST is better, but from a regulatory point of view they were used to this old one. So now translate that to real-world data, and what do we need to do? And how do we need to come together as a community to disease by disease think about it… and in real-world data, it's very hard because you're not going to have this old method, but it's almost you would want to say what is feasible to collect? What impact does it measure on the patient and benefit for a patient? And then you could maybe say how it correlates with these strict clinical trials endpoints…but what you really want to*

		understand what matters to patients, and I agree more as a broader community that this is actually a good measure of effectiveness. - Regulatory advisor to industry

Note. FDA = Food and Drug Administration, RWE = real-world evidence

Supplementary Table 6

Interview results: What actions are needed to achieve this solution?

Themes	**Concepts**	**Quotes**
Incentivize stakeholders	Provide incentives for novel methods	*I also don't think that we're going to get anywhere unless we start to incentivize in a real way the use of these kind of innovative methods for assessment and data collection, and I think that has to come down to how FDA collaborates not only with sponsors, but how they collaborate with payers to make sure that the undertaking of a clinical trial is acceptable not only to the regulator, but also acceptable for payment decision making in the end.* - Digital healthcare and policy expert … *I think it does require the collaboration of all the partners in a space where it's transparent. So it can't be within an individual, IND or NDA because that doesn't come to light until 6 years from now. So I don't know if it's FDA funded like they're doing with the core outcome… So they have those core outcome sets for clinical outcome assessments, and the FDA has funded it with grant money. I think that that's really*

		helpful because it eliminates some of the risk. It assumes some of the financial risk or at least shares it, and then it forces whomever's doing it to be public about it because you're working with that FDA, and that's just a requirement. - Drug and device manufacturer research director specializing in clinical outcome assessments
	Align evidentiary standards for regulators and payers	*The only way we're going to de-risk the use of some of these novel trial methodologies and novel clinical tools for measurement is to get aligned there on payment and evidentiary standards for both… I think that there needs to be some sort of de-risking and coordination between FDA and CMS to enhance our overall ability to generate decision-grade evidence.* - Digital healthcare and policy expert
	Form and work through a community	*It's this bringing the community to get communities together. So it's the disease and patients and physicians. And that's creating… this pre-competitive idea of, okay, this could be this endpoint, right? So bringing these communities together to develop something that everybody uses versus everybody comes up with their own best way…*

		I think by creating something that is more acceptable by all, we are going to make it easier for them, and then eventually easier for everybody else. - Regulatory advisor to industry … *I don't know if it's any life sciences companies or like ISPOR type activities and best practices because it's a membership organization that brings together academics, data companies, and life science companies in a collaborative effort to actually put forth good practices, and to enable FDA to endorse or adopt that as guidance, or even (and FDA is allowed to outsource guidance development) to ask a group like that to develop guidance, and then FDA gets to decide if that's what…* - Drug and device manufacturer research senior executive … *Trying to think who else can do it. I guess professional societies like ISPOR, and they do issue best practices. They have issued reporting guidelines and templates. I think those things are helpful.* - Drug and device manufacturer leader and former FDA representative

	Initiate congressional action to advance this space	*It does seem like in part of the PDUFA [Prescription Drug User Fee Act] reauthorization, so that's Congress acting versus a standalone bill, that requiring additional guidance or more complete guidance on these specific questions is needed. Otherwise, the subjectivity that FDA likes to have is going to remain.* - US government policy and industry legal counsel and former FDA representative *…* *I think another policy idea would be as part of PDUFA [Prescription Drug User Fee Act], you should probably know there's a lot of commitments around meetings and sponsor-FDA interactions, and what the timing of those and the substance of those and when… you could imagine a world where FDA has much clearer policies around, coming to alignment and working with sponsors on an RWE study. FDA talks in the guidance a lot about the need to meet early with FDA and the need to do this, but I think they could have more granular processes about how to do that, and when to do it, and what kind of feedback they would be giving, and how because that… in some ways, if sponsors know how early enough in the program to get alignment with FDA or not, that adds some at least early predictability, even though it's not a public level predictability, you know, it gives that particular sponsor early predictability.*

		- US government policy and industry legal counsel and former FDA representative … *I think you'll have to have multiple levers all working in sync.* - US government policy and industry legal counsel and former FDA representative
Remove barriers	Address FDA's heavy workload	*Not sure how to do this with their [FDA] workload. Maybe they need to figure out their workload issues.* - FDA representative
	Assure RWD providers of confidentiality of information between sponsors and FDA	*Getting clear that we're not asking them [RWD providers] to post their trade secrets out on Google. It's like you're going to be in a comforting them that whatever confidential information they're going to be sharing is going to be shared with us and FDA.* - Drug and device manufacturer director
Accelerate stakeholder efforts versus give it time	Accelerate (speed)	*We need to be moving faster to it. It [real-world data] has got so many benefits. It's how we get to a real learning health care system where actually we've got a healthcare system that learns. All the technology's there… The health sector and drug sectors are*

		behind other sectors like finance and retail and other things, and we just- we're behind. We don't know why, but it's just time for this to happen. - Drug and device manufacturer research executive … *I've always seen it to be really productive scientific discussions that are better had in real time than going back and forth on paper every 3 months.* - Drug and device manufacturer research director specializing in clinical outcome assessments
	Give it time	*I don't know if there's anything more that needs to be done. Maybe we just need to be patient. I don't know. It moves slowly.* - Drug and device manufacturer director … *I'm aware of some work that regulators are doing themselves. I don't think it's public yet so I can't talk about it, but to try and create greater clarity and early engagement.* - Professor and research scientist in epidemiology

Note. FDA = Food and Drug Administration, RWE = real-world evidence

Supplementary Table 7

Interview results: Who are the stakeholders?

Theme	**Quotes**
Academic experts	*There's also academia because I think that's where they could be an unbiased third party. They've got some of the really good analytic expertise…probably physicians too because also just to understand it… and maybe that can be where the academia, maybe put those together, because I think there could be the scientific and the epidemiologist that probably have some deep expertise and certain methods, and not that we [drug and device manufacturers] don't have it, but they probably have it there, and then maybe the physician academics where they've got some insight to just how does that endpoint get collected even?* - Drug and device manufacturer research executive … *For the PFDD [Patient-focused Drug Development] guidance series, they've brought on special employees who are academics but specialists. They bring them on half time, but I've also seen them over the past… fund training from top academics from Northwestern or from Duke who train on the methods, and they're the same people who are at the meetings as well. So, it's not like they [FDA] are getting access to training we don't have. I think they're*

	recognizing the field is moving forward, and they need to move forward with it. And so, we're all kind of trying to do it together. - Drug and device manufacturer research director specializing in clinical outcome assessments … *If you're thinking about who are the stakeholders that need to be, or maybe you can actually propose that it goes beyond just the FDA, because we need academic expertise to also come up with something that can be helpful… The main thing is this has to be outside just the regulators deciding because this is not really a regulatory question. At the end of the day, it's about do you believe what you see or not? If you believe it, it should be acceptable. So, to get there, maybe this needs some kind of academic societal discussion. I mean an open discussion to decide on what are the rules, the thresholds, the boundaries, the acceptable level of validity. I know some academicians, I won't mention names, they were actually talking about the threshold of tolerance of various findings and evidence… FDA has a very good network of academics and scientists that they can engage.* - Drug and device manufacturer senior executive and former FDA reviewer
Congress	*I think Congress correcting them [FDA] just like Congress corrected them to do the RWE Program in the first place. I think you could think about it. Congress in the next years could think about an enhancement.* - US government policy and industry legal counsel and former FDA representative

FDA and other regulatory authorities	*I think FDA is supposed to aggregate information on real-world uses and publish that under the user fee commitments. I think that will help, and to the extent that they could continue to go over use cases with the industry, I think that would be very helpful. I know that ICH [International Conference on Harmonization] has a reflection paper out there right now, where they're moving towards global alignment on real-world quality principles, real-world data quality principles, and then acceptable use cases for real[-world] data, and I think that's going to go a long way as well like. Just have a discussion out in the open about when it's appropriate to use real-world data. What does it mean to have high enough quality data to make decisions? So, I think that will be helpful, and they're going to build on cases where it has been used for regulatory decision making already. So, I think the regulators do have a role to play.* - Drug and device manufacturer leader and former FDA representative … *I think the FDA should [sponsor the pilot studies] because they're the ones that get everybody to the table because whenever there's something put together that I see, at least in it, if it's going to be across industry and other people, my first question, and if it's meant to like influence FDA or to change something…. My first question is who's plugged in from the agency? So, I think they're the ones that have to always put this together and with the express objective that you know this is going- they don't have to make commitments- but this is going to influence our thinking on this.*

	- Drug and device manufacturer research executive
Healthcare providers	*Probably health care providers in terms of improving the understanding as to why certain data elements need to be collected, as they are not necessarily thought to be a component of that health care encounter. It doesn't mean they're not invaluable in the long run, and I think having some alignment around that could be helpful, because what's bound to happen, I think, is people are going to want more and more data being collected, and the people who have to collect it are going to be under greater resource strains, be that time or any other to be able to do that.* - Patient advocacy organization executive leader
Patient groups	*I think this is where advocacy groups play a great role because we don't have any vested…. We don't have a molecule that we're interested in bringing to market. You know what we're really ultimately interested in is how people access treatments efficiently, as long as they're safe and effective. That we're not putting drugs out to market that- where the evidence was weak. And then we find out once they're out for use in the general population that we made a mistake. No one wants to be there. So, I feel like groups that don't have that vested interest are able to bring together stakeholders from different drug companies who don't like to play together too much just on their own. Some are better than others. But then you can bring them together, and then we also have connections with FDA and payers to bring them to the table… and you can have these conversations about doing pilot projects or writing policy. So, I think that the nonprofits are well positioned to this kind of work.*

	- Patient advocacy research director and former FDA reviewer … *Let's think about rare disease. It could be NORD [National Organization for Rare Disorders]. Maybe some common diseases that we want to do something. Maybe it could be the National Academy of Sciences. Create like this forum that for the next 2 years, let's meet regularly and develop something… they [NORD] do conferences and other things, and they do specific ones. They have projects, initiatives, and why not? Right then, they're specific organizations for the specific, rare diseases, and they could also drive that. Some non-profits that are built. It would have to come up that, those groups that are most interested, for me, it should be pharma sponsors but also payers, that they provide some in-kind contribution, and then there's a governance created by all, but it's run by this independent group, and then you have the academics to join or the physicians to provide this scientific, maybe unbiased because it's not tainted by pharma, but at least it could be looked at that it's not just tainted by pharma, not just tainted by payers that want to develop something that is good for them.* - Regulatory advisor to industry … *I think patient groups obviously play an important role because patients are the ones that are going to get treatments that work more quickly if this program [a dashboard for sharing FDA reviews of RWE] is successful, so I think*

	there's some patient groups. I don't think the patient groups have been playing in RWE as much as they should, candidly. I think there's some opportunity there. - US government policy and industry legal counsel and former FDA representative … *And then patients. Because some of these, I think, there should be some look at well, when you're looking at endpoints, and maybe they can't scientifically say this leads to that clinical benefit, but they should get the patient perspective on it.* - Drug and device manufacturer research executive … *I do think patient groups… I think there are certain ways that patient groups can be added here in terms of, I think, articulating why real-world evidence endpoints are important to them because otherwise you get like Patients Like Me and these other groups that also have a vested interest in having their data be used and their approaches and patient preferences. Like that all clouds the stuff, but if you can get alignment on the patient side of why this is important, why having that information and indications and labeling is important for their doctor-patient conversations and shared decision making, to almost validate my example of like staying out of the emergency room is more important in some areas than FEV1 [forced expiratory volume in the first second], like that kind of information from the patient community, and I know if FDA's tried to do that with the patient or the patient focused*

	drug development, but so many of those have then been co-opted into these clinical outcome assessments and things like that that aren't specific to these kinds of endpoints that you're talking about. - Drug and device manufacturer research senior executive
Payer organizations	*I could say payers probably too because I think… we think of them in the US outside the purview of the FDA, but…if we're going to make… it will be short-sighted not to get their input because then it would, just it helps to see what's valuable there because from our perspective it's not great if we get something approved and nobody wants to pay for it.* - Drug and device manufacturer research executive … *If you're talking about stakeholders who'll put pony up something for it, I think it's going to be so interesting, watching the push-pull with the payers with the prices of the gene therapies, for example. Well, hopefully they're always looking at the same thing.* - Real-world data and analytic company executive leader
Professional societies	*I guess professional societies like ISPOR [International Society for Pharmacoeconomics and Outcomes Research], and they do issue best practices. They have issued reporting guidelines and templates. I think those things are helpful.* - Drug and device manufacturer leader and former FDA representative

Real-world data and analytics organizations	*99 out of 100 times, a pharmaceutical sponsor will not own the dataset that they hope to use for a regulatory decision that's based on real-world data. So, that data provider, whether it's IBM or it's Flatiron or it's CPRD [Clinical Practice Research Datalink] or the Japan Medical Data Vision, that that data provider's voice is really important. So, it's a missing piece in our sort of understanding to date, I think, of the acceptability of regulatory anything because we don't talk to the data providers.* - Drug and device manufacturer director … *I think the data providers would really be- it would be helpful if they also kind of align on best practices amongst themselves and share those because until they do, I find it a little bit challenging for regulators to use information if it's like comparing apples and oranges across these different studies. So, I think that needs to happen.* - Drug and device manufacturer leader and former FDA representative … *In the long run it may be valuable to include EHR developers in those discussions so that they are prioritizing those same metrics and what needs to be collected.* - Patient advocacy organization executive leader
Regulatory experts	*I mean it's a huge industry of people that are… That's like all we do. Regulatory experts… because it's this really interesting combination of you have to say, look the data don't exist, like no, it's one. It might be it's unethical. Okay, now we have to show it's unethical to do it. It would take way too long, even if you could start enrolling people*

	because the disease is so rare. You can't possibly get a hundred people to be in the study. The regulatory, the regulatory consult is how do you say this nicely to the FDA, so they'll believe you? Like what kind of meeting should you ask for? Is it a Type B meeting? Is it a Type C meeting? Is it like…they don't care if it costs you a lot of money. That can't be… It harms public health could be a reason. So you have… then there's this like this whole set of folks who think through how do I go back to the FDA to negotiate something reasonable, whether it's to show efficacy or it's a confirmatory trial… - Real-world data and analytics company executive and former FDA scientist
Stephan Lanes	*He [Stephan Lanes] does a lot. He does a lot of chart validation. He does a lot of validation studies.* - Real-world data and analytics company executive and former FDA scientist

Note. FDA = Food and Drug Administration, RWE = real-world evidence

Supplementary Table 8

Interview results: What are good ways to engage the stakeholders?

Theme	**Quotes**
Choose a recognized facilitator for pilot projects	*Once there is defined, and there's someone who is a recognized, not even leader, but the recognized conductor or facilitator…So I think Critical Path Institute served, I mean, beautifully in that way from a COA [clinical outcomes assessment] perspective. It was just a clear facilitator for communication.* - Drug and device manufacturer research director specializing in clinical outcome assessments … *I think this is where advocacy groups play a great role because we don't have any vested…. We don't have a molecule that we're interested in bringing to market. What we're really ultimately interested in is how people access treatments efficiently, as long as they're safe and effective. That we're not putting drugs out to market where the evidence was weak. And then we find out once they're out for use in the general population that we made a mistake. No one wants to be there. So, I feel like groups that don't have that vested interest are able to bring together stakeholders from different drug companies who don't like to play together too much just on their own. Some are better than others. Then you can bring them together, and then we also have connections with FDA and payers to*

	bring them to the table… and you can have these conversations about doing pilot projects or writing policy. So, I think that the nonprofits are well positioned to this kind of work. - Patient advocacy research director and former FDA reviewer … *I thought of NORD [National Organization for Rare Disorders] as one. Definitely something if you're talking oncology- Friends of Cancer Research with its big outreach. It's not exactly a patient group. It's a patient advocacy group, and they could pull patients into it. So yes, you need groups that have this policy outreach probably to do this.* - Regulatory advisor to industry
Identify the value(s) and implications for each stakeholder	*Where I think things are successful is when FDA is bought in and excited, and I think there are a lot of people at FDA now that are working on RWE a lot, and I think the more people internally at FDA that are working on it, the more excitement there is internally, the more the agency is going to be behind, making these decisions and providing clarity on when's it going to be acceptable or not.* - US government policy and industry legal counsel and former FDA representative … *I think it is just sort of working through some of these use cases in determining if there is value for utilization of these metrics. And I think they have to have some degree of value for each of the stakeholders or at least perceived value in order to optimize them into the future, or they'll be kind of gaps in the collection of the evidence and the utilization*

	and the data quality if there's not sort of an attempt at a cohesive sort of end-to-end for collecting and analyzing this type of information to make it useful. - Patient advocacy organization executive leader … *So, it's just these blanket policies, and I know the FDA more and more has even to their credit asked the question, what are the implications within industry if we say this? Because they realize they're unintended. They don't know. I've told them. I was like you think you're being helpful with some of the feedback, but we spend hours and hours and hours in meetings trying to decipher what you mean by this sentence or that sentence, and it's not clear to us always how to just reach out and clarify. You know just little things like that that they don't mean it, and they don't know that it's an issue until we tell them.* - Drug and device manufacturer research director specializing in clinical outcome assessments … *Make it really clear that, if appropriate, this will lead to, progress- that it will influence their thinking because, for instance, right now… in our company, we're trying to put together 2 or 3 possibilities to submit as an RWE pilot for their latest call, and I think they did a much better job about this is going to make a difference. So, we're scrambling and throwing elbows and they want to be involved in this because they see it being valuable because I think they've gotten the signal from FDA that, hey, this is going to be consequential; this is going to have an impact.*

	- Drug and device manufacturer research executive … *Understanding the context of the therapeutic area, why things might look that way by therapeutic area, what's the angst that shows up in cardiology. And then, having a bit of understanding of the politics also matters. Like why do CDER [Center for Drug Evaluation and Research] and CBER [Center for Biologics Evaluation and Research] look different? Science is your friend, though, in these things. FDA sees itself as a science-based regulatory agency. When you need to go from here to there, let science be your friend. Build the methods. Run the experiments. Cross-check. I absolutely think that science should be a friend. That's the first thing… FDA and other regulators around the world are science-based public health agencies.* - Real-world data and analytics company executive and former FDA representative
Engage the full stakeholder community, especially FDA	*There's a Digital Medicine Society, and they sort of have over time established themselves as the closest thing that I think we have, and they have because they've been consistent. They put science first. They include all stakeholders… They're just broad in their thinking, but it's still not endorsed by FDA. And when it's not endorsed and you're not guaranteed FDA collaboration, then it's like, well, I'm glad we have these standards… or even in ISPOR, we just finished this good research practice report, this task force report. If we had done it without FDA, I would say it's great, but now the next step is to make sure that FDA agrees. But the beauty of it is we do have FDA on the task force, and even though they can't speak for the entire agency, that is representative of the current thinking, the*

	current expectations, and it influences that as well, and that they're aware of what the sort of good research practice is, and we don't, as far as I know, have a forum like that now for digital that includes all of the people it needs to include, especially FDA. - Drug and device manufacturer research director specializing in clinical outcome assessments … *In our case we worked very closely with the FDA. They were involved pretty much at every step of the way. So, very close collaboration, and in our new project I also anticipate it to be a very close collaboration as they often bring things back to the team that we're working with for internal discussions among larger teams within the agency and separate teams. So, there's teams within teams that are working together on this.* - Professor and research scientist in epidemiology … *I think that if the community would come together, then… and I say community meaning, okay, the pharma, the payer, the researchers, we're going to do this and agree that let's not compete about who developed this and whose idea gets the IP [intellectual property], then they could find the patient community. Now, how to do it? I don't know.* - Regulatory advisor to industry

Note. FDA = Food and Drug Administration, RWE = real-world evidence

Supplementary Table 9

Interview results: What would help enable this solution?

Themes	Concepts	Quotes
Incentives for stakeholders will lead to action	Financial support for pilot projects (e.g., FDA BAAs and CERSI, industry sponsors)	*We're not a contractor with FDA. It sort of would limit some of our policy engagement and other projects, so we haven't done that. Most of our support is from unrestricted grants. But for the [anonymized] project as an example, I think the participants who are contributing data also see value in the partnership, so they frequently provide additional funding in order to support the partnership.* - Patient advocacy organization executive leader … *Broader agency announcements… for grants, so people can apply for grants. They also have the CERSI [Centers of Excellence in Regulatory Science and Innovation] program which is where there's institutions that are being kind of pre-approved to do work for the FDA, like to answer research questions.* - Patient advocacy research director and former FDA reviewer

	Congressional action	*Get members, key members of Congress interested, and typically they're members that are the ones that historically have played on certain policy issues. I don't know who pushed this RWE stuff at the time. I can't totally remember, but Senator Braun from Indiana, for example, plays on life sciences issues quite a bit, like a member who's on key committees deciding it's important can try to get it into a package. I think every 5 years with the PFUFA [Prescription Drug User Fee Act] reauthorization that happens, and it just happened in '22 but '27 will be here before you know it, and you can think about that as well. It's stakeholders like PhRMA [Pharmaceutical Research and Manufacturers of America], but also patient groups, others getting involved and making sure Congress, recognizing… it's something that needs to be addressed.* - US government policy and industry legal counsel and former FDA representative … … *It's going to be 10 years since the program [21st Century Cures Act] was put in place very soon, and so I think you could think about further direction to FDA about how to keep the momentum going.* - US government policy and industry legal counsel and former FDA representative

		… *One thing that is facilitated [by the Prescription Drug User Fee Act VII] is that FDA asked a few years ago, maybe in 2019 or something, they have sponsors to flag applications that contain real-world data, so that should make it easier for them [FDA] to locate the information.* - Drug and device manufacturer leader and former FDA representative
	Incentives for improved RWD quality	*So that's how you fix this long term is that doctors need to have an incentive to capture the data reliably and accurately.* - Real-world data and analytics company director … *MCode means minimal common oncology data elements. So, it really is analyzing treatment across the EHR and cancer practices to improve quality and care coordination within health systems. I do think that's a big incentive for some of these integrated health systems that are really interested in improving on quality metrics, which their revenue is tied to. And if they've got value-based arrangements, they certainly are. So, I think on the health system level there is an incentive to adopt this kind of platform within their EHR is because they can use that information to inform, not only clinical decision making, but kind of C-suite executive level*

		decision making on how to improve on quality metrics within their system. So, I think there's a health system incentive there to get more standardized, to get more interoperable, especially as you think about some of these large integrated health systems. - Digital healthcare and policy expert
Supportive organizational structures and cultures can help optimize the probability of success	Optimal FDA structure	*I think it can get there, but do you have champions in the FDA who are working with you and not just listening to you? That's a huge—that was a big distinction…. one effort was it used to be the COA [clinical outcomes assessment] group within FDA, was kind of an internal group, almost like a COE [Center of Excellence], an internal group, and the review divisions could reach out to if they wanted kind of. And now it's a COA division where those COA reviewers, while they still report up to the same division, really sit in each of the review divisions, and they have relationships with the rest of the review group. And I think that's really helpful, because it takes away that separation.* - Drug and device manufacturer research director specializing in clinical outcome assessments
	Community involvement	*Factors for success would be having good collaborations, good working relationship, good team on our end, willing to dig in because it was big, a pretty big, project. Yeah, I think well-functioning teams is probably top of mind.*

		- Professor and research scientist in epidemiology … *I really think the big thing is getting the patients involved and having that patient's voice in the process. When you think of a lot of the big legislative changes were because of patient's voice. The orphan disease, it was because of patients. Accelerated approval, it was because of patients. So, I think that patients impacted the legislation. Regulators? Well, we could use the patients or ask the patients to help us impact because I almost feel this impasse that everybody is competing with everybody, but the patients don't benefit, and it's a lot harder because it's easy for patients to go to the Congress and say we need a change, so that there is orphan drug designation for these real diseases. But how do they impact on that that broader community so you guys come together and say, What is an endpoint that can be used so that we can then utilize this data for maybe, if not new approval, at least for us, learning how to use the drug in the future and what it does to patients that were never in studies? It's much harder because they don't have a place to go.* - Regulatory advisor to industry
	Good facilitators	*…who at the end of the week or the end of the year they [device experts] will say, Oh, I was a huge success because I put this wearable in a clinical trial, and I got all this great data. End*

		of story, right? And then you're like, well…okay… [Interviewer: Where did it go from there?] And then- but they don't- that's not their job. Their job is the device piece, and so they kind of look to somebody else. They hand it off, and they're like, Well, but you do the rest of it, and they just assume that it can be done, or that it's easy, or that because Philips said this is what they're measuring, that's what they're measuring, which is fine. Like we figured it out in the COA world because we've been around it long enough that somebody is putting the pieces together. Nobody is putting the pieces together yet for digital and thinking about it from beginning to end and what it really takes. They're just focused on their piece. It might be the same for real-world because you have everybody using it for what they're using it for, but in a regulatory setting, your definition of evidence is not the same as my definition of evidence, and your definition of expertise is not the same as mine, and so it becomes an issue within any organization, I think. - Drug and device manufacturer research director specializing in clinical outcome assessments … *There's an FDA person who does the coordination of meetings between FDA and our team. Internally, I had a sort of project coordinator who is helping to manage on the admin end, and then multiple sub-teams that were working on things as well. So, regular meetings,*

		overall meetings, as well as sub-team meetings to keep things on track and an admin followed me around to make sure I stayed on track… So, I had overall oversight to make sure things kept moving, and so if I spotted a problem, I just wanted to make sure it was headed off before it had too much downstream effect. - Professor and research scientist in epidemiology
	Transparency and inclusivity	*I think what we've done [with the current patient-focused drug development draft guidance], and I credit the FDA with this, is full transparency and collaboration from beginning to end. So, workshops on each of the guidance documents. Many opportunities for feedback in many different venues, and the FDA has been accessible. So, they're at the conferences at ISPOR [International Society for Pharmacoeconomics and Outcomes Research], they're at ISOQOL [International Society for Quality of Life Research], they're at PRO [Patient-reported Outcome] Consortium. They're listening and clearly, every time FDA would set up a panel they would invite someone from industry. They would have patients. They would have providers. FDA hasn't ignored the payer, which is huge, because they recognize that we can't just think about the FDA, and so I don't think it's perfect, but it at least it's not in a vacuum like it was before, and I think it's made it a lot more successful.* - Drug and device manufacturer research director specializing in clinical outcome assessments

	Needs that are well understood and communicated clearly	*[What would help enable this solution is…] Director of the OMP [Office of Medical Policy] and leadership in each of the review divisions decide which areas are most ripe for leveraging RWD. What area where there is not a lot but most in need?* - FDA representative … *Pre-competitive collaborations usually have a longer timeline before any return on that investment is realized, and organizations may have competing priorities, so to be able to identify those areas that are the problems that are ripe for solving, and those problems that will have meaningful impact if they are solved, I think, is important. And trying to understand that and articulate it upfront. You know some of these things, or just they ideally aren't just like 'wouldn't it be nice if'.* - Patient advocacy organization executive leader
	Stakeholders perceive there is value	*Facilitators- they [FDA] are required [by the Prescription Drug User Fee Act VII] to do it [publicly share information about RWE used in its decision making]. They're committed to it. It's important because it's a public like public health tool or public policy tool.* - Drug and device manufacturer leader and former FDA representative …

		I'm hopeful that we'll be able to delineate sort of the framework for successful validation of these types of metrics. I acknowledged that they are probably less precise than what is collected in the clinical trial, so the likelihood that real-world evidence will replace the clinical trial is low and probably should not be the goal here. But I still think there is value and questions that can be answered, maybe even better from real-world data, depending on what that question is than a typical clinical trial, so that they kind of have to go hand-in-hand in order to help improve our health care learning. - Patient advocacy organization executive leader … *The other thing is, I mean in my mind, just keeping in mind what we're trying to achieve here. I mean, for me this is about in some ways—like there's a bigger why here… because we want data that will not just give a favorable opinion about a regulatory decision for X company or Y company, but the right one. We want it to be right for patients. I don't know. Maybe there's just got to be more messaging around, Well, we're all in this to try to—a reminder why we're here, like we want to furnish evidence that will influence a decision in the right way. Not just a 'yes' decision.* - Drug and device manufacturer director

		… *I think when I hear from colleagues that have been at the FDA is—so there starts with they've clearly got a need to demonstrate some things and do some learning, and they can't do it all. They could maybe do through the Sentinel some work, but they've got limited bandwidth. So probably the rationale is to say, Well, look, there's all these companies out there. They can do these things. As long as we direct it a certain way, we should get them involved. So, I think it probably starts with identifying a need to test some methods, test some things, demonstrate some things, and then getting into like, Well, we need—maybe it's two pronged. We need the capacity. It's out there with the manufacturers. We need them to be involved, and they may bring some good perspectives, some things we aren't thinking about.* - Drug and device manufacturer research executive
	Valuing incremental innovation	*What I could say is, if I were the FDA, you learn by experience, and you take baby steps as opposed to big leaps.* - RWE consultant to industry
	Learning mindset	*It's going to take a while, because what's going to happen in the short term is sponsors are going to ask those questions, and data providers are going to say, Well, we can do most of it,*

		but not all of it. But let's see if it's good enough. and there'll be some test-to-learn approaches and things like that. That's what will happen in the short term. - Real-world data and analytics company director … *A good demonstration project hopefully generates a lot of learning from new insights that can help inform sort of guidance or decision making that they need to make… There's always things that happen that are unexpected, and you may get results that are unexpected when you're trying to demonstrate, that even if you think it's going to happen one way, it may not, and it's all very public, and those are some risks, but I think, trying to see everything as learning, whatever you do, whatever comes out, you're learning something, and if you're not, then it wasn't a successful project.* - Professor and research scientist in epidemiology … *I think it [learning from pilot projects] is helpful. It might not be what everyone wants to learn. You know, I'm okay with that. I'm not an evangelist for real-world data. It's just, Okay, if we want to use this, you've got to look at all the warts, and you've got to figure out when you can use it. When is it appropriate? What is it telling you? So, I think it's just really*

		opening people's eyes to what's out there? What are the pros and cons? What's the low hanging fruit? - Drug and device manufacturer leader and former FDA representative
Procedural improvements can accelerate solutions	Mechanisms for interdisciplinary FDA reviews	*They [FDA reviewers in CDER] are not trained on devices and technology. It's the measurement science. And so, are they going to their counterparts in the device world to get feedback on the device part? They're supposed to be, and there's a mechanism for it, but I don't know how well it's working.* - Drug and device manufacturer research director specializing in clinical outcome assessments
	Real-time FDA-sponsor interactions	*But PRO consortium, like the beauty of that is that it's an ongoing forum with a workshop every year with a lot of FDA involvement. And so it's just a continued conversation because you can't just have the conversation and close the door if it's going to build on itself.* - Drug and device manufacturer research director specializing in clinical outcome assessments
Prior knowledge and experience facilitate solutions	FDA's prior experience with real-world endpoints	*There aren't a lot of well known examples and approval letters so far where we can all point to and say, Look, FDA has accepted that endpoint, and again, it's sort of one of those tensions that I think once they do, probably Sponsors 2, 3, 4, and 5 can use it because we know that it*

		is comfortable, and they probably aren't going to have to do as much as Sponsor 1, the canary in the coal mine. That's the place we're at right now. - US government policy and industry legal counsel and former FDA representative
	A landscape assessment	*We've identified them [the research questions] and then go through sort of, in both those of those instances, a little bit of sort of a landscaping process to understand whether the necessary data would be available and whether the owners of that data would be willing to share it, and sort of scope out what that project would conceptually need to look like. If there's interest, then, we may take it on to try and stand it up ourselves, which is what's happened in both the real-world evidence and the [anonymized] project.* - Patient advocacy organization executive leader
	Time to acquire experience	*Some of this, I think, is just going to take time. And I've kind of come across that after just watching the way things play out. It just takes a while for new ideas to kind of trickle down.* - Drug and device manufacturer leader and former FDA representative … *From the real-world endpoint question, I think there just needs to be more experience with them.*

		- Patient advocacy organization executive leader
	Understanding RWD	*I think this was something you could think about with respect to the Friends of Cancer Research paper on endpoints—getting companies together or getting vendors together to talk about how to define endpoints and then to compare them and see if you're measuring the same things. It's really important so there could be more transparency on how endpoints are defined and derived, especially where there's an algorithm involved… I think it's good for everyone to realize the potential like similarities and differences in the way that they're approaching the same thing. So, if you're all looking at survival, we know it's not that straightforward to figure out if someone died in the US like with electronic health records or claims, believe it or not, it's just not that straightforward. It's a lot of missing data, so I think it's a good idea to get everyone together to start aligning on maybe potentially best practices and then to figure out whether or not you can compare that endpoint across data sources. So, I think it's a good way to get away from the theoretical and start really kicking the tires on these real-world data.* - Drug and device manufacturer leader and former FDA representative …

		Where is the data collected? Is there a technology issue that certain medical centers have the equipment, others don't? Are there even barriers related to patient's socioeconomic status? Then some patients are going to follow the instructions better, and they're going to come and adhere with whatever assessment is required versus others may not have the time, may not have the interest. So, it's really the patients and how do you work with them so that you really get the viable data. - Regulatory advisor to industry
Mechanisms that reduce legal risks enable collaboration	Reduced legal risk	*I think the thinking from the regulator's point of view is this: If we get too specific, we box ourselves in, and we want to always reserve some point of subjective judgment. And so, I don't know if we give them… an off ramp… why don't we agree on these principles, and it's not a recipe, and you still got your subjective judgment, but at least we know what to send you, when not to send you. Something like that?* - Drug and device manufacturer research executive … *I'm not seeing a lot of EHR [electronic health records] that have Apple Health metrics downloaded into them that you could then go and take as part of a real-world data study… Well, we ran into this before is health systems don't want information attached to the EHR*

		that they feel like they have a clinical legal responsibility to deal with. So, I go and ask a bunch of pregnant women if they're drinking a lot, and they say, yeah, I have 5 drinks a day. Well, shouldn't your doc know and maybe give you a call or something? So if I stuck that information in the EHR, then that health system felt like they had a responsibility to review the results every time something came in and act on it, which they were not prepared to do, so that information never actually went into the EHR. It was always kept separate, and that was by policy. So even some simple thing like, Hey, you should download all this data. Like what if there's afib [atrial fibrillation] showing up on someone? Your doc never looked to tell you, but it's sitting there in the medical record… [In a registry] you're not caring for them. You're just collecting data for them. You're collecting data and helping support a research endeavor. But you're not a provider. Lots of registries pull information out of EHRs, that's okay, or they ask the patient directly, but you're not their provider, so you don't have the responsibility to intervene. - Real-world data and analytics company executive and former FDA scientist … *I think the tension there is that, but if Gilead, I'll just keep using them, if they're the ones that sort of put the evidence package together, not just purchasing the data and performing the*

		analytics on it, but whatever other evidence FDA required for them to get comfortable with that being an acceptable endpoint, would FDA really require Sponsor 2 to do everything the same way? Or now that we know Sponsor 1 got FDA comfortable with it, that now someone could just point and say, You did that already with Gilead. You know we're giving you the same data and the same analytics; you should just be comfortable with it again. FDA has not been clear really, publicly about that, about their willingness to do that… I think there's a way to do it to say, Hey, we've accepted this for Gilead, you obviously would have to come with your own evidence package. We would do our own independent assessment there. We aren't going to pick up any of Gilead's evidence, but as a good frame of reference, there's a way to frame what FDA is doing that I think still is legally okay. So those are hurdles, but I think they all can be worked through. - US government policy and industry legal counsel and former FDA representative … *Try to bring them, these 2 or 3 companies, say, Look, let's do this together. Let's have this registry that not you own or you own because if 4 of us own it, and 4 of us have the same access and, right, then we can all use it. And eventually, if somebody else wants to join, let them pay a subscription. Maybe it's higher than what we paid to start it, but it should be a*

		good for everybody, and make sure that we are all working on it because otherwise it's just not going to take us anywhere. - Regulatory advisor to industry
	Build in flexibility	*The most interesting element here is how the technology and capabilities are changing, and how that's making the way that we do this work and our and even the application of the rules developed today shift as we think about where we go tomorrow, and so building frameworks that are prepared a different tomorrow is going to be really important in this. Let me give you a really tactical example. CBER [Center for Biologics Evaluation and Research] has asked for 15 years of longitudinal follow-up for cell and gene therapies. Talk about a built to last use case for real-world evidence and real-world data and real-world endpoints. Well, what happens when you're talking about 15 years of longitudinal follow-up, and your biomarkers are going to change across time? Your scanners are going to change across time. Who pays for what in health care delivery is going to change across time? The fact that people do everything by telemedicine is going to change across time. Oh, by the way, there might be a COVID pandemic. So, you get my point. And so, having methodological approaches that accommodate for how we think about how healthcare and technology changes across time is going to be really important.*

		- Real-world data and analytics company executive and former FDA representative
Favorable real-world data circumstances help achieve solutions	Favorable RWD circumstances	*And the fact that [anonymized name] had one [RWE submitted to FDA to inform a regulatory decision] work is not just—it had to work because he found the endpoints he needed, to your point. That study found complete remission data on a lot of people as well as overall survival on a lot of people. Complete remission is very hard to find.* - Real-world data and analytic company executive leader … *I just feel like start with the smaller rare diseases community… So, it's the data source, but also the data sources come from these different clinics and you only have data on patients that have data because for different reasons they were better in following things. So, it's really working through this of how do we get data on everybody? And that's why I said bringing in the patients into these discussions is so important. And that's why for me, starting it from smaller rare diseases is probably better than the large common diseases.* - Regulatory advisor to industry

Note. FDA = Food and Drug Administration, RWE = real-world evidence, US = United States

Supplementary Table 10

Interview results: What are barriers or risks to the solution?

Themes	**Concepts**	**Quotes**
Lack of right incentives for stakeholders retrains action	Lack of right incentives	*Pre-competitive collaborations usually have a longer timeline before any return on that investment is realized, and organizations may have competing priorities, so to be able to identify those areas that are the problems that are ripe for solving, and those problems that will have meaningful impact if they are solved, I think, is important. And trying to understand that and articulate it upfront. You know some of these things, or just they ideally aren't just like 'wouldn't it be nice if'. There has to be some sort of pathway forward, and I think what we're trying to do with some of our endpoint work is to create that path forward and to better understand what the what the steps toward validation would look like, but then actually try it, not just sort of talk about.* - Patient advocacy organization executive leader … *It [pilot project] is a resource intensive project. It's pulling them [RWD companies] off of other work that they might be doing, frankly other work that they might be doing that they're*

		getting paid for at least to some—where they're under some sort of contractual obligation with a sponsor. - Patient advocacy organization executive leader … *The biggest barriers are kind of internal to each individual company. We play better outside. We play better when we're external to our company sometimes than we do within our own organizations, and that's true for the FDA, but yet we talk about it like the FDA was at the table. We told X company—well, we told one group at that company, and that doesn't always work. So, I think the barrier is sometimes our own organizational system of motivation and reward because we reward silos and don't recognize the importance of the collaboration sometimes. I think that's the biggest issue.* - Drug and device manufacturer research director specializing in clinical outcome assessments … *If Gilead, I'll just keep using them, if they're the ones that sort of put the evidence package together, not just purchasing the data and performing the analytics on it, but whatever other evidence FDA required for them to get comfortable with that being an acceptable endpoint, would FDA really require Sponsor 2 to do everything the same way? Or now that we know*

		Sponsor 1 got FDA comfortable with it, that now someone could just point and say, You did that already with Gilead. You know we're giving you the same data and the same analytics; you should just be comfortable with it again. FDA has not been clear, really, publicly about that about their willingness to do that, and I also don't know the industry- how the industry would feel about that because if you're number 1, you're not loving it. If you're number 2, you do, and there's probably also different therapeutic programs that all the companies, where maybe even within the company, they have a different view. - US government policy and industry legal counsel and former FDA representative … *I don't know whose remit that is, but this [improved healthcare data collection in health records] is what they're really pushing in Europe right now. This is why Europe is actually going to catch us and pass us on this is because their health care system is engineered in a way where they can make physicians do it, and that's the only way they're going to get paid, and we're just so fractured here that that'll never happen in this country.* - Real-world data and analytics company director …

		I think that it's going to take an overhaul of the data collection infrastructure to be able to use real-world evidence as right source data. I think it's going to take a large infrastructure investment to get us to a place where we're using this type of measurement for safety and effective[ness]… I do wonder if we're going to need to better invest in data collection infrastructure and standards to be able to effectively use the systems we've got in place that support care delivery, but not evidence generation for earlier phase trials. I wonder if we're going to be stuck in this post-market label expansion portion of RWE fitness for use without any large investment in the way we collect clinical information within our healthcare systems. - Digital healthcare and policy expert … *I think some of the challenges have been there are other more pressing issues that are getting Congress's attention these days and same with FDA… there's just so many things that FDA is responding to that the use of real-world evidence, I don't know that it's been as high up on the priority radar of late for FDA. So, that's a barrier and elevating that as an issue and getting people who are really talking about the Inflation Reduction Act and the threats on accelerated approval, and all of those things are taking over and taking attention off of this, I think, to some extent.*

		- Drug and device manufacturer research senior executive
Organizational structure and culture can inhibit action	Culture	*The review committees are not necessarily the FDA, and they don't speak with one voice, and they've never seen real-world data, and they're skeptical, and they don't have anything to allay their fears because they're just skeptical of all they've heard… Their fears wouldn't know how to get allayed.* - Real-world data and analytic company executive leader … *FDA is staffed by folk who don't trust real-world data. The decision makers or staff, that staff doesn't really trust real-world data… In fact, you could take an algorithm that FDA has used to make a regulatory decision and use it, and the other people at FDA might say, 'Nah, I don't want to use that one. I don't believe it. I want to use a different one.' So, it's all case specific.* - Real-world data and analytics company executive and former FDA scientist … *I used to say to drug companies when I was at FDA, It's guidance, not regulations. People treat them a little bit like they are like the regs but they are not the regs. If you have a really solid reason, and I am your reviewer, and you have put together a rationale for why you're deviating and doing this thing here, I'm going to consider it. I'm not going to say that, No, you*

		didn't follow the guidance. Bad you. I'm going to say, Okay, you put a rationale, but don't just tell me you're going to do it because you feel like doing it. You have to say we're going against the guidance because we believe and have the references there and show the reason…. Drug sponsors need to remember that too, not getting so hung up on the guidance documents… but I think it's tough, and people want to hedge their bets, and it's hard. I do understand that. - Patient advocacy research director and former FDA reviewer … *I think oftentimes when we're about regulatory policy, it's FDA waiting on industry to set some precedents so they can assess on a case-by-case basis… I think industry is often risk averse in the opposite way. They're waiting for guidance from FDA to come down so that they don't invest time and resources in something that's not ultimately regulatory acceptable.* - Digital healthcare and policy expert … *They [FDA] don't get any credit for moving too fast and they rarely, if ever, get criticized for going too slow because if we don't realize some benefit and we don't have it, we don't know about it, but if they do something and they make a mistake, they get trashed. So, they're very risk averse.*

		- RWE consultant to industry … *Intention with a regulatory agency, particularly FDA, that likes to preserve all flexibility it possibly can to the last moment, so that it has all options on the table.* - US government policy and industry legal counsel and former FDA representative … *I think FDA is a conservative organization at core, and I think there's been a worry- I think real-world evidence, when it first became a thing, there was a worry that somehow it could undermine the gold standard of approval. There were certain stakeholders that thought it was somehow substandard. I think those working in the RWE space know that's not the case…I think one of the things that FDA has been very careful of is to try to make sure they project that RWE is not undermining their standards for approval for decision making… I think they're pretty conservative, and they did the press release last fall with one of their—I think it was the supplemental approval for lung transplant patients, and they were very clear to say this is still meeting the substantial evidence standard and all that because they are worried. They don't want people to somehow think it's a lesser decision because it's not.* - US government policy and industry legal counsel and former FDA representative

		… *The two randomized control trials [requirement] was really sort of, it came out of essentially habit, and the need to build more confidence. So, what's interesting is that over time we have built solutions to accommodate for the fact that the habit doesn't make sense… we kind of developed habit of how to get to safety and effectiveness in line with the FD&C (Food Drug and Cosmetic Act]. That's why I sort of described DESI [Drug Efficacy Study Implementation] as this kind of codification activity, but it was basically codified habit.* - Real-world data and analytics company executive and former FDA representative … *There's a big debate in this debate we used to, I used to, have with FDA all the time, but would you rather know something or nothing? Would you rather have something now that's really pretty good? Or you just don't believe any of it and you'd rather just shut your eyes? And some people would rather shut their eyes. They would rather not know anything if it wasn't perfect. Then other people are willing to accept a little bit of imperfection. It will always come to a head on oncology, rare disease, high unmet need types of scenarios.* - Real-world data and analytics company executive and former FDA scientist …

		The information is only as good as the submissions that they [FDA] got, so if companies are reluctant to submit real-world data, then we won't learn as much. We're kind of dependent on whatever they received, whatever companies perceived as being useful for their submissions. So, maybe there's some kind of selection bias there. - Drug and device manufacturer leader and former FDA representative … *I feel like there shouldn't be, but there's competition there, for sure… because you can't really just say we're going to have Pfizer come be part of it. You probably want to have Pfizer, Genentech, maybe somebody small, not just—a mix of those kinds of companies, and how do you bring them to the table without creating—So, there's some issues there. I think that can be because they are competitors.* - Patient advocacy research director and former FDA reviewer … *One big barrier, I mean, it's a cultural shift. I'm competing with you. You're competing with me. And I'm this academic. I'm this expert. So, it's not just companies, pharma companies competing, but it's also the academics competing in their research and everything. So that's just sort of the competition.*

		- Regulatory advisor to industry … *I think it [improved healthcare data collection in health records] takes a bent towards the culture of research and a real clear tie between, Hey, we're already generating a ton of data on our patients that we can leverage in a way that'll help us improve clinical decision making and inform a learning kind of healthcare system, at least internally kind of going forward. So, I think it'll be that culture shift as well there.* - Digital healthcare and policy expert … *You can't get them [Congress] to agree on anything.* - US government policy and industry legal counsel and former FDA representative … *I hope it's changed, and I think it was moving to it, but nobody was thinking about anything but quick win. It was quick win, quick impact, but you have to play the long game in the regulatory space because regulatory precedent isn't a quick win. It requires time. And validity is not a one and done. It's the constant building of a body of evidence. So, we need to agree on what that evidence looks like and how we're building that body of evidence and what we agree is*

		appropriate. Digital is not there. Everybody is trying to be Google, and Google has its place, but you can't make public health decisions on like that. - Drug and device manufacturer research director specializing in clinical outcome assessments … *In my experience in safety studies, FDA is hesitant to a priori define a RWD outcome definition as acceptable.* - Real-world data and analytics company executive and former FDA scientist … *FDA is going to have to get more and more comfortable to where you have like, it's a close call… you don't want it to where the treatment effect seen through RWE has to be a magnitude greater than traditional clinical trials because just that it's an RWE study.* - US government policy and industry legal counsel and former FDA representative
	Slow pace of some organizations	*I don't know what's the average tenure of an FDA reviewer? I don't know. I could stay there forever. So, it takes a long time for an agency like that to change.* - Real-world data and analytics company executive and former FDA scientist …

		[About global guidance on real-world effectiveness endpoints]: *I don't know if we're ready for it yet either, but I feel like we're getting close. We need something.* - Patient advocacy research director and former FDA reviewer … *It takes time, like a guidance takes probably on average, 5 years maybe… This space is evolving really quickly and changing a little bit too still as people are getting more experience, because as you say, the data has been around for a really long time. This idea that the RCT could supplement and you could pill into this, that is a newer idea. There is science around this that is developing and changing. If you write a guidance, the problem is, if it takes years to get it through the process of the bureaucratic processes, and then it changes.* - Patient advocacy research director and former FDA reviewer … *It [a solution] can't be within an individual, IND or NDA because that doesn't come to light until 6 years from now.* - Drug and device manufacturer research director specializing in clinical outcome assessments …

		In the regulated space with these regulators, like FDA, changing the way of thinking and doing business is a slow process, and that's the nature of this regulator, and there are reasons why that's not necessarily all a bad thing. There's good and bad with that. - US government policy and industry legal counsel and former FDA representative … *CPATH [Critical Path Institute] could be another group. I just heard like, okay, some people it takes forever to work with them, and maybe it just takes forever to work with anything.* - Regulatory advisor to industry
	Workload	*There's many other elements that I think prevent participation in research beyond the fact that providers may not be able to see the connection to their work directly. I think there's a time issue. I think there's a bandwidth and administrative burden issue. It's difficult to participate in research, but on an individual level, it is going to take providers who are interested in seeing and can see the results of evidence generation as part of their decision-making process. And I think that's oftentimes only happening in academic settings where we are conducting the majority of our trials, and less and less so in terms of community settings where providers are providing routine care and are overworked and overstretched and don't have time for much else.*

		- Digital healthcare and policy expert … *In our country, physicians don't want to enter information into an EHR. It's too much work. Take community oncology, for example. These practices are struggling to keep afloat, stay profitable. They're understaffed. They need to see more patients. Why does a physician want to spend more time putting information in the EHR? Roughly, throughout this industry 30% of the race and ethnicity data is missing. That means that in an EHR, the doctor doesn't even put what race the patient is. 20% of it is wrong, like a black female may be classified as a white male. So, how reliable is the data from the EHR when nobody is paying attention to it?* - Real-world data and analytics company director
	Lack of community	*I think early on was an example of how not to do it. So, if we look back at 2006 when the draft FDA guidance [on patient-reported outcomes] was put out, and then that time to 2009 when it was finalized, it was kind of a closed door process, even within the FDA, and it was sort of done within what's now a COA [clinical outcomes assessment] division, but it was a COA group then, and then the COA group within the FDA kind of went to the divisions. It was like, here's what you need to do, and then they also came to industry. It was like, this is what we decided with the 4 brains that be in the field. It's just no ownership. There's no uptake.*

		- Drug and device manufacturer research director specializing in clinical outcome assessments … *I work with a lot of biopharma sponsors, too, and I know how seriously they take every single interaction with the agency, and people are prepped, like this is their role, this is their role, and to bring in third parties [real-world data companies], even if they might be a close partner, it's sort of a level of trust that just people don't necessarily want to have to extend because these interactions are taken so seriously, and they are that important. So, I think there are a lot of layers… to why that isn't always happening.* - US government policy and industry legal counsel and former FDA representative
	Lack of transparency	*I guess what I would want to know is, because I've seen these things like, I know Aetion talks with the FDA and advises them, and they talk back and forth, and other groups. But what never becomes apparent is what does FDA think? So even like you're talking about the Flatiron Health stuff. I'm sure the FDA has seen that. Well, what did they—what was their take on it? Maybe they could publicly say what their take is on it.* - Drug and device manufacturer research executive …

		You're going to have different divisions reviewing stuff and for instance, if something goes through CBER [Center for Biologics Evaluation and Research], CDER [Center for Drug Evaluation and Research] may not know that there was real-world evidence if it goes through OCE [Oncology Center of Excellence], CDER may not know, like broad CDER…[Interview question: If it's a non-approved, like new molecule not approved, we won't have insights into the review at all, I'm guessing, right?] Right. They don't post the documents until after approval anyway. - Real-world data and analytics company director … *FDA submitted or announced those [draft guidance] documents. They had a period of public comment. I don't know what they're going to do with those comments. Do you know? Like they going to respond ever? Are they going to issue a new guidance? It's like it goes into a black hole. So, maybe one of the things would be, I don't know, issue a statement on, Okay, we heard these things. This is what we're—This is our plan… maybe they heard 3 pieces of feedback that they're going to action. I feel like draft guidance, sometimes it's draft guidance forever.* - Drug and device manufacturer director …

		We [FDA] go through everything in one to be able to see if we can include it in the—and we actually, we did internal modifications, rewording in the guidance, to make sure that if there is understanding, if not it's clarified, if something's missing it's added. [Interviewer question: But you don't reply back to every single person who submitted a comment, right?] Yeah, see, this piece is not clear to me. Maybe somebody in the background, but I mean my role was mostly of focusing on the contents and the making the guidance better. Whether somebody actually take—because we do, we do actually, for if we comment we have like a common response—whether this is sent back or not, I mean, it's not transparent to me. I don't know. I submit a comment. Sometimes I don't know where they go. - Drug and device manufacturer senior executive and former FDA reviewer … *I think if you go back to the PRO [patient-reported outcomes] initiative or guidance, I don't think we even acknowledge—see this this one thing bothers me about FDA. Nobody acknowledges you as an author at all. I mean, you spend like 5 years of your life with the guidance, and your name is nowhere.* - Drug and device manufacturer senior executive and former FDA reviewer …

		I have to look at the [Prescription Drug User Fee Act (PDUFA) VII] commitment letter again because I forget exactly the way it was worded, but if it [[the FDA-issued RWE report required under PDUFA VII] comes out like a checklist where they [FDA] say, 'Yeah, we received 50 applications, and 30 of them were rejected,' and like they stopped there, that won't be that helpful. It will give us ammunition to complain but, or look you really don't want to use real-world evidence, but it won't give anything meaningful. So, I feel like they have to at least give a little bit of insight into decision making. So, maybe all 30 were not useful because 50% of the data was missing. I think they have to tell us why they made the decisions that they made, not just the numbers or information that doesn't provide insights. - Drug and device manufacturer leader and former FDA representative
	Organizational structures	*So, I wonder if there's not some mechanism where the FDA can set some priorities, because I don't know, I'm like just looking down like my very narrow lens of oncology. I can see the plan, but I don't know what the plan looks like for cardiology or neurology, or anything like that. And how much overlap is there? There might be some. It seems like it would be foolish to have 3 different groups working independently where there was learnings that could be taken from the other group like, let's say, 80% of it is not applicable to cardiology, but 20% is. Like why duplicate that 20% if you can just sort of then take what that bit?*

		- Patient advocacy research director and former FDA reviewer … *We have never been asked or never being given a piece of the FDA regulatory document and asked our opinion about whether the data collected and the way we collected qualified for that. The decision is made higher than my level.* - Director and research scientist at an academic healthcare organization
Lack of knowledge and experience limits achieving solutions	Lack of experience(s)	*There's a serious lack of expertise at the right spots inside FDA on the space. There's actually really deep real-world data expertise in the Office of Safety, Office of Surveillance and Epi [Epidemiology]. In CDER [Center for Drug Evaluation and Research], they know real-world data really well. Office of Medical policy knows it pretty well. There's a couple of people in the Office of the Commissioner that know it pretty well, and then it's one-sies and two-sies around the divisions that really understand. Like the reviewing divisions, there's just not, as far as I can tell, there's just not a lot of deep expertise, familiarity with it. I've done studies, seen them. So, it is my impression also that the people who know it best are not the ones responsible for writing the guidance for what it's worth. For what it's worth, that guidance seems to come out, and it surprises. I have colleagues, old colleagues from FDA who I trust fully of understanding real-world data, deep deep expertise, and I know that they were not involved in writing*

		guidance about the real-world data. So, there is a lack of expertise… The Commissioner understands real-world data very well, but that doesn't matter. - Real-world data and analytics company executive and former FDA scientist … *What I hear from regulators a lot is that there's a lot of variability. Some groups seem to have spot on and they know what they're doing, but they see a lot of things that are—that's why the guidance is needed, and that's why the early engagement is needed because they [industry] can spend tons of money going down a rabbit hole when if they just engaged early they could have said that's not going to fly.* - Professor and research scientist in epidemiology … *The last thing I'd say is that when we [my previous real-world data company] first started doing this work, it was really avant-garde, as you can imagine, and it's still avant-garde… it was really avant-garde and coming up with ways of walking the world through what we were doing and the 'why' meant we had to have mental models that people could understand. So, for example, the PRO [patient-reported outcomes] framework. We needed to have experiments*

		that we could repeat the use of that endpoint then and make sure that people understand, and we actually had to have other ways of finding corresponding data. - Real-world data and analytics company executive and former FDA representative … *The message from that guidance was that we [FDA] expect real-world data that's used in a study to be the same quality as clinical trial data, and retrospective real-world data is never going to be that because you can't control how it was collected. There's missingness. There's misclassification. There's subject to interpretation, all this other stuff you're never going to meet it, but a real-world endpoint is a lot more difficult, because for instance, if those patients were part of a clinical trial where they were assessed by RECIST [Response Evaluation Criteria in Solid Tumors], there's not going to be a note where the doctor says this patient is responding to therapy because they're assessing by RECIST… there just has to be a realization that they're not going to be perfect, and so they have to kind of work with people to try to understand how is it validated? Is this going to be good enough? And I think that just has to be some clarity around that.* - Real-world data and analytics company director …

		I kind of feel that sometimes people don't understand exactly what they're dealing with because they haven't worked with real-world data before. So, they don't understand necessarily that an algorithm is used to kind of define what an endpoint is, and it might have been captured within a 2-month time period. They might not know that. There is a lot of nuance. - Drug and device manufacturer leader and former FDA representative … *Really basic questions of what is the source data? If it's part of a clinical trial, how does it get put into the trial master file and what gets put in there? Is it the cleaned transcript, or is it the original? We can't have the original because it might identify all that stuff. So, that does cause a bit of an issue because if somebody doesn't know how to do something, they're less likely to do it. It's a real barrier to getting approval to actually doing interviews within trials because nobody knows. Nobody wants to handle the data the wrong way. And so, it's like, Well, we're just not going to do it, which is not ideal.* - Drug and device manufacturer research director specializing in clinical outcome assessments
	Lack of framework	*It's like a belts and suspenders kind of approach. Everyone's going to go to the extreme… I think the community knows what we have to do in order to get past the discussion. I don't know*

		if it's what we need to do… I think the community probably knows how to avoid the debate from the regulator by just doing absolutely everything… I'm trying to say that's different than what I think is probably needed to show to get or generate a robust result. You probably don't need to do all of that every time. No one knows what they're really supposed to do, so we all do the most we can imagine doing. - Real-world data and analytics company executive and former FDA scientist
Legal risks disincentivize collaboration	Legal risks	*Some of that information [about real-world endpoint derivation] is considered proprietary.* - Drug and device manufacturer senior executive and former FDA reviewer … *Our proprietary advantages are drug, not our ruler. Like nobody wants their methods to be their advantage. You want to have the best treatment.* - Drug and device manufacturer research director specializing in clinical outcome assessments … *The thing is, this is where all the endpoints are so proprietary nobody is going to do it [precompetitive validation of real-world endpoints].* - Real-world data and analytics company director …

		I do think there's a level of detail they [FDA] could share that's not proprietary, but they would have to make sure that under their regulations, they can't even say or summarize or enough data if it can be the mosaic effect, if you could piece it together and figure out who you're talking about. So, dashboard challenges are that FDA would have to navigate its own confidentiality rules. I think they're called the disclosure regulations in Part 20 of the C-F… Code of Federal regulations. That's how it's all governed. - US government policy and industry legal counsel and former FDA representative … *A barrier might be that they [FDA] have to respect confidentiality, so it's going to be challenging for them to give too much, too many details for products that weren't approved. They'll have to aggregate the information. So, that could be a barrier to information sharing.* - Drug and device manufacturer leader and former FDA representative … *I think they [real-world data organizations] are going to have come to grips with not being able to keep as many things proprietary. I think it should be, it has to be known, at least for the regulators. I don't know how much they'll be able to conceal from the public, but maybe if you use artificial intelligence to do data mining, those algorithms, they might want to keep that*

		mechanism proprietary. They may want to keep—I want to say definitions of endpoints, but I don't think they'll be able to, but I'm sure everyone has their own proprietary way that they define different endpoints. Yeah, I think it could be a barrier. - Drug and device manufacturer leader and former FDA representative … *We ran into this before is health systems don't want information attached to the EHR that they then feel like they have a clinical legal responsibility to deal with.* - Real-world data and analytics company executive and former FDA scientist … *I just don't see a lot of docs [doctors] asking you to download your data. One, they don't know what to do with it, and there's a very real risk… like docs don't know what to do with it. What are they going to look every day? What are they going to do? [In a registry], you're not caring for them. You're just collecting data for them. You're collecting data and helping support a research endeavor, but you're not a provider. Lots of registries pull information out of EHRs [electronic health records], that's okay, or they ask the patient directly, but you're not their provider, so you don't have the responsibility to intervene.* - Real-world data and analytics company executive and former FDA scientist

		… *There are many barriers. The first is that EHRs are all proprietary developed tools, so they're not interoperative…* - RWE consultant to industry
Complexity of real-world data and science impedes progress	Complexity	*So, real-world response variable 99.5% of the time means that the patient responded… and I think you know there's other considerations like that. It's just complicated, like cancer is such a complicated disease because patient may get a 2 or 3 or 9 lines of therapy, and which one was the result? Which one resulted in response? And so, it's just very complicated. So, I'm not saying the agency [FDA] is being unreasonable. I'm just saying that it's a hard problem to solve.* - Real-world data and analytics company director … *…that level of tolerance will vary [by] the disease being applied in, the nature of the disease, what was known, all the expectations kind of thing.* - Drug and device manufacturer senior executive and former FDA reviewer …

		When I'm guiding clients, the first question I ask them is, Is this going to a regulator or not? What is your use of this study? Is it internal decision making? Okay. Is it for a publication? Is it for—it could be a safety study. But if it's going to a regulator, I have to follow different rules than I would, and it just becomes longer and more expensive basically… You want it to be robust, and to do that you have to show process, and you almost always need a human brain in the system, and that's what's expensive. When you insert a human brain, someone has to read it and understand it and document it. That's what I would have to do for a regulator, but I might not do that for anyone. - Real-world data and analytics company executive and former FDA scientist … *There could be more transparency on how endpoints are defined and derived, especially where there's an algorithm involved. I think they[pilot projects] do [help to achieve clarity], but they're probably not enough.* *It's not always easy to interpret the results of those. So, I think it might just point to more research that needs to be done.* - Drug and device manufacturer leader and former FDA representative …

		When it comes to every other endpoint, the new imaging endpoint that we want to develop for some of the diseases like the neurological diseases- every company is thinking, Oh, you know this imaging, that imaging, but again, it's so hard for the regulator. Why is your diagnostic better than these other companies? And how do we put it out there for patients? And it's the same thing with real-world data. - Regulatory advisor to industry … *I would say there is not having focus. So, trying to do too much. Thinking all right, this is our one chance to do everything because it's a pilot, and then nothing's really pulled through completely. So, I think it would be to make it targeted and focused.* - Drug and device manufacturer research executive … *It [the real-world effectiveness endpoint] doesn't perform exactly the same in every disease. So, for example, trying to calculate real-world PFS [progression-free survival] accurately in lung cancer versus breast cancer, wildly different because in lung cancer, just due to survivability of the disease, you have much more—It's just it's much higher likelihood that the person is going to be in the same health system, and their data is going to show up in the same*

		EHR, and you're actually going to have all the same inputs that you need in order to calculate the PFS. Similarly for others, like glioblastoma. Whereas breast cancer, especially diseases with long times between disease events, then people who tend to essentially, you start going to places like survivorship clinic and other things and have less repeated surveillance, you've got big issues. So, that's why the framework applies differently depending on the therapeutic area. - Real-world data and analytics company executive and former FDA representative … *The other thing that strikes me is when you talk about real-world endpoints, a lot of times the way those are derived, defined, but then derived, differ depending on what vendor you're using potentially. So, they may not measure overall survival in the same way, or they may not define exposure in the same way. And that makes it challenging.* - Drug and device manufacturer senior executive and former FDA reviewer … *We're automating a lot of our work with machine learning, and we're having the machine abstract the information and infer something like progression or whatever, and then we validate it with a human.*

		It's just a matter of do they [FDA] believe in the progression variable or not? I feel like that's really really hard for them to wrap their head around in the situation where they don't have to use that data to make a safety and efficacy determination. - Real-world data and analytics company director … *It sometimes depends on the endpoints… We all know, for example, what time to treatment discontinuation in oncology means. But okay, if we are going to take 4 or 5 different hospitals, are they actually measuring the same thing in the same way because it was the day that collected? It was their day of when the treatment started versus when it ended. How did they decide the day it ended? Is it always the last dose you see that the drug was administered, or was there something else? So, I don't know that there is this this way of saying you should use this, and then you should do these types of studies to confirm it. If you're using 5 different data sources, do you have to come up with this way? That in all these, from these 5 different data sources, you're getting something. That's what I'm saying. I don't think we have this idea, or even guidance, of how to do this.* - Regulatory advisor to industry …

		I think that from the validation perspective, like there's different approaches, so they [FDA] are not going to put out a guidance that says here's how to validate an endpoint because every practice is going to be different, and I think again, it's going to be case dependent, probably because in some indications you're going to have a better maybe measure of response, like in a solid tumor. It's easier because you can actually go back and look at scans and see when a tumor started shrinking. - Real-world data and analytics company director … *We need to systematically deconstruct accumulating examples of RWE for regulatory decision making, keeping in mind that it will keep changing as the technical underpinnings improve.* - Real-world data and analytics company executive and former FDA representative … *Today you talk about CDISC [Clinical Data Interchange Standards Consortium standards]. That's the major difference between the research-oriented clinical trials and the industry-oriented clinical trials, and we try to implement such a standard, but we never actually strictly follow it… We were invited to be the statistical analysis team for our industry-sponsored clinical trial and because of the huge gap between how we handle data and what is expected by*

		FDA, finally, we didn't make an agreement because it'll be too costly for us to run it, to get our staff trained, to get the consulting services to make sure we are aware and following FDA guidelines in data collection, data standardization, data analysis, data locking, and so on. And so, there's too huge a gap here that we couldn't reach an agreement. - Director and research scientist at an academic healthcare organization
	RWD challenges	*There are a lot of real-world data companies that don't have access to a patient chart, and that is a problem, I think, for FDA because they want to understand how was the endpoint validated.* - Real-world data and analytics company director … *There are many barriers. The first is that EHRs are all proprietary developed tools, so they're not interoperative. Even when they actually, you have the same company installing it for one hospital and a different hospital on an outpatient, they don't talk to each other. So, interoperability was something that, this was identified by the IOM [Institute of Medicine], which is now, which is no longer the IOM, when they issued their first thing about the learning health care system.* - RWE consultant to industry

		… *Other barriers have to do with the size of the data itself and its complexity. When I was growing up, a multivariate regression analysis is all you ever needed to look for correlations. Now, as the data sets get larger and have many more dimensions, you're now having to use machine learning or artificial intelligence. We don't clearly know exactly what that is. I mean, we do know what it is, but for a lot of people it's a black box, and so it can come up with insights, but if you can't explain how it came up with that insights, there's more reason to be suspicious of those insights.* - RWE consultant to industry … *The hardware we have is not sufficient to be able to efficiently metabolize the data. So even if you're using machine learning, you have to make choices. When they start looking at correlating different genomic profiles or epigenetic profiles or metabolomic profiles, whatever profile you want, with different disease states, they can't look at everything, because then the runtime would take weeks or months. So, they say, Well, we've known this area over here was interesting before, so we'll look over here. They have to look under the light post. They have to make choices because we cannot really investigate all possibilities of all correlations, and most*

		of the correlations are looking at are first and second order correlations- mostly first-order correlations, less second order correlations. But you know what the most important ones are going to be third and fourth order correlations. It's never about a single gene. It's about an interplay of a whole series. And not only the genes… - RWE consultant to industry … *Now I think we're still trying to work through what to do with more data than we've ever had access to. As a health care community that has a lot of noise, so trying to optimize that, I think, is still a work in progress.* - Patient advocacy organization executive leader … *The reason for anonymizing [the names of real-world datasets in the pilot project] was not necessarily because there was reluctance to participate. I think that's probably how it started, but what we didn't want was for, we wanted these pilots to be about the endpoints, not be a bake off between the different data sources. We weren't looking to generate a marketing tool or something like that that would say so and so is better at this aspect. We didn't want to be about*

		the data sources. We wanted it to be agnostic to the data sources but be more about the endpoints. - Patient advocacy organization executive leader … *The CDISC [Clinical Data Interchange Standards Consortium] data standard format. And what does that mean like? How are you going to? It's just—it's not an answered question, but there's a lot of people up in arms in industry about the CDISC data format, like, we have to reformat all these real-world datasets.* - Drug and device manufacturer research director specializing in clinical outcome assessments
Costs can deter developing optimal solutions	Cost	*…but you see what I'm saying with surrogates, there's a way to validate a surrogate. There's a way to validate a real-world endpoint, probably to say in a similar way, but it's just so complicated like nobody is going to invest the money to do it.* - Real-world data and analytics company director … *For GBS [Guillain-Barre syndrome], we had 2 neurologists each read the note, read the abstracted information, and then we went to see if they agree. If they both agreed this person really did have GBS, and the onset date was November, then that's good, and then we*

		considered it a true case onset November. If they disagreed, it went to the chief of neurology, who would adjudicate that and make the final decision… but that's what we had to do in order to convince the regulator that all of those counted GBS cases were real and that we didn't count ones that weren't…. You want it to be robust, and to do that you have to show process, and you almost always need a human brain in the system, and that's what's expensive. When you insert a human brain, someone has to read it and understand it and document it. That's what I would have to do for a regulator. I might only have one person review [the patient chart in an endpoint validation study] if it was for a health economics journal—someone to do an abstraction and one person reviews. I'm not having 2 neurologists review it. I just doubled the cost of the neurology reviews because they're doing full reviews. So, for health economics outcomes research, I might only have one. In fact, I might just use a code algorithm and say it's pretty good. It's good enough. - Real-world data and analytics company executive and former FDA scientist

Note. FDA = Food and Drug Administration, RWE = real-world evidence, US = United States

Supplementary Table 11

Interview results: What similar efforts have succeeded or failed?

Themes	**Concepts**	**Quotes**
Communities help achieve clarity	Communities	*You have these CPIMs now- these critical path innovation meetings and all of that, and they're talking about these part D meetings or type D meetings, and I think that does really help because it does allow us to have more open conversations that benefit the entire community, not just one company, which nobody wants to do, nobody in the measurement community.* - Drug and device manufacturer research director specializing in clinical outcome assessments … *There's a whole workstream called Getting Better Together, believe it or not, that is centered around eCOA [electronic clinical outcome assessments] or ePRO [electronic patient-reported outcomes] vendors and industry, and how we can communicate more clearly, how we can have better timelines, how we can make things work, and that's for like ePRO.* - Drug and device manufacturer research director specializing in clinical outcome assessments …

		Even the PRO community, they started to finally to come together. How many years we had all these different questionnaires, and FDA for years was saying we'd love to see that? But nothing was happening until the community started together and think of instrument by instrument, how could we validate them? How could we validate the subscales and what they're measuring? - Regulatory advisor to industry … *So there's a PRO consortium but there's also an eCOA consortium. And we had a lot of working groups just around eCOA data structure and eCOA data flow. And I mean, it was vendors or TPOs [third party organizations] and industry and FDA working together to say, what is a standard? What does it look like? Because eCOA data was just flying all over the place. I mean it wasn't that bad, but you don't want to have to restructure. That's a lot of time and money and resources that's just not necessary.* - Drug and device manufacturer research director specializing in clinical outcome assessments … *I'm speaking from all of the Duke Margolis publications that came out, and I was part of some of those, and then ISPOR [International Society for Pharmacoeconomics and Outcomes*

		Research] best practices, and I think the National Academies also developed materials for FDA around this sort of regulatory grade RWE. Partnerships with IQVIA, and I think there IQVIA was leading a company partnership and publications coming to my journal as well as other journal, like all of that has been there, and I know that's what we're saying needs to happen, but you can only go so far but until the agency has—FDA has to take it up and say, get more explicit, and I just think that they haven't. - Drug and device manufacturer research senior executive
FDA guidance helps achieve clarity, but clarity is not always popular	FDA guidance on other topics	*It [2013 Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets] did help us [FDA] actually a lot after because we continuously met with sponsors after that, and we told them that we keep asking the questions and sending them pointing them to the guidance, that made everybody's life much easier.* - Drug and device manufacturer senior executive and former FDA reviewer … *The action was exactly this kind of process behind even your thesis. Give us guidance. We have no idea what to do. What do you want to ask us? Let us know what we need to do and then we will do it. We try to strike a balance not to write the whole textbook because everything we were saying actually exists in some kind of textbook about epidemiology and these analytic*

		approaches, but we were trying to figure out what methods … we tried to make it as narrow a focus as possible on the EMRs…There was more pressure from the scientific community and the need of companies to get the guidance. We were getting tired of getting all kinds of request for clarification… the whole story started in 2007, where FDA got the FDA Act passed, the FDA got higher authority to request… to conduct more safety studies after marketing and after clinical trials… that's where the Sentinel, the Mini center, was created at the time. So, this whole thing created buzz around epi [epidemiological] work, and it was almost recommended there as a kind of guidance. So, maybe in effect I would argue it might have been some kind of at least incentive behind that because we had to tell people what to do. - Drug and device manufacturer senior executive and former FDA reviewer … *I mean the FDA has hosted workshops around like the PFDD [Patient-focused drug development] guidances to try and bring panelists, so they speak, and then audiences (pre-COVID) to have comment and then engagement on what they're doing, but you saw, and I don't know how much you follow the PFDD guidances, but certainly they haven't always been popular. Even though different voices get listened to, perhaps they feel not listened to because at the end of the day, a decision has to be made. And yeah, it's a tough one… FDA guidances*

		tend to be written mostly by the FDA with listening to- but there's always strong voices at the agency, so when someone leaves you'll see a shift in priorities, or shift in thinking, if you will because one person has got the pulse and the power and sway, and can argue for their case fairly well, and that those things can shift and change. It's a tough one. I don't know that there's been any great examples of it. - Patient advocacy research director and former FDA reviewer … *I go back to the example of 8 years ago… Genentech, this was one of the first companies that had antibodies and was starting to produce Rituxan, Herceptin, and then others. At the time there was no guidance of what are the purity metrics and everything. So, when you look at what eventually happened, a lot of the guidance even… I have a friend, she said, they [FDA] use their guidance based on guidance developed at Genentech when they compared and looked at it, and that's where we all struggle. Like we want something, but FDA doesn't know what to say about it.* - Regulatory advisor to industry
	Pilot projects	*Friends of Cancer Research, they have those pilot projects where they look at endpoints from different data sources, and they compare to endpoints, and is that a way of validating? I don't*

Pilot projects and tools do not always create clarity		*know if you call it validation. That was an attempt at validating response. So, it was an attempt, but I think you know the hard thing is that's just work that sponsors participate in and things like that. I don't know that FDA sees it as scientifically credible because- I don't know the details of that project. I'm not sure if they had a statistical analysis plan and an IRB [institutional review board] that surveyed, that like oversaw the work. I don't think it was geared to be like powered to be like a regulatory endpoint type thing.* - Real-world data and analytics company director … *I am not aware of anyone that has done it across multiple different data sources in the same way. Probably that one other organization [Friends of Cancer Research] that has done a fair amount, at least from a definitional standpoint that we've worked with, although their purview has been beyond just oncology, and in some cases excluding oncology is the Duke Margolis Center… I think it was mostly just definitional white papers.* - Patient advocacy organization executive leader … *I haven't seen any demonstration projects where, front and center, it was clear to me what did FDA want to do? How did it influence them? How do they change things? Maybe I'd even say*

		the first round of the pilots too because I feel like the pilots were- they were proposed, and they had their own machinery, and then people said, Okay, well, we're going to make one of those the pilot, but then it—I didn't see FDA involved in it. So, I don't know if it'll change. - Drug and device manufacturer research executive … *I think we've seen success for cross competitor collaborations, for lack of a better word, in the biomarker space. We've run a couple of projects that have cross compared different tests with the same intended use to understand whether there was variability around things like estimating mutational rates in a tumor. Any type of approach where we aligned on a common protocol. In the case of the biomarker space, we had to supply common samples that each test developer ran on their own test, and reported the results back in some agreed upon fashion in which we were able to cross compare to understand whether there was variability in different tests that were measuring TMB out there, and also in the endpoint space we'll see if this is successful, although we have published a prototype…* - Patient advocacy organization executive leader
	Tools	*I once worked on a project for AHRQ, the Agency for Health Care Research and Quality on trying to come up with a uniform endpoint framework, I think, is what it was called, and it was*

		a thankless job, and it really didn't go anywhere because people didn't want it. They were stuck with what they had. There was no reason to use the framework. It's not clear we would have been better off with it… Outcome measures framework is what they called it… but it fizzled. It was like arm to arm, as far as I understood it, fizzled, and we also made an extension to clinical trials.gov for registries, and that pretty much has- nobody uses it. It doesn't search well. It was promoted heavily, but not widely adopted or used. - Real-world data and analytic company executive leader … *There's a lot of tools and guidance and things like that. HARPER [HARmonized Protocol Template to Enhance Reproducibility] has been endorsed by EMA [European Medicines Agency], and they're working on pilot projects, so with FDA Sentinel and so on and so forth. So, in terms of regulatory acceptability, sort of showing one thing that would be acceptable… they [EMA] are building it into their new regulations next year from the GVP [Good pharmacovigilance practices] Module 8, as well as the EMA PASS [post-authorization safety study] template. So, expect a few revisions from a regulatory perspective if it's being built into what is required, so that changes things.* - Professor and research scientist in epidemiology

		… *I know there's some work being done for the project [EHDEN, European Health Data Evidence Network] for EMA [European Medicines Agency] about at least generating metadata about different data resources that they sort of catalog.* - Professor and research scientist in epidemiology
Policy can help create clarity on FDA legal and procedural topics	Policy and legislation	*I think of what I'll call public qualification of endpoints, and this was something that Cures [Act] spent a lot of time doing right around biomarkers and drug development tools, creating a process which FDA has not used that much to qualify endpoints and use of those endpoints that anyone can leverage and sort of point to so that they don't have to recreate in their particular one on one proprietary situation the evidence to validate that particular endpoint… one of the examples that came up a lot was…Solvadi. It was Hep [Hepatitis] C… that the viral load at week 12 had gone down significantly or something. I remember there was an endpoint that they worked and qualified, and then there was this question about like, well, now that FDA has established this for Gilead based on all of their work, can have FDA just kind of pick up and take that knowledge and apply it to someone else without someone else having to recreate that wheel? And is that fair that the second sponsor, that they didn't have to do that work? Or is that qualification really, that endpoint being qualified for FDA decision making, is that really*

		Gilead's property? And FDA has not that very clear guidance on that, and I think on one hand, it's sort of like FDA is not necessarily always picking up this application and this information and giving it the sponsor too, but it's in the heads of the reviewers that they've gotten comfortable. And I think there's a tension within the agency and within the industry of that happening and people kind of knowing that's happening. And I think that that's what the Act tried to do is kind of bring some of that about board to say, Hey, for these ones that multiple stakeholders are going to be using, are there ways that you could have a consortium or a group that together and in partnership? - US government policy and industry legal counsel and former FDA representative … *I think, on the MDUFA [Medical Device User Fee Act] side, med device, I'd have to go back to look so don't quote me on this, but I think as part of MDUFA V that just is now underway, I think if you have a software solution that might be a medical device, and you're meeting with the review division and CDRH [Center for Devices and Radiological Health], I think MDUFA might mandate that a sponsor has the option to bring in someone from the CDRH digital health center of excellence into the meetings. You'd want to verify that, but you could think about things on the drug side where you know there is an RWE Subcommittee, and there's the Office*

		of Medical Policy, and could they be empowered more to be kind of an arbiter of RWE with different divisions from a process perspective? - US government policy and industry legal counsel and former FDA representative
Scientific clarity may be achieved by relating the unknown to the known	Relate the unknown to the known	*I think it [FDA Sentinel] did [help FDA get comfortable with RWE for safety studies] because I think a lot then it got a much more familiarity within the agency. It made sponsors much more comfortable to propose things because—and I know, and I remember advocating for this within the company to say, Look, we're talking about using Healthcore data. Same data FDA is looking at. We're not talking about something that's… [Interviewer: Something they've not seen?] Right. And so, I think the same will help a lot.* - Drug and device manufacturer research executive … *The last thing I'd say is that when we [my previous real-world data company] first started doing this work, it was really avant-garde, as you can imagine, and it's still avant-garde… it was really avant-garde and coming up with ways of walking the world through what we were doing and the 'why' meant we had to have mental models that people could understand. So, for example, the PRO framework. We needed to have experiments that we could repeat the use of*

		that endpoint then, and make sure that people understand, and we actually had to have other ways of finding corresponding data. - Real-world data and analytics company executive and former FDA representative
Perceived urgency can compel action to create clarity	Urgency compels action	*Progression, that's assessed in a very strict way through the RECIST criteria. Response, pathological complete response, very strict way to be assessed. Those are surrogate endpoints where FDA actually did the work in some cases to help validate those surrogate endpoints by confirming that the surrogate endpoints were reflective of the ultimate clinical endpoint, and the thing was is the reason they did that is because they were forced to do it because people started living longer with cancer, and you can't power every trial for overall survival. So, they had to say, like, okay, Well, are we going to make this trial last 15 years? What else can we use? And so that's where PFS [progression-free survival] and pCR [pathological complete response] came from, so it was a necessity, and I think that over time, it may be a necessity with real-world data, and they'll be kind of forced to say, All right, we need to kind of look at this progression variable again, and see if we can use it… they [FDA] partnered with sponsors and some advocacy groups to do pathological complete response. They partnered with people to do that… I mean, that's probably what they're definitely going to be looking at surrogates. Surrogates are such a big deal right now because you want to shorten the duration of trials.*

		You want to have to power trials appropriately but with the smallest patient population you can, and so what the FDA did is that they developed a sort of a protocol for a SAP [statistical analysis plan] to determine if pCR was real and then they have clinical trial data pooled from all the trials that they've ever used and considered, and they can go back and do that, meta-analysis on those. So, that's kind of how they participated. You can envision a situation where maybe they would be willing to do the same. - Real-world data and analytics company director

Note. FDA = Food and Drug Administration, RWE = real-world evidence, US = United States

Supplementary Table 12

Interview results: What would be the impact if clarity were achieved?

Themes	Concepts	Quotes
Clarity will help accelerate patient access to treatment and minimize patient burden in clinical trials	Accelerate patient access to treatment and minimize patient burden in trials	[Interviewer: if we were to just do nothing and just kind of have status quo today, what do you think are some of the risks today and then also downstream in the future?] *I think that if we continue to drag our feet here development timelines will continue to be what they are. I think there is a lost opportunity for compressing development. Timelines to get patients and people, medicines or vaccines they may need, they may benefit from. So, I think that RWE potentially has—RWD and RWE potentially have a place in optimizing development timelines.* - Drug and device manufacturer director … *There continues to be concern in some instances around patients not enrolling because they don't want to be randomized to a standard of care that they could get outside of a clinical trial, so want to take on that additional burden. And it may expedite research by creating tools where information can be collected across a much broader group of individuals outside of that clinical trial which have been limited in scope in terms of the number of people that participate*

		in trials. So, to be able to generate healthcare learning outside of a clinical trial, I think, would be beneficial as well, and help prioritize those clinical trials, for truly answering the questions that need to have a clinical trial, not just because it's the only tool to answer them. - Patient advocacy organization executive leader … *It could also improve research efficiency.* - Patient advocacy organization executive leader … *What it can potentially do is, of course, speed up drug development and bring effective treatments because sometimes, I feel like in rare—again, it goes back more to the rare settings that it can be quite challenging to recruit patients into these studies. There's just not that many. And we are struggling. We have a crisis of recruitment, to be perfectly honest, into research. People don't want to participate in research. I mean, it's abysmal. The rates are abysmal. That's on us, as researchers, to be perfectly frank, to sort out, not on patients.* Professor and research scientist in epidemiology …

		I think if there was improved data quality, there could be a greater acceptance of things like using real-world evidence as some sort of concurrent control. I think that would be of interest to the sponsor, but I think it would also be of interest to clinical trial participants who often enroll in order to have access to the experimental agent, and so to be able to increase that experience. - Patient advocacy organization executive leader … *… I think FDA is the right place to start, but maybe it's a footnote, or because ultimately the Holy Grail here, whatever analogy you want to use, is you could have an RWE package for a validated endpoint and you sort of are able to use that globally in a very streamlined way that will open up new therapies for patients more quickly, and that's a good thing. That's a good policy outcome.* - US government policy and industry legal counsel and former FDA representative … *[If we] Did nothing? I just think it's going to be more canaries in the coal mine or bespoke longer and more painfully. The sooner we have clarity on some of this, the more we can have holistic use of RWE consistently cross-therapeutic areas benefiting patients with all sorts of*

		diseases and conditions. It will just be a longer, more painful journey to that if we—the sooner we get clarity, the better. - US government policy and industry legal counsel and former FDA representative
	Does not matter to patients as long as the quality is there	*Patients at the end of the day kind of don't care how the sausage is made. They want their drugs to be safe and effective. How you get there for the average person is neither—they can't comment on the quality of that, just like I can't comment on the quality of how other regulations are made because I don't know enough about them. I happen to know how these regulations work, but I think for the average patient—we heard this with some of the issues around trials just occurring in China, like there's this idea that patients would be outraged that maybe a trial is being conducted solely in China but turns out maybe not really because as long as it's safe and effective, and if it was to be cheaper especially, maybe those things don't really matter. So, as long as the quality is there. So, I think from the patient perspective, as long as the quality is there, how the drug gets approved, through what mechanisms, doesn't really matter to the average patient… So, I don't know the patients worry too much about whether it's real world. I do wonder if they knew, if you're talking about external control arms, how they feel about the data potentially being used in different ways, like synthetic control arms get away from that, I guess, because it's not one person per se. But again, it seems like*

		people might be concerned. But then, if it leads to more effective treatments, okay. Perhaps lower drug prices, but not that the FDA regulates drug prices, but if there was real competition, I feel like that would, they would worry less about these things. They become more problematic when things cost a lot of money. And there's resource issues. I don't think patients worry about this as long as the quality is there. - Professor and research scientist in epidemiology
Clarity will lead to better healthcare decisions for patients	Better healthcare decisions	*That would enable companies and ultimately labeling, in my view, to be much more reflective of real-world practice, which is what will ultimately benefit patients and providers and payers because there are all often coverage questions that payers have Medicare, in particular, but also private payers, that if these were more, if a lot of these outcomes and studies were conducted earlier in seeking FDA approval, then payers would have this data more readily available, and you could arguably decrease the time from approval to coverage for certain scenarios where payers have required like a coverage of evidence development program or additional evidence before it thinks that the drug is reasonable and necessary, which is more of a payer consideration than an FDA.* - Drug and device manufacturer research senior executive …

		This may enable a better understanding of the potential benefits or risks associated with off label uses, it may help to characterize the performance of products and populations that have not been included in the original clinical trials, which is often the case again, in oncology, where the clinical trials are not necessarily as representative as of the population that ultimately uses the drug. - Patient advocacy organization executive leader … [About the potential impact of an FDA RWE dashboard]: *And you know what, it wouldn't just be helpful to you. It'd be helpful for FDA review staff.* - US government policy and industry legal counsel and former FDA representative
Clarity will help improve RWD and empower a learning health system	Improved RWD quality	*I think it would help improve data quality in the short run because it would sort of demonstrate the value of collecting this evidence and demonstrating that it has additional uses beyond just collecting things that might be nice to know. So, if that were able to happen, I think there would be a greater incentive to collect the data that would reduce things like missing-ness and overall data quality would be greater. And I think that would open up more opportunities and increase confidence around the use of real-world data, and that's sort of one means to the end. I think there is interest around how this could improve understanding outcomes associated with*

		different product uses, particularly in fields like oncology, where you see extensive off label use in certain scenarios. - Patient advocacy organization executive leader … *I don't know how much is really going to change, even if we have more examples and more clarity on endpoints, and I say that only because I think we've got to go a little bit upstream to data collection and improve data collection and have incentives for better data collection or have a more realistic understanding where it's appropriate to use real-world evidence.* - Drug and device manufacturer leader and former FDA representative
	Increased investment in RWD/RWE	*I feel like it would de-risk the decision by companies to invest more in real-world evidence studies and registries and claims data because they have a clear regulatory purpose and a clear regulatory use.* - Drug and device manufacturer research senior executive
Clarity will reduce time, costs, waste, and frustration in	Reduced time and costs	*If we did nothing, I think we'll still be where we're at where drug development takes too long, and it's too expensive for everybody involved.* - Drug and device manufacturer research executive

developing new treatments		… *That's like, FDA, I see the trial you want us to do; it's impossible to do it. FDA asks for studies to be done all the time that are impossible. It can't be done in any reasonable amount of time or any reasonable amount of money. They do it in pre-market and post-market. They're like, No, I need you to do placebo-controlled trial like this. We get it. We see it all the time because the companies come to us and say, Can you do the trial? And we say who agreed to that? But pharma companies agree… It's like, Oh, you want me to do a 5,000 patient—I've actually heard a 50,000 patient real-world data study with every outcome validated. Uh, like okay, we'll do that. Product's on the market. This is a device. And then they came, and then they're like this is 200 million dollar study! Oh, right, like it can't possibly be done, but now FDA has actually asked them to do it. That's an extreme. That's in real-world data. But I've seen this in accelerated approval, they want a randomized trial. Like who's, what clinician is putting their patient in a randomized trial when the product's on the market, and FDA just holds its breath and stomps its feet and says but you have to do it. And then the company goes and tries to do it. It's a horrible waste of everyone. It's not just like I care about the drug company's money. It's just a horrible waste of resources. It's a waste of the patient's resources. It's a waste of the pharmaceutical company resources. It's a waste of doctors' resources.*

		- Real-world data and analytics company executive and former FDA scientist … *That's the certainty is you do everything. You have human brains read it, and then you curate it and double-check it and make sure no one made any transcription errors basically… Like if I don't want to have this debate, I'm going to have double data entry. I'm going to double all this stuff. I'll get a super duper, make sure that there's no errors in that outcome. Is that really what we need to do? Probably not. But no one will tell me I have to—I could do less. So, you always just do... Noone wants to do a whole study, and then to have FDA say, I really wish you would have done double data entry. You just do it. Even if you don't need to do it, and they may not say that. But I think the community probably knows how to avoid the debate from the regulator by just doing absolutely everything, which is, I'm trying to say that's different than what I think, is probably needed to show to get or generate a robust result. You probably don't need to do all of that every time.* - Real-world data and analytics company executive and former FDA scientist
	Reduced frustration and greater confidence	*If we did nothing, just let it all go, I mean, we would just continue this state of everybody trying to do something and being frustrated…So, I almost feel that we would continue being this case by case land where there continues to be no clarity of what is a good case, and what is not.*

		That it's not exactly, Oh, you were lucky because you had a good drug and you just got a great effect, so it worked. It would just continue to be this describe in a mundane way, step by step, and how what you did, and how you did it and okay, and yes, you have a huge effect—we'll accept this endpoint. - Regulatory advisor to industry … *…it's this really interesting combination of you have to say, Look the data don't exist. Like no it's one, it might be it's unethical. Okay, now we have to show this unethical to do it. It would take way too long, even if you could start enrolling people because the disease is so rare. You can't possibly get a hundred people to be in the study… I've done this for safety studies. These, all these pregnancy registries, are all waste of everyone's time, but FDA continues to demand them, and they will until this one person retires because there's one person at FDA will demand a pregnancy registry even though they know.* - Real-world data and analytics company executive and former FDA scientist … [About the impact of pilot projects related to real-world endpoints]: *I think it was some general things around the ability to align on specific populations across different data sources and*

		even understand how different those underlying populations were or were not—we actually saw relative consistency across the populations from the various different data sources. So, just understanding who's receiving these treatments frankly in the real world, I think, was one demographic understanding that benefited from this type of collaboration. I can't think of too many other scenarios where the data partners would actually cross compare results with each other. You know they typically utilize their data for specific research questions, I suppose at the request of someone who is funding that research or a specific sponsor. I'm also not aware why a sponsor would go out to 7 different partners to ask the same question. But from our vantage point it was important to explore the ability to have reproducibility between the different observations in order to create some confidence and also help understand what some of the underlying differences between the datasets were to identify things that might contribute to future challenges. So, things like rates of missingness of data, which has been a regular concern that FDA has identified with real-world data sets, but are there ways that different data partners could align on those types of challenges? Were different results seen across different data partners that had missing variables of things that were being included in these types of assessments? And then also to show sort of the performance of these endpoints as well

		to understand whether these types of endpoints could be used to distinguish between 2 different treatment options. - Patient advocacy organization executive leader

Note. FDA = Food and Drug Administration, RWE = real-world evidence, US = United States

Supplementary Table 13

Interview results: Other perspectives you wish to share?

Themes	Concepts	Quotes
Context of use influences the validation needed to demonstrate fit-for-purpose real-world endpoints	There are different levels of validation needed, depending on the context of use	*I think safety signals carry a different level of validation- whether it is cause enough to be an indicator that there is potential risk at hand, so probably would not be held to the same standards to be validated as an efficacy endpoint would.* - Patient advocacy organization executive leader … *I'm not expecting that in guidance, like for FDA to go in and outline that. Okay, sensitivity and specificity need to both be above 80% in order for this to be accepted. That's goofy because it really depends on, my epidemiology sort of is failing me now but really what you need in terms of the balance of sensitivity, specificity really depends on the disease you're talking about. So, anyway. So, I think that that's very context and regulatory question dependent, and I'm okay—I'm comfortable with that.* - Drug and device manufacturer director …

		For GBS [Guillain-Barre syndrome], we had 2 neurologists each read the note, read the abstracted information, and then we went to see if they agree. If they both agreed this person really did have GBS, and the onset date was November. Then that's good, and then we considered it a true case onset November. If they disagreed, it went to a it went to the chief of neurology, who would adjudicate that and make the final decision… but that's what we had to do in order to convince the regulator that all of those counted GBS cases were real and that we didn't count ones that weren't…. You want it to be robust, and to do that you have to show process, and you almost always need a human brain in the system, and that's what's expensive. When you insert a human brain, someone has to read it and understand it and document it. That's what I would have to do for a regulator. I might only have one person review [the patient chart in an endpoint validation study] if it was for a health economics journal- someone to do an abstraction and one person reviews. I'm not having 2 neurologists review it. I just doubled the cost of the neurology reviews, right, because they're doing full reviews. So for health economics outcomes research, I might only have one. In fact, I might just use a code algorithm and say it's pretty good. It's good enough. - Real-world data and analytics company executive and former FDA scientist …

		That's actually kind of how we do with real-world variables, too. I mean, they're validated against overall survival, or real-world OS [overall survival] is validated against overall survival, because we have the death index, but with response and things like that, it's a little bit harder because the response in a clinical trial is through RECIST, and a community oncology clinic where we're pulling our data from, that short of running a clinical trial where they measure like a patient goes and sees a doctor and the doctor says think you're in, you're responding to therapy, and then they have to leave and go to an academic medical center where somebody assesses them on the RECIST criteria. That's the only way to do that kind of surrogate validation model with a real-world endpoint. - Real-world data and analytics company director … *From our perspective, when we have access to a patient chart and we have a medical professional reviewing that patient chart and we have that medical professional saying, Ah, I see this in the chart, this is evidence of progression from our perspective, that abstraction process is a validation that that happened because if you think about, there's no validation to say the tumor regressed other than like a scan or something that's available, but that's part of our abstraction process is looking at scans…*

		I do think our organization was inspected once before by the FDA... so in the event that as a sponsor uses an external control arm that uses real- world data, that would be considered a clinical trial under regulations which would fall under the FDA's regulations for clinical trials, meaning that not only do the sponsors have to give patient-level, analyzable data to FDA, but FDA will come and inspect the data source, which means that they could come to our organization, knock on the door, say Here's the data set, show me how you got it, and we would have to say, Okay, well, this is how we got it. But that's not- it's not what I mean by validating the variable. Validating the variable to me is a process where we've developed abstraction protocols to define that variable. So this is what you look for to define response, here are terminologies that are used… all those things, and then, generally speaking, we will have something like a publication that would highlight not- it wouldn't give out the proprietary abstraction methods, but it would be something that says, Here's our approach to validation. That's how it kind of needs to be- it's a scientific process. You did it. If the agency has questions about it, then they're welcome to have us in, and we'll talk more detail under confidentiality. - Real-world data and analytics company director …

		We had to have mental models that people could understand. So, for example, the PRO [patient-reported outcomes] framework. We needed to have experiments that we could repeat the use of that endpoint then, and make sure that people understand, and we actually had to have other ways of finding corresponding data. And one of the best ones that I always go back to… is I remember how important it was to have third-party reviewers read the narrative, the transcript from, for example, electronic health record and cross-check that that endpoint made sense when I read the transcript. So essentially what I call qualitative and quantitative review. And I remember back in the early days of some of the EBM [evidence-based medicine] papers in the British Medical Journal, there was a series by, I believe, Trish Greenlaw, Greenhalgh, in the UK about QualQuant, and I'll never forget it because it turned out in my mind that the kind of QualQuant review of these real-world endpoints was really really important to make sure that they made sense and could make sense in context. Now, that's not what I would say the FDA would tell you because there's a bit of squishiness in all that. But I think that the real value of understanding qualitatively and quantitatively how things perform in concert was really important. - Real-world data and analytics company executive and former FDA representative

Stakeholders should focus on patient-centric endpoints	We need to focus on patient-centered endpoints	*Speaking as a patient advocate, I think it's important that we stay flexible on the endpoints because the endpoints that matter to patients are often highly functional and overlooked. So, I think that the context is so much, but we fall into wanting to come up with our codes for our databases. I get it, and we need to narrow the pool of potential subjects, but I think that we really need to- a big focus is the patient-centered endpoints. Maybe that's the phrase everybody's using. But I think we lose track of that. We've seen more presentations, or somebody was telling me about our presentation. They saw that that was all about saving the doctors time. Oh, it's about using what do you call it when it has a multi-drugs in one tablet drug combinations. He was talking about using combination products… It was lively discussion. But the topic was fixed dose combination pills for whatever condition and patients, saying that combination doesn't work for me. I need more of this and less of that. It needs to be tweaked. It needs to be individualized, and I can't do that with your product. And the response was, But this- it's better. My combination is better because it saves time for physicians. They actually said that at the podium! [Another example is] at a conference on neuros, neuro stimulation devices, neuro modulation, stimulated devices, devices they plant in in the brains of people who can't move, and then also they can move. It's such a strong reminder of the outcomes, different outcomes. One guy was wheelchair bound, and he said, I use this product, and I can play guitar.*

		- Real-world data and analytic company executive leader
Stakeholders should put science first and adapt the regulatory system accordingly	Put science first, adapt regulatory system accordingly	*I think the more we can learn from what came before us- one mistake that COA did make early on it was almost trying to regulator-ize, if that's a word, measurement science, instead of looking at this whole area of measurement science that up until recently has really been mainly focused on educational testing and that kind of thing. And now we're- someone realized it doesn't really make any sense. And so, you see the world's coming together. So, I think one important thing to keep in mind is, if the science is there, you don't change the science to make it regulatory approval. You change your regulatory system to embrace the science, and that wasn't done initially in COA, and it caused some issues because then the field couldn't move forward scientifically because regulators wanted something else. And so, once we sort of got it on a better track, it allowed for the field to move forward with our regulatory colleagues. But I could see that happening, even with data structure, with real-world evidence, like if it's not what the field is, don't change it, like you don't change the dog into a cat when you adopt it. You just you change your environment…* - Drug and device manufacturer research director specializing in clinical outcome assessments …

		There's also, I think, that clarity we don't want to lock ourselves into. Tell me now this is what it's got to be, and then what happens is then you're chasing clinicians for 10 for 15 years to go chase down, Mary, who you saw you gave her that gene therapy changed her life, you know she's not coming back to see you. - Real-world data and analytic company executive leader
Stakeholders need to right-size their expectations of RWD/RWE	Even clinical trials have lots of subjectivity	*Interestingly enough, every clinical trial we expect things to be incredibly objective, and in fact there's a ton of subjectivity built into traditional clinical trial.* - Real-world data and analytics company executive and former FDA representative
	How to accelerate drug development and patient access	*My mind like yours goes right to secondary use of data because I just think that that's where the transformational change can be for regulatory because just the speed and the volume and so, I mean, there may be instances where the pragmatic trial, just it's so compelling and it'll make all the difference, that's great, but I just think it's- I don't know. I usually go to thinking how can we use the existing data?* - Drug and device manufacturer research executive
	Many RWE submissions to	*...they [some review articles] say there's been 100 decisions based on real-world data. It's just not true. The regulatory decision, FDA will say, has to say we used it as a primary- I don't know*

	FDA may not be used for decision making	*what terminology- like as a primary resource or a primary source for the decision. There's very few where real-world data are used. Our data are submitted all the time with submissions. Doesn't mean it was used for FDA's regulatory decision. They're really careful about that. Very few, I think, meet the- your definition.* - Real-world data and analytics company executive and former FDA scientist
	Right-size expectations of RWD/RWE	*FDA is going to have to get more and more comfortable to where you have like, it's a close call… you don't want it to where the treatment effect seen through RWE has to be a magnitude greater than traditional clinical trials because just that it's an RWE study.* - US government policy and industry legal counsel and former FDA representative … *I don't know how to say this a nice way, but like I don't know- when we go to the doctor's office, I don't worry about what's put in my chart so that drug developers can use it. I guess- it's just the way. It's just candid. So, I think it's important to collect the best data possible, but we always have to realize that if it's for like secondary use of data, what has to be perfect and what's used to direct my care so I get the best care. Like it's not all about drug development, and that's just being realistic, too, about how much you can do. I do think we have to make people understand that data is important. Contributing to data will benefit them. Have*

		physicians understand that better data collection is going to help everybody in the long run, but we've also got to be realistic. It might not- certain patient data might not meet every purpose that we hope it will. - Drug and device manufacturer leader and former FDA representative
The solutions for achieving clarity are inter-dependent	Solutions are inter-dependent	*They [potential solutions] are all very closely intertwined and interrelated, so it's hard to disentangle the effect of one alone.* - Professor and research scientist in epidemiology
Stakeholders may consider alternative approaches to RWD/RWE and regulatory approval	Consider alternative approaches to obtaining RWD on patients	*There's great skepticism among the real-world evidence users about what patients can say about their own self, but there, if you did direct-to-patient follow up, they can tell you a lot about themselves. They don't answer the phone, and you go to next of kin and or their best friend, and they tell you they're dead right away, you have survival. So there are a number of ways you can do long-term follow up that are informative. And when you can ask patients questions, Can you get out of bed? Does it keep you up all night? Activities of daily living kinds of things and quality of life. They're tremendously useful.* - Real-world data and analytic company executive leader

	Consider alternative paradigms for new drug approvals	*I like some of the more radical ideas even then too. I don't know. One of them was like progressive approval where somebody would say, Look, as long as you make sure things are completely—the drug's initially safe, you give, you put the drug out there, and you let the real-world evidence, you just, you collect the real-world evidence, and that's your approval, to get things out there even faster.* - Drug and device manufacturer research executive … *You would think that if a patient's having premature ventricular contractions suppressing those premature ventricular contractions would decrease the likelihood they would go into Vtac [ventricular tachycardia] or Vfib [ventricular fibrillation] or whatever and die. But some drugs came along that were able to suppress those PVCs [premature ventricular contractions]. But guess what? When they did the studies, death rate was higher. Took them a while to explain that. Another—theoretically lowering your blood pressure should increase your life expectancy because we know that blood pressure adds on to a whole bunch of other things and increases cardiovascular mortality. But then there long came some drugs that lowered blood pressure. But guess what? They increased mortality. So now, if you asked anybody, is the scientific underpinning for these presumptions that these are good surrogate endpoints, good ones they*

		would say, yes. What happened here? Well, it turned out that these drugs had other effects aside from affecting the surrogate endpoint, which overcompensated for their good effects. So, is a surrogate endpoint good enough? That's a question we're going to be facing, more and more. And I don't know the answer to that. What I do know is that we're increasingly moving to personalized medicine, which is that instead of using a drug or a therapy that works in 70% of people, and we don't know which 70%, we're trying to get use it in a smaller group of people where it works at 80 or 90 or 95% and in that world it may be better able to disentangle benefit from harm. - RWE consultant to industry
Not applicable	See 2022 conference session on real-world endpoints	*See ISPE session from Denmark/Aetion session on real-world endpoints.* - FDA representative

Note. FDA = Food and Drug Administration, RWE = real-world evidence, US = United States

MASTER CURRICULUM VITAE FOR JULIE BEYRER

Education

December 2023

Indiana University, Doctorate in Public Health (DrPH), Global Health Leadership

August 2013

Indiana University, Master of Public Health (MPH), Epidemiology

December 2004

Miami University (Oxford, Ohio), Master of Technical and Scientific Communication (MTSC)

May 2002

Hanover College, Bachelor of Arts (BA)

Major: German

Minors: Chemistry, History

July 2001

Philipps-Universität Marburg (University of Marburg, Germany), Certificate

June 2000

Goethe Institute (Rothenburg, Germany), Certificate

Employment (Eli Lilly and Company, 2004-Present)

January 2023-Present

Senior Advisor- Real-world Evidence (RWE), Value, Evidence, and Outcomes (VEO), Strategic Innovation

RWE scientist in Lilly's VEO Center of Innovation. Pilot and scale emerging capabilities that advance RWE for regulator decision-making and healthcare system partnerships across Lilly's therapeutic areas.

September 2020- December 2022

Senior Research Scientist/Senior Advisor- Real-world Evidence (RWE), Value, Evidence, and Outcomes (VEO), Oncology Strada Platform

- Led a virtual team of RWD (real world data) and statistical analysts in coordinating fulfillment of oncology RWE requests.
- Delivered expert, credible, and timely RWE guidance to researchers in the Oncology Business Unit (OBU) and other internal business partners for clinical development, clinical trial planning, payer evidence including value-based agreements, regulatory support, and more. This included the following:
    - Review and provide input to the RWE strategic plan.
    - Identify and evaluate novel RWD sources and applications.
    - Characterize real world data quality and relevancy. Evaluate 'fit for purpose' of potential and newly acquired real world datasets.
    - Develop observational research protocols.

    - Consulting on study design, methods, analytics, and results interpretation.
    - Analyze real world data.
    - Communicate results to internal and external audiences.
    - Author/co-author scientific disclosures.
- Monitored the external environment and contributed through scientific disclosure and participation in industry organizations.
- Advanced Lilly's innovative RWE capabilities by proposing and delivering on RWE transformation to develop and promote new standards, pilot nontraditional data sources, or experiment with new methods to derive RWE value.
- Collaborated with academic researchers and commercial third parties to augment Lilly's RWE and RWD expertise and scientific capabilities.

October 2016-September 2020

Research Scientist- Global Patient Outcomes & Real World Evidence (GPORWE), Oncology Strada Platform

Core responsibilities similar to those listed above.

November 2013-September 2016

Consultant Scientist- Global Patient Outcomes & Real World Evidence (GPORWE), Oncology Strada Platform

Core responsibilities similar to those listed above.

September 2009-October 2013

Scientific Communications Consultant, Oncology Business Unit (OBU)

- Led cross-functional, cross-company teams through development of communication strategies and plans.
- Led primary document development for external scientific publications (including, but not limited to, abstracts, posters, manuscripts and presentations), and/or regulatory documents (including, but not limited to, protocols, clinical study reports, briefing documents, regulatory responses, and marketing authorization applications).
- Wrote and edited regulatory and commercial documents. Developed communications strategy and influential scientific-based messages with medical experts. Authored first drafts. Distributed drafts for review to project teams, Lilly affiliates, external business partners, and vendors. Incorporated author input and facilitated decision-making across teams. Managed editing, finalization, approval, and disclosure of communications.
- Facilitated and influenced decision-making across multiple levels, regions, functions, and companies to ensure answers to customers' (health care providers, regulators, payers, etc) questions were timely, accurate, and of the highest quality. Ensured development of consistent and relevant medical scientific information on Lilly product(s) to multiple audiences.
- Provided oversight of vendor writers, including peer review and project management. Communicated regularly with vendors to provide project requirements and needs, monitor progress, and share constructive feedback.
- Served as a regulatory submission lead for global regulatory submissions of 2 oncology products:

  - Represented Global Scientific Communications (GSC) in developing submission strategy and cross-functional project plans.
  - Monitored and regularly update submission workplans.
  - Reviewed statistical analysis plans and output. Contributed to developing strategy, content, and formatting of tables, figures, listing (TFLs) to statistical analysts and project teams.
  - Communicated strategy and plans to medical writing team and coordinated the writing team efforts.
  - Reviewed and provided feedback on colleagues' drafts.
  - Ensured writing team members had access to systems and other resources needed for creating submission dossiers.
  - Communicated, collaborated, and negotiated with team leaders on expectations, team needs, capacity, timelines, quality delivery of project milestones to effectively manage the document process and progress.
  - Represented the GSC organization at related OBU operational and strategy meetings.
- Lilly SME (Subject Matter Expert) for medical regulatory communications (e.g., internally, American Medical Writers Association, etc.).
- Supported capacity planning and sourcing of deliverables with internal staff and external staff (contractors and third party organizations).
  - Coached and mentored other writers.
  - Co-developed and maintained Lilly's late phase oncology protocol template over time.
  - Participated in Lilly Six Sigma and related initiatives, including Medical Quality System projects.

April 2008-August 2009

Senior Scientific Communications Associate, Multiple Sclerosis Platform Team

- Served as global Secondary Progressive Multiple Sclerosis (SPMS) submission lead writer. Many of the same submission lead responsibilities described previously.
- Ensured appropriate division of medical writing responsibilities between Lilly and alliance partner per the Master Service Agreement.

2008-2009

Third Party Organization (TPO) Assessor

- Assessed vendor capabilities for developing regulatory, commercial, and medical information deliverables on behalf of Lilly.
- Visited vendor sites throughout the United States to assess capability.
- Met with vendor management and staff to review vendor policies and procedures, role descriptions, job qualifications, and training records to ensure quality infrastructure for developing medical communications on behalf of Lilly.
- Trained other TPO assessors at Lilly.

April-July 2008

Substitute Team Leader, ADAPT (ADHD, Depression, Anxiety, Pain Team) Product Team

Served as substitute team leader for team of medical writers and editors while team supervisor was on medical leave:

- Assigned internal or outsourced medical writing support to regulatory medical communications based on team needs, internal capacity, and GMC outsourcing strategy.
- Developed Requests for Quotations (RFQs) for work sourced to third parties. Identified and contracted with vendors and monitored project progress and invoicing.
- Forecasted quarterly medical writing deliverables, anticipated effort, and resource needs. Managed team metrics.
- Communicated and resolved team issues with GMC lead team and leads of other departments supporting ADAPT molecule development.
- Served as an initial point of contact with writing vendors, delegated oversight of vendor writers to internal writers, and monitored progress on medical writing deliverables.
- Facilitated internal staff meetings and project updates.
- Shared vendor performance feedback with external supervisors of medical writing vendors.

January 2004-March 2008

Scientific Communications Associate, ADAPT Global Product Team

- Authored medical regulatory documents, including regulatory marketing applications/submission (5 neuroscience submissions for US, EU, and Canada drug approvals), Investigator Brochures, protocols, briefing documents, regulatory responses, etc.
- Peer reviewed and quality checked others' deliverables.
- Many of the same writing responsibilities previously described.

September 2002-December 2003

Miami University of Ohio, Instructor, Business Writing

- Planned and developed instructional lessons, activities, and assignments in business writing.
- Taught informative and persuasive business writing principles and practices to 3rd- and 4th-year students in Miami University's Farmer School of Business and other university students.
- Evaluated student learning and performance on writing projects and assigned student grades.
- Facilitated classroom discussion and supervised activities.
- Attended teaching seminars focused on improving teaching methods.

June 2002-August 2002

Eli Lilly and Company, Intern in GSIC-R Global Scientific Information and Communications – Regulatory

- Assisted in editing text in Clinical Study Reports (CSRs).
- Assisted in preparing the results section of an article for the American Journal of Respiratory and Critical Care Medicine.
- Researched cardiovascular drugs to inform myself about drugs in my therapeutic area.
- Wrote the Introduction of a Clinical Investigator's Brochure (CIB).
- Met with cross-functional teams to participate in online reviews and discuss timelines and new action items for documentation projects.
- Learned about the documentation processes and regulatory guidelines involved with developing and marketing new drugs.

- Developed and delivered a final internship presentation on the CIB.

Presentations and abstracts

1. Singh S., Beyrer J., Zhou X., Swerdel J.N., Harvey R.A., Hornbuckle, K., Russo, L., Ghauri K., Abi-Elias I-H., Rodriguez-Watson C. Development and Evaluation of the ALgorithm CErtainty Tool KIT (ACE-IT) to Evaluate Safety Outcomes Using Electronic Medical Record and Claims-based Algorithms. 38th International Society of Pharmacoepidemiology Annual Meeting. Aug 24-28, 2022.
2. Acknowledged for content contribution. Campbell U, Kim S, Toh S, Kent S, Brown J, Rodriguez-Watson C. What do real world data validation best practices look like? Operationalizing guidance for real-world studies intended for decision-making. (United States). 38th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) August 28, 2022.
3. Nagasaka M., Cui Z., Stefaniak V., Li X., Kim S., Lee H.-Y. Beyrer J., Molife C. Reweighting ORIENT-11 Trial (O-11) Results to a US Patient Population. ESMO-IO conference. Dec 8-11, 2021.
4. Andre F, Aggarwal A, Rao X, Chen Y, Beyrer J, Smyth EN, Guimaraes CM, Litchfield LM, Bowman L. Characterizing Demographics, Clinical, and Genomic Characteristics for US Patients with HR+, HER2- Metastatic Breast Cancer Following Progression on a CDK4 and 6 inhibitor. American Society of Clinical Oncology (ASCO) June 3-7, 2021.
5. Liepa, AM, Zhanglin LC, Beyrer J, Hadden E, Chatterjee A. US real-world ramucirumab and immune checkpoint inhibitor (ICI) treatment sequences in advanced gastric, gastroesophageal junction (GEJ), or esophageal cancer. 23rd World Congress on Gastrointestinal Cancer June 30-July 3, 2021.

6. Hess LM, Beyrer JK, Abedtash H. ST69.Biomarker Testing and Overall Survival Among Patients Diagnosed with Advanced or Metastatic Non-small Cell Lung Cancer. Association for Molecular Pathology 2020 Annual Meeting Abstracts, The Journal of Molecular Diagnostics, Volume 22, Issue 11, Supplement, 2020, Page S79, https://doi.org/10.1016/S1525-1578(20)30513-4.
7. Saverno KR, Beyrer J, Smyth EN, Abedtash H, DeLuca A, Zhu YE, Rybowski S. Real-world patient characteristics, utilization patterns, and outcomes of US patients with HR+/HER2- metastatic breast cancer treated with abemaciclib. San Antonio Breast Cancer Symposium (SABCS) Dec 8-11, 2020.
8. Winfree KB, Molife C, Peterson P, Chen Y, Visseren-Grul C, Leusch M, Beyrer J, Dimou A. Real-World Characteristics and Outcomes in Patients with Advanced Non-small Cell Lung Cancer and Exon 19 or 21 EGFR Mutations. International Association for the Study of Lung Cancer - 2020 North America Conference on Lung Cancer. Journal of Thoracic Oncology, Volume 16, Issue 1, S23.
9. Beyrer J, Manjelievskaia J, Bonafede M, Lenhart G, Nolot S, Haldane D, Johnston J. Validation of an ICD-10 coding adaptation for the Charlson Comorbidity Index in United States healthcare administrative data. ISPOR International Society for Pharmacoeconomics and Outcomes Research – 25th International Meeting. May 18-20, 2020.
10. Murray J, Beyrer J, Abedtash H, Hornbuckle K. RWE algorithms – the building blocks of RWE quality. Accepted ISPOR 2020. ISPOR International Society for Pharmacoeconomics and Outcomes Research – 25th International Meeting. May 18-20, 2020.
11. Eli Lilly and Company, GPORWE Lunch & Learn. Beyrer J. Nelson DR. Yes, we can! Building and validating RWE algorithms for claims data (and some novel methods). Oral Presentation. Nov 2019.

12. Eli Lilly and Company, Global Patient Safety phamacoepidemiology staff meeting. Beyrer J. Nelson DR. Yes, we can! Building and validating RWE algorithms for claims data (and some novel methods). Oral Presentation. Nov 2019.
13. Rao X, Gupta S, Sheffield K, Beyrer J, Ebert P, Calley J, Chen Y, Peachey J, Smyth E, Aggarwal A, Bowman L, Iyer M, Blackwell K. Genomics Datasets Linked to Electronic Medical Records: Challenges and Opportunities. OTTR Science Days, Eli Lilly and Company, Indianapolis, IN, October 7-8, 2019.
14. Encore presentation. Barzi A; Hess LM; Zhu YE; Liepa AM; Fang Y; Kuder C; Beyrer J; Chao J. Treatment and outcomes in patients with advanced gastric, esophageal, or gastroesophageal junction adenocarcinoma in the United States. Simposio Latinoamericano de Gastroenterologia Oncologia. April 2019.
15. Kuehne F, Arvandi M, Hess L, Faries D, Matteucci Gothe R, Gothe H, Beyrer J, Zeimet AG, Stojkov I, Muehlberger N, Oberaigner W, Marth C, Siebert U. ASSESSING TYPE AND IMPACT OF BIASES POTENTIALLY OCCURRING WHEN ANALYZING REAL WORLD EVIDENCE: THE CASE OF SECOND LINE TREATMENT FOR OVARIAN CANCER. 2019 European Causal Inference Meeting. (Encore presentation).
16. Genomic characterization of lung tumors and metastatic (Met) sites in advanced (Adv) NSCLC. Willard MD, Smyth EN, Tiu RV, Beyrer J, Zhu YE, Bowman L, Sheffield KM, Han Y, Brastianos P. American Society of Clinical Oncology (ASCO). June 2, 2019.
17. Clinical Characteristics, Treatment Patterns, and Overall Survival in Advanced NSCLC Patients With and Without Brain Metastases. Smyth EN, Tiu RV, Willard MD, Beyrer J, Zhu YE, Bowman L, Sheffield KM, Han Y, Brastianos P. American Society of Clinical Oncology (ASCO). June 2, 2019.

18. Hess LM, Cui ZL, Li XI, Goodloe R, Liepa AM, Beyrer J, Oton A, Schelman W. Defining treatment regimens and lines of therapy using real-world data in oncology. 40th annual meeting of the Society for Medical Decision Making. October 14 - October 17, 2018. Oral presentation.
19. Barzi A, Hess LM, Zhu YE, Liepa AM, Fang Y, Kuder C, Beyrer J, Chao J. Real world outcomes and patient characteristics for the second-line treatment of gastric, esophageal, or gastroesophageal junction (GEJ) adenocarcinoma (EGAC). American Society of Clinical Oncology (ASCO). June 1, 2018.
20. Siebert U, Kuehne F, Arvandi M, Hess L, Faries D, Beyrer J, Matteucci Gothe R, Gothe H, Stojkov I, Rochau, U, Oberaigner W, Zeimet AG, Marth C. Comparative effectiveness analysis using real world evidence (RWE) and applying a causal marginal structural model: the case of second-line treatment in patients with ovarian cancer. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) - 23rd International Meeting. May 22, 2018.
21. Siebert U, Kuehne F, Arvandi M, Hess L, Faries D, Beyrer J, Matteucci Gothe R, Gothe H, Stojkov I, Rochau, U, Oberaigner W, Zeimet AG, Marth C. Assessing type and impact of biases potentially occurring when analyzing real world evidence: the case of second line treatment for ovarian cancer. ISPOR International Society for Pharmacoeconomics and Outcomes Research - 23rd International Meeting. May 21, 2018.
22. Golden L, Winfree K, Beyrer J. Real World Erlotinib Outcomes in Advanced Non-Small Cell Lung Cancer Patients with EGFR Mutations. Indiana University Master of Public Health (MPH) candidate poster presentations (Dec 8, 2017).
23. Siebert U, Kuehne F, Arvandi M, Hess L, Faries D, Beyrer J, Matteucci Gothe R, Gothe H, Stojkov I, Rochau, U, Oberaigner W, Zeimet AG, Marth C. Comparative effectiveness analysis applying a causal marginal structural model in a large database: the case of second-line treatment of patients with ovarian cancer. 39th annual meeting of the Society for Medical Decision Making (SMDM). Oct 25-28, 2017.

24. Kuehne F, Arvandi M, Hess L, Faries D, Matteucci Gothe R, Gothe H, Beyrer J, Zeimet AG, Stojkov I, Muehlberger N, Oberaigner W, Marth C, Siebert U. Assessing immortal time bias and time-dependent confounding in the causal evaluation of second line treatment for ovarian cancer using real world evidence. 39th annual meeting of the Society for Medical Decision Making (SMDM). Oct 25-28, 2017.
25. Zhang L, Carter GC, Beyrer J, Li L, Sheffield KM, Muehlenbein C, Boye M, Frantz K, John W, Gadgeel SM. Characterization of KRAS mutations and their impact on treatment and clinical outcomes in patients with advanced non-small cell lung cancer (NSCLC). Chicago Multidisciplinary Symposium in Thoracic Oncology. Sept 14-16, 2017.
26. Afsaneh Barzi, Lisa Hess, Yajun Zhu, Astra Liepa, Yun Fang, Craig Kuder, Julie Beyrer, Joseph Chao; P-081. Treatment and outcomes of patients with advanced gastric, esophageal, or gastroesophageal junction adenocarcinoma in the United States, Annals of Oncology, Volume 28, Issue suppl_3, 1 June 2017, mdx261.080, https://doi.org/10.1093/annonc/mdx261.080.
27. Zhu YE, Fang Y, Nicol S, Beyrer JK, Hess LM. Challenges of identifying treatment patterns of patients with advanced soft tissue sarcoma using claims data in the United States. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – 22nd international meeting. May 22-24, 2017.
28. Ali AK, Beyrer JK, Shroeder KM, Wu J, Haldane DC, Mitchell L. Case studies on the impact of ICD-9-CM to ICD-10-CM coding transitions on studies using real-world data in the United States. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – 22nd international meeting. May 22-24, 2017.
29. Beyrer J, Nolot S, Haldane DC, Johnston J. Developing an ICD-10-CM Version of Charlson Comorbidities for United States Real-world Healthcare Data. Value in Health. 2017;20(5):A315.

30. Herren C, Beyrer JK, Chen L, Li L, Heaton PC, Bowman L, Girvan A. Characteristics and adverse events of patients with hepatocellular carcinoma reciving one sorafenib prescription. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – 22nd international meeting. May 22-24, 2017.
31. Herren C, Beyrer JK, Chen L, Li L, Heaton PC, Bowman L, Girvan A. Sorafenib tolerance and adverse events in the first line treatment of hepatocellular carcinoma. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – 22nd international meeting. May 22-24, 2017.
32. Hess LM, Cui ZL, Li X, Beyrer J, Oton AB; Eli Lilly and Company, Indianapolis, IN; Eli Lilly & Company, Indianapolis, IN. Treatment sequences in non-small cell lung cancer in the US from 2014-2016. 2017 ASCO Quality Care Symposium. March 3-4, 2017.
33. Sheffield K, Watson I, Beyrer J, Stafford S, Mills B, Ale-Ali A. Using real-world data to minimize drug waste: olaratumab for soft tissue sarcoma. Am J Health Syst Pharm. 2017 Jun 1;74(11):832-842.
34. Zhu Y, Fang Y, Nicol S, Beyrer J, Hess LM. Challenges in the diagnosis of soft tissue sarcoma: a comparison of pre-diagnosis conditions and health care resource use between known soft tissue sarcoma patients and matched controls in claims data. 39th annual meeting of the Society for Medical Decision Making (SMDM). Oct 23-26, 2016.
35. Hess LM, Michael D, Mytelka DS, Beyrer J, Liepa AM, Nicol S. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. Gastric Cancer. 2016 Apr;19(2):607-15. doi: 10.1007/s10120-015-0486-z.

36. Eli Lilly and Company. Beyrer J and Watson D. Improving your personal effectiveness through the Lilly/GPORWE leadership principles and behaviors. Oral presentation.
37. Hess LM, Goodloe R, Cui ZL, Carter GC, Beyrer J, Treat J. Comparative effectiveness of second-line treatment for non-small cell lung cancer (NSCLC) among patients ≥70 versus <70 years of age. Journal of Clinical Oncology, Vol 33, No 15_suppl (May 20 Supplement), 2015: e19018.
38. Eli Lilly and Company. GPORWE Town Hall. Using real-world data to minimize drug wastage (olaratumab). Sheffield K and Beyrer J. Oral Presentation.
39. Hess LM, Michael D, Mytelka DS, Beyrer J, Nicol S. Treatment Patterns and Outcomes of Patients with Gastric Cancer in the U.S.: A Retrospective Analysis of Electronic Medical Record (EMR) Data. Poster P-0067. European Society of Medical Oncology – Gastrointestinal Conference. June 2014.
40. Hess LM, Michael D, Mytelka DS, Beyrer J, Nicol S. Costs and Patterns of Gastric Cancer Care in the U.S.:
41. A Retrospective Analysis of Administrative Claims Data. Poster P-0069. European Society of Medical Oncology – Gastrointestinal Conference. June 2014.
42. Indiana University Richard M. Fairbanks School of Public Health, Indianapolis, IN. Identifying Patients With Advanced Gastric and Gastroesophageal Junction Adenocarcinoma Using an Insurance Claims Database. Beyrer J. Poster. July 2013.
43. Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN. Development Of Algorithms To Identify Gastric Cancer Stage In An Insurance Claims Database. Beyrer J. Poster. May 2013.

44. Eli Lilly and Company. Planting the SEED in Benefit-Risk Assessment. Ellis B, Noel R, Acharya N, Beyrer J, Murray I, Gazak M, Fredborg T, Alyea J. Poster. September 2012.
45. Gridelli C, de Marinis F, Pujol J-L, Reck M, Ramlau R, Parente B, Pieters T, Middleton G, Winfree K, Melemed S, Zimmermann A, John W, Beyrer J, Chouaki N, Visseren-Grul C, Paz-Ares LG. 2011. Safety, resource use, and quality of life (Qol) results from PARAMOUNT: A phase III study of maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pemetrexed cisplatin for advanced nonsquamous non-small cell lung cancer (NSCLC). Oral Presentation (my role: developed slides to support oral presentation by primary author). World Conference on Lung Cancer, Amsterdam, the Netherlands. July 2011.
46. Gridelli C, de Marinis F, Pujol J-L, Reck M, Ramlau R, Parente B, Pieters T, Middleton G, Winfree K, Melemed S, Zimmermann A, John W, Beyrer J, Chouaki N, Visseren-Grul C, Paz-Ares LG. 2011. Safety, resource use, and quality of life (Qol) results from PARAMOUNT: A phase III study of maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pemetrexed cisplatin for advanced nonsquamous non-small cell lung cancer (NSCLC). Abstract. World Conference on Lung Cancer, Amsterdam, the Netherlands. July 2011.
47. Eli Lilly and Company. New Medical Quality Systems “Clinical Study Reports” procedure. Beyrer J.
48. Eli Lilly and Company. Deviation Management. Beyrer J and Steiger M. Oral Presentation
49. Eli Lilly and Company. Intercontinental Information Sciences staff meeting. Tables, Figures, Listings (TFL) Auto-insertion macro. Beyrer J and Steiger M. Oral Presentation.

50. Eli Lilly and Company. US Regulatory Affairs/Global Medical Communication joint staff meeting. 21 CFR 312.120 Foreign Non-IND Study Requirements. Beyrer J and Wojcieszek R. Oral Presentation.
51. Eli Lilly and Company. Vendor Webinar. Granular Clinical Study Report. Beyrer J and Ruiz K. Oral Presentation.
52. American Medical Writers Association – 68th Annual National Conference. How to Effectively Lead Teams on Medical Writing Projects. Beyrer J. Oral Presentation.
53. Eli Lilly and Company. FarisFest. Clinical Study Reports with eCTD Granularity: Leveraging Lifecycle Management to Deliver Medicines to Patients at the Right Time. Hensley I, Garni-Wagner B, Beyrer J, Maxwell S, Ruiz K, Frisby D. Poster.
54. Miami University, Master of Technical and Scientific Communication (MTSC) program. Outsourcing of Technical/Scientific Communication. Beyrer J. Oral presentation.
55. Eli Lilly and Company. GMC Community of Practice Summit. Meet the Vendors: GMC Transformation Through Vendor Collaborations. Bakken R, Beyer J, Dominguez S, Frisby D, Heraty K, Sprague R, Webb D. Oral presentation.
56. Eli Lilly and Company. GMC Community of Practice Summit. From 1 to 22! The CSR has gone to pieces, honestly! Garni-Wagner B, Beyrer J, Maxwell S, Ruiz K, Hensley I, Frisby D. Poster.
57. Eli Lilly and Company. GMC Community of Practice Summit. Assessing Vendors' Quality Management Systems Via TPO Assessments. Beyrer J, Hile L, Murray I, Sprague R. Poster.
58. Eli Lilly and Company. Internal Training through Lilly University. Facilitator for Study Report Optimization workshop. Beyrer J and Heraty K. Oral Presentation.

59. Toastmasters International Lilly Corporate Club. Speeches on various topics presented at club meetings. Beyrer J. Oral Presentation.
60. Eli Lilly and Company, GSIC-R Neuroscience staff meeting. How to Effectively Lead Teams on Medical Writing Projects. Beyrer J. Oral Presentation.
61. American Medical Writers Association – 67th Annual National Conference, Louisville, KY. Writing with International Partners and Contributors. Beyrer J. Oral Presentation.
62. Eli Lilly and Company, GSIC-R Neuroscience staff meeting. Outsourcing Discussion. Beyrer J. Rohe M. Oral Presentation.
63. Eli Lilly and Company, GSIC-R Neuroscience staff meeting. GSIC-R
64. Neuroscience Records Retention. Beyrer J. Holdridge K. Oral Presentation.
65. Eli Lilly and Company. Global Patient Safety (GPS) Conference. Successful
66. Development and Maintenance of a Risk Management Plan: Shared Learning. Beyrer J. Acharya N. Jones M. Holdridge K. Thomas L. Witte M. Poster.
67. Eli Lilly and Company. FarisFest. Successful Development and Maintenance of a Risk Management Plan. Beyrer J. Holdridge K. Witte M. Poster.
68. Eli Lilly and Company. GMC Community of Practice Summit. Successful Development and Maintenance of a Risk Management Plan. Beyrer J. Holdridge K. Witte M. Poster.
69. Eli Lilly and Company, GSIC-R Neuroscience staff meeting. Project/Document Management Strategies. Beyrer J. Oral presentation.

70. American Medical Writers Association – 67th Annual National Conference. Writing with International Partners and Contributors. Beyrer J. Oral presentation.
71. Eli Lilly and Company, Corporate Clinical Operations staff meeting. The Clinical Study Report and QCing (quality checking) the Clinical Study Report. Beyrer J. Willey C. Oral Presentation.
72. Eli Lilly and Company, GSIC-R Neuroscience staff meeting. Stress: Just Dealing With It. Beyrer J. McGregor S. Oral Presentation.
73. Eli Lilly and Company GMC Town Hall. Shared Learning from the 64th Annual National Conference of the American Medical Writers Association. Beyrer J. Babu N. Oral Presentation.
74. Eli Lilly and Company, GSIC-R Neuroscience staff meeting. FDA: Facts, Details, Audience; Putting a Human Face on the US Food and Drug Administration. Crowder J. Kasper K. Oral Presentation.
75. Eli Lilly and Company, GMC Community of Practice poster. Best Practice: QC of Tables of Completed and Ongoing Studies. Crowder J. Poster.

Publications

1. Smyth EN, John J, Tiu RV, et al. Clinicogenomic factors and treatment patterns among patients with advanced non-small cell lung cancer with or without brain metastases in the United States. Oncologist. 2023;28(11):e1075-e1091. doi:10.1093/oncolo/oyad170.
2. Rao X, Chen Y, Beyrer J, et al. Clinical and Genomic Characteristics of Patients with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Following Progression on Cyclin-Dependent Kinase 4 and 6 Inhibitors. Clin Cancer Res. 2023;29(17):3372-3383. doi:10.1158/1078-0432.CCR-22-3843.
3. Liepa AM, Cui ZL, Beyrer JK, Hadden EL, Chatterjee A. Real-world ramucirumab and immune checkpoint inhibitor sequences in US patients with advanced gastroesophageal cancer. Future Oncol. 2023;19(18):1277-1291. doi:10.2217/fon-2022-0604.
4. Beyrer J, Nelson DR, Sheffield KM, Huang YJ, Lau YK, Hincapie AL. Development and Validation of Coding Algorithms to Identify Patients with Incident Non-Small Cell Lung Cancer in United States Healthcare Claims Data. Clin Epidemiol. 2023;15:73-89. https://doi.org/10.2147/CLEP.S389824.
5. Singh S, Beyrer J, Zhou X, Swerdel J, Harvey RA, Hornbuckle K, Russo L, Ghauri K, Abi-Elias IH, Cox JS, Rodriguez-Watson C. Development and Evaluation of the Algorithm CErtaInty Tool (ACE-IT) to Assess Electronic Medical Record and Claims-based Algorithms' Fit for Purpose for Safety Outcomes. Drug Safety. (2022). https://doi.org/10.1007/s40264-022-01254-4.
6. Smyth EN; Beyrer J; Saverno KR; Hadden E; Abedtash H; DeLuca A; Lawrence GW; Rybowski S. Real-world patient characteristics, utilization patterns, and outcomes of US patients with HR+, HER2- metastatic breast cancer treated with abemaciclib. Drugs - Real World Outcomes. (2022). https://doi.org/10.1007/s40801-022-00327-1.

7. Beyrer J, Abedtash H, Hornbuckle K, Murray JF. A review of stakeholder recommendations for defining fit-for-purpose real-world evidence algorithms. J Comp Eff Res. 2022 May;11(7):499-511. doi: 10.2217/cer-2022-0006.
8. Nagasaka M, Molife C, Cui ZL, Stefaniak V, Li X, Kim S, Lee HY, Beyrer J, Blumenschein G. Generalizability of ORIENT-11 trial results to a US standard-of-care cohort with advanced non-small-cell lung cancer. Future Oncol. 2022 May;18(16):1963-1977. doi: 10.2217/fon-2022-0099.
9. Kuehne F, Arvandi M, Hess LM, Faries DE, Gothe RM, Gothe H, Beyrer J, Zeimet AG, Stojkov I, Mühlberger N, Oberaigner W, Marth C, Siebert U. Causal analyses with target trial emulation for real-world evidence removed large self-inflicted biases: Systematic bias assessment of ovarian cancer treatment effectiveness. J Clin Epidemiol. 2022 Oct 14:S0895-4356(22)00246-3. doi: 10.1016/j.jclinepi.2022.10.005.
10. Winfree KB, Molife C, Peterson PM, Chen Y, Visseren-Grul CM, Leusch ML, Beyrer J, Dimou A. Real-world characteristics and outcomes of advanced non-small-cell lung cancer patients with EGFR exon 19 deletions or exon 21 mutations. Future Oncol. 2021 Aug;17(22):2867-2881. doi: 10.2217/fon-2021-0218. Epub 2021 Apr 19.
11. Beyrer J, Manjelievskaia J, Bonafede M, Lenhart G, Nolot S, Haldane D, Johnston J. Validation of an International Classification of Disease, 10th revision coding adaptation for the Charlson Comorbidity Index in United States healthcare claims data. Pharmacoepidemiol Drug Saf. 2021;30(5):582-593. doi:10.1002/pds.5204.
12. Beyrer J, Nelson D, Sheffield KM, Huang Y, Ellington T, Hincapie A. Development and validation of coding algorithms to identify patients with incident lung cancer in United States healthcare claims data. Pharmacoepidemiol Drug Saf. 2020 Nov;29(11):1465-1479. doi: 10.1002/pds.5137.

13. Bowman L, Tiu R, Smyth EN, Willard MD, Li L, Beyrer J, Han Y, Singh, A. Clinical Characteristics, Treatments, and Concurrent Mutations in Non–Small Cell Lung Cancer Patients With NF1 Mutations. Clin Lung Cancer. 2021 Jan;22(1):32-41.e1. doi: 10.1016/j.cllc.2020.09.011. Epub 2020 Sep 18.
14. Molife C, Hess LM, Cui ZL, et al. Sequential therapy with ramucirumab and/or checkpoint inhibitors for non-small-cell lung cancer in routine practice. Future oncology (London, England). 2019.
15. Barzi A, Hess LM, Zhu YE, et al. Real-World Outcomes and Factors Associated With the Second-Line Treatment of Patients With Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma. Cancer control : journal of the Moffitt Cancer Center. 2019;26(1):1073274819847642.
16. Kuehne F, Arvandi M, Hess LM, et al. Assessing Type and Impact of Biases Potentially Occurring when Analyzing Real World Evidence: The Case of Second Line Treatment for Ovarian Cancer. Value in Health. 2018;21:S213.
17. Acknowledged (for scientific peer review). Cui ZL, Hess LM, Goodloe R, Faries D. Application and comparison of generalized propensity score matching versus pairwise propensity score matching. Journal of Comparative Effectiveness Research. 2018;7(9):923-934.
18. Hess LM, Cui ZL, Li X, Beyrer J, Oton AB. Treatment sequences in non-small cell lung cancer in the United States from 2014-2016. Journal of Clinical Oncology. 2017;35(8_suppl):237-237.
19. Sheffield KM, Beyrer JK, Watson IA, Stafford K, Mills BJ, Ale-Ali A. Minimization of olaratumab drug waste using real-world data. Am J Health Syst Pharm. 2017 Jun 1;74(11):832-842.

20. Hess LM, Michael D, Mytelka DS, Beyrer J, Liepa AM, Nicol S. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. Gastric cancer. 2016;19(2):607-615.
21. Acknowledged (for writing support). Shah M, Winfree KB, Peterson P, Gruschkus SK, Eaddy M, Green MR. 2013. Cost effectiveness of first-line pemetrexed plus platinum compared with other regimens in the treatment of patients with nonsquamous non-small cell lung cancer in the US outpatient setting. Lung Cancer 82:1, 121–127.
22. Beyrer J. 2012. How to Effectively Lead Your Team as the Medical Writer. Journal of the American Medical Writers Association. 27 (3), 118-122.
23. Acknowledged (for writing support). Schnabel PA, Smit E, de Castro Carpeño J, Leśniewski-Kmak K, Aerts J, Kraaij K, Visseren-Grul C, Dyachkova Y, Taipale K Girvan A, Moro-Sibilot D. Influence of histology and biomarkers on first-line treatment of advanced non-small cell lung cancer in routine care setting: Baseline results of an observational study (FRAME). Lung Cancer 78 (2012) 263– 269.
24. Gridelli C, de Marinis F, Pujol JL, Reck M, Ramlau R, Parente B, Pieters T, Middleton G, Corral J, Winfree K, Melemed S, Zimmermann A, John W, Beyrer J, Chouaki N, Visseren-Grul C, Paz-Ares LG. 2012. Safety, resource use, and quality of life in paramount: a phase III study of maintenance pemetrexed versus placebo after induction pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol. 2012 Nov;7(11):1713-21.
25. Acknowledged (for editorial review). Rahardja D and Young DM. 2011. Bayesian Inference of Risk Ratio of Two Proportions Using a Double Sampling Scheme. Journal of Biopharmaceutical Statistics. Vol. 21, No. 3, 393-404.

26. Beyrer J. 2009. AMWA Annual Conference Student Scholarship Winners: Where Are They Now? Journal of the American Medical Writers Association. Volume 24, Number 1, pp. 9-12.
27. Haley H. 2008. Professional Development: Voices of Experience (Interviewee: Julie Beyrer). Journal of the American Medical Writers Association. Volume 23, Number 3, pp. 131-133.
28. Acknowledged (for editorial review). Rahardja D. Zhao Y.D. 2009. Unified Sample Size Calculations Using the Competing Probability. Statistics in Biopharmaceutical Research. Statistics in Biopharmaceutical Research. Vol. 1, No. 3, 323-327.
29. Lin AT, Sun MJ, Tai HL, Chuang YC, Huang ST, Wang N, Zhao YD, Beyrer J, Wulster-Radcliffe M, Levine L, Chang C, Viktrup L. 2008. Duloxetine versus placebo for the treatment of women with stress predominant urinary incontinence in Taiwan: a double-blind, randomized, placebo-controlled trial. BMC Urology 8:2.
30. Acknowledged (for review). Perahia D, Acharya N, Wang F, Strombom I, D'Souza D, Wernicke J. 2008. Hepatic Effects of Duloxetine-III: Analysis of Hepatic Events Using External Data Sources. Current Drug Safety, Volume 3, Number 2, pp. 154-162(9).
31. Kornstein S, Dunner D, Meyers A, Whitmyer V, Mallinckrodt C, Wohlreich M, Beyrer J, Greist J, Detke M. 2007. Comparison of Increasing or Maintaining Duloxetine Dose in Patients Without Remission of Major Depressive Disorder After Initial Duloxetine Therapy. Presented at NCDEU Annual Meeting in Boca Raton, Florida.
32. Acknowledged (for editorial review). Rahardja D. Zhao Y.D. Sampling scheme for locating two-dimensional parts. 2007. International Journal of Manufacturing Research 2(4): 484 – 498.

33. Mah SY, Lee KS, Choo MS, Seo JT, Lee JZ, Park WH, Kim JC, Lee SY, Zhao YD, Beyrer J, Wulster-Radcliffe M, Levine L, Viktrup L. 2006. Duloxetine versus placebo for the treatment of Korean women with stress predominant urinary incontinence. The Korean Journal of Urology 47(05): 527-535.
34. Crowder J. 2004. An Internship as a Scientific Communications Associate at Eli Lilly and Company [master's thesis]. Oxford, OH: Miami University. Available at http://www.ohiolink.edu/etd/view.cgi?acc_num=miami1101594503. Accessed 22 January 2007.
35. Crowder J. 2003. Converting a Newsletter from Print to Electronic Form. Journal of the American Medical Writers Association 18 (4) 2003, 167-168.
36. Crowder J. 2003. Honesty is the Best Policy: Why Audience Analysis and Self-Honesty Are Important for Biomedical Communicators. Journal of the American Medical Writers Association 18 (4), 183-184.

Professional Affiliations

Value, Evidence, Outcomes (VEO) Health Equity Community of Practice	2023-present
Lilly Influencers of Change community of practice	2021-present
Flatiron Health Equity Board	2021
International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Member	2017-present
ISPOR, RWE and health equity special interest groups	2019-present
American Medical Writers Association (AMWA)	2002-2014
AMWA, Member (Indiana Chapter)	2002-2014
AMWA, Treasurer (Indiana Chapter)	2009-2011
AMWA, national chair for student scholarship to the AMWA annual conference	2009
AMWA, President (Indiana Chapter)	2008-2009
AMWA national selection committee member for student scholarship to the AMWA annual conference	2008
AMWA national task force member for spending of interest on the AMWA endowment fund	2008

AMWA, President-Elect (Indiana Chapter)	2007-2008
AMWA, Student scholarship chair (Indiana Chapter)	2007-2008
AMWA, student scholarship judge (Indiana Chapter)	2006-2007
AMWA, program chair (Indiana Chapter)	2005-2007
Toastmasters International	2006-2009
Toastmasters International, Member (Lilly Corporate Club)	2006-2009
Toastmasters International, Vice President of Education (Lilly Corporate Club)	2008-2009
Toastmasters International, Mentor Liaison (Lilly Corporate Club)	2007-2008
Toastmasters International, Secretary (Lilly Corporate Club)	2006-2007
Other former affiliations	
Lilly Global Medical Communications (GMC) Community of Practice	2004-2013
Lilly GMC Community of Practice, Annual Summit Co-chair	2007
Society for Technical Communication (STC), Member (Miami University student chapter)	2002-2003
STC, Program Chair (Miami University student chapter)	2002-2003