

A Framework for Regulatory Use of Real-World Evidence

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WHITE PAPER

A FRAMEWORK FOR REGULATORY USE OF REAL-WORLD EVIDENCE

CONTRIBUTING AUTHORS

Marc Berger

International Society for Pharmacoeconomics and
Outcomes Research

Greg Daniel

Duke-Margolis Center for Health Policy

Katherine Frank

Duke-Margolis Center for Health Policy

Adrian Hernandez

Duke Clinical Research Institute

Mark McClellan

Duke-Margolis Center for Health Policy

Sally Okun

PatientsLikeMe

Marc Overhage

Cerner

Richard Platt

Harvard Medical School

Morgan Romine

Duke-Margolis Center for Health Policy

Sean Tunis

Center for Medical Technology Policy

Marcus Wilson

HealthCore

INTRODUCTION

As the American health care system continues to innovate, there is untapped potential for utilizing new and maturing sources of data to provide evidence that supports patient care and medical product development. Routine collection of electronic data in hospital billing, medical records, and other clinical and administrative data allows examination of information more broadly representative of clinical settings and patient populations than those found in traditional clinical trials*. New technologies are enabling patients to generate their own health data, providing opportunities to learn from patient experiences with treatments and their impact on day-to-day life. These data hold the potential to address a number of evidentiary gaps related to the effectiveness, safety, and utility of treatments for patients in real-world settings.

These gaps in knowledge combined with increasingly sophisticated methods for turning electronic health data into evidence that could be more relevant to patients and their unique clinical circumstances, are together motivating stakeholders to explore the application of these data sources within a regulatory decision-making framework. How the U.S. Food and Drug Administration (FDA) can take into account data and evidence collected during routine care is a growing area of interest and debate. Legislative requirements passed in the 21st Century Cures Act (which will require FDA to explore the use of such evidence for additional indications of approved drugs and post-approval study requirements),¹ commitments negotiated between the pharmaceutical industry and FDA as part of the sixth Prescription Drug User Fee Act (PDUFA VI),^{2,3} and countless conference sessions, working groups, and emerging research collaborations^{4,5,6,7} have revolved around the same broad question: *How can real-world evidence (RWE) better support regulatory decisions?*

While the Agency has spoken publicly about the potential for real world data (RWD) and RWE to inform regulatory decisions,^{8,9,10,11} discussion to date is limited by both an imprecise characterization of the kinds of RWD and RWE that could be useful and a clear assessment of how future types of RWD or RWE could be applied in specific regulatory contexts. In this white paper, we lay out distinct definitions for what constitutes RWD and RWE, the considerations that should guide the development of RWE that is fit for regulatory purposes, and high priority opportunities to improve such development and use. A number of scientific and policy challenges remain, but continued multi-stakeholder collaboration can build on this foundation to support the FDA, industry, researchers, payers, providers, and patients as they seek to further the utility of information that is gleaned from clinical experience.

DEFINING REAL-WORLD DATA AND REAL-WORLD EVIDENCE

An immediate barrier to precise discussion of the potential role of RWE in stakeholder decision making is the inconsistent use of the term to represent a number of different concepts or types of information.¹² Often, RWE is simply used as a placeholder term for either evidence derived from retrospective studies in observational data sets or “anecdotal” information gathered from case report forms – definitions that do not reflect the epidemiological and other scientific insights that can be achieved through rigorous use of RWD. These definitions of RWE often devalue serious consideration of such evidence and conflate the term with non-randomized study

* For purposes of this paper, a traditional clinical trial (either randomized or non-randomized) typically has a trial infrastructure that is largely separate from the routine delivery of health care. There are specific eligibility requirements (which can be broad or narrow) and a protocol for intervention and follow-up (which includes efforts to ensure adherence). Further, the clinical interventions and data collection on study endpoints and adverse effects are almost exclusively performed by investigators and other associated clinical trial staff.

settings. As such, they fail to capture the wider variety of evidence that can be embodied by the term, including randomized trials within health care settings.

Furthermore, the term RWE is often used when stakeholders are actually describing the development or use of RWD for a variety of purposes. Data and evidence are not the same; RWD is necessary but not sufficient for generating RWE. There is a clear need to separate these concepts from one another *and* to clarify the full range of RWE itself. This has important implications for the ways that RWD and RWE are used by regulators.

We define RWD as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. This includes data elements captured in a patient’s electronic health record (EHR), in a hospital or insurance company’s administrative and claims data, directly from patients or providers in the course of an observational study, from sources of patient-generated information outside of clinical settings (e.g., in-home monitoring devices, wearable technologies, fitness trackers), and in registries that support various aspects of care and research. It may also include data on contextual metrics not typically considered part of a patient’s routine clinical experience, such as environmental exposures and socio-economic indicators. Importantly, this baseline definition does not preclude incorporation of routinely collected data in traditional randomized clinical trials (RCTs) from being considered RWD.

In addition to their primary role in health care delivery, reimbursement, and health status assessment and improvement, RWD elements serve a wide range of secondary uses. They can support health plan and health system administrative operations and quality reporting, quality improvement and cost management activities, direct-to-patient or provider communications, patient self-care management, and epidemiologic and health services research. In addition, RWD can have an important role in designing more efficient clinical trials by identifying potential patients for randomized studies, targeting site selection, and selecting inclusion and exclusion criteria, though this use does not constitute the development and use of RWE as we have defined it below.^{13,14}

We define RWE as evidence derived from RWD through the application of research methods. For regulatory applications, RWE can further be defined as clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of RWD. RWE is not simply “anecdotes” based on RWD – it involves data curation, validation, and standardization to ensure that the data themselves are adequately fit-for-purpose. It requires thoughtful study designs to assess the effects of the treatments on the outcomes of interest, and an understanding of the context in which the treatments are used.

Importantly, this definition of RWE reflects evidence generation that is broader than passively-collected observational data and retrospective analytical approaches. It conceptually allows for prospective capture of a wider variety of data, and utilization of study designs that are embedded in clinical practice but retain randomization. This definition of RWE does not characterize good versus bad evidence and what “kind” of RWE is suitable for regulatory decisions. The development and application of RWE that is fit for a specific regulatory purpose may be contingent upon the set of factors explored below.

With clear definitions established, it is important to return to the questions or evidence gaps that robust RWD and RWE development efforts can shed light on and how broader application of such evidence within FDA's regulatory framework could make an important contribution to the agency's public health and regulatory mission. Rigorous RWE may be able to provide insight into questions that are difficult, infeasible, unethical, or cost-prohibitive to address through traditional RCTs, making development more feasible for rare diseases and other areas. Following approval, both RWD and RWE can make continued contributions to a more comprehensive safety and effectiveness profile that is increasingly useful for patients and providers compared to less generalizable evidence available from traditional RCTs (e.g., tracking long-term outcomes, understanding real-world use in patients with multiple comorbidities, etc.). Furthermore, both can be developed through patient-facing tools that capture information about their experiences, expanding sources of patient-related data and evidence for decision making and labeling. Ideally, reliable RWD and RWE can enable more efficient and timely development of actionable evidence that supports a range of FDA decisions.¹⁵

Potential Benefits of RWD/RWE in Regulatory Decision-Making

- Enables evidence development in settings where traditional RCTs are impractical to conduct (e.g. rare diseases, etc.)
- Fills important evidentiary gaps that are not typically addressed with traditional RCTs (e.g. real-world uses of products in patients with multiple comorbidities, long-term outcomes, etc.)
- May allow sponsors to generate evidence in support of an efficacy claim that is potentially more useful to payers and patients
- May significantly reduce time and cost of evidence development for some regulatory decisions

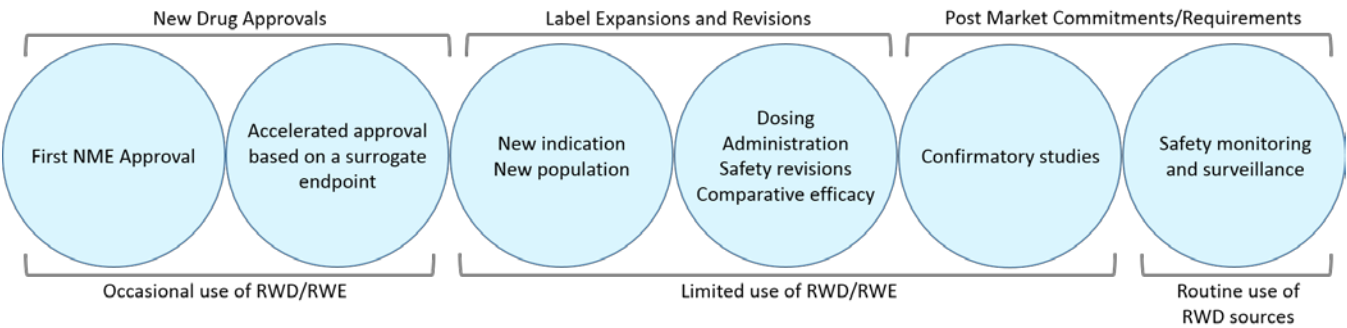
To date, FDA has made progress on using RWE within particular parameters related to rare disease drug development and post-market safety surveillance. It has been used, for example, to support the approval of New Drug Application (NDA) submissions for rare diseases or in small population settings in which an understanding of pathophysiology and natural history data, large effect sizes, and high unmet need combine to justify the acceptance of historically-controlled trials.^{16,17} There has also been considerable FDA use of RWE derived from retrospective claims data from Medicare and within the Sentinel System, a distributed data network that largely consists of claims and claims-linked EHR data that can be queried rapidly to better understand potential safety signals related to a medical product of interest.¹⁸ These use cases represent important tools and methods that FDA and sponsors should continue to support and evolve. The more policy-relevant question at hand then is *how* and *when* RWE could be used by FDA across the broader range of decisions that fall under the agency's remit.

While the use of RWE in epidemiological studies of medical product safety has been well established within regulatory settings,^{19, 20} interpreting results or determining causal inference in these studies can sometimes prove challenging for industry and regulators. In contrast, regulatory considerations for utilizing RWE from studies of effectiveness are still needed. The possibilities range from externally controlled studies (e.g., epidemiological studies that can credibly detect large effects common for adverse events but not commonly used for effectiveness) to randomized or observational designs in the clinical setting with endpoints based on RWD that aim to better understand effectiveness.

The pathway for pursuing such RWE development efforts to support a regulatory decision should not be overly prescriptive, however, and will necessarily depend upon a number of factors or contexts unique to each potential evidentiary and regulatory need. These include the ultimate intended regulatory application of the RWE, the underlying clinical question of interest spurring RWE development, the credibility of the data and attendant

collection “hygiene,” and the study design and analytical methods used to translate the RWD collected into credible RWE for that application. Here, we walk through the major guiding factors that sponsors should consider jointly with FDA when weighing RWE as a potentially viable option.

Experience Utilizing RWD and RWE for Regulatory Purposes



To date, there has been varying experience utilizing RWD and RWE to inform a range of regulatory use cases. For example, FDA has used both to support a small number of approval decisions in rare diseases or areas of high unmet need (e.g. through the use of historical controls in studies with small patient populations). Following a first-time approval, RWD and RWE have been used on a very limited basis to support label changes such as indication expansions, dosing modifications, or safety revisions. RWD sources are routinely used to monitor the safety of medical products on the market through systems such as Sentinel, which leverages EHRs, claims data, and registries from a diverse group of data partners.

REGULATORY CONTEXT

Stakeholders are currently most interested in those regulatory uses for which there has not yet been systematic application of RWE and for which improved efficiency or relevance of RWE development could potentially benefit both FDA’s decision-making process and treatment decisions for patients. This narrows the focus to those regulatory decisions that can follow a full first-time approval of an NDA, such as those related to refining the label for an approved product with an already well-described benefit-risk profile. This could mean utilizing RWE to expand an indication to a new population, or to a new clinically-meaningful or patient-relevant endpoint within the approved population. It could also include other label revisions that are more focused on enhancing the approved product label, like updates to drug-drug interaction, safety, or dosing information. Improved RWE strategies for fulfilling post-market commitments or requirements (PMCs and PMRs, respectively), including those PMRs that are required for drugs given an accelerated approval based on a surrogate endpoint, are also of interest to sponsors. While there are significant opportunities for leveraging RWD and RWE in premarket development programs, full approval for a wholly new drug or biologic based solely on RWE remains difficult to envision.

Viability of RWE-enabled approaches will depend upon which of these regulatory questions a sponsor would like to answer, and sponsors will need to ensure an appropriate match between the regulatory context in which the RWE will be used and the intended clinical context for RWE development. Each potential application will dictate both RWE’s suitability and value for achieving a sponsor’s desired aim, as well as the data collection and study design considerations discussed below.

CLINICAL CONTEXT

The specific clinical question of interest and the surrounding clinical context will drive much of the remaining consideration regarding whether an RWE approach is sufficient and robust enough for the regulatory question at hand. The desired or necessary endpoints, as well as any other key variables relevant to answering the question, will need to be available and adequately accessible in an RWD source. Valid and reliable RWD collection and methodological approaches will need to be able to identify and account for potential biases inherent in the chosen clinical setting.

These requirements – that the underlying RWD within a specific clinical context be valid and reliable for the regulatory application – may immediately preclude certain disease areas or clinical questions of interest from being considered for RWE development. Certain symptoms like fatigue or sexual dysfunction, for example, are rarely captured in clinical records and would not lend themselves to being included in a RWE study unless patient-generated data on such symptoms could be adequately incorporated. Elsewhere low-severity diseases or low-prevalence diseases not treated in specialty care centers may not have as deliberate or comprehensive data collected during routine clinical care as common, severe illnesses; there may simply be less data available. Patients with asymptomatic illnesses may be less likely to seek care and thus, again, have less data collected in electronic records. Even variability in what a clinician chooses to measure and record during a visit could lead to problems with missing data that makes RWE approaches infeasible in certain settings.

Failure to capture certain signs and symptoms of disease might be remedied in prospective studies through the addition of research specific modules that could be imbedded in electronic medical records. In these situations, providers could be prompted to enter necessary information or other data augmentation methods, such as systematically collected patient-reported data, could be used in order to overcome context-specific data deficiencies.

After an RWE approach is deemed promising for the regulatory purpose and clinical question at hand, clinical characteristics will also drive many of a sponsor's methodological considerations. For example, questions dealing with high prevalence outcomes may limit the ability to detect a meaningful treatment effect in nonrandomized settings. For some safety-related questions, the relationship between the outcome of interest and the disease pathway itself may prevent the ability to distinguish between the drug's effects versus disease progression.²¹ A lack of clinical equipoise between treatment alternatives can also give rise to selection biases that must be accounted for with a range of analytic approaches. This is especially true in non-randomized designs.

DATA COLLECTION CONSIDERATIONS

Once sponsors have examined both the clinical and regulatory contexts within which RWE will be developed, they will need to assess the context in which the data themselves are collected. The ability to collect reliable and timely data on patient outcomes will vary by a number of characteristics related to the availability and consistency of data across provider types and settings, types of benefits coverage, and even system-wide difficulties in definitively determining events like death in RWD sources. It will further depend on the adequacy with which relevant information for the intended use is documented within clinical work flow or patient experience data and, as highlighted above, on whether individual patients seek care.

Determining validity and reliability of the RWD against its source or set of standards will therefore be essential. The U.S. health care system has decades of experience standardizing, validating, and using claims data for public health and research purposes. This has led to a relatively strong understanding of what claims data can and can't

answer, how claims data have strengths and limitations compared to other RWD sources, and when linkage to clinical records is necessary.^{22,23} Less well-characterized is the state of readiness of research-grade EHR data, especially in relation to standardization methods, comprehensiveness, degree of validity, and the extent to which the patient perspective is filtered through the provider. More work also needs to be done to understand and validate potential applications for patient-reported outcomes assessments and patient-generated health data (e.g., from wearable devices, social media, and other online patient communities) in generating RWE.

Extensive data hygiene practices and tools developed for using claims data (e.g., through Sentinel, Observational Medical Outcomes Partnership, Observational Health Data Sciences and Informatics, Electronic Data Methods Forum, etc.) may help to bridge the data methods gaps between such RWD sources, but sponsors will need to characterize how well a given RWD source may be able to contribute to RWE efforts. Additional data standardization techniques, quality checking tools, and steps for mitigating erroneous data will need to be developed and applied across diverse RWE efforts in order to further establish best practices.

STUDY DESIGN AND CONDUCT CONSIDERATIONS

A final set of considerations for assessing the suitability of RWE for regulatory purposes relate to the tools that enable its creation: study designs and analytical methods that translate RWD into evidence. There are several approaches available to researchers, with a number of fundamental design elements that can combine to generate evidence with the necessary credibility for their needs. This includes elements related to treatment assignment and comparison group selection in interventional studies, use of prospective versus retrospective observational designs, and choice of analytical and statistical methods.

The most critical element that researchers must consider is whether an interventional or observational (i.e., non-interventional) design is best suited for generating sufficient evidence to meet the regulatory and clinical questions at hand. Interventional studies are those where a researcher intercedes as part of the study design. Typically, these studies utilize randomization techniques, either at the patient level or the health care provider or plan level (e.g., cluster randomization), to determine treatment assignment. A complicating factor for randomized designs is the potential for bias in assessment of endpoints if blinding is not performed during the treatment assignment process. Blinding prevents bias in certain settings but has significant impact on a study's ability to be integrated into a real world setting due to drug accountability or complexity. In some cases blinding may not be necessary, such as in a trial with all-cause mortality where bias may be less likely.

There may be situations in which an intervention is necessary but randomization is considered unethical, such as in very rare disease settings with small patient populations. In these cases, a comparison group from a patient registry or natural history study may be selected in order to assess the impact of the intervention on the study subjects. As previously noted, these types of designs represent an area where industry and FDA have already exhibited progress in utilizing RWD and RWE.

Observational designs, on the other hand, do not introduce an intervention but instead observe the natural relationship between exposure and outcome variables of interest. These studies can be conducted prospectively or retrospectively, both of which come with their own strengths, limitations, and ability to control treatment exposure and important covariates. Prospective designs follow subjects forward in time and are well suited for RWE development in which researchers need greater certainty around the temporal relationship between the exposure and outcome variables and purposeful data collection of elements not routinely captured in RWD sources is essential to the study. These designs mitigate the potential for data mining because researchers must

define the treatment effect hypothesis and are limited to a defined set of subjects from the study's inception, helping to increase confidence around the study findings.

Retrospective designs, on the other hand, often rely on existing databases of routinely collected data used for public health, academic research, or patient management by hospital systems or payers. Unlike prospective designs, retrospective approaches start with an observation period that is already complete. This feature makes retrospective studies well-suited for investigations that require longer timeframes for the relationship between the exposure and outcome variables to become observable. They are also typically less expensive and faster to conduct but may lack the variable control and temporal certainty that characterizes prospective studies. The validity of RWE from retrospective observational studies will hinge on prespecification of the analysis plan, the strength and diversity of the RWD utilized, and the reproducibility of results across different databases.

Finally, researchers will need to choose from a variety of analytical techniques that seek to control for known and unknown differences in baseline characteristics between treatment groups. While observational studies (both prospective and retrospective) can have the potential for bias and confounding, new study designs and analytic techniques that include matching, stratification, weighting, and/or multivariate regression models have made progress in managing such limitations over the last decade. These methods may be able to address some of the potential biases inherent in non-randomized studies and potentially increase the applicability of these studies in the regulatory context. Considerations for assessing or reducing measurement error and understanding the impact that certain data limitations may have on the ability to make inferences (e.g., confounding due to treatment modifications that occurred during the study) will also be integral to selecting appropriate analytical techniques.

The interplay of these elements and evidentiary needs will dictate the general type of study design chosen as a starting point for generating fit-for-purpose RWE. There will be many distinct factors that guide specific design decisions within individual RWE development programs and, in keeping with our definition that RWE is developed from different combinations of RWD and study designs, it is important to underscore that not all RWE will be the same. Credible RWE developed for and applied within a specific context of use may not look the same as credible RWE developed for a different type of clinical or regulatory purpose.

THE FUTURE ENVIRONMENT: ESTABLISHING A VISION FOR ENHANCED REGULATORY USE OF RWE

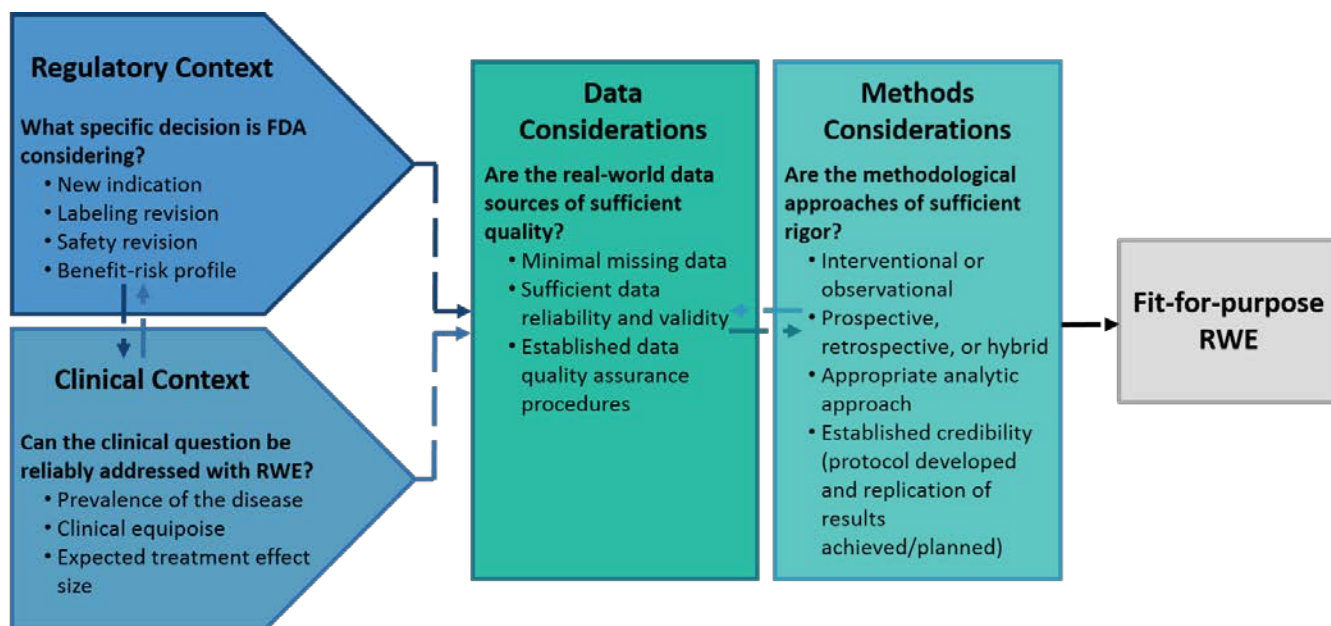
Taken together, the stepwise considerations for RWE development outlined above provide a framework for applying RWE to support a variety of regulatory decisions. Given near-term challenges and opportunities, it is instructive to establish the situations in which FDA decision-making could be supported by either of two main types of RWE development strategies: those requiring intervention and those that are considered observational. What are the situations in which an interventional design is truly needed? What are the situations in which observational approaches may be sufficient for supporting the decision at hand?

We note that exploring these uses and applications for RWE presumes a future health system with an infrastructure that enables efficient use of high quality RWD for research. This assumes research-sufficient EHRs, links between the EHR and payment data capable of complete longitudinal data capture, and the capacity for upfront patient consent and randomization to meet all types of study needs.

Some of these advancements are already being made in pockets of the US health care system, and we believe most are achievable in the near term for a number of collaborations and integrated health systems with a vested interest in improving the quality of RWD development to improve patient care, outcomes, and value. Further

development of best practices, data standards, and a networked research infrastructure will be needed to make RWE development feasible on a larger and more sustainable national scale, but at least some baseline assumptions about future health systems' ability to support RWE activities must underpin our assessment of where such efforts could support regulatory decisions in the years to come.

Considerations for Generating RWE Fit for Regulatory Purposes



As manufacturers consider pursuing an RWE development strategy to support regulatory use, there are a number of interlocking considerations that they should address to ensure that an RWE approach is sensible. First, they must examine the intended regulatory use and the clinical context within which RWE will be developed. Once they have decided that RWE may be sufficiently robust for regulatory decision-making, they will need to consider the strength of available RWD data sources and study methods for generating fit-for-purpose evidence. Matching data sources and appropriate methods to answer specific clinical and regulatory questions will result in different “types” of RWE for different use cases.

MATCHING INTERVENTIONAL RWE STUDIES WITH REGULATORY USES

Because interventional studies have a stronger ability to demonstrate causality, they are likely to be most immediately applicable for RWE development efforts aimed at answering clinical and regulatory questions underpinning expansions of a drug's approved labeling – namely, regulatory decisions related to a new indication or population. Such decisions would require a higher degree of certainty that the study has adequately demonstrated the anticipated clinical effect and achieved statistically significant results. The clinical question of interest in such cases, i.e. “What is the safety and effectiveness of this drug in a new population or indication?” will also require a strong baseline level of safety information on which to build additional evidence around effectiveness.

From there, researchers will need to ensure that the key outcomes that can establish effectiveness are reliably observed in RWD sources. Whether the data can be easily collected from EHRs, claims, hospital records or other patient-generated data sources will impact the overall interventional design as well as its clinical and cost burden. For example, it may be necessary for researchers to request that a new field be incorporated in an EHR or a bio specimen be collected and stored for later analysis.

If a sponsor anticipates a significant though small effect in the new population or indication, can guarantee that the necessary RWD will be accessible, and anticipates that a traditional RCT to support label expansion is either infeasible or less optimal for generating the desired evidence, then subsequent decisions around study design will likely lead them to consider pragmatic clinical trials (PCTs) as an option.²⁴ These designs, in which randomization is maintained as a critical design element of a study that takes place within routine clinical care, have gained increasing attention in the last several years as an incremental step toward more fully embedding clinical research in clinical practice. Projects like the Salford Lung Study²⁵ and PCORnet's ADAPTABLE²⁶ have demonstrated the potential advancements that PCTs can make in generating RWE, but have also uncovered a number of challenges related to infrastructure and financial resources that will need to be addressed before PCTs can be more easily pursued.

One area for such applications would be a drug approved for patients with diabetes mellitus based on improving glycemic control (HgbA1c), for which a sponsor seeks an indication expansion to include beneficial effects on cardiac events with modest treatment effects over usual therapy. For example, new medications such as SGLT-2 inhibitors for the treatment of diabetes may have plausible benefits for cardiovascular outcomes or other related conditions such as heart failure or chronic kidney disease. However, a full-scale RCT for such an expansion may prove challenging because the drug is already on the market with expanded use making it difficult to enroll patients or to rely on a resource- and time-intensive new registry. A prospective PCT that utilizes RWD from claims and EHRs and includes randomization could therefore be harnessed to generate RWE. A PCT design would allow multiple endpoints, including cardiac events and HgbA1c, to be tracked in the setting of routine care. Further expansion could also be considered in related conditions where the drug may be of benefit.

Another clinical example is within the field of anticoagulation. As direct oral anticoagulants have been developed, several have expanded beyond their initial indication from venous thromboprophylaxis in a specific setting to prevention of stroke in patients with atrial fibrillation. With each successive indication, the use of direct oral anticoagulants grows, making it more difficult or more expensive to study due to challenges in recruitment. For example, the benefits and risks for patients with atrial fibrillation and percutaneous coronary interventions are unknown regarding oral anticoagulation and dual anti-platelet therapy. The challenges of enrollment in a normal trial setting are large and the patient profile with the greatest risk profile for bleeding (older patients or women) are the most challenging to recruit into traditional trials with frequent in-person visits, making this a highly relevant clinical question that could lend itself to a PCT.^{27,28}

MATCHING OBSERVATIONAL RWE STUDIES WITH REGULATORY USES

There are other situations in which, based on the underlying clinical question and existing evidence on the medical product under study, purely observational approaches may eventually be suitable for generating RWE for regulatory use. In these cases, the regulatory decision at hand will likely be a label change that incorporates new information closely associated with the accepted clinical evidence in the label or makes revisions to that information (e.g., drug-drug interactions, dosing).

Pursuing an observational approach will then depend on the interplay of a number of factors related to the clinical context and underlying RWD. For example, strong candidates for an observational RWE approach will probably have a high level of scientific understanding around the given disease (e.g., pathophysiology and natural history) and a drug with a well-understood safety and efficacy profile. They may be most attractive for studies where there is a large anticipated effect size or when repeated and consistent treatment effects are already being observed in practice across multiple trusted data sets or patient populations. There must be valid and reliable RWD, rigorous analytical methods, and, as established above, a high level of reproducibility. In short, a sponsor must be able to trust that the signals they see are credible.

A key to overcoming known limitations of observational approaches, and to ultimately generating observational RWE acceptable for regulatory use, will be replication. The credibility of such RWE will be best established through multiple observational studies considered together as a body of actionable evidence. Ideally this should also mean transparent reporting of study designs, methods, and data by sponsors – all to allow others to also replicate the observational findings. The combination of trusted observational methods and replication have allowed sponsors and FDA to make safety-related decisions and label revisions based on RWD and RWE, but making broader use of such approaches for efficacy-related label changes or other types of clinical questions around effectiveness will take additional standards and methods development.

Here, an illustrative regulatory application could be a sponsor seeking to add efficacy claims on endpoints relevant to payers and/or patients to the label for an already approved drug with completed confirmatory studies. In a clinical area like chronic obstructive pulmonary disease (COPD), for example, a sponsor may wish to generate RWE supporting claims of reduced exacerbation-related hospitalizations or improved quality of life – endpoints more readily useful in clinical decision-making and coverage decisions than the forced expiratory volume in one minute (FEV1) endpoint used for initial drug approval. Because these endpoints may be measured using RWD with good validity and reliability and would be captured in the same indicated population, they could lend themselves to a rigorous observational study design that harnesses EHRs and claims. Another area may be the expanded use of cancer treatments where the outcome of interest is very clear, such as survival.

OPPORTUNITIES FOR NEAR-TERM PROGRESS

Moving toward an ideal state in which consistently robust and reliable RWD and RWE can be utilized for specific regulatory purposes will require addressing a number of critical challenges. While these challenges may be different depending on the type of RWE being developed or have varying implications across regulatory use cases, some are overarching and will necessitate engagement from all sides to solve.

These efforts can be synergistic with other overarching FDA priorities related to improving the overall efficiency of drug development and regulatory review. Work related to adaptive and novel clinical trial designs, the expanded use of model-informed drug development, the advancement of Bayesian statistical analyses, and the qualification of drug development tools like biomarkers, all reinforce the push to better elucidate where RWE could contribute meaningful scientific evidence to the drug development process.²⁹ With FDA as a key and willing partner in tackling these issues through scientifically rigorous and transparent collaborations, we feel that tangible progress can be made in the coming months and years.

REGULATORY OPPORTUNITIES

Agency Guidance Development

Under both the Cures Act and PDUFA VI provisions, FDA will have established timetables for developing guidance around the enhanced use of RWE within their regulatory framework. Over the next few months and years, it will be important for FDA to continue such guidance development with as much external collaboration and input as possible. This should include where possible public meetings and external engagement on challenges related to data and methods development. Groundwork for much of this has already been laid with the release of several FDA guidance documents on topics such as the use of electronic source data, electronic informed consent, and electronic health records in clinical trials.^{30,31,32,33}

DATA DEVELOPMENT OPPORTUNITIES

Improving Data Collection and Standardization

First, improvements to the collection and potential standardization of real-world data elements will pave the way for further success in regulatory applications of RWE. The format, quality, and validity of RWD can vary significantly by practice, insurer, EHR vendor, and provider, and nascent efforts to address these challenges have yet to align on a path forward. Appropriate curation and validation techniques are needed, as well as criteria for what is appropriate for particular purposes, and could potentially be implemented within specific disease areas or for specific outcomes of interest as pilot opportunities for establishing broader consistency in data capture across health systems. Emerging tools through which patients can actively monitor and offer corrections to their EHR (e.g., “open notes”) will need to be further validated.³⁴ There is little doubt that RWD will be more valuable and credible for some endpoints than others.

In the clinical setting, additional work is needed to help standardize a set of data elements that both meet research needs and help to provide clear value for frontline medical care providers. Data capture must be meaningful and better integrated into provider workflow in order to reduce burden and the potential for data to be omitted due to time and resource constraints at the point of care. More research is also needed in assessing the credibility and value of RWD when curated and normalized without any enhancements.

These efforts will ultimately hinge on establishing a clear business case and value-add for those who create, curate, and improve data for RWE applications. Stronger incentives need to be developed for physicians and other providers, health care systems, payers, and patients to become fully-vested partners in the development and use of RWD and RWE. These might include incentives for reporting on patient outcomes, for providing RWD for studies, and for further adoption of payments based on outcomes.

Utilizing RWD in Traditional Clinical Trials

In tandem with improvements to RWD collection in real-world settings, near-term opportunities to gain greater experience with the use of these data to support traditional RCTs could further inform best practices for its use in generating RWE. For example, RWD could be leveraged to increase the efficiency of RCTs through faster EHR-enabled identification and recruitment of study participants, or to increase retention by using physician appointments as opportunities to collect data throughout the study. These applications can not only cut down on time and cost for the study sponsor, but also reduce participant burden. Moreover, this progressive incorporation of RWD into randomized studies can serve as important proof-of-concept opportunities for broader applications of RWD in the future.

STUDY DESIGN AND CONDUCT OPPORTUNITIES

Strengthening Methods for Randomization in the Clinical Setting

As previously highlighted, RWE development that makes use of randomization within the clinical setting (e.g., PCTs) can allow for more meaningful comparisons, diverse study populations and settings, and potential collection of more representative outcomes data – while also streamlining clinical trials and allowing for randomization between different practices or formularies. Yet randomization at the point of care requires significant personnel effort and administrative resources, and the methods and study designs underpinning these approaches need to mature.^{35, 36, 37} Researchers should consider and further develop the use of umbrella or platform trials to overcome these challenges. Umbrella trials allow for randomization across a variety of groups (e.g. by drug or disease mutation) in a real-world setting, while platform trials enable randomization of multiple medical products in a given condition.³⁸ Strengthening these approaches in real-world settings with continuous data collection will likely provide the highest value and most efficient study conduct for many RWE development activities. Further methods work around the use of cluster randomization may also increase study efficiency and feasibility for certain settings and questions.

Increasing the Credibility of Observational Studies

Observational studies are leveraged by a variety of stakeholders to make important health and policy decisions but, as discussed above, are generally not used within regulatory frameworks outside of safety monitoring. While this may still be the case in a regulatory framework that harnesses RWD and RWE more often across a range of decisions, credibility of such approaches is still uncertain. Researchers must address the challenges inherent in these designs that make it difficult to detect random variation versus systematic bias, for example, or that result in loss of longitudinality because of the difficulty in data integration across different systems or sources. This will be especially important for utilizing EHR data within observational approaches, as these data typically provide more clinical detail than other sources but have yet to be fully utilized in or standardized for observational research. In recent years groups such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) have developed best practices for payers and providers generating data in this space, but the suitability of these approaches for regulatory purposes will need to be further explored.³⁹

While many may perceive observational approaches as lacking credibility, there are a number of steps that researchers can take to overcome these concerns and improve the overall rigor of observational studies and subsequent results. Publishing detailed protocols that pre-specify the study population, exposure and outcome variables, other key covariates, and the analytical techniques that will be utilized a priori can increase the validity of study results by ensuring the decisions made during the study process are not arbitrary or made in light of interim findings. Additionally, publishing comprehensive protocols enables the replication of studies across a range of databases. Replication of results and conclusions using different data or with different analytical methods allows evaluation of the consistency of findings between multiple studies, which lessens the impact of systematic error in one study coloring the entire body of research on a given topic.

DEVELOPING PILOT AND DEMONSTRATION PROJECTS

Lastly, many of these potential opportunities can be advanced through pilot and demonstration projects that move analyses around the regulatory acceptability of different types of RWE past the current primarily theoretical stages. This will require clearly defined study questions, stepwise improvement to methods, and a willingness on the part of stakeholders to approach pilot development as a transparent learning process for all involved. Pilots that compare the results from randomized studies using RWD and observational studies within the same system will be especially useful in illuminating data and methods gaps. Industry and FDA will need to engage the broader

health care community in both prioritizing near-term opportunities and building collaborations capable of making strategic use of existing data infrastructure and resources. The lessons learned through these activities can in turn strengthen study and methodological approaches, clarify the specifics of potential regulatory use cases, and ultimately inform future guidance and best practices.

CONCLUSION

The increasing availability of RWD, and the increasing desire to translate it into RWE useful for all stakeholders, represent a timely and important opportunity to enhance regulators' ability to leverage multiple types of RWE across a range of decisions. To make these regulatory applications a scientifically-sound reality that maintains FDA's long-held standards of ensuring the safety and efficacy of the medical products it regulates, a more nuanced approach to defining or categorizing RWE is needed.

Here, we advance the idea that RWE is the output from the combination of a variety of different RWD sources and methods for evidence development, and that the resultant applicability of RWE will necessarily vary across regulatory contexts of use. Appropriately matching data and methods to potential uses will take time and input from all stakeholders involved in the development and use of medical products, but progress can be made if thoughtful and transparent collaborations can improve underlying challenges in data collection, study design, and shared infrastructure.

The wealth of real-world information currently being generated through routine patient care is already of use to a wide array of stakeholders – making it suitably reliable for regulators and, ultimately, the patients who benefit from more treatment options is the next step toward fully realizing the learning health care system.

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