SUMMARY OF PUBLIC COMMENT

A FRAMEWORK FOR REGULATORY USE OF REAL-WORLD EVIDENCE

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The Robert J. Margolis, MD, Center for Health Policy at Duke University is directed by Mark McClellan, MD, PhD, and brings together expertise from the Washington, DC policy community, Duke University, and Duke Health to address the most pressing issues in health policy.

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INTRODUCTION

In September 2017, the Duke-Margolis Center for Health Policy released "A Framework for Regulatory Use of Real-World Evidence," a white paper outlining considerations for stakeholders exploring the potential for regulatory applications of real-world evidence. The release coincided with a public workshop co-hosted by Duke-Margolis and the U.S. Food and Drug Administration, "Developing a Framework for Regulatory Use of Real-World Evidence," which was designed to explore the use of real-world data (RWD) and evidence (RWE) in drug development and regulatory decision-making. In order to give stakeholders the chance to provide comment on the white paper's concepts and framework, and to ensure a wide array of expert and organizational perspectives are included in its further refinement, Duke-Margolis opened a month-long informal comment period that closed on October 11, 2017. Comments were solicited via email at Margolis.RWE@Duke.edu.

Twenty responses were received from a variety of stakeholders across the biomedical community including industry representatives, academic researchers, providers, and regulators. This supplement aims to synthesize the comments received and lay out additional considerations for how the framework in the original white paper may be applied moving forward.

COMMENT SUMMARY

Comments on the paper spanned a wide range of topics. They can largely be categorized into four common areas:

- Continued work to clarify definitional issues underlying RWD and RWE concepts;
- Additional data and methods development challenges;
- Further engagement activities that would strengthen RWD and RWE approaches;
- The potential alignment of efforts to improve regulatory applications of RWD and RWE with their use to support other high priority health policy efforts.

What follows is a summary of these comments and additional observations on how to potentially address them moving forward.

DEFINITIONAL ISSUES AROUND KEY TERMINOLOGY

Through the Duke-Margolis white paper, publications authored by FDA, and work by other stakeholders there is an emerging consensus on standard definitions of real-world data and evidence and greater clarity around how regulators will use both terms within their framework and eventual guidance.* However, there continue to be

* The Duke-Margolis white paper defines 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 electronic health records (EHRs), administrative and claims data, observational studies, patient-generated data (e.g., in-home monitoring devices, wearable technologies), and in registries. It may also include data on contextual metrics, such as environmental exposures and socio-economic indicators. The paper defines 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.

questions surrounding certain subcategories of each term or additional nuance that may not be captured in baseline definitions. In some cases, this may reflect inconsistent use of the terms and their definitions because, by design, they are necessarily broad in order to apply to a variety of RWD and RWE sources.

Stakeholders requested further clarification around the distinctions between RWD and RWE, especially at the boundary between RWD "becoming" RWE. While the baseline definitions establish RWE as being the output of rigorous methods applied to sources of RWD, some questioned situations in which RWD may be used for an interim analysis or to inform another analysis – but not necessarily generate actionable RWE. If RWE is RWD analyzed through methods, is this an application of RWE?

Definitional challenges around RWD extend to a number of stakeholder comments that the term RWD itself would benefit from additional subdivision or clarification. As it stands, not only are there a number of sources of RWD (payer claims, electronic health records, mobile health technologies, patient generated health data, disease registries), but also different stages of processing the data for specific uses. For example, there is raw data output and then cleaned data that has been subjected to various logic checks and evaluated in terms of the availability and completeness of key data elements. This clean RWD is further processed into transformed data sets via normalization, imputation, and fitting to common data models and definitions. More complex, linked datasets or databases are then created for specific purposes, such as payer claims that have been enriched by clinical data from Electronic Health Records (EHRs). These all represent types of RWD and can be fit for a variety of purposes dependent upon the stakeholder's needs. To the extent that stakeholders continue to poorly characterize which data type or stage of processing they are referring to or wish to use when discussing RWD, however, confusion will remain.

There were similar comments about better clarifying the type and variety of study designs or methods that could be considered within the definition of pragmatic clinical trials. There is a great deal of literature related to degrees of pragmatism (e.g., PRECIS), how pragmatic clinical trials (PCTs) and large simple trials (LSTs) differ from traditional randomized controlled trials (RCTs), and the components of studies that maintain randomization in the clinical setting. However, the eventual utilization of PCTs within a RWE regulatory framework need to be more clearly established or defined due to differences in how stakeholders interpret the term.

Some stakeholders also commented on the definitions surrounding patient-generated health data (PGHD). These data are currently coming from a wide variety of sources (e.g., wearables, monitors, smartphone apps, social media, etc.) and are being generated via different means (e.g., passive sensing versus active patient input). Some commenters would appreciate further elucidation of whether all are considered PGHD within an RWE framework. Finally, commenters suggested additional consistency in how terminology related to efficacy and effectiveness are utilized in discussions around regulatory acceptability of RWE. Within biomedical research, efficacy is often used to describe a desirable outcome in the clinical trial setting, while effectiveness is often used to represent patient benefit and harm when the product is applied in a real-world setting. While these are not universal definitions, stakeholders may need to more clearly establish context and definitions within an RWE context.

DATA CHALLENGES

Commenters raised a number of topics related to the development, characterization, and use of RWD. For example, some felt that descriptions of RWD as "valid and reliable" would benefit from further elaboration of the underlying components that contribute to this description. This extended in some comments to further descriptive work on when RWD is "sufficient" to generate RWE, including a better understanding of any underlying power, sample size, endpoint, or exposure data considerations. Furthermore, one commenter raised questions

about whether or how availability of individual patient-level data may be a regulatory requirement for adjudicating when an RWD data source is appropriate for the research purpose at hand.

Still others suggested that the white paper did not include enough detail around processes that will be important when utilizing RWD, such as data curation, data integration from multiple sources, data linkages, and even data visualization. Along the same lines, some comments outlined the need for additional discussion about the impacts of missing data, particularly data that are missing systematically or fields that are missing as a result of the integration of multiple datasets. Multiple stakeholders felt that eventual guidance may be needed in these areas to assist industry.

One commenter raised important considerations that should be taken into account when discussing collection and use of RWD in pediatric settings. When considering RWD-enabled pediatric studies, stakeholders will need to ensure the availability of databases with adequate numbers of children that include critical developmental data elements such as birth date, birth weight, gestational age, and other variables. Linkages to parental and sibling data may be useful to explore, as well as to additional information within other care or educational settings.

Many commenters touched on the need for a more robust discussion of the various strengths and limitations of different sources of RWD. While the white paper highlights some limitations for each, especially in relation to EHRs, there are often useful data within these sources that go beyond data generated by a RCT and could be used to support a variety of RWE approaches. Similarly, commenters called for a more thorough characterization of when and where advantages could be found in registry or observational data.

OUTSTANDING METHODS QUESTIONS

The white paper laid out baseline methods considerations for generating RWE, and commenters raised a number of study design and process questions to be addressed. In particular, they called for establishing best practices for when and how to utilize a given analytical technique based on the study's underlying RWD. As sponsors make choices related to source RWD and study design or analytical method, it would be helpful to have additional recommendations for controlling for confounding variables, propensity score matching, endpoint identification, and other study characteristics that could ensure the RWE is sufficient for the regulatory application. Some commenters specifically called for additional work to be done in the PCT space in order to better understand how different study design elements could impact a PCT's overall acceptability for generating regulatory-grade evidence.

Additional comments related to the need for validation of endpoints used in non-RCT study designs. Because some approaches may rely on already-collected data (e.g., data from registries) and not pre-specified, prospective data capture, properly characterizing the differences between the intended study endpoints and more commonly used or well-understood endpoints from traditional RCTs will be essential to making progress.

Duke-Margolis has previously discussed stakeholder calls for additional research aimed at replicating results from RCTs in EHR and other sources of data through observational approaches. While many researchers are actively exploring this issue,[1,2,3,4] one commenter challenged stakeholders to better define how variation between RCTs and observational findings might be handled, and what an acceptable level of variation might be given the regulatory or clinical contexts at play.

Finally, commenters pointed out that there is a wealth of experience and literature in comparative effectiveness research (CER) that could greatly inform future discussions about the generation and regulatory acceptability of

RWE. Recommendations and guidelines from ISPOR, ISPE, and other organizations have outlined how to conduct robust CER and high-quality observational studies. These previous efforts should be utilized to identify remaining methods gaps for applying resultant RWE within regulatory contexts.

PATIENT ENGAGEMENT OPPORTUNITIES

In keeping with ongoing efforts across the health care ecosystem to move toward greater patient engagement, many commentators advocated for involving patients and caregivers at every stage of the RWE development process. It was pointed out that patients can be a true catalyst for change, and that adding their voice to discussions of regulatory acceptability will not only strengthen RWE-enabled decision-making, but ultimately help sponsors and regulators to better develop evidence and information that is truly meaningful for patients.

Commenters challenged researchers, sponsors, and regulators to bring patients to the table for discussions about RWE development. This includes patient input across a range of decisions related to data capture, data use, endpoint selection, and study design. Many felt that patients should be involved in early-stage pilot and demonstration projects in order to establish best practices for patient engagement prior to moving toward more systematic or widespread RWE efforts.

Questions about the ways in which patients understand and interact with RWE were threaded throughout comments and were the focus of a parallel white paper by the National Health Council (NHC).[5] The NHC's work pointed to a clear need for tools and capacity building within and among patient groups to support their engagement in RWE development and to ensure that there is a clear understanding of the strengths and limitations of RWD and RWE. If patient groups are unable to trust RWE, or if there are not adequate pathways for explaining downstream decisions that may be made because of RWE, many of these concepts for utilizing real-world data and evidence within broader contexts may not achieve patient buy-in or could collapse under privacy concerns.

INTERNATIONAL HARMONIZATION

As efforts progress for potentially utilizing RWE within the US FDA's regulatory framework, commenters pushed for stronger and earlier discussions with international regulatory bodies in order to lay the groundwork for eventual harmonization efforts. There are already projects in Europe, for example, focused on the use of RWD and RWE by the European Medicines Agency (EMA). The Innovative Medicines Initiative's (IMI) GetReal program has been actively exploring many of the same data and methods issues described in the Duke-Margolis white paper and other FDA statements about regulatory acceptability.[6] It may be helpful, therefore, to establish an engagement cluster between FDA and EMA that is focused more squarely on RWD and RWE, similar to other clusters that have been created on topics such as rare disease drug development and pharmacovigilance. Some commenters suggested the International Conference on Harmonization (ICH) as a potential home for greater coordination on a multi-national level.

The RWD challenges and the need for international collaboration also intersect when considering potential issues surrounding the eventual use of RWD that has been developed across many different countries and regulatory settings. The business of drug development and clinical research is increasingly global, and commenters pointed out that RWD and RWE discussions have not yet delved into the potential acceptability within a US context of RWD from non-US settings and populations. How FDA and US stakeholders grapple with such data considerations remains an open question.

ALIGNMENT WITH OTHER HEALTH POLICY EFFORTS

Stakeholders noted that the potential regulatory uses of RWD and RWE should not be explored in a vacuum, and that other areas of health policy that actively draw from sources of RWD and RWE could be important touch points for making progress. For example, the broad push by the US health care system to move toward value-based payment and contracting across a range of services and medical products has many of the same underlying data and methods challenges. If payments for a drug are to be based on achieving certain patient outcomes, for example, how should those outcomes be tracked and through what kind of RWD source? What meaningful endpoints or proxy measures are routinely captured in EHRs or registries that also could be used in a value-based payment decision? As payers, pharmacy benefit managers, and hospital systems work with sponsors to better understand the best practices for these types of value- or outcomes-based arrangements, there may be important lessons learned that could translate to discussions of regulatory use of RWD.

Similarly, some commenters linked improvements to the RWD and RWE development process to ongoing challenges pertaining to off-label communication. While this is currently a highly unsettled policy topic, the potential application of RWE to further refine or expand product labeling has important implications for how we understand off-label issues (i.e., RWE may enable more efficient movement of off-label uses onto the label itself, obviating some of the current challenges related to communication and scientific dissemination). Stakeholders will also need to grapple with how RWD is generated through off-label use, and the extent to which this may impact potential RWE studies pursued for regulatory purposes.

CONCLUSION

Throughout the public comment period, experts and organizations provided Duke-Margolis with valuable input and additional considerations that will help to further strengthen a framework for utilizing RWD and RWE within regulatory decision making. The Center looks forward to finding solutions to many of these challenges in the coming months and years as all stakeholders work toward the generation of better evidence, better treatments, and better patient care.

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