ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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March 9, 2022

Docket Number FDA-2021-D-1214

Dear FDA:

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to your consultation entitled **"Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry."**

ISPOR is a scientific and educational society with many of its members engaged in evaluating health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership living and working in 110 countries globally, across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government, and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

The response to this consultation was led by the Policy Outlook Committee of our most senior advisory body, the Health Science Policy Council. To engage our membership, we consulted with interested members of our Real-World Evidence Steering Committee, Institutional Council (i.e., industry and consulting), as well as our Real-World Evidence, Rare Disease, and Patient-Centered Special Interest Groups, and solicited our general membership for comments. The attached document provides both summary and line-by-line responses based on their comments. We hope they prove useful.

ISPOR would be happy to answer any questions about our response, and to participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Nancy S. Berg
CEO & Executive Director
ISPOR

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Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry; Availability.
FDA Draft Guidance for Industry

ISPOR Summary Comments, March 9, 2022

- **Overview**
  - We agree that there is a distinction between the requirements for Interventional Clinical Trials, Pragmatic Trials, and Interventional Clinical Trials that collect additional RWD from Non-interventional observational Clinical Studies and that the latter do need IND approval. However, if such studies collect additional RWD, consenting of patients and strict protection of patient information may be required.

  - The guidance does answer some important logistical questions for study sponsors with respect to study conduct and reporting requirements. FDA's expectations for public posting of study protocols and for study monitoring are appropriate. However, the lack of content on appropriate regulatory and clinical contexts of use, study designs, and analytical approaches limits the relevance of this guidance for some important considerations. For instance, sponsors need to understand how a non-interventional study can be 'adequate and well-controlled'. We trust that these areas will be addressed in other guidances.

- **Transparency Regarding Data Collection and Analysis**
  - We agree with the recommendations that a protocol and data analysis plan should be created prior to execution of a study as proposed in the joint ISPOR-ISPE taskforce good practice recommendations and transparency initiatives.[1] We also agree that consultation with the FDA for review and comment would be an important step in finalizing these documents and conducting analyses. In addition, any revisions to the protocol should be appropriately documented.

  - While clinicaltrials.gov and the ENCePP registry are the most established protocol registries, they tend to be most applicable to prospective observational studies and can be cumbersome to use for retrospective studies such as cohort studies. A collaboration between ISPOR, ISPE, Duke-Margolis and NPC has recently established the “RWE Registry” on the Center for Open Science’s registry platform, Open Science Forum.[2] It is located at https://osf.io/registries/rwe/discover. It is specifically designed to be fit-for-purpose for retrospective database studies, provides a registration number, date-stamping of revisions, and makes protocol characteristics available to the public, unless designated to be confidential for some specified period of time. We recommend that you review this as a registration option and consider including it in this guidance.

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[1] Berger ML, Sox H, Willke RJ, et al. Recommendations for Good Procedural Practices for Real World Data Studies of Treatment Effectiveness and/or Comparative Effectiveness Designed to Inform Healthcare Decisions: Report of the joint ISPOR-ISPE Special Task Force on Real World Evidence in Health Care Decision Making. Value in Health 2017; 20(8):1003-1008.
[2] Willke RJ, Wang SV. Registering Study Protocols: Helping RWE Come of Age. Value & Outcomes Spotlight. Nov/Dec 2021.

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- We suggest that the feasibility assessment be reported in a separate document (rather than included in the study protocol). This document could also describe the plan for database options and the criteria for selection. Clarification would be helpful on "all data sources accessed" as well as on the nature of audit trials for accessing data sets. During selection of an appropriate data source, sponsors may reach approach various data providers, some of whom would provide only a rough estimate for feasibility and would be screened out at an early stage. Does FDA expect documentation of those early explorations as well? Feasibility assessment vs reviewing outcome data prior to the SAP/protocol can be a fine line. Should the feasibility assessment and selection of appropriate data source be agreed with the FDA prior to the development of the study protocol? We suggest that FDA provide more detail on defining the feasibility work a priori, so it is clear what is being done in its entirety to ensure it does not cross over into the review of outcomes that should not be done in advance.

- **RWD Data Access**
  - The guidance states that "source data necessary to verify RWD are made available for inspection as applicable." It is unclear exactly what source data must be available for FDA inspection. Is the source data the database with full patient identifiers from which an anonymized analytic data set was ultimately derived? Is it the patient medical records? A sponsor usually does not have access to either. A data aggregator may not be permitted to routinely audit their data with the electronic health records of individual patients. We would note that for medical claims data, it is generally accepted that the anonymized claims level data are the source data.

- **Data Validation and Verification**
  - RWD is most often collected, aggregated and curated by third parties. We agree that transparency is required to ensure that data are valid and fit-for-purpose. Appropriate documentation should be provided to the FDA. It might be useful for the FDA to engage with sponsors and data curators to develop a publicly available list or database of prior successful validation methods and approaches that can be referenced for a variety of unique data sources.

  - As part of the PDUFA VII pilot program, the FDA should also consider sponsoring convenings on the topic of data quality to promote alignment between FDA, sponsors, and data curators on appropriate data quality benchmarks and standards. These convenings could discuss approaches for the validation and verification of key variables or data elements. Even this may require a renegotiation of agreements between data collectors, aggregators and health plans/providers. To the extent that it is feasible, a consensus among sponsors, database providers, and health providers about a risk-based approach will be important.

  - In addition, for data sources that might be used repeatedly, a special certification process that allows sponsors or data source owners to complete validation and verification processes for key data elements, followed by periodic reviews to ensure data standards are maintained, could be one approach to facilitate an efficient review process. This certification process would not only drive transparency around data quality and offer opportunities to reference prior validated work, but also create or maintain data

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processing efficiencies for evidence generation within critical timeframes. This recommendation contrasts with the proposed processes outlined in the draft guidance. Both this certification process recommendation and the validation approach database described in the previous section are potential approaches to avoid the need to start from scratch each time validation or verification is required. Absent a certification process, it should still be possible for sponsors to leverage prior validation and verification work on a given data source (supplementing with new work as necessary). The ability to build on prior high-quality work where appropriate will help make processes more efficient.

- **Missing Data**
  - The guidance states that "the protocol and the statistical analysis plan should be developed and based on an understanding of reasons for the presence and absence of information. Descriptive analyses should be included to characterize the missing data." Additional clarification from FDA on what the agency would like to see in these descriptive analyses and what are considered acceptable analytic approaches to address missing data.

- **Safety reporting**
  - It would be helpful if FDA clarified whether this guidance applies specifically to non-interventional studies intended to provide primary or supportive evidence of the safety and effectiveness of marketed drugs for new or expanded indications and does not apply to studies that examine a disease state to understand unmet medical need or disease progression.

  - Frequently, the databases from which analytical data sets are derived have been anonymized and some databases do not contain adverse event data. In these cases, sponsors do not have access to information necessary to identify and report adverse events. The FDA should clarify that they are not recommending that sponsors seek the requisite additional data to identify adverse events.

ISPOR Detailed Comments

General. Overall, the draft guidance is well written and reasonable even if some additional detail would be desirable (as reflected in our comments below). In addition, as a somewhat overarching FDA guidance document, it touches on a few topics that are addressed in more detail in other FDA guidance documents. It would be helpful to reference those other FDA guidance documents where applicable.

General. The guidance does answer some important logistical questions for study sponsors with respect to study conduct and reporting requirements. FDA's expectations for public posting of study protocols and for study monitoring are appropriate. However, the lack of content on appropriate regulatory and clinical contexts of use, study designs, and analytical approaches limits the relevance of this guidance for some important considerations. For instance, sponsors need to understand how a non-interventional study can be 'adequate and well-controlled'. This concept has been referenced in a recent approval (Prograf) but absent from the draft guidance documents. We trust that these areas will be addressed in other guidances.

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General. From an industry sponsor perspective, the most problematic aspect of this draft guidance is the lack of clarity and explicit flexibility in FDA's expectation for access to "source data," as it is commonly the case that the industry sponsor neither owns nor has direct access to the "source data" in non-interventional studies. Source data is a particularly relevant issue in the rare and orphan disease setting where there is additional risk of re-identification of patients. It would be helpful for the guidance to recognize this concern by stating that sponsors should consult with the relevant review division to discuss other acceptable approaches in such circumstances.

32-36, We would suggest recognizing that digital clinical data or evidence (diagnostic and/or patient monitoring wearables), as well as artificial intelligence-related data, are emerging considerations here, and incorporating wording related to them into the RWD/RWE statements if appropriate.

38-44, The definition of "clinical study" in footnote 6 seems to include safety signal detection and monitoring, suggesting that these activities would be in scope for this guidance. However, many of the guidance recommendations would not be applicable or realistic for these activities. Please clarify that safety signal detection and near real time safety monitoring are out of scope.

93-97, FDA recognizes the use of RWD as control arms in interventional studies and the corresponding applicability of Part 312, but does not make it clear whether any of section B of this guidance applies to these control arms.

93-97, Consider adding clinical trials with a synthetic control arm as an example so it is clear where these studies fall in the dichotomy of interventional vs non-interventional.

99, How would a non-interventional study that also includes the use of marketed drugs administered in routine clinical practice outside the licensed indication be classified?

105, 141-148, Eventually, it would be good to have the forthcoming FDA guidance on RWD study protocols and SAP linked here

120-125, We would suggest considering the mention of linkages as a way to collect additional data (e.g., linking health care data to the National Death Index) here as well. This recommendation also applies to health care data-only studies. This could link to the final guidance on Assessing EHR and Claims Data to Support Regulatory Decision Making for Drug and Biological Products.

127, It would also be useful to provide some common data privacy considerations for imaging, lab tests, etc., as mentioned in the previous paragraph.

136, Is there an RWE expert group at FDA to consult with under certain circumstances, as opposed to a Type C meeting with the appropriate review division? For example, it may be useful to have a discussion in early R&D stages especially when RWD is being considered for

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several molecules in a similar disease area.

132-177, Transparency section. It would be helpful if FDA clarified whether this section applies to any non-interventional study intended to support a marketing application (e.g., disease state study to demonstrate unmet need) or whether it is intended to cover studies investigating the drug or a comparator to provide primary or supportive evidence for the marketing application. Can FDA please clarify whether they are recommending that sponsors seek additional data (e.g. via chart review) to identify adverse events?

147, Recommending that "any" revisions to the protocol be date-stamped seems overly broad and could be onerous. Please clarify what level of revisions to the protocol would warrant a new date-stamp.

150-167, We suggest that the feasibility assessment be reported in a separate document (rather than included in the study protocol). This document could also describe the plan for database options and the criteria for selection. Clarification would be helpful on "all data sources accessed". During selection of an appropriate data source, sponsors may reach out to many data providers, some of whom would provide only a rough estimate for feasibility and would be screened out at an early stage. Does FDA expect documentation of those early explorations as well? Feasibility assessment vs reviewing outcome data prior to the SAP/protocol can be a fine line. Suggest that FDA provide more detail on defining the feasibility work a priori, so it is clear what is being done in its entirety to ensure it does not cross over into the review of outcomes that should not be done in advance.

150-167, Further to the previous comment, while we understand and appreciate the need for regulatory confidence that a non-interventional study was not designed, and particular data sources were not selected, to achieve a predetermined conclusion, an expectation to describe in the protocol "all" data sources accessed during the study design phase can be overly burdensome. It is unclear what level of detail is needed in the protocol to describe data sources and what is the benefit and relevance of describing all feasibility evaluations or exploratory analyses of every data source. Please limit the information included in the protocol to what is necessary and clarify why information on every data source accessed and the results of all feasibility evaluations and analyses should be included in the protocol.

150-167, Also on this same point - due to widespread access to some datasets combined with communication, intentional or unintentional, about findings between analysts and researchers, these requirements could result in optimal data sources being considered ineligible for some studies. Some finer guardrails and possibly creative solutions may need to be considered.

174-177, While clinicaltrials.gov and the ENCePP registry are the most established protocol registries, they tend to be most applicable to prospective observational studies and can be cumbersome to use for retrospective studies such as cohort studies. A collaboration between

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183-192, It is unclear what "patient-level data" a sponsor should be able to submit or provide (or arrange to submit or provide) to FDA for RWD that have been analyzed as part of a clinical study. Does "patient-level data" in this context refer to the anonymized patient-level analytic files, or something more (e.g., patient medical records)? A sponsor might not have access to patient-level data beyond what is in the anonymized analytic file. Please clarify the meaning and scope of "patient-level data" in this context.

188- 191, This is generally beyond what data vendors currently provide and would become a new deliverable for them. There is little incentive for vendors to share their data accrual, creation and transformation processes as this could raise and highlight other potential challenges with their approach and systems that will have implications beyond any individual study. These few lines have major implications for data vendors as well as sponsors and much more attention will be needed to define and enable compliance with them.

201-202, In order for this to work well, a standard process would need to be required of each vendor in general instead of for individual studies.

213-231, This section seems to imply that all records from subjects included in the study should be screened for adverse events. In an extreme situation, it would mean that all events reported after exposure and until the end of the individual eligibility period should be submitted as Individual Case Safety Reports (ICSR). Generally these events cannot be traced back to identifiable individuals for additional information that may be needed for safety reporting. Please clarify what is considered an adverse event in the context of non-interventional studies and what should be submitted to FDA.

292, We suggest saying "similar or same time period" instead of just same time period. That is the definition FDA commonly uses.

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