

**2021–2022
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Docket Number FDA-2021-D-1146

President-ElectJan Elias Hansen, PhD
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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 “**Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products.**”

Past PresidentJens Grueger, PhD
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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.

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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
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Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products. *FDA Draft Guidance for Industry*

ISPOR Summary Comments

- **Overview**

- This draft guidance discusses key considerations in using registry data for regulatory purposes that will be most helpful for sponsors, researchers, patients, and other stakeholders. We agree with the importance of the primary points here and with the general direction of the guidance but do seek greater clarity on some specifics.
- Clearer definitions, particularly regarding demonstration of reliability and a delineation between registry data types, with substantive differences, would be of great benefit. These considerations are essential for sponsors planning to include registry data in their studies.
- Existing documents such as the AHRQ User's Guide that provide detailed information on registries and pertinent topics, including linkage with registry data, would be relevant to cite in this guidance to direct sponsors to helpful information sources.

- **Relevance and Reliability**

- A more significant discussion of both the limitations and the strengths of registry data would enhance the usefulness of this document. For example, registries are often an important source of information about rare diseases. On the other hand, data heterogeneity and, in general, the lack of data validation are known limitations.
- We encourage FDA to amend their comments regarding registries being better suited for objective endpoints. The collection of patient-reported outcomes (PROs) represents a potential advantage for registries, so we believe that PROs should be included in a list of examples of possible data types to include in registries. The comments regarding pain's subjectivity compared to death or hospitalization are general rather than registry-specific. If the implicit concern is that unblinded treatment makes subjective endpoints more prone to bias, it would be helpful to be more explicit about that.
- We agree with the importance placed on standardized measurement. Examples regarding this, particularly with respect to PRO data, would be helpful.
- Since registries are especially relevant for rare diseases, we encourage the FDA to discuss rare diseases' considerations in more detail.
- Clarification regarding the demonstration of the reliability of registry data would be very beneficial. This includes providing a definition of what might be construed "appropriate" policies and procedures" and expectations regarding the documentation and sharing of these procedures with the FDA. Furthermore, expectations regarding validation in situations when industry sponsors may not own the data should be clarified.
- A clearer definition of source data would be beneficial. Furthermore, the FDA's requirements about confirming source data would be helpful, and such requirements should consider situations when this may be infeasible.

- **Data linkage and integration**

- The AHRQ's comprehensive guide to registries is a very beneficial document, and it should be cited in this guidance. The document discusses the legal and technical feasibility of linking registry data.
- Sponsors should include a plan for addressing the adequacy of data linkage, including the standard approach for data linkage and documentation of deviation from the plan. We encourage reference to the AHRQ's user guide for information on this topic.

- **Registry definitions**
 - The guidance document would be improved if existing registries and purpose-built registries or registry-based studies were differentiated due to substantive differences, including requirements for consent and the ability to design core data elements rather than evaluating the fitness of existing elements for a study.
 - The type of registry (i.e., existing or purpose-built) may also have implications for the sponsor's ability to provide data to the FDA and sponsor ability to affect registry operations. Furthermore, the statement regarding procedures enabling FDA and "persons interested in using the registry's data" is overly broad and may be infeasible in some cases due to privacy legislation. We recommend that this statement be deleted.
- **Regulatory considerations**
 - Clarification regarding the acceptability of global data in registries for informing regulatory decision-making would be helpful.
 - The consent statement should be modified to acknowledge that not all registries are subject to consent requirements in a limited number of cases where this is legally permissible. Examples include the anti-retroviral pregnancy registry or population-based cancer registries where cancer is a legally reportable condition.

ISPOR Detailed Comments

- **General section comments**
 - General, AHRQ has a very comprehensive guide for "design, implementation, analysis, interpretation, and quality evaluation of registries created to increase understanding of patient outcomes." It systematically addresses topics raised in this FDA guidance and additional ones that FDA may want to incorporate. Wherever possible, we suggest aligning the two documents and referencing the AHRQ guide. Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. 16, Linking Registry Data With Other Data Sources To Support New Studies. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK208613/>.
 - General, It would be helpful for the guidance to differentiate between a "registry" and a "registry-based study" (as the EMA guidance on registry-based studies does). A registry usually has more general objectives and a data collection approach that is open-ended, while a registry-based study generally will have objectives separate from the original registry and bespoke design and analytic elements. This matters because there will be some nuances depending on whether it is a registry or registry-based study, e.g., consent, approvals, ability to design core data elements versus assessing whether existing registry core data elements are fit-for-purpose for a specific study. * Most industry-sponsored studies utilize existing registries rather than purpose-built de novo registries. The draft guidance seems to assume that industry sponsors have more influence and capacity to shape the operations of existing registries than they actually have.
 - General, It would also be helpful to introduce a time line/flow chart of key steps outlined in the guidance document as one reviews registry design, execution and data use.
 - 26-30, Clarity is needed on the definition of "sponsor" for when the industry marketing authorization holder (MAH) is not the sole sponsor of the registry. Some expectations in the draft guidance may be

- more suited to the owner of the registry than the MAH. We ask that FDA clarify terms when the industry MAH is not the sole sponsor of the study.
- 43-52, Clarity is needed on the acceptance of data from a global registry or a registry representing specific geographic regions beyond the United States. This is particularly important for rare diseases or outcomes. Please clarify that data from global registries and geographic-specific regions may be acceptable to support regulatory decisions (with the understanding that, as with other aspects of working with registries, a sponsor should discuss this with FDA).
 - 77-78, There is no mention here (although there is later, eg, l. 142) of direct input from patients, such as PRO data, as a supplement to registry data. Also, many registries are patient-led – should this be referenced?
 - 117-122, There are some reasons why using existing registries may be a better approach. For example, for many diseases, there is a limited pool of available patients, with academics, vendors, and sponsors all competing to enroll them. Moreover, industry-sponsored registries can experience challenges with enrollment and fail to enroll sufficient number of patients to answer the research question. The EMA’s Patient Registries Initiative and efforts to use existing registries when appropriate could be referenced here: [Patient registries | European Medicines Agency \(europa.eu\)](#)
 - 127-154, It may be worth mentioning upfront that, as a common limitation, lack validation is a key consideration for suitability within a regulatory context. Another limitation worth mentioning is the complexity of privacy issues in some situations.
 - 152, We suggest that FDA acknowledge that a strength of using registries is the ability to collect data about a sufficient number of patients, especially when studying rare diseases or rare outcomes, and that data heterogeneity may be inherent in these circumstances and may be an acceptable limitation.
 - 156-164, Another strength worth mentioning explicitly is that registries are often an essential data source for rare diseases.
 - 156-159, “In general, registries are better suited as a data source for regulatory purposes when sponsors aim to capture objective endpoints, such as death or hospitalization. Subjective endpoints, such as pain, can be collected in a registry, but additional challenges are involved to standardize such measurements.” Comment: The statement is too general and not specific to registries; it is a comment about data objectiveness rather than the suitability of a registry to help answer a specific question. If the implicit concern is that the unblinded treatment in a registry makes subjective endpoints more prone to bias, it would be helpful to be more explicit about that.
 - 156-158, Since rare disease registries may not be developed with one objective in mind, death is not always objectively collected in registries. Sometimes patients are lost to follow up or transition from pediatric care to adult care, and clinicians do not always know if they are still alive. This endpoint is particularly hard to track in rare diseases.
 - 157-159, The guidance uses pain measurement as an example of a subjective endpoint with challenges to collect standardized measurements – are there additional details regarding standardized measurements for this example? If patient reported pain is captured from all patients using a 0-10 NRS at regular intervals, would this be considered standardized (realizing, of course, the potential for missing data)? It is also important to note that while objective measures may be easier to capture, it is very important to measure endpoints that are meaningful to patients, which are likely to involve subjective measurements.
 - 159-163, The reference to study design may merit a broader reference to a framework for the design and execution of RWE studies (such as the FDA’s framework mentioned in footnote 4). Ultimately, sponsors will be in a better position to evaluate the relevance and reliability of RWD in the context of such framework. This would improve the research quality and evidence quality.

- 161-164, As an aside, registry data should generally not be used if the data could be reasonably collected in the pivotal study. As the document alludes to, registry data should be discussed in advance of the trial being locked down. Registry data used with the aim of addressing data uncertainties as a result of a poorly designed registration trial should be considered only in specific circumstances.
- 173-259, The guidance in general does not focus on the nuances/challenges inherent of rare diseases and does not provide guidance on these considerations. It would be helpful to note and account for these factors:
 - Disease heterogeneity, mutation sub-types, misdiagnosis, lack of understanding of prognostic factors, lack of definition of progression and response, importance of disease stabilization vs. deterioration, heterogeneity in outcomes measures, insufficient specific coding system, differences in the use and definition of standard of care, lack of validated PRO instruments, access to care etc.
- 173-259, Considerations for pediatric registries, e.g., consent and data collection issues, should be addressed.
- 175-178, The purpose of any registry and particularly rare disease registries should be made clear from the beginning. This can help ensure that information on prevalence, clinical course of disease, prognostic subgroups and relevance of surrogate endpoints (when collected) or other outcome measures is captured fully and completely. The sponsor should also consider how any data will be analyzed and processed in advance, taking account of the difficulties in rare diseases and ensuring the SAP is fit for purpose. Accessibility of the data to patients should also be considered.
- 175-178, Registry developers should demonstrate they have considered if there are existing rare disease registries to build upon instead of developing a treatment specific one – an existing registry will build on knowledge already secured and provide a stronger foundation to demonstrate treatment effect.
- 180-184, It may be helpful to recognize that in ultra-rare diseases where RCTs are not viable, a rare disease registry could be used as a control arm or historical control to inform trials and further research.
- 180-187, Sponsors should carefully consider the data elements captured by the registry and report rationale for use in review of registries being used prior to engagement.
- 183-184, Registries utilized to inform trials should capture reasons when patients choose not to continue on therapy if patient has opted out of trial or other treatment option. This is particularly relevant in rare diseases – especially if another trial becomes available.
- 183-184, For rare disease registries the identification of relevant endpoints and the use as a data source for the design of a therapeutic clinical trial are two ways a registry can support the identification of an appropriate sample for epidemiological and/or clinical research.
- 186-187, Sponsors should work with registry owners to support retention of participants where possible - particularly relevant in rare diseases where patient numbers are low - taking account of factors that will enable patients to participate. Sponsors should develop a plan to reduce loss to follow-up of registry participants but if it's an existing registry not run or coordinated by the sponsor then it may be difficult for sponsors to implement such a plan.
- 191, This section would be more comprehensive if the importance of complete data elements and efforts to maximize complete data elements were also emphasized here. Consider adding “and recruitment and retention where relevant” after patient selection.
- 192-194, The inclusion and exclusion criteria used to enter patients into a registry are influenced by the research question. But the recommendations on the design and execution of RWE studies are outside the scope of this guidance. It might be beneficial to either focus exclusively on the data quality, relevance and reliability (governance, data quality, curation, consent) or expand this guidance to cover the design and execution of RWE studies.

- 198-202, Some registries may be exempt from consent requirements and provisions should be allowed for these instances. For example, it is our understanding that the anti-retroviral pregnancy registry is exempt from obtaining consent. Please clarify and acknowledge that some registries may be exempt from informed consent requirements where permitted by law.
- 207, FDA should consider calling out socioeconomic status under patient demographics, which may impact not only health but adherence to the program and be very valuable in informing future trials/patient care.
- 224, Adherence should be recorded in a registry where possible.
- 238-239, Quality of life measures should include patient-relevant and disease-specific as well as non-disease-specific measures.
- 243-258, “Pregnancy-related information” – is there a compelling reason for including this detailed information, when the guidance is supposed to cover many disease situations and outcomes?
- 260-360, The section on reliability of registry data is comprehensive including advice on process and procedures, human protection and data privacy, data collection and management. One point that is missing throughout this section is the distinction between primary and secondary data collection and any issues between retrospective and prospective data collection and handling. For example, in terms of defined process and procedures, if the data are already collected for another/prior purpose, sponsors will have very little ability to influence versus de novo data collection for a specified research question. This is especially salient in areas (like rare disease) where sponsors need to work with existing data sources. These distinctions should be enumerated in each section.
- 274, Is it possible to discuss introducing a level of blinding such that the individual recording the information for the registry is blind to the intended use and so cannot bias the data towards an outcome?
- 274-276, Source data can vary based on data collection methodology. For example, if a patient-reported outcome or HCP-reported outcome is entered directly into an electronic data collection system, the source data would be difficult to confirm (i.e., no medical chart notes). Similarly, de-identified data abstracted from an electronic medical record would also be difficult to confirm. Please clarify what is required for “confirming” source data and consider situations when this might not be possible.
- 290, An important aspect is how to obtain permission to share patient level data with the FDA. Sponsor or registry holders should incorporate this element into the reliability aspect of their registry. This also means that sites, ie, registry holders, should be willing to accept an audit from the agency. This aspect is critical for regulatory use of registry data.
- 306-313, The data dictionary should also include reasons for missingness if the data could not be collected.
- 320-322, It is unclear what FDA considers to be “appropriate policies and procedures.” Expectations for validating electronic health care systems (e.g., validating hospital EMR data) are also unclear and might not be feasible for industry sponsors in any case. Please: (1) Clarify expectations for “appropriate policies and procedures” and if these policies and procedures are expected to be documented and shared. (2) Delete the recommendation to “validat[e] electronic systems” or at least clarify expectations for when the industry sponsor does not own the data.
- 322-326, Under the HIPAA privacy rule, access to registry could be restricted to FDA and the industry sponsor on an absolutely “as needed” basis. Therefore, the reference to “and persons interested in using the registry’s data” is overly broad and vague. Please consider changing “interesting in using” to “authorized to use.”

- 322-326, This sentence is unclear. Does that mean that FDA should have the authority to modify and transform the primary data source? Or be allowed to modify the content and address errors once data are submitted to the agency? Or simply have an opportunity to provide feedback to the registry holders?
- 322-326, It would be helpful for the FDA to bring in an actual quality scale assessment for data to enable provision as objective a rating of data quality as possible.
- 362-419, While a good outline and recommendations with respect to registry data linkage have been provided in this draft guidance, the agency needs to clarify the depth of details that it would require in terms of data linkage process as there can be some data tokenization methods that are proprietary and certain stakeholders may have reservations in sharing them.
- 362-419, Reconsenting the registry participants either post data collection initiation or post data collection completion can be challenging. The agency should also comment on its viewpoint regarding reconsenting the registry participants in these situations.
- 362-419, There is published guidance from AHRQ on the legal and technical feasibility of linking registry data with other sources. This is worth mentioning and/or referencing. The technical and legal feasibility should be considered in appropriateness. In addition to a plan for addressing the adequacy of the linkages, the plan should include the standard approach for linking databases (see five key components for identifying matching pairs of records across two databases in AHRQ User Guide) or where the plan deviated.
- 362-419, Individual level data -- Comment: Individual level data may be owned by a third party and not available to the industry sponsor for submission. Also, when the data come from a registry, it is unclear how FDA's expectations might vary depending on if (A) the industry sponsor is the sole sponsor, (B) it is a multi-stakeholder sponsored registry, or (C) the data are owned by an external party. Please clarify expectations for individual level data when the data come from a registry under three different scenarios: (A) the industry sponsor is the sole sponsor, (B) it is a multi-stakeholder sponsored registry, and (C) the data are owned by an external party. * Data dictionary -- Comment: If the industry MAH does not own the data or the registry is linked to a second data source, it is unclear what is an acceptable level of detail in the data dictionary. Data sources may have different levels of detail, and the industry MAH might not have the ability to mandate certain data standards (e.g., National Death Index). In these cases, the industry MAH can link the data but cannot guarantee similar data standards. Ask: Clarify what is an acceptable level of detail in a data dictionary and acknowledge that the level of detail may vary based on the source of registry data.
- 374, Linking other data and registries particularly internationally may be an important consideration for rare diseases due to the lack of evidence and data available. Sponsors should document from where the linkage was made and contextualize any differences.
- 374, Acknowledge that in rare disease registries the linking of stakeholder interests may create conflicts of interest for rare disease registries. Regulators should be aware and develop guiding principles to address and overcome these. These partnerships can be a powerful agent in the success of understanding natural history, product in development or evaluation.
- 378-379, The main concern with data linkage is the ability to identify patients. In certain instances, particularly in rare diseases, only a handful of patients have the same diagnosis, same age, and similar disease progression status in a given geographic area.
- 391, Should be made available to patients to bring with them into other registries/trials
- 421-445, The requirement that all patient-level data can be provided to FDA may result in the inability to use or create the optimal registry. In such instances, creative solutions (e.g., aggregate data to FDA or federated queries) should be considered.

- 441-445, This last paragraph is critical for the reliability aspect of registry, but not even discussed in the relevant section of this guidance.
- 443-444, Whether or not this is an absolute requirement that data be made available to FDA by a 3rd party may depend on the purpose of the registry in the study. For example, it may be appropriate to require this for a registry being used as an external control arm compared to using a registry to inform the selection of endpoints for a trial.
- 446-500, A definition of data quality and of data cleaning may be useful

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