REGULATORY CONSIDERATIONS FOR USING PATIENT REGISTRIES

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NATIONAL ACADEMIES Sciences Engineering Medicine

OUR MISSION at NORD

We improve the health and well-being of people with rare diseases by driving advances in care, research, and policy.

OUTLINE

- Definition of a “Registry”
- NORD’s “IAMRARE” Patient Registry and Natural History Study Platform and Program
- Key Guidance Documents and other References
- 2023 FDA Guidance
- 2021 EMA Guideline
- Challenges and Opportunities: Some Examples
- Lessons Learned?

DEFINITION OF A "REGISTRY"

– According the 2018 Framework for FDA's Real-World Evidence Program[1] –

"A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves one or more predetermined scientific, clinical, or policy purposes. Registries are generally defined either by diagnosis of a disease (disease registry) or usage of a drug, device, or other treatment (exposure registry)."

Note: The EMA uses a very similar definition, and parts of this shared definition are derived / cited from prior AHRQ[2] and CITTI[3] recommendation documents.

NORD'S "IAMRARE" REGISTRY PROGRAM

- Developed to empower patient advocacy groups to build patient registries and collect patient/caregiver-reported natural history data on their diseases
- Proprietary, secure, mobile-friendly, online data collection platform, developed by NORD
- First study launched in 2014, with support from FDA
- IAMRARE core data dictionary includes validated assessments and other standardized data elements
- Each IAMRARE registry is also includes surveys customized for its patient advocacy group (PAG)
- Now includes ~50 registry studies and data on ~18,000 patients representing ~75 rare diseases

What Others Are Saying

"Our IAMRARE registry currently contains seven surveys, 2,000 registered users and became the anchor of PDSA's research program." - Caroline Kruse, President & CEO, Platelet Disorder Support Association (PDSA)

KEY GUIDANCE DOCUMENTS / REFERENCES

FDA (US):	**Framework for FDA's Real-World Evidence Program (Dec 2018)[1]**
	Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry (Final - Dec 2023)[4]
EMA (EU):	**Guideline on Registry-Based Studies (Final – Sep 2021)[5]**
	Contribution of patient registries to regulatory decision making on rare diseases medicinal products in Europe. 2022. (Journal article by 4 EMA authors)[6]
ARHQ (US):	**Registries for Evaluating Patient Outcomes: A User's Guide. (4 editions 2007-2020). 4th ed. (426 pages)[2]**

2023 FDA GUIDANCE (Part 1: Scope)

"Real World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry"[1]

- Considerations for design a new registry or use of existing registry to support regulatory decisions
- Does not provide recommendations on statistical methods used to analyze data from registries
- Rather, focuses what attributes make registry data **relevant** and **reliable**
- "Registry data can be used to inform the design and support the conduct of either interventional studies (clinical trials) or non-interventional (observational) studies." Examples include:
  - —Characterizing the natural history of a disease
  - —Providing information to help determine study sample size, selection criteria, and trial endpoints
  - —Identifying biomarkers or clinical characteristics relevant to designing clinical studies or trials
  - —Supporting inferences about safety and effectiveness (e.g., when including registry data as an external control for an interventional trial[7])
  - —Evaluating a drug received during routine medical practice (e.g., to evaluate clinical outcomes in populations underrepresented in clinical trials

2023 FDA GUIDANCE (Part 2: Some key points)

A. Using Registry Data to Support Regulatory Decisions

- Sponsors should consult with the appropriate FDA review division regarding the appropriateness of using a specific registry (whether newly designed registry or a pre-existing one) before conducting the {related} study
- For regulatory purposes, "registries are generally better suited… to capture objective data."[8]
- **Relevance** includes the availability of data for key study variables (exposures, outcomes, covariants) and sufficient sample size; **Reliability** includes accuracy, completeness & traceability.

B. Relevance of Registry Data

- The specific data elements that should be captured depend on the sponsor's intended use (e.g., more data elements are required for an external control than to identify participants for a trial)

C. Reliability of Registry Data

- Whether new or pre-existing, to be used registries must have procedures to support Reliability
- Registries should use data standards;[9] and Sponsors should have access to registry metadata[10]

D. Considerations When Linking a Registry to Another Registry or Another Data System

- When linking to another data source/system, consider the impact on overall data integrity; procedures should be used to account for missing or redundant data, and for secure data transfer

E. Considerations for Regulatory Review

- Before conducting a study using registry data, sponsors should submit protocols & statistical analysis plans; and should ensure FDA access to appropriate patient-level data, metadata, and source records

2021 EMA GUIDANCE (additional items vs FDA)

"Guideline on Registry-Based Studies"[5]

Scope: "To provide recommendations on key methodological aspects that are specific to the use of patient registries by marketing authorisation applicants and holders planning to conduct registry-based studies."

- More clearly distinguishes a 'Registry-Based Study' from a 'Registry'
- A **product registry** when used by MAAs/MAHs to evaluate use, safety, or effectiveness "typically falls outside of normal routine follow-up of patients and therefore corresponds to a **clinical trial** or **non-interventional study** in the targeted population. It is therefore preferable to avoid using the term 'product registry' in this situation."
- **Registry-based randomized trial (RRCT)** definition: Randomized trial embedded in the data collection infrastructure of one or several registries (e.g., for randomization, data collection, and/or follow-up).
- "Open questions remain regarding the validity and relevance of RRCTs.[11,12] It is therefore recommended to obtain Scientific Advice from EMA and, where applicable, from the concerned NCAs, health technology assessment (HTA) bodies and health insurance schemes as payers on the acceptability of the chosen approach for evidence generation in case deviations from a traditional randomised clinical trial (RCT) design are considered"
- A detailed table of Legal/Regulatory Requirements table
- An annex of Registry design considerations
- Registry checklist & link to **REQueST** Registry Evaluation and Quality Standard Tool (developed by EUnetHTA)[13]

My Reflections

- Challenges and Opportunities: Some Examples

- Lessons Learned

REFERENCES (part 1)

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4. In Dec 2023, FDA issued the guidance: Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-registries-support-regulatory-decision-making-drug-and-biological-products
5. In Sep 2021, EMA (CHMP) adopted as final its: Guideline on registry-based studies. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf
6. Jonker CJ, Bakker E, Kurz X and Plueschke K (2022). Contribution of patient registries to regulatory decision making on rare diseases medicinal products in Europe. Front. Pharmacol. 13:924648.
7. For additional discussion on the use of external controls, see the draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023). When final, this guidance will represent FDA's current thinking on this topic. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

REFERENCES (part 2)

8. For additional discussion on how FDA reviews patient-reported outcome instruments, see the guidance Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (December 2009). This guidance will be replaced by a series of guidances on patient-focused drug development (PFDD) when those PFDD guidances are finalized. For additional information, see https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical
9. See FDA's Study Data Standards Resources web page, available at: https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm and the Dec 2023 final guidance: Data Standards for Drug and Biological Product Submissions Containing Real-World Data https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-drug-and-biological-product-submissions-containing-real-world-data
10. For additional discussion of metadata, see the draft guidance Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers (March 2023). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-systems-electronic-records-and-electronic-signatures-clinical-investigations-questions
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