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Natural History Studies and Registries in the Development of Rare Disease Treatments

Key Takeaways

What Are Registries and Natural History Studies?

Dominique Pichard, MD, MS, National Center for Advancing Translational Sciences, NIH

- **Natural history of a disease:** the course a disease takes in the absence of intervention in individuals with the disease, from disease onset until either the disease's resolution or death.
- **Natural history study:** a preplanned observational study intended to track the course of a disease over time.
- **Registry:** a collection of information about a specified group of people
    - Example: contact registry, disease registry, population registry
- Examples of different types of registries include disease specific registries (e.g., Rett Syndrome Registry, CDC's National Amyotrophic Lateral Sclerosis Registry) and larger multi-disease registries (e.g., National Cancer Institute's Surveillance, Epidemiology, and End Results Program)

Why Registries and Natural History Studies are Critical to Rare Disease Treatment Development

Kerry Jo Lee, MD, Center for Drug Evaluation and Research, FDA

- Common challenges faced in rare disease drug development include:
    - Natural history is often poorly understood
    - Diseases are progressive, serious, life-limiting and often lack adequate approved therapies – urgent unmet medical needs, many have pediatric onset
    - Small populations often restrict study design options
    - Phenotypic and genotypic diversity within a disorder
    - Development programs often lack solid translational background
    - Drug development tools –well-defined outcome measures and biomarkers- often lacking
    - Lack of precedent, including clinically meaningful endpoints, for drug development in many rare diseases

Getting Started: Developing Registries & Designing Natural History Studies

Leslie Gordon, MD, PhD, The Progeria Research Foundation
Elieen King, PhD, Cincinnati Children's Hospital Medical Center
Michael Wagner, PhD, Cincinnati Children's Hospital Medical Center
Kristen Wheeden, MBA, United Porphyrias Association

Keys to successful collaboration include

1) defining clear roles and responsibilities,
2) open communication,
3) transparency among stakeholders, and
4) recognizing the value of patient advocacy groups

Data collection

Data should be collected and managed using systems, processes, and procedures that ensure high quality data

- Always assume your data will be used to support drug approval so utilize a data collection platform like REDCap (Research Electronic Data Capture) or a similar database system
- Safeguard your source data as raw data will be useful many times over

Data sharing

Data sharing with the general research community maximizes its value for clinical trial readiness and approval of treatments

"Patient families are passionate partners. We can't do it without them. They can't do it without us. It is a partnership."

-Leslie Gordon

"Stakeholder engagement … is absolutely critical. You need to understand your key stakeholders and engage them all early and often throughout a patient registry process."

-Kristen Wheeden

Addressing Challenges in Registry and Natural History Data Collection

Benjamin Forred, MBA, ACRP-CP, Sanford Research
Zohreh Talebizadeh, PhD, Global Genes
Reactor Panel
Henry Kaminski, MD, George Washington University
Suzanne Pattee, Office of the Commissioner, FDA
Dominique Pichard, MD, MS, National Center for Advancing Translational Sciences, NIH

Examples of data collection and rare disease registries

- CoRDS: CoRDs is a patient registry for all rare diseases, unaffected carriers and the undiagnosed – it ties together patients, advocacy groups, and researchers
    - CoRDS is made available at no cost to patients, advocacy groups, and researchers
- RARE-X: RARE-X is a program of Global Genes to accelerate rare disease research and treatments by removing barriers for data collection and sharing.
    - To date, RARE-X has attracted approximately 7,700 participants, representing 67 disease communities and 106 patient advocacy groups from almost 90 countries.

Data interoperability

- Balancing data interoperability in rare diseases involves the utilization of common data elements for standardization while incorporating condition-specific questions and adopting a flexible, iterative approach to ensure relevance and comprehensiveness.

Informed consent

"… the consent form and the consent process [are] nothing if [they're] not approachable."
– Benjamin Forred

- Considerations for consent
    - A lay person should be able to read and understand the consent form.
    - Depending on the study, it is important to ensure that the patient knows what they are agreeing to and that they have the option to have their data used in other ways in the future.
- March 2024 FDA draft guidance: *Key Information and Facilitating Understanding in Informed Consent Guidance for Sponsors, Investigators, and Institutional Review Boards*. This guidance aids organizations in the consent process, including the writing of consent documents and engaging in the oral consent discussion.

Funding Opportunities

Tiina Urv, PhD, National Center for Advancing Translational Sciences, NIH
Katherine Needleman, PhD, RAC, Office of Orphan Products Development, FDA

- NCATS Rare Disease Clinical Research Network (RDCRN): Currently, there are 18 trials funded by the RDCRN program
    - The RDCRN has helped provide 12 FDA-approved treatments for 11 different rare diseases
- FDA Natural History Grants Program: Launched in 2016, FDA's Natural History Grants Program currently funds 14 ongoing grants

Collecting Fit for Purpose Data to Inform Regulatory Decision Making

Collin Hovinga, PharmD, MS, FCCP, Critical Path Institute
Jennifer Farmer, MS, Friedreich's Ataxia Research Alliance
Reactor Panel
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Donna Rivera, PharmD, MSc, Oncology Center of Excellence, FDA
Kimberly Smith, MD, MS, Center for Drug Evaluation and Research, FDA
Tiina Urv, PhD, National Center for Advancing Translational Sciences, NIH

- **Data collection for rare diseases:** Structured data collection advances research and meets regulatory needs for new therapies. Structured data collection can help advance research and is more likely to be helpful for regulatory purposes to develop new therapies.
- **Fit-for-purpose data:** Data from registries must be reliable, relevant, timely, and auditable for regulatory submissions, with clear goals ensuring credibility and trustworthiness.
- **Data collection and quality control:** Strategies should minimize patient burden and include quality control measures like standardized protocols, cross-site reliability, and rigorous auditing.
- **Value and complexity of using natural history and registry data:** These data are invaluable for drug development, but using them for regulatory decisions adds complexity, requiring careful planning, rigorous data collection, and FDA engagement.
- **Registry data for regulatory approval:** The Friedreich's Ataxia Research Alliance's (FARA) Natural History data was crucial in gaining approval of Skyclarys

(omaveloxolone) by providing confirmatory evidence and focusing on accessibility, standardized formats, and partnerships.
- **Successful use of registry data:** In oncology, registry and real-world data supported approvals for treatments like Abatacept for acute graft versus host disease and Alpelisib for PIK3CA related overgrowth spectrum, exemplifying the importance of predefined statistical plans and objective endpoints.
- **Early and continuous regulatory engagement:** Regular communication with agencies like the FDA ensures data meet regulatory standards, prevents issues like outdated consent forms, and provides valuable feedback throughout the process.
- **Collaboration and inclusivity:** Collaboration with patients, researchers, and advocacy groups is key, with special attention to enrolling children and underrepresented populations.

Natural History Studies and Registries that Informed Regulatory Decision Making

Example: Nulibry for Molybdenum Cofactor Deficiency
Ronen Spiegel, MD, Emek Medical Center
Liza Squires, MD, Sentynl Therapeutics

Example: Lumasiran and Nedosiran for Primary Hyperoxaluria
John Lieske, MD, Mayo Clinic Hospital – Rochester

Reactor Panel
Catherine Lerro, PhD, MPH, Oncology Center for Excellence, FDA
Kirtida Mistry, MBBCh, DCH, MRCPCH, Center for Drug Evaluation and Research, FDA
Jill Morris, PhD, National Institute of Neurological Disorders and Stroke, NIH
Catherine Pilgrim-Grayson, MD, MPH, Center for Drug Evaluation and Research, FDA

- Natural History Studies provide an opportunity to
    - Characterize ultra-rare and rare disorders
    - Develop appropriate disease biomarkers
    - Ethically study potentially life-saving treatments
    - Facilitate the development of therapeutics in ultra-rare and rare disorders
- Different types of stakeholders can design, conduct, and use natural history studies and registries to generate data for drug development:
    - Nulibry example: An academic medical center and industry collaboration

    - Lumasiran and Nedosiran example: A patient advocacy group and Kidney Health Initiative collaboration
- Sponsors can use the data from natural history studies and registries in various aspects of drug development:
    - The placebo (untreated control) group in the full analysis set for the Nulibry drug development program was composed of patients with Molybdenum Cofactor Deficiency type A who were enrolled in a multinational, multicenter, retrospective/prospective natural history study.
    - Data from primary hyperoxaluria registries increased understanding of the natural history of primary oxaluria and helped to identify a surrogate endpoint for clinical trials.

More information on FDA's current thinking regarding registries and natural history studies is available in the final guidance ***Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products*** (December 2023) and draft guidance ***Rare Diseases: Natural History Studies for Drug Development*** (March 2019).[1]

To find Guidance documents relevant to rare disease drug development which are organized by topic, please access the **ARC Program's** **Guidance Documents for Rare Disease Drug Development** **web page**.

More comprehensive information regarding natural history studies and registries is available in the **FDA and NIH Resources** list for this meeting.

[1] To search for the most recent versions of FDA guidance documents: https://www.fda.gov/regulatory-information/search-fda-guidance-documents