E24: Natural History Studies and Patient Registries to Advance Rare Disease Drug Development

Endorsed by the Management Committee on 15 November 2026

1. Background to the proposal and statement of the perceived problem

Rare disease applications constitute a significant share of New Active Substances (NAS) and indication expansions reviewed by regulatory authorities. Regulatory agencies have observed a consistent upward trend in the proportion of NAS marketing applications and approvals for rare diseases.

These marketing applications are often for serious and life-threatening rare conditions with limited or no available therapies. Clinical trials in rare disease drug development are conducted in small or very small study populations and are further complicated by heterogeneous disease manifestations. Consequently, generating and leveraging fit-for-use natural history and registry data is imperative to advance drug development in rare diseases. These data can be critical to inform the design and conduct of clinical trials and can contribute to assessments of safety and efficacy.

Despite the increasing use of natural history and registry data in rare disease drug development, natural history studies and patient registries are often established without a clear understanding of the requirements for their intended regulatory use. As a result, generated data may not be suitable for regulatory use, resulting in limited utility in supporting the development of rare disease treatments.

2. Type of harmonisation action proposed

The new Guideline will provide high-level, harmonised, principles-based guidance to support the appropriate use of natural history and registry data for rare disease drug development. Establishing harmonised expectations for different regulatory uses will inform the design and conduct of natural history studies and patient registries, increasing the potential for the data generated to be fit-for-use.

3. Issues to be resolved and expected deliverable(s)

Issues to be resolved:

Challenges with Rare Disease Drug Development

The lack of a well-characterised natural history, including information on disease course, clinical outcomes, biomarkers, and prognostic factors, limits the ability to inform clinical trial design in rare diseases. In addition, the small and often heterogeneous patient populations pose challenges to conducting adequately sized, randomised clinical trials. Given these challenges, it is critical to strive for high-quality natural history and registry data to inform rare disease drug development.

Regulatory Use of Natural History and Registry Data

Expectations for the acceptability of natural history and registry data differ across regulatory authorities and across intended uses, so data generated for one purpose or region are often unusable for another purpose or region. As a result, many existing data are deemed not fit-for-use for regulatory decision-making due to various deficiencies, such as those in terminology, study design, data quality, and analytic methods. This issue is further complicated when regulatory use of these data requires accounting for representativeness across regions and changing standards of care.

Scope of the issues to be resolved:

This Guideline will provide high-level principles on the use of natural history and registry data for different regulatory uses in rare disease drug development and on design and conduct of natural history studies and patient registries needed to generate such data. The regulatory uses include: a) informing the design and conduct of clinical trials by guiding key elements such as patient selection, trial duration, endpoint selection, factors relevant to randomisation, and statistical planning; b) supporting the development and use of biomarkers and clinical outcome assessments; c) contributing to the evaluation of a product's efficacy and safety; d) forming the foundation for long-term follow-up, including post-marketing studies for approved therapies.

Deliverables:

High-level principles Guideline including:

a) Definitions and types of natural history studies and registries
b) Principles for generating and evaluating natural history and registry data for regulatory uses in rare disease drug development
c) Principles for analysing natural history and registry data for regulatory uses in rare disease drug development

4. Planning

4.1. Resources and Expertise

Development of this Guideline requires experts from regulatory agencies, industry, and observers with experience in design and conduct of natural history studies and patient registries as well as regulatory use of natural history and registry data for rare disease drug development. Core disciplines include pharmacoepidemiology, biostatistics, clinical trial design, real-world evidence/data, and clinical medicine.

4.2.Planned Interactions/Data Generation

This working group will coordinate with the E23 EWG to ensure alignment and avoid duplication on general principles of RWD collection and quality. E24 will be aligned with and cross-reference E23 or other relevant Guidelines on the use of real-world

evidence and address only considerations specific to natural history and registry data in rare diseases.

4.3. Stakeholder Engagement and Impact

As this guidance is expected to be heavily utilised by patients, patient advocacy groups, and academic researchers who often initiate these studies, a stakeholder engagement plan will be developed.

4.4. Timeframe and Key Milestones

The aim is to complete this Guideline within 3 years from the appointment of the working group including approximately 24 months to reach *Steps 2a* (Final Technical Document) and *2b* (Draft Guideline).

Key Milestone	Estimated Timeframe
Step 1 sign-off of E24 Technical Document / *Step 2 a/b* endorsement of draft E24 Guideline and release for public consultation	Q2 2028
Begin development of E24 EWG Training Materials/Stakeholder Engagement etc.	Q4 2028
Step 3 documents and sign-off of draft E24 Guideline / *Step 4* adoption of Final E24 Guideline	Q2 2029

5. Impacts of the project and post-hoc evaluation

The rare disease community (including patients, patient advocacy groups, academic researchers, and foundations) and industry sponsors are increasingly looking for early engagement with regulatory agencies when initiating and utilising natural history studies and patient registries. Given the typically global nature of rare disease drug development and the limited patient populations available to participate in studies, harmonised guidance across regulatory authorities will increase the potential for the data to be fit-for-use, thereby supporting advancement in rare disease drug development.