HOW TO USE REAL-WORLD DATA FOR REGULATORY PURPOSES

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BACKGROUND

- The EMA's "Reflection paper on the use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes" provides essential guidance on the methodological approach to ensure the generation of reliable real-world evidence (RWE). This supports stakeholders involved in planning, conducting, and analyzing non-interventional studies (NIS) using real-world data (RWD).
- Additionally, the draft version of annex 2 of ICH GCP – Good Clinical Practice E6 (R3) introduces specific considerations for clinical trials incorporating RWD. It emphasizes the importance of Quality by Design (QbD), particularly identifying critical-to-quality factors to generate fit-for-purpose evidence that supports regulatory decision-making.
- The awareness on the applicable legal obligations, regulatory requirements, standards, guidelines for good and recognized practices and the use of reliable data sources are the main element to be considered by Marketing Authorization Holders (MAHs) and Applicants in a NIS using RWD (**Figure 1**).

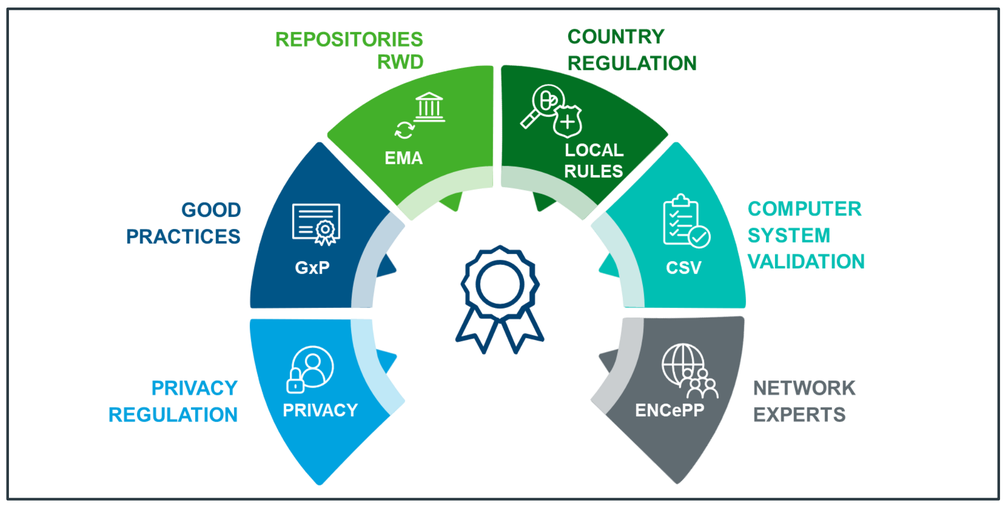

Figure 1: Governance and Transparency in NIS

METHODS

- A systematic review of recent regulatory guidelines was integrated with over 20 years of experience as a service provider in the design and management of more than 175 NIS.
- NIS studies involved primary and secondary data collection and analysis of RWD from over 385,151 patients, in collaboration with 4,594 investigational sites across 28 countries, with a highly diverse regulatory landscape.
- The design of NIS should focus on obtaining reliable evidence for the research question considering the regulatory objectives.
- The MAH must justify the appropriateness and feasibility of using RWD to meet the study objectives stating in the study protocol methodological requirements.
- The study design must be selected considering descriptive and causal objective and the use of primary and secondary data useful to answer the research question (**Figure 2**).

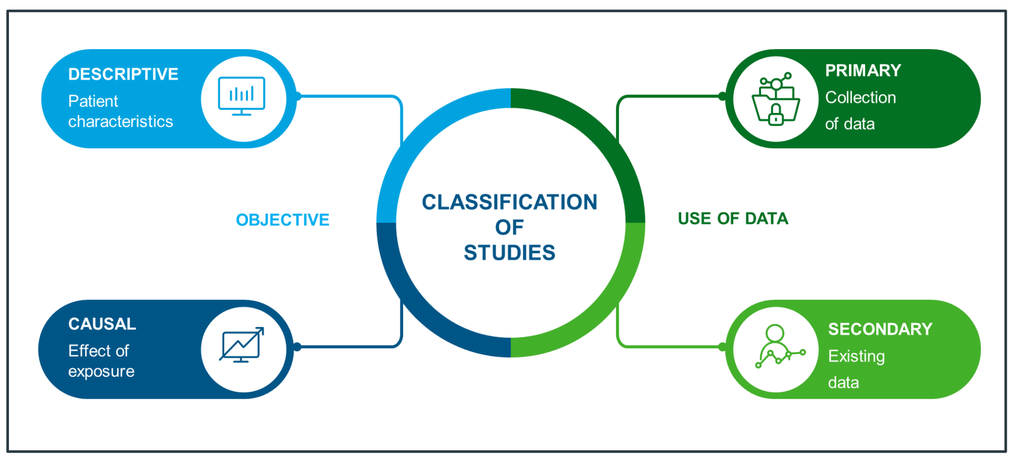

Figure 2: Classification of clinical studies

RESULTS

- Key considerations for designing NIS that generate regulatory-grade RWE include:
  - ✓ Clearly defining regulatory objectives and addressing gaps in knowledge or uncertainties about a product's safety and effectiveness.
  - ✓ Designing methodologically sound studies aligned with these objectives.
  - ✓ Selecting appropriate data sources by evaluating their reliability and relevance.
  - ✓ Assessing study feasibility with preliminary analyses for protocol development.
  - ✓ Mitigating bias and confounding by ensuring accurate measurement of key variables and applying appropriate adjustment methods.
  - ✓ Evaluating data reliability in terms of completeness, trustworthiness and credibility.
  - ✓ Ensuring governance and transparency by adhering to ethical standards, complying with data protection regulations, registering studies and data sources and making protocols and results publicly accessible.
  - ✓ Applying rigorous statistical methodologies, including clear specifications of assumptions, model structures, sensitivity analyses and appropriate handling of missing data (**Figure 3**).

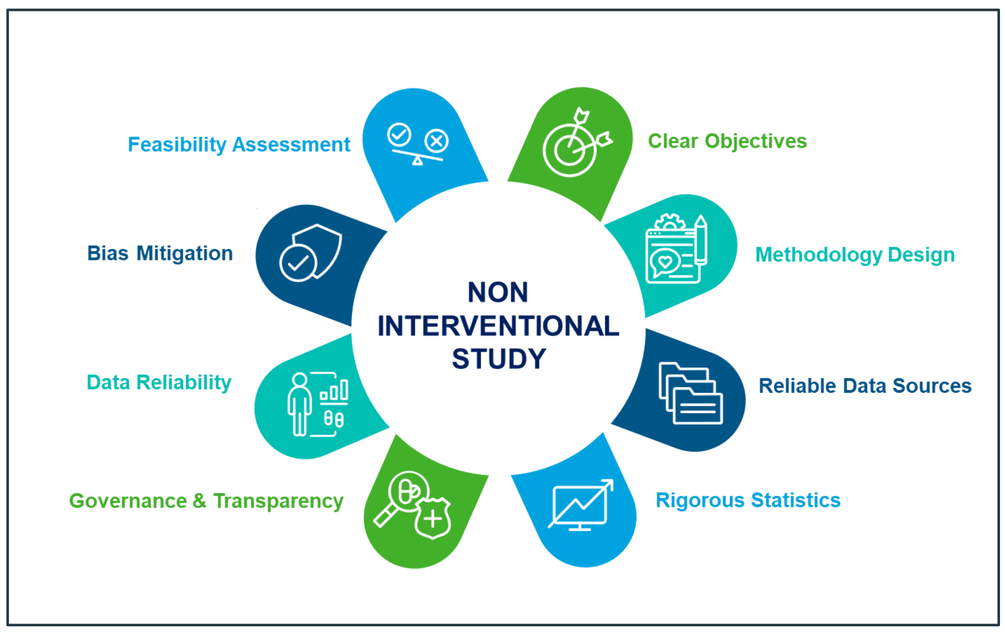

Figure 3. Key factors for NIS with regulatory purposes

CONCLUSIONS

- **The value of RWE is increasingly recognized by regulatory authorities. Stakeholders involved in NIS are now guided by explicit regulatory expectations. To ensure the quality, compliance and reliability of RWE, the design and execution of NIS must incorporate all the aforementioned considerations, thereby enhancing their impact on regulatory decision-making.**
- **Knowledge gaps can be addressed by NIS utilizing RWD that are appropriate for the regulatory objective. These studies should integrate and validate information from various data sources while adhering to legal requirements and agreements among involved parties. This ensures the data's availability over time for regulators and inspectors (Figure 4).**

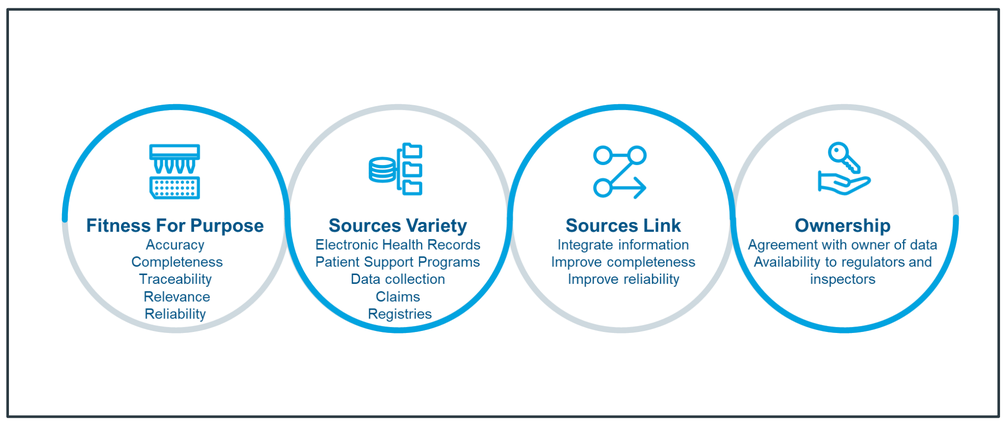

Figure 4. RWD in NIS

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1. EMA - Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes, 17th March 2025
2. EMA - Real-world evidence provided by EMA, 10th April 2024
3. ICH E6 (R3) - Guideline for Good Clinical Practice – Annex 2 - Step 2b, Draft version endorsed on 06th November 2024

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