Registry-based studies in practice: Enhancing real-world evidence generation in rare disease and personalized medicine

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Background

- In September 2020, the European Medicines Agency (EMA) issued a draft guideline on registry-based studies (RBS)[1].
- The EMA has now issued the final guideline dated 22 October 2021, confirming the agency's interest in using patient registries (PRs) for pharmacoepidemiologic safety and effectiveness research [2]. New points of focus include ethics/consent, safety reporting and feasibility.
- This guideline is the result of a joint effort between the EMA Patient Registry Initiative and the Cross-Committee Task Force on Registries aimed at improving the use of existing registries in order to support the benefit-risk evaluation of medicinal products.
- Several workshops that have focused on rare diseases and precision medicine (e.g. in oncology) have been held as a preamble to the guideline development [3-7].
- The EMA guideline includes:
  - Definitions of:

Patient registry (PR): "Data collection system on a group of people defined by a particular disease or condition, established for a specific purpose and used to conduct a registry-based study"

Registry-based study (RBS): "A registry-based study is an investigation of a research question using the infrastructure of (a) new or (an) existing registry(-ies) for patient recruitment and data collection"

  - Clarification on how registries can support post-authorization safety studies
  - Details on the scientific design and collaboration aspects of RBS
- A RBS can be a clinical trial or an observational study based on either primary or secondary data.
- In parallel, a process of registry qualification has been launched, with the objective of ensuring that existing registries meet the requirements for regulatory-grade registry-based studies. To date, two registries have their qualification opinion published on the EMA website [8,9].

Objective

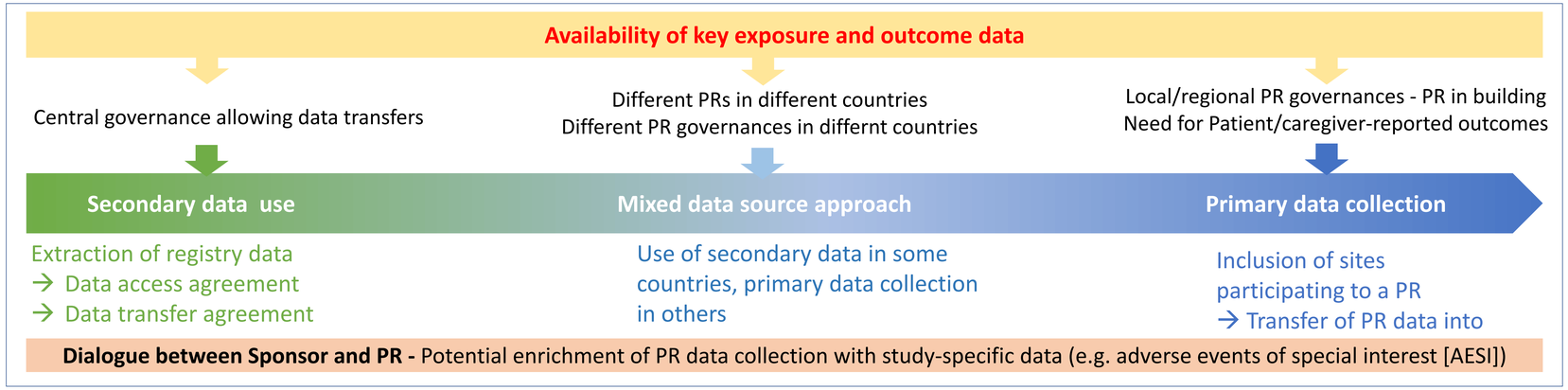
To present our experience and learnings designing **observational RBS** and integrating feed-back received from regulatory authorities.

Methods

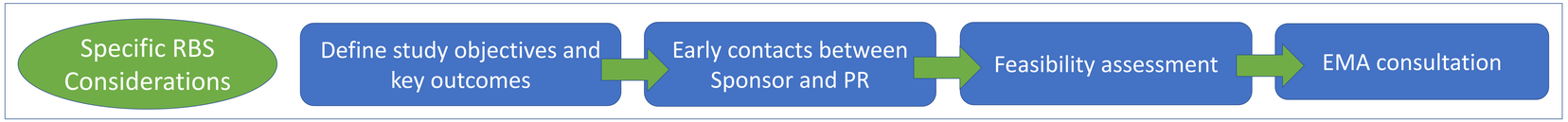
- We reviewed the design of the ten RBS we either designed or supported since September 2020.
- We present a synthesis of the context, objectives, methodological approaches, and EMA feedback received, as applicable.

Results

- The majority of RBS were multi-country observational post-authorisation safety studies (**PASS**, voluntary or mandatory) or post-authorisation efficacy studies (**PAES**).
  - We also designed patient registries (PRs) that aimed to become data sources for future studies.
- **Most studies were within an indication related to a rare disease or a precision medicine.**
- The RBS design was selected based on the ability of the PR to address the study objectives, a key criterion being the **availability of key exposure and outcome data**. The main study designs are presented below:



- Most frequently, PRs were few and clearly identified. However, a **feasibility assessment** was always needed to confirm the availability of key data elements and models of collaboration.
- EMA (PRAC or CHMP) feed-back for the use of PR as a data source for both prospective and retrospective approaches was favourable, even when the PR was not qualified by the agency.
- The main EMA questions related to:
  - the availability and quality of exposure, outcome data and covariates in the PRs
  - the status of the collaboration between the sponsor and the PR.



Conclusion

RBS are becoming increasingly used to generate regulatory-grade real-world evidence (RWE) in Europe and are encouraged by the EMA. RBS foster academic-industry collaborations and expand research in rare diseases beyond regulatory purposes. Early collaboration with PRs facilitates feasibility, data collection and evidence generation planning.

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