EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP Guideline on registry-based studies

Kelly Plüschke
EMA Data Analytics and Methods Task Force

In this presentation:

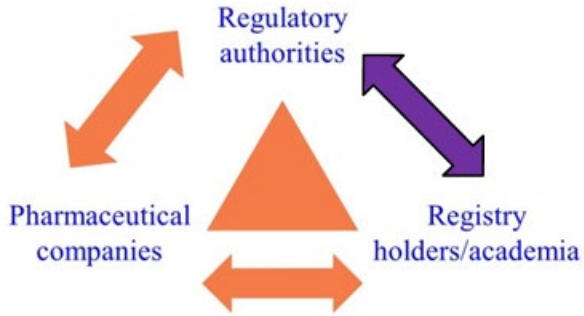
- EMA Patient Registry Initiative
- Timelines for development of the guideline
- Insight into the guideline's sections
- Any questions?

EMA Patient Registry Initiative - LINK

- Launched in September 2015
- EMA Cross-Committee Task Force on Registries
- Aims to facilitate use of disease registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines

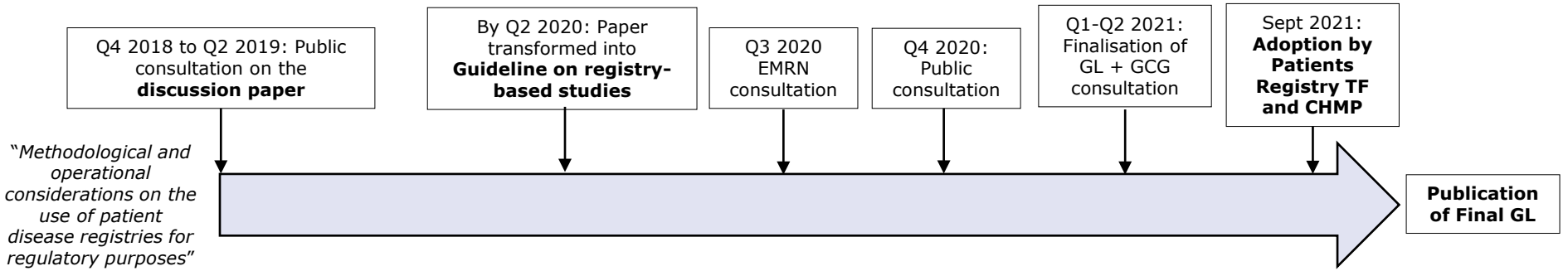
Key components of the initiative

- To promote dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries.
- To provide guidance to clarify methodological concepts and requirements for use of registries for regulatory purpose



Source: Nicola Ruperto, PRINTO

Timelines for the development of the guideline



- Q4 2020 public consultation: 960 comments from 68 organisations
- Large number of editorial comments – useful and acceptable

Table of content (core guideline)

Abbreviations **3**

Glossary **4**

1. Introduction **5**

2. Scope and objective **5**

3. Methods and processes **6**

3.1. Differences between a registry-based study and a patient registry 6
3.2. Use of registry-based studies for evidence generation 7
3.3. Planning a registry-based study 8
3.4. Study protocol 9
3.5. Study population 10
3.5.1. Informed consent 11
3.6. Data collection 11
3.7. Data quality management 11
3.8. Data analysis 12
3.9. Data reporting 14

4. Legal basis and regulatory requirements **14**

Objectives, scope, glossary

- **Objective**: To provide recommendations on **key methodological aspects** of registry-based studies, and to highlight **relevant legal bases and regulatory requirements**. Main target audience: MAAs/MAHs, but also relevant to other stakeholders
- **Scope**: Studies based on patients' registries (including disease or specific conditions registries)
- **Patient registry** (in line with US FDA and US Agency for Healthcare Research and Quality)

> *"Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure. The term 'patient' highlights the focus of the registry on health information. It is broadly defined and may include patients with a certain disease, pregnant or lactating women or individuals presenting with another condition such as a birth defect or a molecular or genomic feature."*

"Product registry": system of data collection by MAAs/MAHs targeting patients exposed to a specific medicinal product or substance to evaluate its use, safety, effectiveness. It is preferable to use the appropriate terminology, i.e. "clinical trial" or "non-interventional study"

Objectives, scope, glossary

- **Registry-based study**

  "Investigation of a research question using the data collection infrastructure or patient population of one or several patient registries.

  A registry-based study is a clinical trial or a non-interventional study as defined in Article 2 of Regulation (EU) No 536/2014"

Methods and processes - *Registry-based study versus patient registry*

Important differences that should be well understood to design a registry-based study

	Registry-based study	Patient registry
1. Definition	Investigation of a research question using the data collection infrastructure or patient population of one or more patient registries.	Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure
2. Duration of follow-up	Timelines driven by the study objectives, the collection/extraction and analysis of the relevant study data.	Timelines driven by schedules for data collection and any anticipated data analyses which prompted the registry.
3. Patient enrolment	Defined by research objective(s) and may be a subset of a registry population; in case of a clinical trial, allocation to treatment arm (e.g. with randomisation) is to be documented; generalisability of the study results to be documented.	Aimed at enrolment of all patients with the particular disease or condition; generalisability of registry data to be documented.
4. Data collection	Restricted to what is needed by the research question including data on potential confounders and effect modifiers; collection of additional data not routinely collected in the registry may be required; if such additional data includes subject monitoring outside the terms of the SmPC and normal clinical practice, the legislation for clinical trials may apply; study may involve primary data collection in addition to secondary use of data.	Data collected based on the purpose of the registry; agreed core set of data elements to be collected with documented definitions, coding system and data entry procedures; data collected for the purpose of a registry can involve primary collection of data or secondary use of data.

Methods and processes - *Registry-based study versus patient registry*

	Registry-based study	Patient registry
5. Analysis plan	Detailed statistical considerations most commonly defined in separate document in addition to study protocol and to registry protocol; descriptive or hypothesis driven statistical analysis plan.	Statistical analysis plan with analyses often performed routinely at intervals based on patient accrual or analyses of pre-defined outcomes at time points described in the registry protocol.
6. Data quality management	Study-specific data quality management to be prospectively defined and implemented with a risk-based approach.	Quality management applied routinely to data and processes with a focus on core set of data elements; data systems to ensure data integrity, completeness and security; data quality management to be prospectively defined and documented.

Methods and processes – *Role of registries in evidence generation*

To complement the evidence generated in the pre-authorisation phase and provide evidence in the post-authorisation phase, e.g.:

- Contextualisation through information on standards or real-world practice of care for the disease, incidence, prevalence and determinants of disease outcomes in clinical practice, or the characteristics of the registry population
- Patient recruitment (e.g. to identify patients meeting inclusion/exclusion criteria)
- Randomisation allocation, sample size calculation
- Identification of relevant endpoints
- Quantification/characterisation of risks, identification of risk factors for the occurrence of AESI
- Evaluation of long-term effectiveness and safety profile of a medicinal product
- Assessment of patterns of medicines utilisation
- Assessment of the risk minimisation measures effectiveness

Methods and processes - *Planning a registry-based study*

- First step: **identify the scientific question(s)** and critically consider if a registry-based study is appropriate to provide the relevant answers
- **Feasibility analysis** to identify the suitable registry/ies to answer the study question(s)
- **Early consultation** with national competent authorities and EMA (e.g. Scientific Advice and Protocol Assistance procedures)
- Primary data collection versus secondary use of data

Primary data collection in the context of a registry	Primary data collection in the context of a registry-based study	Secondary use of data in a registry-based study
Collection of data directly from patients, caregivers, HCPs to address the registry's purpose	Data not routinely captured by the registry needed: • Implications on potential sources of bias, confounding, missing data, safety reporting requirements, patients informed consent, audit/inspections etc… • Study-specific primary data collection methods to clearly be described in the study protocol	Use of existing data for a different purpose than the one for which they were originally collected. The study entirely uses data already collected in the registry

Methods and processes - *Planning a registry-based study*

Feasibility analysis

- To be performed by the MAA/MAH or research organisation initiating the registry-based study in collaboration with registry holders to facilitate the discussion with regulators and other parties
- Can help answer essential questions on suitability to use the infrastructure of the registry for a specific registry-based study. If any doubts, another study design could be a better choice.

  - ✓ Is the governance model in place appropriate?
  - ✓ Is the registry population appropriately representative?
  - ✓ Are the requirements for additional informed consent feasible?
  - ✓ Is primary data collection feasible, e.g. in terms of collecting and reporting safety data?
  - ✓ Are the collected data sufficient for the purpose of the study ?
  - ✓ Is the time lag for the availability of the data suitable?
  - ✓ Are the data of demonstrated quality?

Methods and processes - *Planning a registry-based study*

Feasibility analysis, including checklist describing the registry, analysis of the availability of the data elements needed for the study and analysis of the capacity to collect any additional ones if needed

Examples of information to be provided

Data on the numbers of registered patients, active patients and patient flows	Potential selection bias due to incl./exclusion criteria
Analysis of the quality and completeness of the available data elements	Potential confounding if some data elements are not available
Any data privacy and governance-related issues	Analytical issues that may arise
Processes in place for AEs/ADRs	Overall evaluation of the suitability of the registry for the specific study

Potential difficulties acknowledged (e.g. burdensome for small registries, need for collaboration with MAA/MAH without contract, quickly outdated) **but added value, e.g.**:

- Time saving (preliminary discussions with registry holders/regulators, feasibility analysis fit in protocol)
- Quality of outputs (choice of the most suitable registry/-ies, limitations of registry-data already known before start and can be adjusted for)

Annex ***Considerations on patient registries*** and appendices

A.1. Introduction 18
A.2. Registry population 18
A.3. Data elements 19
A.4. Quality management in patient registries 21
A.5. Governance 23
A.6. Data sharing outside the context of registry-based studies 24

References 26

Appendices 30
Appendix 1. Checklist for evaluating the suitability of registries for registry-based studies . 30
Appendix 2. Safety reporting 32
Appendix 3. Examples of recommended international terminologies for data elements 33

Any questions?

Further information

EMAregistries@ema.europa.eu

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

Follow us on **@EMA_News**

Back-up slides

Specific disease related multi-stakeholder workshops:

- LINK
- Cystic fibrosis registries: 2017
- Multiple sclerosis registries: 2017
- Registries for CAR T cell therapies: 2018
- Haemophilia (Factor VIII) registries: 2018
- Use of registries in the monitoring of cancer therapies based on tumours' genetic and molecular features: 2019

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 September 2018
EMA/487643/2018
Pharmacovigilance and Epidemiology and Regulatory and Science Management Departments
Inspections, Human Medicines, Pharmacovigilance and Committees and Evaluation Divisions

Report on Haemophilia Registries
Workshop 8 June 2018
Patient Registries Initiative

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 Facsimil +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact
An agency of the European Union