EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Final Guideline on registry-based studies

Kelly Plueschke, Xavier Kurz, Carla Jonker
EMA Data Analytics and Methods Task Force

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EMA Cross-Committee Task Force on Registries

Peter Mol – Chair – SAWP (CBG-MEB)

Christian Gartner – CHMP, BSWP (AGES)

Jan Span - CAT (CBG-MEB)

Milena Stain - CHMP (AGES)

Sabine Straus – PRAC (CBG–MEB)

Ulla Wändel Liminga – PRAC (MPA)

Brigitte Keller-Stanislawski – PRAC (PEI)

Virginie Hivert – PRAC (Eurordis)

Kieran Breen – CAT, PCWP (European Parkinson's Disease Association)

Dolores Montero (AEMPS)

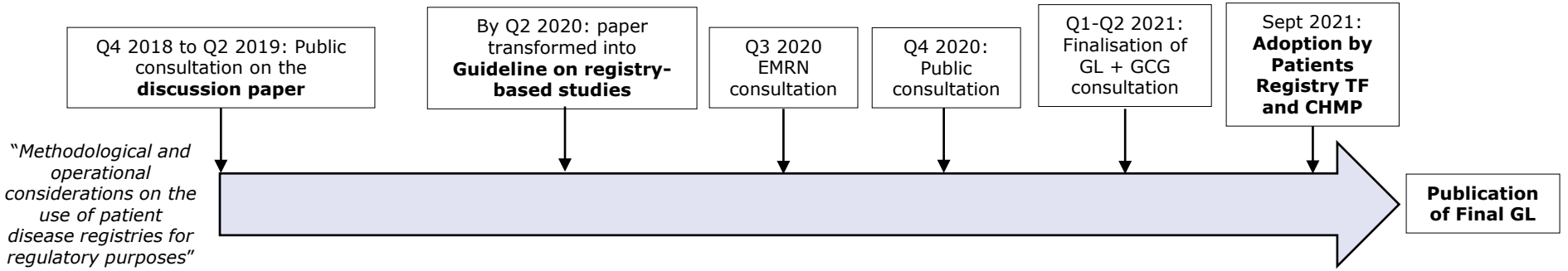
Carla Jonker (CBG-MEB)

EMA: Xavier Kurz (Co-Chair), Priya Bahri, Julianna Fogd, Karin Hedenmalm, Jane Moseley, Kelly Plueschke, Valerie Strassmann, Robert De Lisa

Background

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 *disease registries* or studies characterised by the presence or occurrence of a particular condition (e.g. pregnancy or birth defect) or exposure (e.g. vaccine)



- Q4 2020 public consultation: 960 comments from 68 organisations
- Large number of editorial comments – useful and acceptable – will not be presented

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Main comments and changes made

Definitions

1. **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."

Was : *"Organised system that collects data and information on a group of patients defined by a particular disease, condition or exposure, and that serves a pre-determined scientific, clinical and/or public health (policy) purpose. […]."""*

Main comments and changes made

Definitions

2. 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"

Registry-based randomised clinical trial

"Randomised clinical trial embedded in the data collection infrastructure of one or several patient registries" (e.g. identify patients meeting inclusion/exclusion criteria, randomisation, data collection or follow-up)

Main comments and changes made

Definitions

3. Primary data collection versus secondary use of data

- **Primary data collection in the context of a registry**: Collection of data directly from patients, caregivers, healthcare professionals or other persons involved in patient care to address the registry's purpose.
- **Primary data collection in the context of a registry-based study**: the study requires additional study-specific primary data collection not already routinely captured by the registry
    - *Data collection methods applied to clearly be described in the study protocol due to implications on potential sources of bias and confounding, retrieval of missing data, safety reporting requirements and possibly on patients informed consent;*
    - *Additional study-specific data collection may affect the ongoing registries' data collection and maintenance, and may require audit and validation*
- **Secondary use of data in a registry-based study**: Use of existing data for a different purpose than the one for which it was originally collected. The study entirely uses data already collected in the registry.

Main comments and changes made

Use of registry-based studies for evidence generation

The first step is to identify the scientific question(s) to be addressed by the study and critically consider if a registry-based study is appropriate to provide answers.

The acceptability of registry-based studies as a source of evidence for regulatory purposes depends on several factors related to the ***specific regulatory assessment procedure*** *for the concerned medicinal product, the* ***characteristics of the concerned registry*** *(see Annex) and the* ***objectives, design and analytical plan*** *of the proposed study. Early consultation with national competent authorities (NCAs), where applicable, and with EMA (via the procedure for Scientific Advice and Protocol Assistance) is recommended when a registry-based study is proposed to be used and study protocols should be published.*

Main comments and changes made

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?

Main comments and changes made

Planning a registry-based study: Feasibility analysis

Content

Description of the registry(-ies) (check list proposed) including analysis of the availability of the data elements needed for the study and of the capacity to collect any additional ones	
Processes in place for AEs/ADRs	Analytical issues that may arise
Data on the numbers of registered patients, active patients and patient flows	Analysis of the quality and completeness of the available data elements
Potential selection bias due to incl/exclu criteria	Any data privacy and governance-related issues
Potential confounding if some data elements are not available	Overall evaluation of the suitability of the registry for the specific study

Comments from public consultation

Generally strongly supported - proposals to use for all studies using RWE	
Different views: to be made mandatory vs. optional; additional vs. less information	Registry holders may not collaborate before contract with applicants is in place – burdensome for small registries
Need to involve HTA bodies/ payers in early discussions	Feasibility Analysis may become quickly outdated
Proposals for improving quality of disease registries may not well be accepted by registry holders due to practical difficulties	Need for better interactions between registry holders, MAAs/MAHs and regulators
Patient registries not designed for AEs and SAEs recording and reporting in real time, except for new registries with processes in place	

Main comments and changes made

New sub-section on Informed consent

*Informed consent **may need to be collected** from patients participating in a registry-based study **in addition** to the consent given for participating in the registry, unless a legal basis or the consent obtained for the registry adequately covers the potential use of the data for the research purposes of the study. The informed consent should explain the **intended use of their data** and c**over all data to be used**, as specified in the study protocol. Use of additional data sources for the follow-up of patients through record-linkage of registry data by means of unique identifiers (e.g. to cancer registries) may also require patients' additional consent.*

The patients' consent to allow use of registry data and access to source data and source documents should also cover access to data for monitoring, auditing or inspections by competent authorities.

Next steps

- September 2021:
    - Adoption by EMA Cross-Committee Task Force on Registries + **CHMP**
    - Presentation to EMA committees/WPs
- Early Q4 2021: Publication
- Q4 2021: Communication

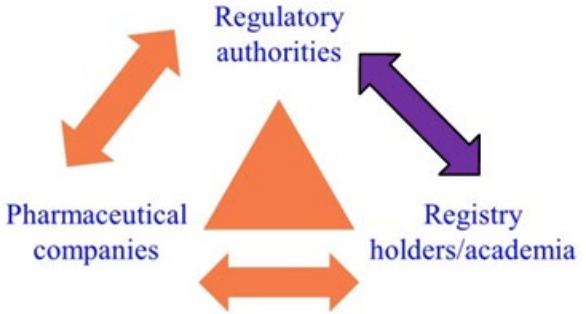
ANY QUESTIONS?

Back-up slides

- EMA Patient Registry Initiative launched, September 2015: LINK
- 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 regulatory requirements



Source: Nicola Ruperto, PRINTO

- Specific disease related multi-stakeholder workshops on :
  - 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

- Follow-up actions:
  - Survey on safety data collection in registries
  - Further work on essential data elements for the cancer registries
  - Interactions with other disease registries based on lessons learned from the workshops