EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on registry-based studies

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In this presentation:

- Background
- Use of registries in pharmaceutical industry applications
- Insight into the guideline's sections
- Any questions?

Why did we initiated the EMA patient registry initiative?

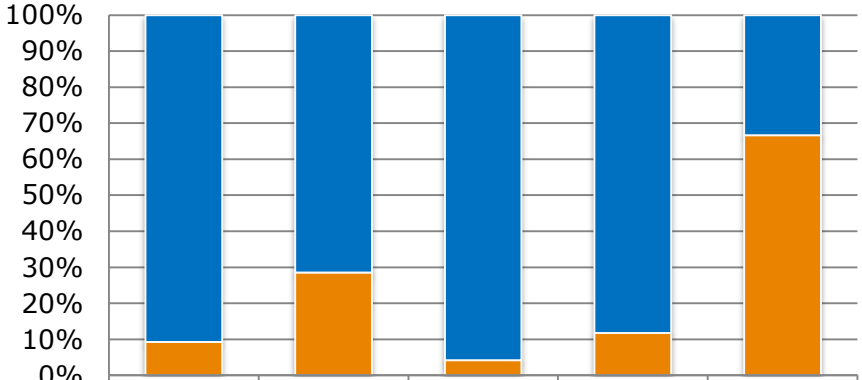
Number of registries imposed as an obligation at the time of autorisation for centrally-authorised products, 2005-2013

Overall, use of a registry imposed for **9% of the products authorised**

65% of registries are product registries

80% of registries are new registries

Problems encountered	%
No problem encountered	37.5
Delayed start	37.5
Low accrual rate	54.2
Protocol amendment required	37.5
Low data quality or missing data	12.5
Low use of the product	12.5
Low enrolment due to other issues	12.5



	all (n=335)	orphan (n=70)	non-orphan (n=265)	conditional (n=17)	exceptional circumstances (n=21)
no registry	304	50	254	15	7
registies	31	20	11	2	14

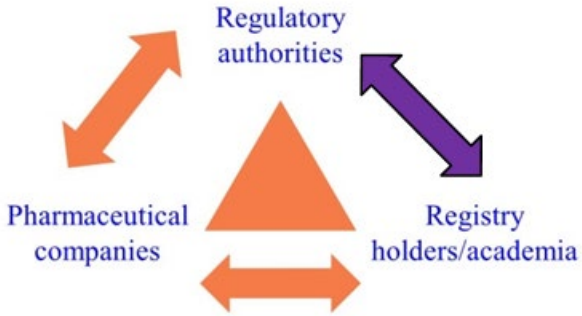
2 *Bouvy et al. PDS 2017;26(12):1442-50*

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

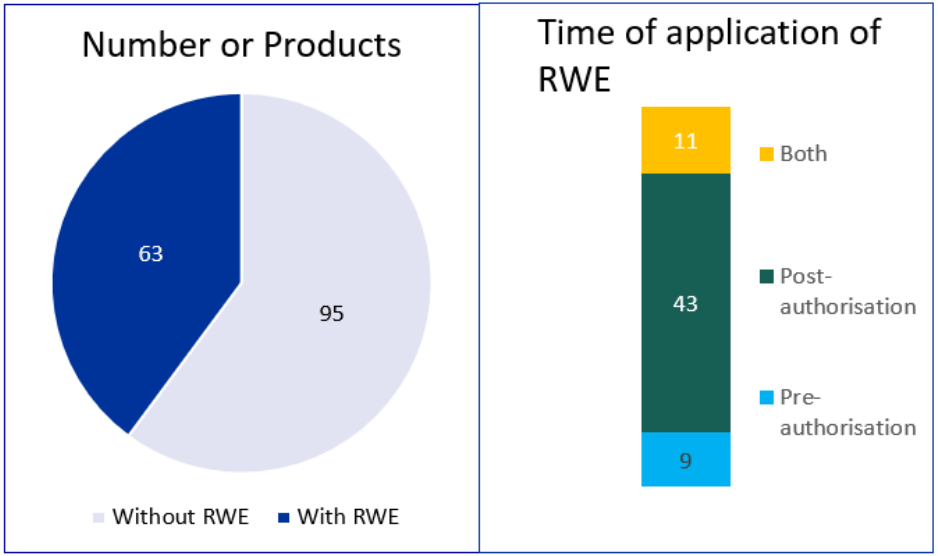
- To promote dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries.
- To provide guidance to clarify methodological concepts and requirements for use of registries for regulatory purpose



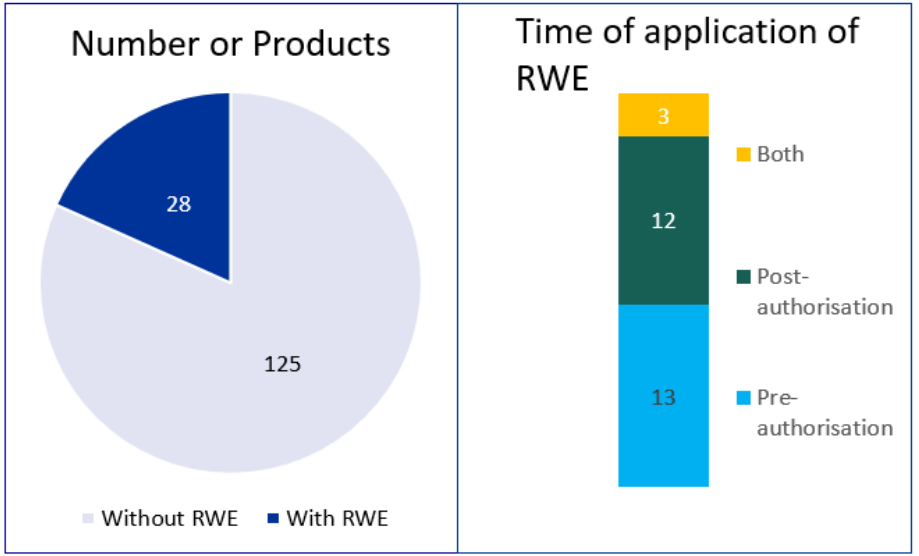
Source: Nicola Ruperto, PRINTO

EMA study on RWE in marketing authorisation applications* (Phase 1)

Initial MA Applications (n=158)



Extensions of indications (n=153)



** Accepted manuscript to be published shortly in Clinical Pharmacology & Therapeutics: "Marketing authorisation applications made to the European Medicines Agency in 2018 - 2019: what was the contribution of Real-World Evidence?" by Robert Flynn, Kelly Plueschke, Chantal Quinten, Valerie Strassmann, Ruben Duijnhoven, Maria Gordillo-Marañon, Marcia Rueckbeil, Catherine Cohet, and Xavier Kurz [Paper #2021-0170CR]*

Data sources used in RWE

RWD/RWE used in:

- **40% of new MA applications** (mainly post-authorisation)
- **18% of EoI applications** (mainly pre- or post-authorisation)

Characteristics of RWD/RWE studies used	Initial MAAs n (%) total MAAs = 63	EoI n (%) total EoI = 28
Data sources		
Electronic health care records from primary care	8 / 63 (12.7)	2 / 28 (7.1)
Electronic health care records from secondary care	8 / 63 (12.7)	0 / 28 (0.0)
Medical records from primary care *	8 / 63 (12.7)	5 / 28 (17.9)
Hospital data	20 / 63 (31.7)	7 / 28 (27.0)
Claims data	5 / 63 (7.9)	2 / 28 (7.1)
Prescription data	6 / 63 (9.5)	3 / 28 (10.7)
Dispensing data	5 / 63 (7.9)	1 / 28 (3.6)
All registries †	38 / 63 (60.3)	13 / 28 (46.4)
Disease registry	21 / 63 (33.3)	9 / 28 (32.1)
Product registry	9 / 63 (14.3)	3 / 28 (10.7)
Other registries ‡	13 / 63 (20.6)	2 / 28 (7.1)
Data from compassionate use programme	2 / 63 (3.2)	1 / 28 (3.5)
Spontaneous reports §	4 / 63 (6.3)	3 / 28 (10.7)
Re-use of data from observational studies	4 / 63 (6.3)	1 / 28 (3.6)
Linked data sources	3 / 63 (4.7)	1 / 28 (3.6)
Other data sources ‖	18 / 63 (28.6)	5 / 28 (17.9)

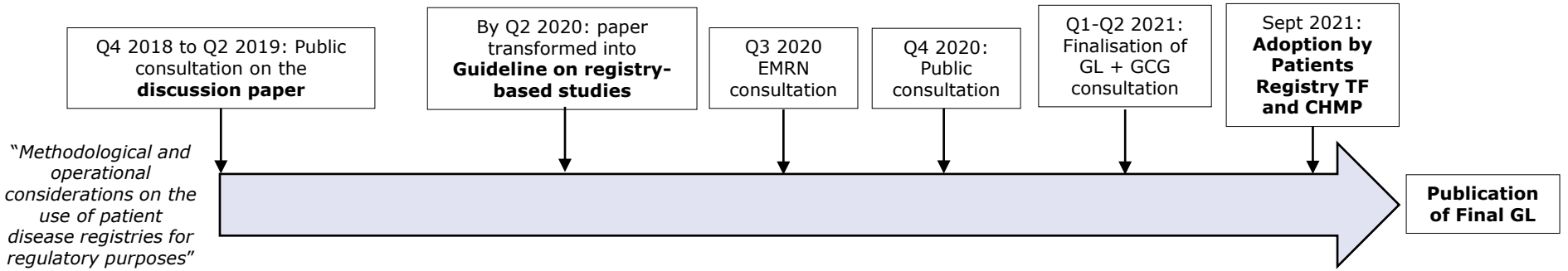
Registries used as source of RWE for 24% of products with new MAA

RWE Real world evidence; MA Marketing authorisation; MAAs Marketing Authorisation Applications; EoI Extensions of Indication

* Primary care medical records were not always identified as electronic or paper based
† Products might be associated with registries of multiple different types
‡ Other registries: pregnancy registry, birth defect registry, population registries, other patient registries (unspecified)
§ Use of spontaneous reports for purposes other than routine pharmacovigilance: typically, these were included as part of wider safety databases incorporating data from multiple sources
‖ Example of other data sources: medical charts or combination of different data sources

Study Phase 2: Further characterise RWD used by applicants to support efficacy / effectiveness claims and disease epidemiology to analyse their impact on CHMP decision making on marketing authorisation and extension of indications applications

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)

Objectives, scope, glossary

- **Objective**: 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)
- **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"

- **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)

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 - *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)

Methods and processes – *Study protocol*

- Should describe:
  - ✓ How the registry infrastructure and population will be used to address the research question(s) of interest
  - ✓ How the study will be conducted and how the validity (both internal and external) of the results will be ensured
  - ✓ Roles and responsibility of all persons involved

- Structure and content should follow existing applicable regulatory and methodological requirements (e.g. ICH guidelines, Good pharmacovigilance practices Module VIII PASS, Scientific Guidance on PAES, ENCePP Guide on Methodological Standards)
- If multiple registries are used: common study protocol and common design recommended, even if aspects of the study may vary according to the registry and not all outcomes may be assessed in all registries --→ description of the differences, sensitivity analyses addressing heterogeneities

Methods and processes – *Study population*

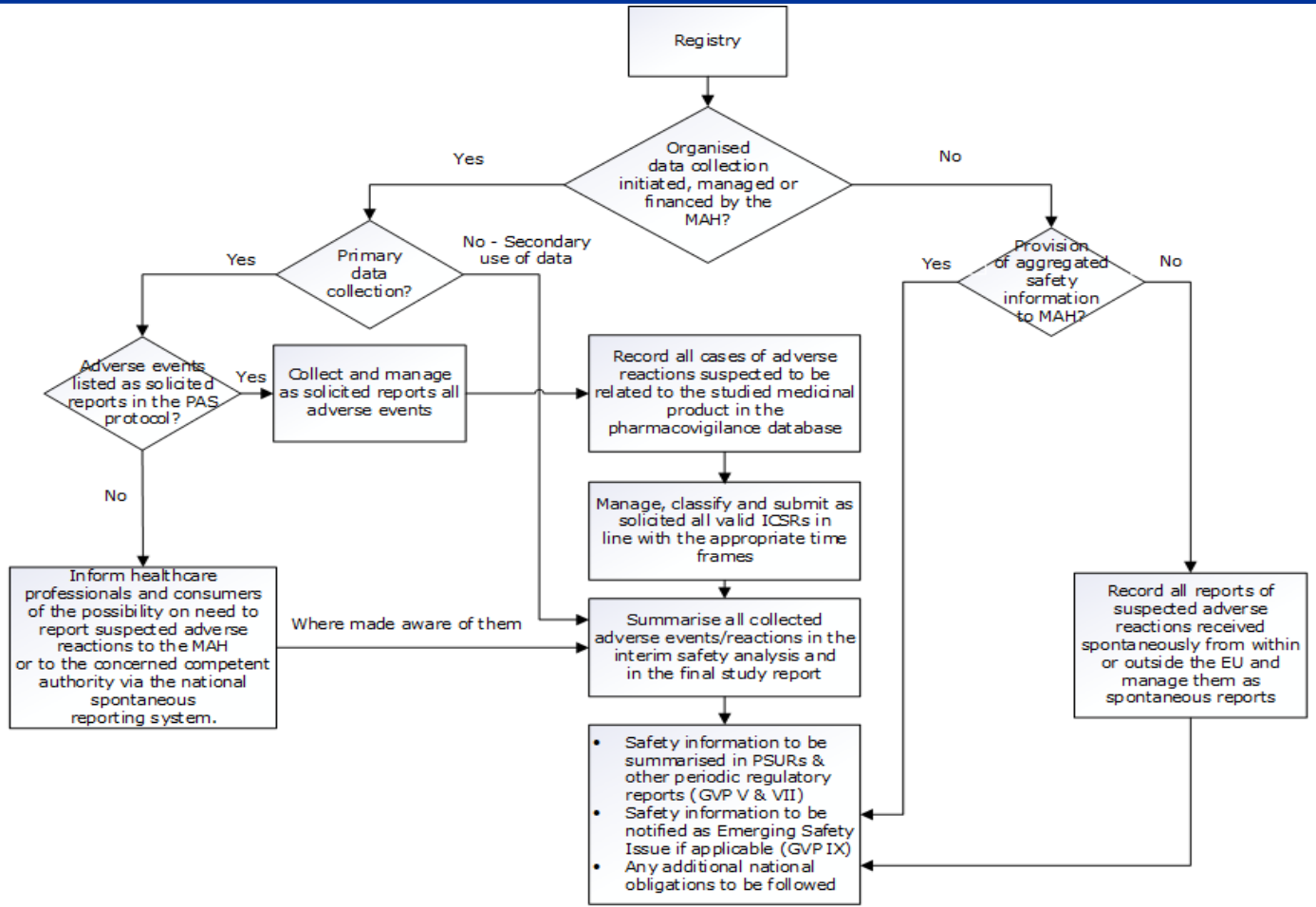
- Driven by the study objectives
- ***Informed consent***:
  - ✓ Additional consent may be needed from patients participating in a registry-based study
  - ✓ Clearly explain the intended use of patients' data and cover all data to be used, as specified in the study protocol (including cases of record-linkage of registry data by means of unique identifiers)
  - ✓ Should also cover access to data for monitoring, auditing or inspections by competent authorities.
- ***Data protection*** requirements at each step of the processing of personal data, including the option for data sharing/pooling between registries and other stakeholders like competent authorities and MAAs/MAHs (GDPR, EUDPR)

Methods and processes – *Data reporting*

- National + EU obligations on reporting requirements for clinical trials and non-interventional studies
- Principles of scientific independence and transparency for reporting study results:
  - ✓ Clinical trials: ***European database*** (EudraCT or CTIS: protocol, report)
  - ✓ Non-interventional studies: ***EU PAS Register*** (protocol/SAP, report + ideally feasibility analysis and summary in lay language)

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

MAH responsibilities for safety reporting in non-interventional study



Any questions?

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