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Workshop on the draft guideline on registry-based studies

EMA 25 years

Virtual meeting - 19 October 2020 - 12:30 – 17:00 (CET)

Welcome to all the participants

Dr. Peter Arlett
Head of Data Analytics and Methods task Force
European Medicines Agency

Drug Safety (2019) 42:1343–1351
https://doi.org/10.1007/s40264-019-00848-9

ORIGINAL RESEARCH ARTICLE

Patient Registries: An Underused Resource for Medicines Evaluation

Operational proposals for increasing the use of patient registries in regulatory assessments

Patricia McGettigan[1] · Carla Alonso Olmo[2] · Kelly Plueschke[2] · Mireia Castillon[2] · Daniel Nogueras Zondag[2] · Priya Bahri[2] · Xavier Kurz[2] · Peter G. M. Mol[3,4]

Published online: 13 July 2019

Abstract

Introduction Patient registries, 'organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time', are potentially valuable sources of data for supporting regulatory decision-making, especially for products to treat rare diseases. Nevertheless, patient registries are greatly underused in regulatory assessments. Reasons include heterogeneity in registry design and in the data collected, even across registries for the same disease, as well as unreliable data quality and data sharing impediments. The Patient Registries Initiative was established by the European Medicines Agency in 2015 to support registries in collecting data suitable to contribute to regulatory assessments, especially post-authorisation safety and effectiveness studies.

McGettigan P, Alonso Olmo C, Plueschke K, Castillon M, Nogueras Zondag D, Bahri P, Kurz X, Mol PGM. Patient Registries: An Underused Resource for Medicines Evaluation: : Operational proposals for increasing the use of patient registries in regulatory assessments. Drug Saf. 2019 Nov;42(11):1343-1351.

Plan for the afternoon

Dr. Peter Mol
Co-Chair of the EMA Cross-Committee Task Force on Registries; Scientific Advice Working Party (SAWP) member; Medicines Evaluation Board (MEB – NL)

Objectives of the workshop

Respond to key questions and requests for clarification

Present stakeholders' perspectives on the usefulness of the Guideline for registry-based studies

Present recent experience on methodological aspects of registry-based studies

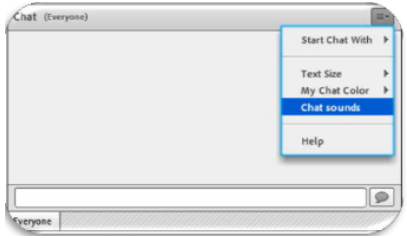
SESSION 1: **Overview of core recommendations of the draft Guideline and comments received** ***Chair: Peter Mol***			
3.	Overview of the main recommendations of the draft Guideline on registry-based studies	Xavier Kurz	13.00
4.	Summary of the comments received from stakeholders by October 9th, 2020	Valerie Strassmann	13.15
5.	Plenary discussion, Questions and Answers	All	13.30
BREAK – 14.00			

SESSION 2: **Stakeholders' perspective on the use of the Guideline for registry-based studies** ***Chair: Sabine Straus***			
6.	- Regulator - Regulator - Registry holder - Pharmaceutical industry - Patients association	- Milena Stain - Marion Haberkamp - Eoin McGrath - Chris Chinn - Mariette Driessens	14.15
7.	Plenary discussion and summary	All	15.15
BREAK – 15.40			

SESSION 3: **Recent experience on methodological aspects of registry-based studies** ***Chair: Xavier Kurz***			
8.	Experience of randomisation within a registry	Barbara Casadei	15.50
9.	Data quality and data verification in registries: results of a stakeholders' survey	Carla Jonker	16.05
10.	Collection of safety information linked to medicinal products through registries: results of a survey among registries listed in the ENCEPP Resources database	Kelly Plueschke	16.20
11.	Plenary discussion	All	16.35
12.	Summary of meeting and next steps	Peter Mol	16.50
End of meeting – 17.00			

Housekeeping notes

- 100 participants in the virtual meeting room (620 requests)
- Q&A at the end of each sessions
- For Q: Please raise your hands (top of screen)
- You can also write in the chat box (bottom left)



- We aim at responding to all questions, either during the workshop or afterwards in writing
- Live broadcast
- Presentations and summary report will be published on EMA website after the meeting
- In case of technical issues, please contact virtualmeetings@ema.europa.eu

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Guideline on registry-based studies

Presented by: Xavier Kurz,
Head of Data Analytics, Data Analytics and Methods Task Force

EMA 25 years

In this presentation:

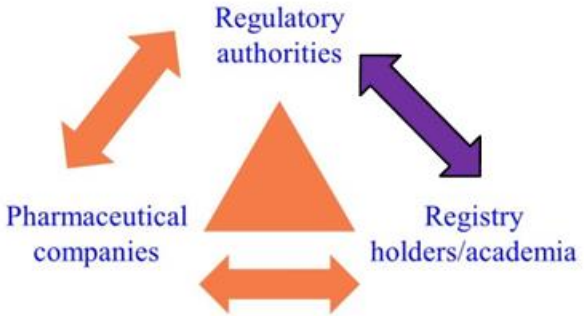
- History
- Objectives
- Scope
- Contents (selected sections)
- Annex: considerations on patient registries
- Appendix 3: safety reporting

History (1)

- EMA Patient registry Initiative launched, September 2015
- 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

History (2)

June 2017 to November 2019: five workshops on disease specific registries

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

November 2018 to June 2019: Public consultation on the Discussion paper "Methodological and operational considerations on the use of patient disease registries for regulatory purposes"

May 2020: Draft of the Guideline adopted by the Cross-Committee Task Force

June 2020: EMA internal consultation

June to August 2020: consultation of EMA Committees and EC

September 2020: publication for public consultation.

October 2020: webinar on the Guideline for registry-based studies

History (3)

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Basis for recommendations

- Existing legislation and regulatory guidelines
- Lessons learned from the disease-specific registries workshops
- CHMP Qualification Opinions for the European Cystic Fibrosis Society Patient- Registry (ECFSPR) and the Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry
- Interactions with marketing authorisation applicants/holders, registry holders, patients' and health care professional associations
- Discussions in EMA Committees and working parties, esp. Scientific Advice WP, CHMP, PRAC
- Existing guidance, incl.
    - PARENT Joint Action Methodological Guidance on Patient registries
    - EUnetHTA's Registry Evaluation and Quality Standards Tool (REQueST)
    - US Agency for Healthcare Research and Quality (AHRQ)'s Users' Guide on registries
    - European Platform on Rare Diseases Registration

Objectives

To provide recommendations on key methodological aspects of **registry-based studies** and the relevant legal basis and regulatory requirements for MAAs/MAHs

- Focus on specific aspects related to use of registries (often include cohorts of patients with pre-defined selection criteria and collection of pre-defined data elements)
- Focus on frequent issues or questions identified in regulatory procedures or discussions with companies and registry holders
- Also relevant to patients and to persons involved in the funding, creation and management of registries, those participating in the collection and analysis of registry data, and those planning to use the registry to perform registry-based studies with a possible regulatory purpose.
- Aspects of patient registries considered important for their use in registry-based studies are included as an Annex.

Scope (1)

Registry-based study

Investigation of a research question using the infrastructure of (a) new or existing registry(-ies) for patient recruitment and data collection.

A registry-based study may be a clinical trial or a non-interventional trial/study.

A registry-based study may apply primary data collection and/or secondary use of data collected through a registry for a purpose other than that of the given study.

The Guideline focusses on studies based on *disease registries* or *condition registries* to study the utilisation, safety and effectiveness of medicines.

From a regulatory perspective: product registry = clinical trial or non-interventional study

Content of guideline

Content: differences between registry-based study and registry

	Registry-based study	Patient registry
1. Definition	Table that highlights differences in methods and processes between a registry-based study and a registry, e.g. • timelines may differ • additional data elements may be required in a study • additional quality control measures may be required in a study	
2. Timelines		
3. Patient enrolment		
4. Data collection		
5. Analysis plan		
6. Data quality control		

Content: planning a registry-based study (1)

Early discussions with regulators about the feasibility of the use of the registry(-ies) to meet regulatory needs.

Scientific Advice, the PRIME procedure, if applicable, and pre-submission meetings should be used in the pre-authorisation phase.

Early discussions should also take place if registry-based studies are planned post-authorisation; they should involve the concerned Rapporteurs or Lead Member States as well as the registry holders and HTA bodies if relevant.

It is the responsibility of the MAA/MAH to involve in the discussion the holders of the registry(-ies) intended to be used.

Content: planning a registry-based study (2)

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Feasibility analysis: performed by the MAA/MAH or research organisation initiating the registry-based study in collaboration with registry holders

Not an obligation but will facilitate the discussion with regulators and other parties

- Description of the registry(-ies) (check list proposed), incl. safety reporting
- Availability of the data elements needed for the study and of the capacity to collect any additional ones or introduce additional data collection
- Processes in place for AEs/ADRs and capacity to introduce additional data collection if needed.
- Data on the numbers of registered patients, active patients and patient flows
- Potential selection bias due to inclusion/exclusion criteria
- Potential confounding if some data elements are not available
- Analytical issues that may arise
- Any data privacy issues and governance-related issues
- Overall evaluation of the suitability of the registry for the specific study.

Differences to be made between elements specific to the registry and elements specific to the registry-based study (e.g. unmeasured potential confounders)

Content: study population

- Choice of study population to be driven by study objective(s)
- Different study populations have different implications, e.g.:
  - newly diagnosed patients entering the registry with a first prescription of the drug of interest
  - patients already diagnosed with the disease and switched from another treatment
  - patients who already received the drug of interest (e.g. in a clinical trial).
- Objective: participation of all individual centres enrolling the population of interest and inclusion and follow-up of all eligible patients treated in these centres.
- Eligible patients not recruited in the study or withdrawing from the study could consent in writing to provide a small set of baseline data.
  - comparison of important socio-demographic and clinical characteristics between recruited patients, withdrawn patients and non-recruited eligible patients
  - documentation of possible selection bias and generalisability of study results.

Content: data analysis

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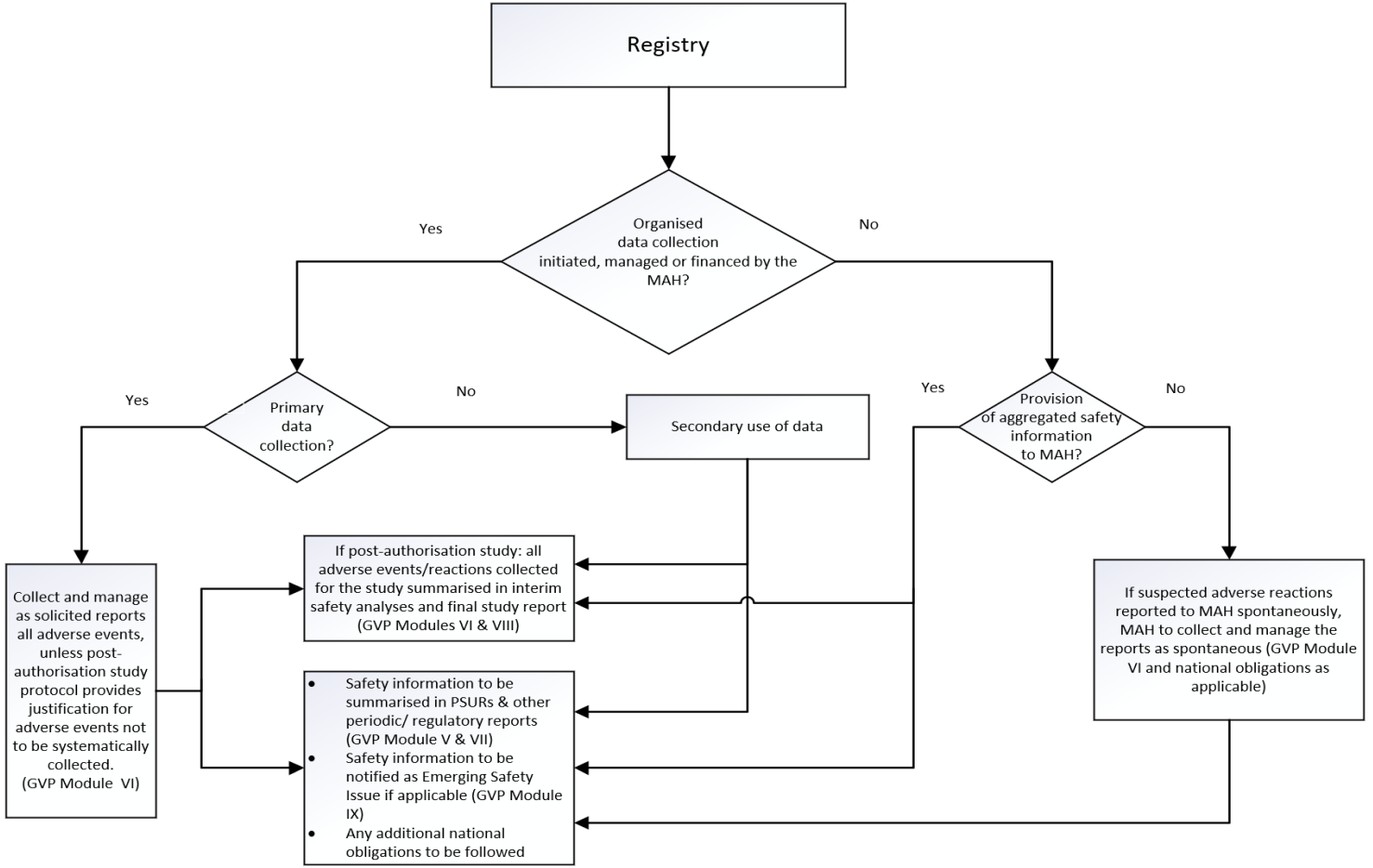
For non-interventional studies:

- Difference between number of individuals experiencing an event and number of events
- Confounding by indication to be addressed as much as possible, e.g. data collection, time-dependent analyses, sensitivity analyses
- Use of prevalent drug users for comparison may introduce bias; incident drug users may reduce sample size and limit duration of follow-up period.
- Immortal time bias to be considered when the follow-up period starts before initiation of the treatment under study; time-dependent analyses may be needed
- Time-related bias and information bias may also occur in a comparison to a historic control group; need to consider changes in treatment options, diagnosis, medical practice in choice of treatments, secular trends, etc.
- Use of a comparative non-exposed control group from outside the registry should ensure that underlying differences between the two populations influencing the risk of outcome occurrence are adequately measured and accounted for in the analysis.

Annex

Safety reporting for non-interventional registry-based study



Further information

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Guideline on registry-based studies – Overview of main comments

Presented by: Valerie Strassmann
EMA Data Analytics and Methods Task Force

Discussion paper: Use of patient disease registries for regulatory purposes – methodological and operational considerations

- September 2019-March 2020: revision by Cross-Committee Task Force on Registries following comments
- Decision to develop a **Guideline on registry-based studies**
- Consultation of the EMA committees and other parties over the summer 2020

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5 November 2018
EMA/763513/2018

Discussion paper:

Use of patient disease registries for regulatory purposes – methodological and operational considerations

The Cross-Committee Task Force on Patient Registries

- **Comments from more than 20 internal stakeholders received**
  - **EMA Scientific Committees,**
  - **EU National Competent Authorities,**
  - **HCP and patient representatives**

Main comments received so far

1. Level of recommendations on registries and registry-based studies
2. Role of "product registries"
3. Distinction between non-interventional and interventional studies
4. Informed consent and GDPR
5. Quality and governance
6. Acceptability of registries for B/R evaluation

1. Level of recommendation on registries versus registry-based studies

- The scope of recommendations from regulatory agencies lies primarily with studies performed by marketing authorisation holders or applicants

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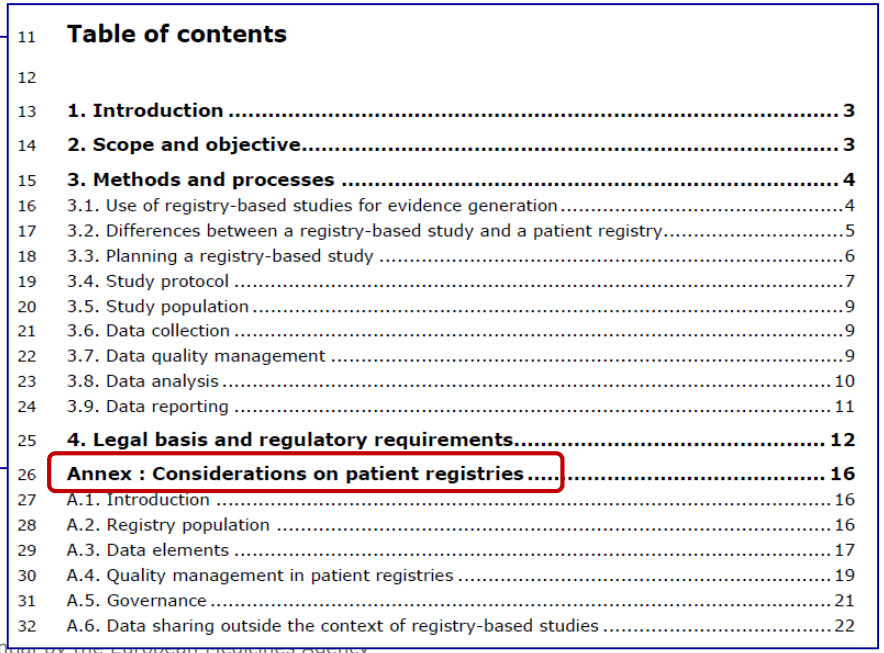
24 September 2020
EMA/502388/2020

Guideline on registry-based studies
Draft



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2. Role of 'product registries'

The term product registry is sometimes used to indicate a system of data collection targeting patients exposed to a specific medicinal product, single substance or therapeutic class and who are followed over time with the aim to evaluate the use, safety, effectiveness or another outcome of this exposure.

This type of data collection system corresponds to a clinical trial or a non-interventional study and does not include specific aspects related to the use of patient registries.

For these reasons, the term product registry is not used in this Guideline.

2. Role of 'product registries'

- **Regulatory perspective:**

  product registry = clinical trial or non-interventional study

  ➔ "product registry-based study" = "study based on study"

  ➔ "product registry" not used and removed from registry definition to avoid confusion

- **Studies focussing on products only ('product registries') are addressed as part of existing guidance on PASS, PAES and clinical trials as applicable**

- **For clarity, use of the wording 'product registry' should be avoided – instead the correct term related to the intended study should be used**

3. Distinction between non-interventional and interventional studies

- Directive 2001/20/EC or Regulation (EU) No 536/2014 (when it becomes applicable) apply (definition of non-interventional studies provided there): see also Annex of Questions & Answers document, Version 11.0
- The guideline on registry-based studies does not change legal interpretation and responsibilities that follow Directive 2001/20/EC or Regulation (EU) No 536/2014

1.10. Question: What can be considered a "non-interventional trial"?

33. **Answer:** According to Article 1(1), 2nd period of Directive 2001/20/EC, non-interventional clinical trials are excluded from the scope of this Directive.

34. "Non-interventional trial" is defined in Article 2(c) of Directive 2001/20/EC as follows: "*a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data*".

35. Thus, a trial is non-interventional if the following requirements are cumulatively fulfilled:

- The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

4. General Data Protection Regulation and informed consent

The guideline on registry-based studies does not change legal interpretation and responsibilities that follow General Data Protection Regulation (GDPR)

Designing a registry-based study also implies to consider how the requirements of the data protection legislation will be fulfilled in terms of adequate ***procurement of patient informed consent****, depending on the type of study (clinical trial vs. non-interventional study) and the* ***patient information consent that was signed when the patient initially registered****.*
The ***study protocol should specify how the data protection regulation will be followed****, e.g. if the data is not already provided in an anonymised way excluding the identification of the patient. […]*

Some registry-based studies ***may require modifications*** *to the existing registry data collection system to address a particular research question, e.g.* ***by adding a specific data collection*** *form or module for additional data collection. The impact of this modification on the legal status of the study should be taken into account as it* ***may require additional informed consent*** *[…]*

5. Data Quality Management (1)

The **nature and extent of the data quality management** for a registry-based study depends on **various factors**, including the **planned use of the study results** and whether the study makes **primary or secondary use** of registry data.

Risk-based methodologies and measures should be planned. In case of a **local data extraction process or manual data entry, routine data quality checks should be performed** to alert on erroneous, missing or out-of-range values and logical inconsistencies, and trigger prompt data verification and remedial measure if needed. The validity of any data cleaning, extraction and transformation processes performed centrally should be verified and monitored, especially if it involves mapping of data to a common terminology. The collected information per time interval for the main outcome parameters should be compared to the amount of expected information. **Other possible measures include random source data verification, on-site review of processes and computerised systems used for data collection and management, and internal or external audit of the registry-based study.**

5. Data Quality Management (2)

The **European Commission's Risk proportionate approaches in clinical trials**, the **EMA Reflection paper on risk-based quality management in clinical trials** and the **GVP Module III on Pharmacovigilance inspections** should be **consulted** on these aspects.

The **thresholds** of data quality measures, the **level** of data verification and the **measures** to be taken in case relevant findings are observed should be **agreed upfront** with the **registry holders**. This **information should be included in the study protocol**.

6. Acceptability of registry-based evidence for regulatory evaluation

On a **case by case** basis, **objectives** may include aspects such as:

- to study natural history of disease
- to provide external or historical control data for clinical trials
- to evaluate effectiveness and/or safety of medicinal products
- to evaluate utilisation of medicinal products

Regulatory context of use

- Supportive evidence
- Main evidence

Feasibility of use

- Feasibility and timing of data generation within registry data to answer the research question

Strength of evidence provided by registry-based data

- Data quality, granularity and amount of data

6. Acceptability of registry-based evidence for regulatory evaluation

- Aspects of use of registry-based data in regulatory evaluations are **complex and need evaluation on a case by case** basis by regulators and the responsible committees
- The use of registry-based data should be **discussed** with rapporteurs and committees **from early stages on** (e.g. seek Scientific Advice, within PRIME discussions, etc.),
- **Proposals** for registry-based studies should be **submitted as early as possible** with as much **details** as possible during applications and procedures to allow for appropriate feedback and planning
- Research question and intended regulatory use should guide the choice of the most appropriate data source

Next steps

- Public consultation has been launched on 24th September:

  https://www.ema.europa.eu/en/news/guideline-registry-based-studies-launch-public-consultation

- **Deadline for comments: 31/12/2020**

- Multi-stakeholders workshop on the draft guideline today
- Q1 2021: update of the guideline based on comments received, following by adoption by the EMA scientific committees later in 2021

Thank you for your attention

Further information

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