CBG MEB
MEDICINES EVALUATION BOARD

Registry-based Real World Data in regulatory decision making

Qualification of Novel Methodology Workshop

Prof. Dr. Peter G.M. Mol

GOOD MEDICINES USED BETTER

university of groningen

University Medical Center Groningen

Looking forward

'By 2025 the use of Real-World Evidence (RWE) will have been enabled and the value will have been established across the spectrum of regulatory use cases'

European Medicines Regulatory Network (EMRN) strategy to 2025

PERSPECTIVES

Clinical Pharmacology & Therapeutics

PERSPECTIVE

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Peter Arlett[1,*], Jesper Kjær[2], Karl Broich[3] and Emer Cooke[1]

regulatory partners. This work also needs to be seen in the wider EU policy context, most notably the European Commission's plans for a European Health Data Space.[7]

Acknowledging different frameworks to conceptualize the challenges and opportunities of RWE, we believe the two main priorities for the European Union are to enable its use and establish its value for regulatory decision making. The EMRN is working to deliver on both priorities

EMA Patient Registry Initiative - 2022

Aims to facilitate use of patient (disease) registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines

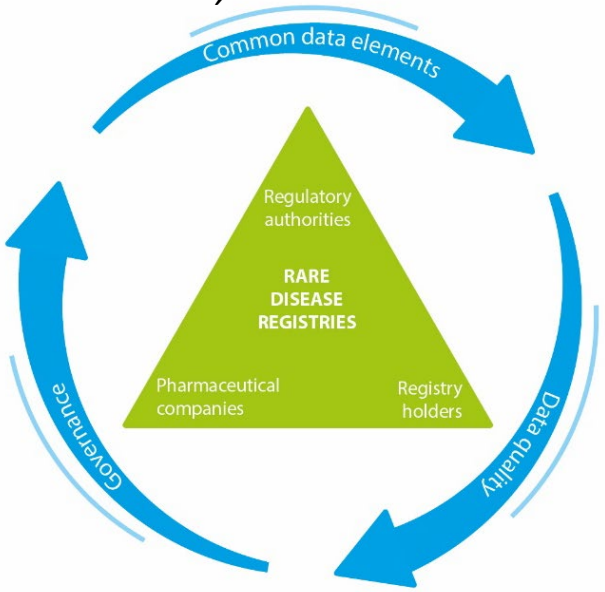
To promote dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries.

To clarify concepts: **registry vs. study** that may be registry-based

Guideline on registry-based studies

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf

Rare disease registries:
a must for regulatory decision making.
Carla Jonker, PhD thesis 2022



https://bit.ly/3HXbqOC

Registries – a lot of effort, heterogeneous data, difficult access

For example, a global review of cardiovascular RWD sources, identified ***322 heart failure data sources*** [Figure], that had ***near complete demographics*** data (94%), ***good coverage of comorbidities*** (77%), **but** where ***drug codes (10%)*** and ***caregiver involvement (6%)*** were ***poorly reported***. Moreover, only few data sources provided information on access to the data for other researchers (11%) – or health authorities – and whether data may be linked to other data sources (20%) [Studer et al., 2021].

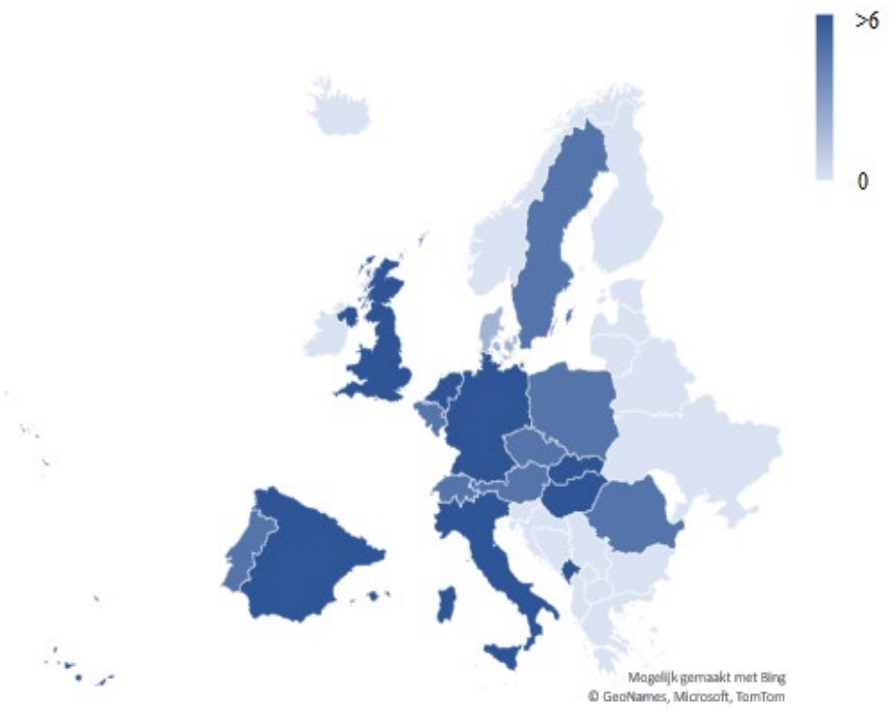
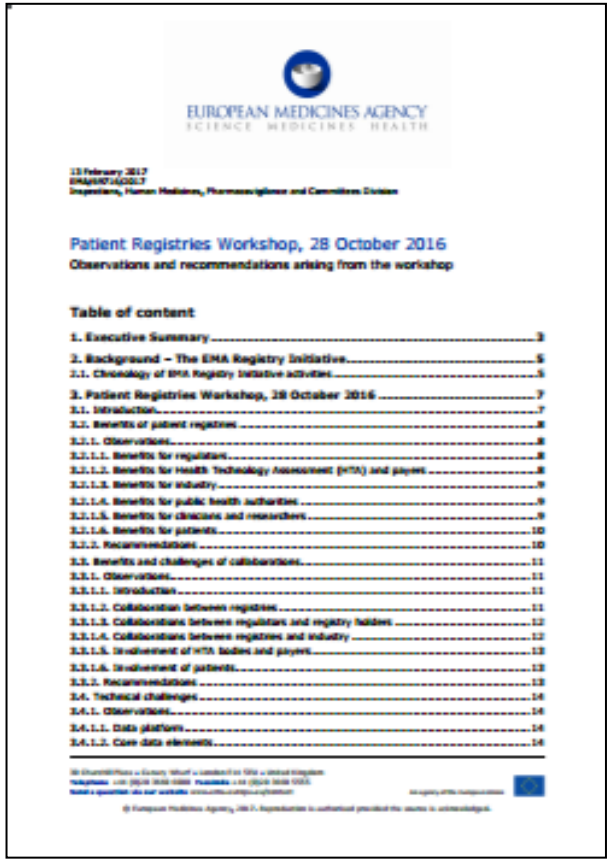


Figure. *Geographical distribution of heart failure data sources in Europe, with darker shades of colour representing more data sources. Adapted from Studer et al., 2022.*

The EMA's Patient Registry Initiative

- Launched, September 2015 – Cross-Committee Task Force
- ***Aims to facilitate use of patient (disease) registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines***
- **Pilot phase, 2016**: Stakeholder feedback encouraged an active role of EU network in supporting collaboration for greater utilisation of disease registries



EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

Patient Registries Workshop, 28 October 2016

Observations and recommendations arising from the workshop

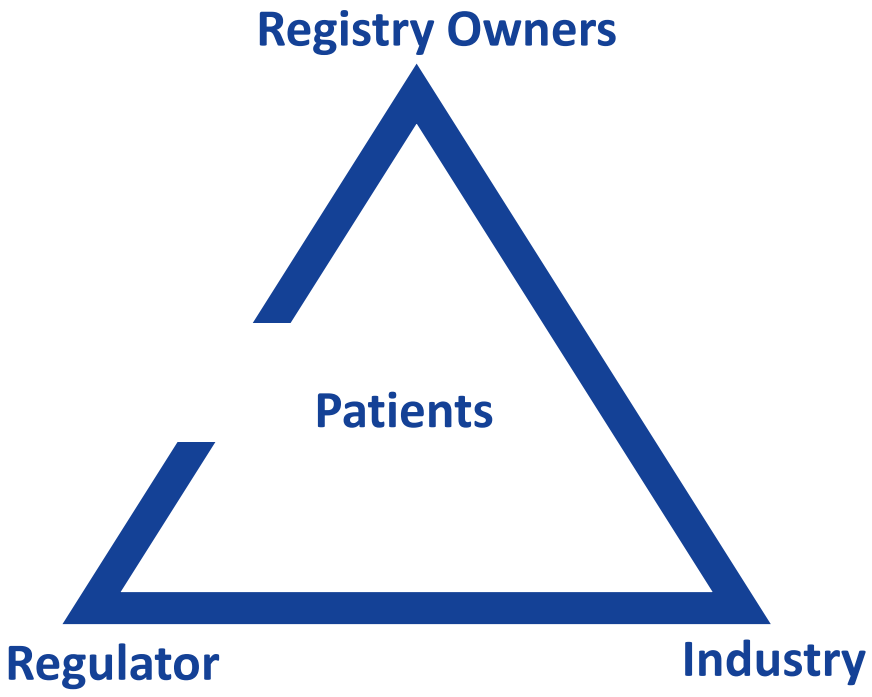
Table of content

Strategy

Patient Registry Initiative strategy - key components

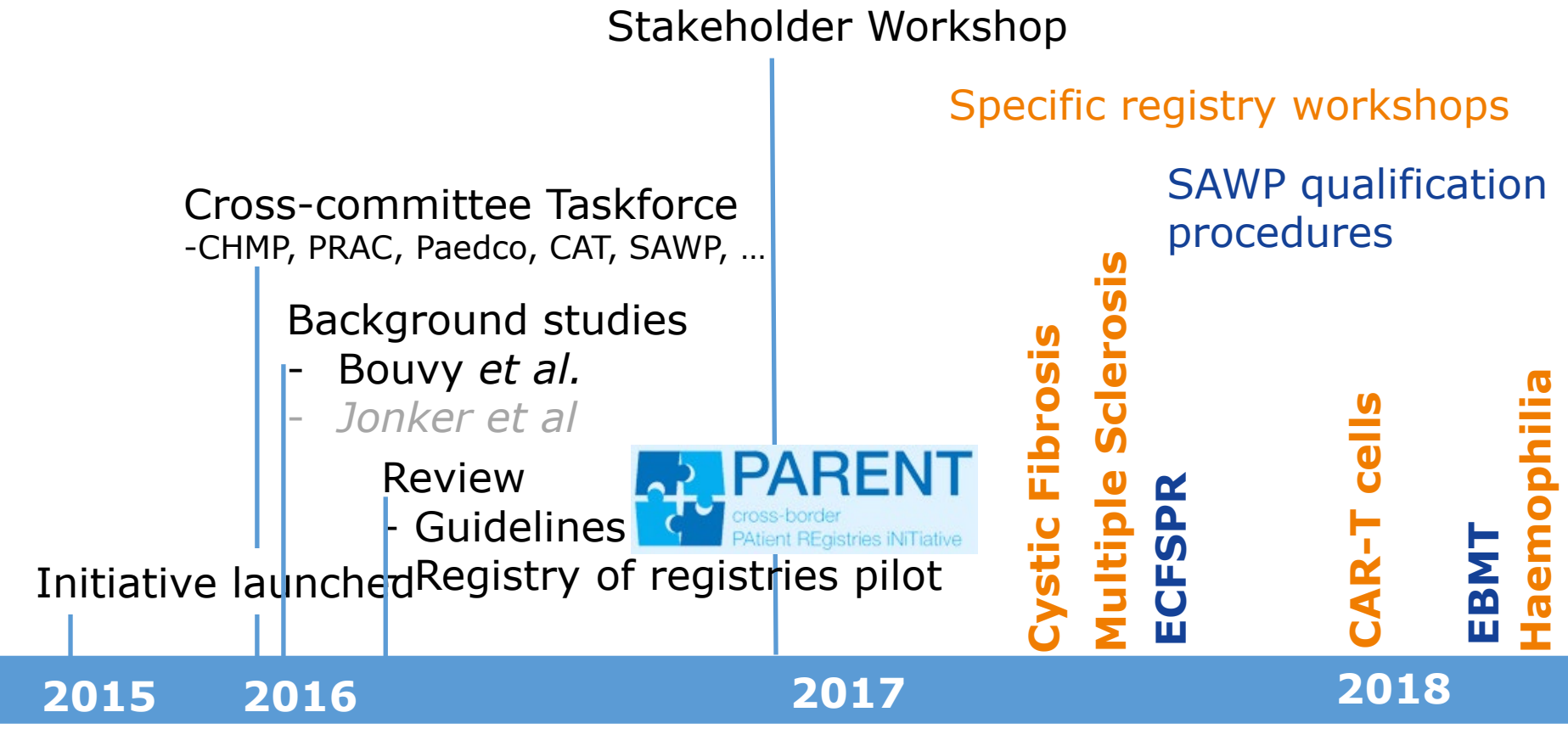
- To promote dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries.

- To clarify concepts: **registry vs. study** that may be registry-based



Source: Nicola Ruperto, PRINTO

Patient Registry Initiative



EMA registries workshops

Cystic Fibrosis Registries Workshop: 14th June 2017

Multiple-Sclerosis Registries Workshop: 7th July 2017

CAR T-Cell therapies Registries Workshop: 9th February 2018

Haemophilia Registries Workshop: 8th June 2018

Participants: regulators, companies, registry holders, health technology assessment bodies, patient and health care representatives

Diseases selection?

- ✓ Products recently authorised or authorisation process ongoing
- ✓ New products - business pipeline
- ✓ EU disease registries have requested support for harmonisation
- ✓ On-going qualification procedures for two EU-wide registry platforms

McGettigan, P *et al. 2019 Drug Safety* https://doi.org/10.1007/s40264-019-00848-9

Tumour-independent …

SCIENCE MEDICINES HEALTH

Medicines | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

Workshop on the role of registries in the monitoring of cancer therapies based on genetic and molecular features

Share

Date: 29/11/2019

Location: European Medicines Agency, Amsterdam, the Netherlands

The aim of the workshop is to investigate the feasibility of using disease registries for cancer therapies based on genetic and molecular features.

The objectives are to agree on:

- core data elements that should be collected in cancer registries to support regulatory assessment of long term safety and effectiveness of new cancer treatments;
- quality assurance measures necessary to ensure registry data are of suitable quality to support regulatory evaluation and to permit registries interoperability;
- practical considerations for accessing and sharing data to be used for regulatory purposes.

Documents

https://www.ema.europa.eu/en/events/workshop-role-registries-monitoring-cancer-therapies-based-genetic-molecular-features

Lessons learned and challenges

Core common data elements

- Participants were able to agree on core data elements to be collected
- Distinction between “must have” and “nice to have” data
- Additional data can be collected if needed to support a study
  - Needs early discussion, flexibility, agreement, registry lead-in time
  - Marketing authorisation applicants need to commit time / personnel long before approval
  - **Careful**: More data ask = more registry workload & risks lower quality data

Lessons learned and challenges

Data Quality

Recurrent concern for registry holders, MAHs/ MAAs and regulators

- Key components of quality:
  - Uniformity, representativeness, consistency, completeness, accuracy, timeliness
- Source data verification procedures needed
- Data quality control system to be established internally
- External audit to be considered
- Data quality indicators to be defined
- Similar data quality in routine collection and in registry-based studies

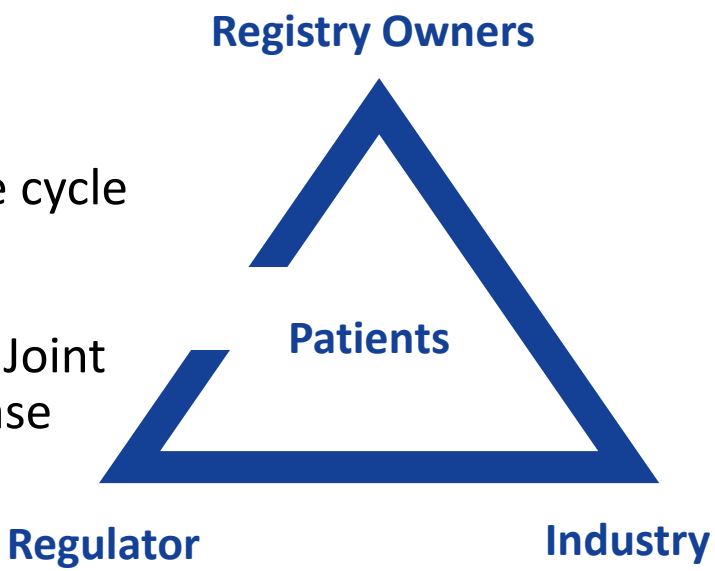
Lessons learned and challenges

Governance

- **Regulators and marketing authorisation holders / applicants (MAHs/MAAs)**
  - Need to be aware of data that can be feasibly be collected by registries
  - Inform registries on their data needs - early discussions
  - Process for collecting and reporting adverse events defined / described in study protocol
- **Registry holders**
  - Consent and governance arrangements align with EU General Data Protection Regulation
  - Develop policy for timely data sharing based on data protection and informed consent
  - Establish a system for centralised data application requests
  - Require sustainable funding for registries
- **All**
  - Transparency on access to, sharing of, and publication of data

How can regulators support use of disease registries?

- **Methodological guidance** on use of disease registries from a regulatory perspective - Will address regulatory requirements and guidance for collecting / reporting AEs and ADRs
- **Scientific Advice** on PASS/PAES study protocol using registries, e.g. joint collaborative studies
- **Inventory of disease registries**
- **Facilitation of interactions** between regulators, industry and registry holders during the entire life cycle of a product
- **Collaboration with EU initiatives**, e.g., EUnetHTA Joint Action 3, EC JRC European Platform on Rare Disease Registration
- **Qualification procedure**



But, no funding of individual registries!

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Guideline on registry-based studies

Draft approved by the Cross-Committee Task Force on Registries	25 May 2020
Draft sent to the EU Regulatory Network for consultation including EMA committees, Patients' and Consumers' Working Party and Healthcare Professionals' Working Party	9 July 2020
Start of public consultation	24 September 2020
End of consultation	31 December 2020
Final guideline agreed by the Cross-Committee Task Force on Registries	7 September 2021
Final guideline adopted by CHMP	16 September 2021

Keywords	**Patient registry, Real World Evidence, Real Word Data, registry-based study, feasibility analysis**

Methodological Guidance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Guideline on registry-based studies

Draft approved by the Cross-Committee Task Force on Registries	25 May 2020
Draft sent to the EU Regulatory Network for consultation including EMA committees, Patients' and Consumers' Working Party and Healthcare Professionals' Working Party	9 July 2020
Start of public consultation	24 September 2020
End of consultation	31 December 2020
Final guideline agreed by the Cross-Committee Task Force on Registries	7 September 2021
Final guideline adopted by CHMP	16 September 2021

Keywords	**Patient registry, Real World Evidence, Real Word Data, registry-based study, feasibility analysis**

Table of contents

Methodological Guidance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2021
EMA/426390/2021
Committee for Human Medicina

Guideline on reg

Draft approved by the Cross-Committee Task Force on Registries	25 May 2020
Draft sent to the EU Regulatory Network for consultation including EMA committees, Patients' and Consumers' Working Party and Healthcare Professionals' Working Party	9 July 2020
Start of public consultation	24 September 2020
End of consultation	31 December 2020
Final guideline agreed by the Cross-Committee Task Force on Registries	7 September 2021
Final guideline adopted by CHMP	16 September 2021

Keywords	**Patient registry, Real World Evidence, Real Word Data, registry-based study, feasibility analysis**

Table of contents

Methodological Guidance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2021
EMA/426390/2021
Committee for Human Medicina

Guideline on reg

Draft approved by the Cross-Committee Task Force on Registries	25 May 2020
Draft sent to the EU Regulatory Network for consultation including EMA committees, Patients' and Consumers' Working Party and Healthcare Professionals' Working Party	9 July 2020
Start of public consultation	24 September 2020
End of consultation	
Final guideline agreed by the Registries	
Final guideline adopted by CHMP	16 September 2021

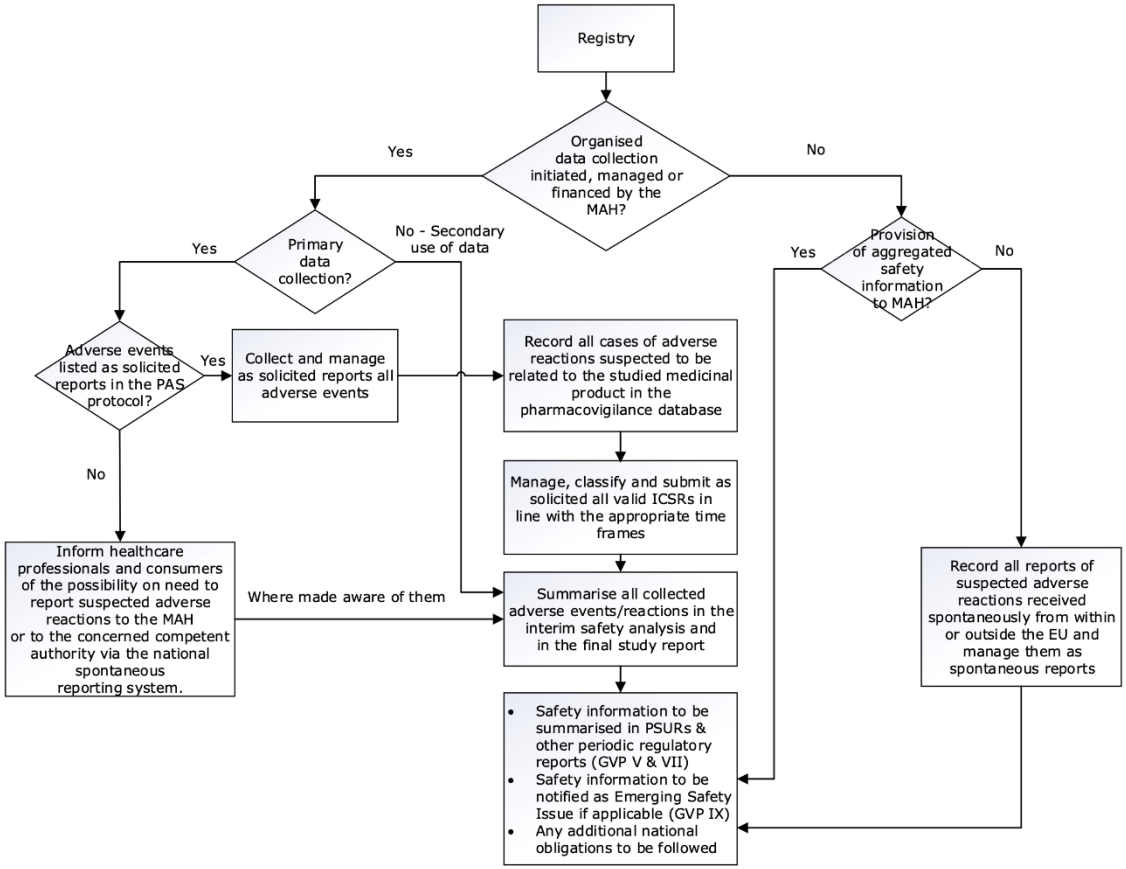
Keywords	**Patient registry, Real World Evidence, Real Word Data, registry-based study, feasibility analysis**

Table of contents

Safety reporting

Appendix 2. *Safety reporting*

Overview of MAH responsibilities for the collection and reporting of adverse events and suspected adverse reactions when a registry-based study fulfils the definition of a non-interventional post-authorisation study according to the clinical trial legislation (GVP Modules VI, VIII).



Qualification of Novel Methodologies

- …on the regulatory validity and acceptability of a specific use of a proposed method in R&D context (in non-clinical and clinical studies)
- Voluntary, scientific pathway for innovative methods or drug development tools (e.g. biomarkers) not yet integrated in the drug development and clinical management paradigm
- One procedure with two outcomes:
  - Qualification Advice, OR
  - Qualification Opinion

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Long-term benefits from EMA perspective: Speed-up the time to regulatory acceptance of novel approaches and time to new marketing authorisations, improve public health

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

Registry Qualification Procedures

Qualified

- Enroll-HD (a Huntington's disease patient registry)
- Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry
- European Cystic Fibrosis Society Patient Registry (ECFSPR)

Letter of Support

- TREAT-NMD Core Dataset for Spinal Muscular Atrophy
- Big MS Data Network (BMSD)

Various other registries got advice only

Registry qualification procedures

Most common proposals

- Post authorisation safety studies

Most common issues

- Data quality ; e.g., source data verification, how guaranteed?
- Data elements – 'need to have' and 'nice to have'
- Comedication / safety data (AEs – SAEs)
- Access to individual patient data

Proof of concept study

- Feasibility
- Missingness

https://doi.org/10.1007/s40264-021-01081-z

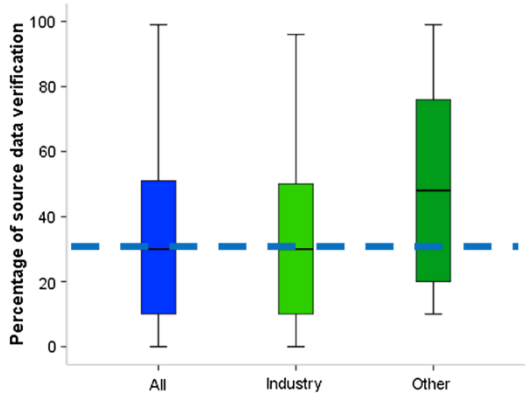


Fig. 3 Percentage of source verification needed that is acceptable by the respondents by stakeholder group (all, industry, other stakeholders)

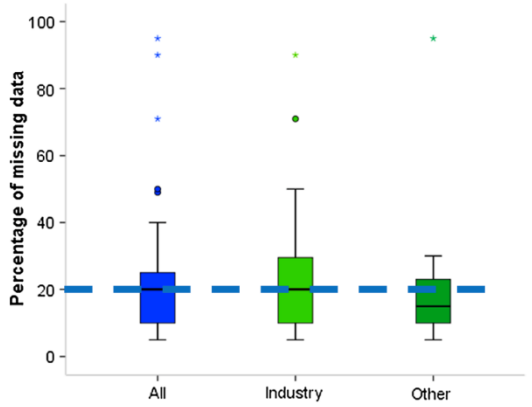
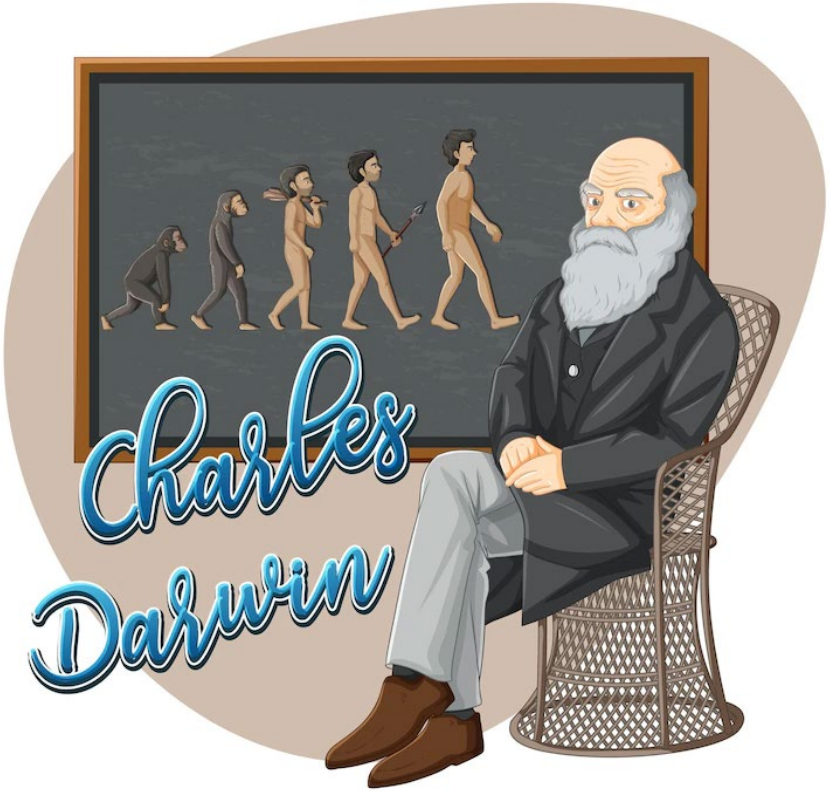


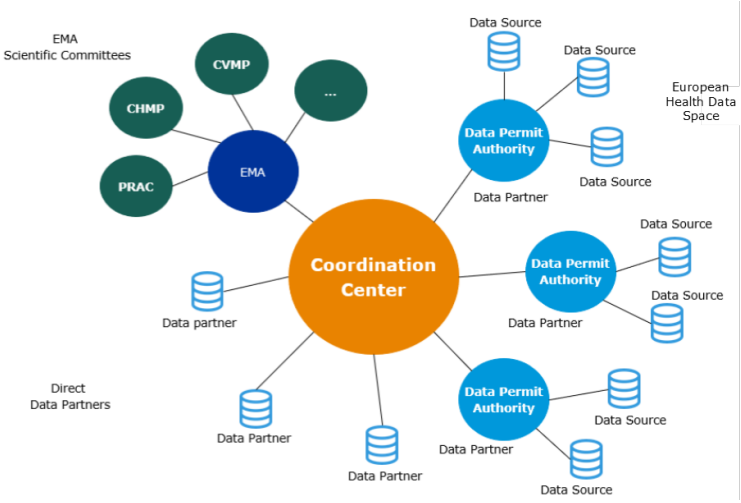
Fig. 4 Percentage of missing data that is acceptable by the respondents by stakeholder group (all, industry, other stakeholders)

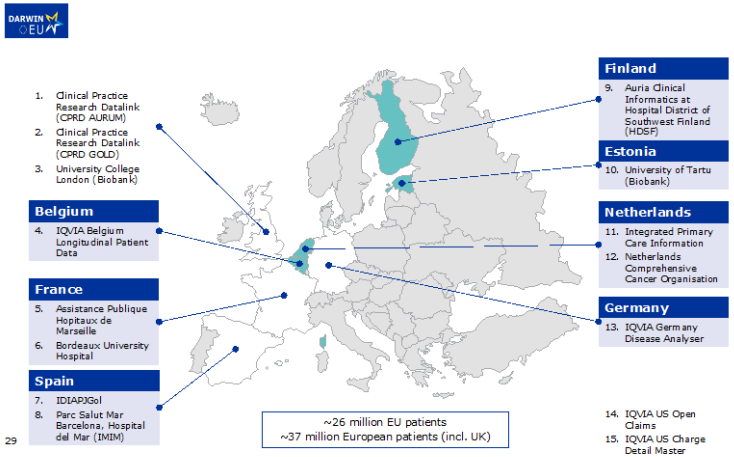
Data Analysis and Real-World Interrogation Network - DARWIN EU®

DARWIN EU is a federated network of data, expertise and services



Achtergrond vector gemaakt door brgfx - nl.freepik.com





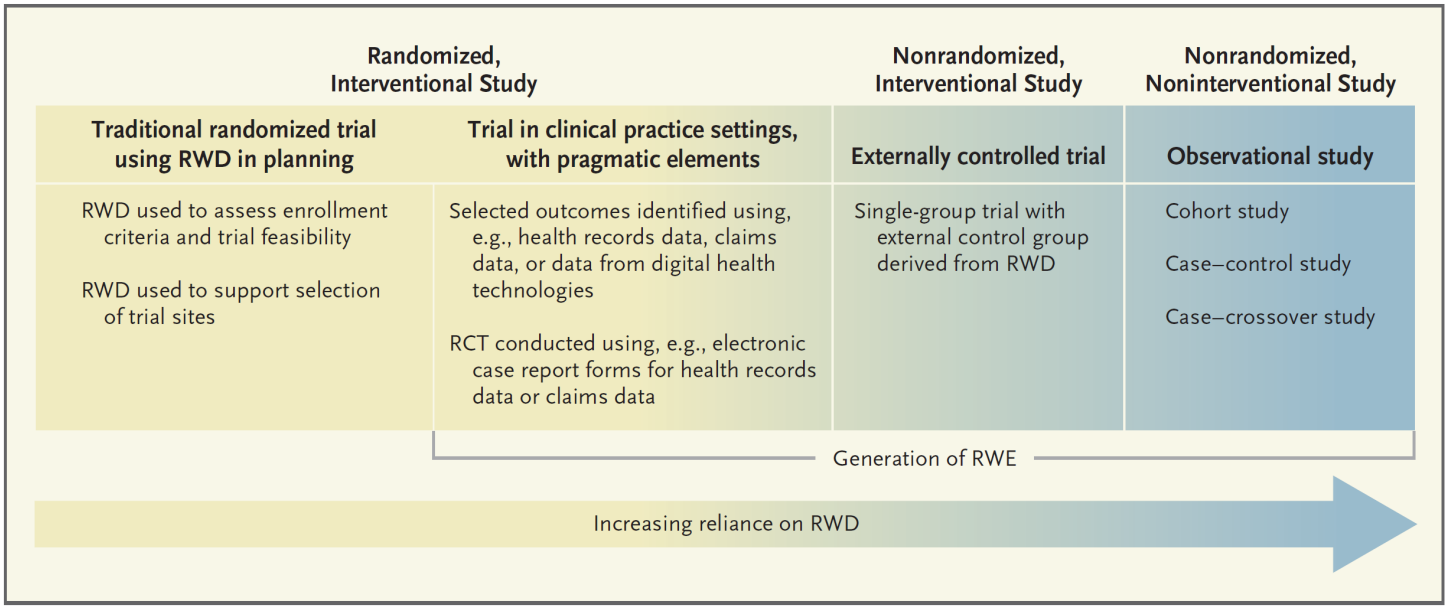
Demand

Three main areas of committees decision-making for which RWE can be requested

Use case objective	Support the planning & validity of applicant studies	Understand clinical context	Investigate associations and impact
Use case category	Design and feasibility of planned studies	Disease epidemiology	Effectiveness and safety studies
	Representativeness and validity of completed studies	Clinical management	Impact of regulatory actions
		Drug utilisation	

Registries could contribute at all these levels

Evidence continuum from trial to RWD



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

Concato *NEJM* 2022 DOI: 10.1056/NEJMp2200089

Evidence continuum from trial to RWD

Randomized, Interventional Study		Nonrandomized, Interventional Study	Nonrandomized, Noninterventional Study
Traditional randomized trial using RWD in planning	**Trial in clinical practice settings, with pragmatic elements**	**Externally controlled trial**	**Observational study**
RWD used to assess enrollment criteria and trial feasibility RWD used to support selection of trial sites	Selected outcomes identified using, e.g., health records data, claims data, or data from digital health technologies RCT conducted using, e.g., electronic case report forms for health records data or claims data	Single-group trial with external control group derived from RWD	Cohort study Case–control study Case–crossover study

Generation of RWE

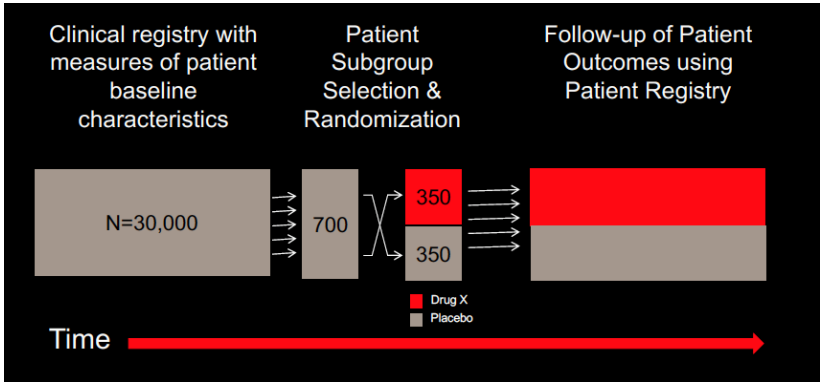
Increasing reliance on RWD

Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

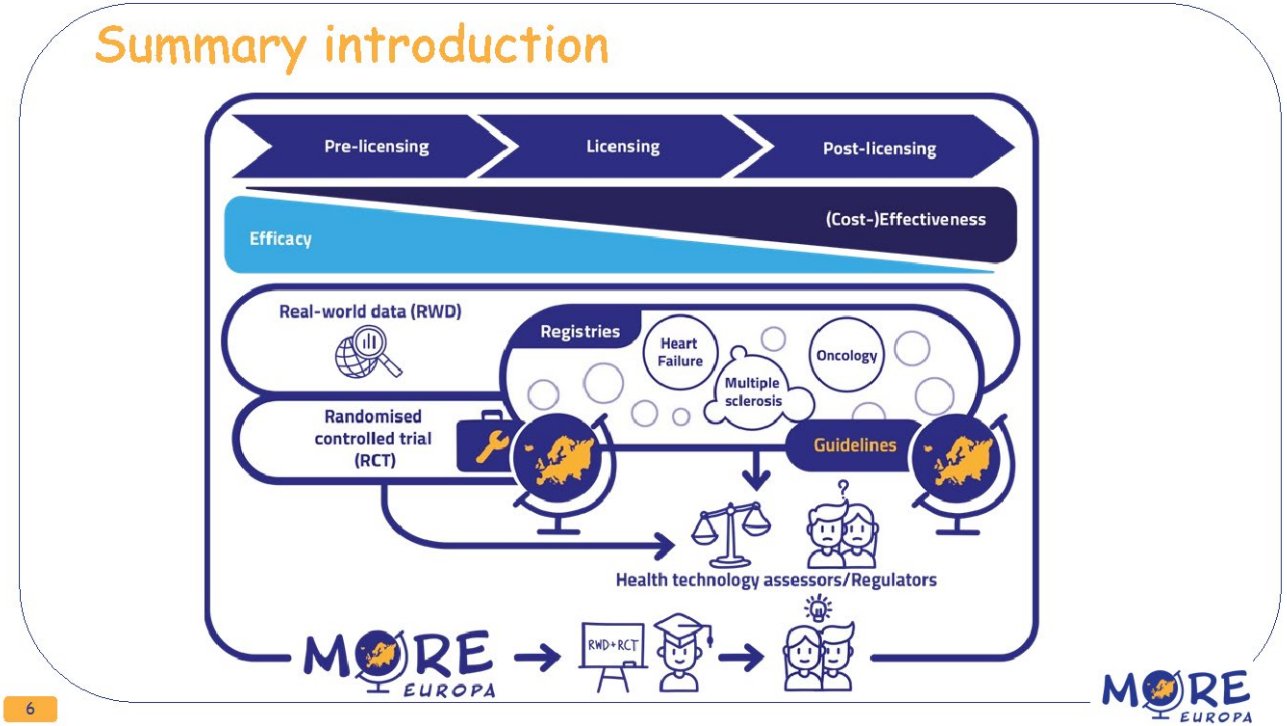
Concato *NEJM* 2022 DOI: 10.1056/NEJMp2200089

Registry-based RCT



(Clinical Trials Transformative Initiative)
https://www.ctti-clinicaltrials.org/projects/registry-trials

- Establish value of registry-based RWD in augmenting RCTs
- Enable more effective and ethical use of registry data to support patient-centered regulatory and health technology assessment decision-making



https://umcgresearch.org/w/more-europa

Registry qualification procedures – take home

Evidentiary standards for regulators are not changed

But, evidence may be derived from multiple data sources

- Electronic Health Records show great promise, but curated ***patient registries*** have (currently) added value [access, governance, more structured outcomes, PROs]
- Qualification:
- Core data elements & quality (defined)
- Timeliness
- Access

- Challenges – safety data collection, timeliness, recruitment/feasibility of registry-based study/ies

CBG MEB
MEDICINES EVALUATION BOARD

Thanks to: Lysbeth Bakker, Kelly Plueschke, Carla Jonker, Viktoriia Starokozhko, Xavier Kurz

GOOD MEDICINES USED BETTER

p.mol@cbg-meb.nl /
p.g.m.mol@umcg.nl

university of groningen

University Medical Center Groningen

Paper just published

ASCPT American Society for Clinical Pharmacology & Therapeutics | Ssc Factuurverwerking En Financiële Dienstverlening | Search | Login / Register

JOURNALS | ASCPT.org

Clinical Pharmacology & Therapeutics

Article | Open Access

Contribution of real-world evidence in EMA regulatory decision making

Elisabeth Bakker, Kelly Plueschke, Carla J. Jonker, Xavier Kurz, Viktoriia Starokozhko, Peter G.M. Mol

First published: 17 October 2022 | https://doi.org/10.1002/cpt.2766

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:10.1002/cpt.2766

PDF TOOLS SHARE

Accepted Articles

Accepted, unedited articles published online and citable. The final edited and typeset version of record will appear in the future.

Related | Information

Recommended

Nonrandomized Real-World Evidence to Support Regulatory Decision Making: Process for a Randomized Trial Replication Project

Jessica M. Franklin, Ajinkya Pawar, David Martin,