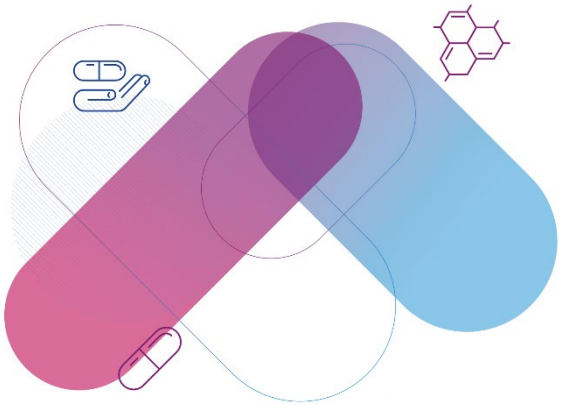
HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Seeing the totality of evidence generation

Bringing better medicines to patients faster



28 November 2024

Session 2 of the HMA/EMA Big Data Forum: Evidence generation to advance regulatory here and now

Presented by Bruno Sepodes
Chair of the Committee of Medicinal Products for Human Use (CHMP), EMA
Co-Chair of the Emergency Task Force (ETF), EMA

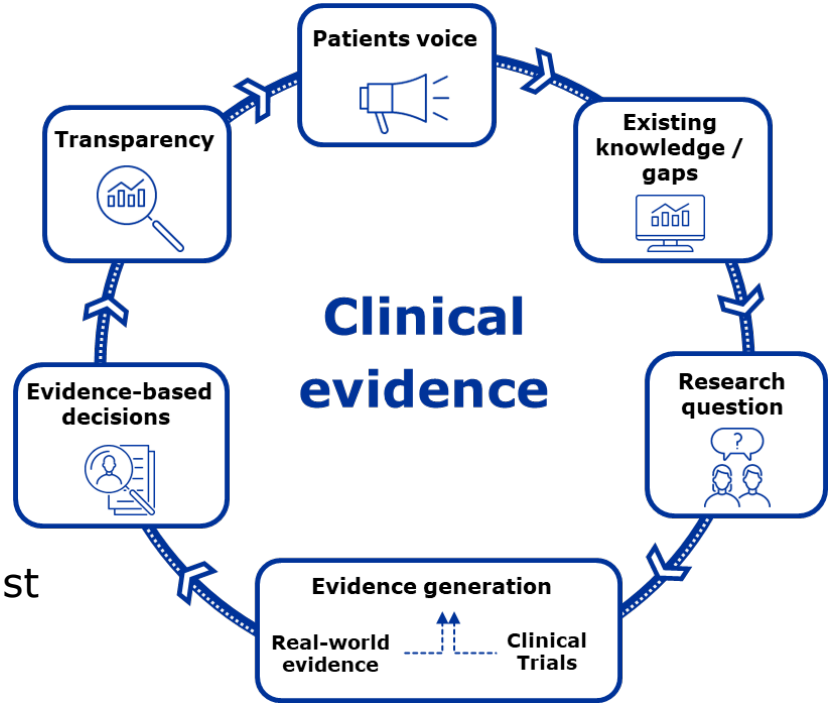
Clinical evidence: drivers for change

- Slow speed and high cost of product development
- Burden of unmet medical need (incl. small pops)
- Changing policy environment (AI, EHDS, NPL)
- Opportunity of greater healthcare data access
- Opportunity of better study methods
- Opportunity of advanced analytics
- Pandemic showed new ways of working

Author: Eoneren | Credits: Getty Images

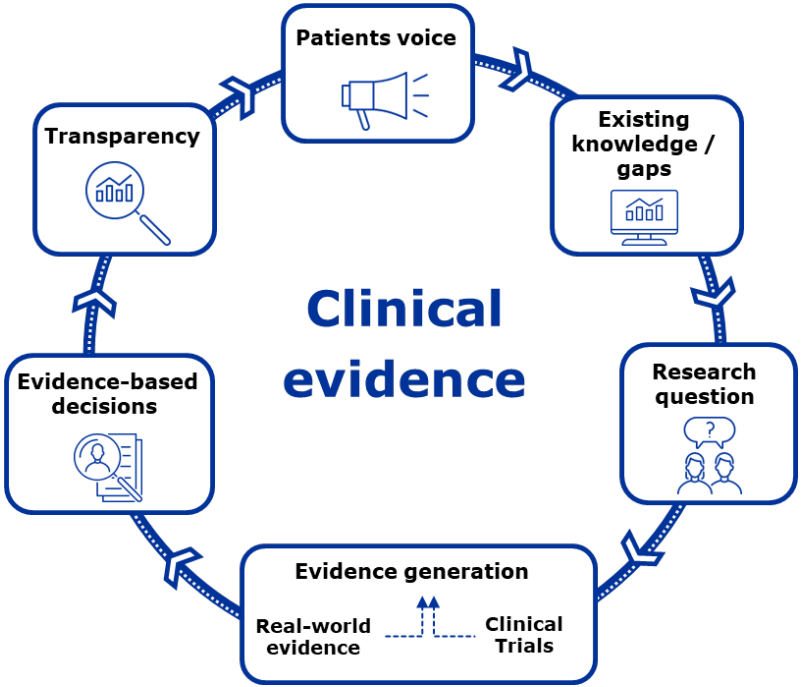
Generating clinical evidence: the shared vision towards 2030

1. Patient voice guides every step of the way
2. Evidence generation is planned and guided by purpose, data, knowledge and expertise
3. Research question drives evidence choice and embraces spectrum of data and methods
4. Clinical trials remain core but are smarter, better and faster
5. Real world evidence is enabled, and its value is established
6. High transparency level underpins societal trust



Patient voice providing guidance

every step of the way:



Multi-stakeholder workshop:
Patient experience data in medicines development and regulatory decision-making

21 September 2022, 10:00 – 16:30 (CEST), EMA, Amsterdam

Background and objectives

Patients have valuable insights and perspectives from living with a condition and its treatment. This includes symptoms, natural history, quality of life, unmet needs, which outcomes are important and preferences for future treatments. Input from patients, as users of medicines, can inform medicine development, enhance regulatory decision making and result in more patient-relevant outcomes.

EMA's Regulatory Science Strategy to 2025 recognises the need to identify optimal approaches for engaging patients in medicines development and benefit-risk assessments, including the development of standards for designing, conducting, analysing and reporting relevant studies incorporating patient experience data for regulatory submission, and to elucidate how such data can best inform regulatory decisions.

This multistakeholder workshop will bring together patients, healthcare professionals, academia, regulators, and industry to discuss ways to improve the collection and use of patient experience data to achieve patient-centred medicine development and regulation.

Patient voice providing guidance

every step of the way:

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 23 May 2024
DOI 10.3389/fmed.2024.1408636

Check for updates

OPEN ACCESS

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RECEIVED 28 March 2024
ACCEPTED 07 May 2024
PUBLISHED 23 May 2024

CITATION
Almeida D, Umuhire D, Gonzalez-Quevedo R,

Leveraging patient experience data to guide medicines development, regulation, access decisions and clinical care in the EU

Diogo Almeida[1,2], Denise Umuhire[3], Rosa Gonzalez-Quevedo[4], Ana António[5], Juan Garcia Burgos[4], Patrice Verpillat[3], Nathalie Bere[6], Bruno Sepodes[1,2†] and Carla Torre[1,2*†]

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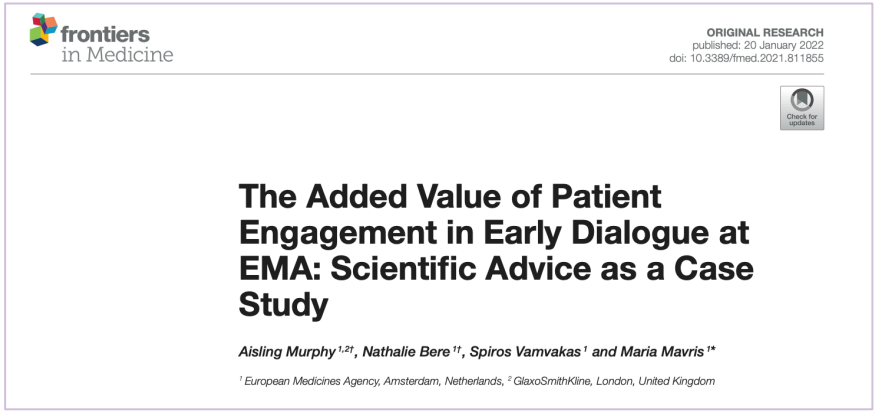

frontiers in Medicine

ORIGINAL RESEARCH
published: 20 January 2022
doi: 10.3389/fmed.2021.811855

Check for updates

The Added Value of Patient Engagement in Early Dialogue at EMA: Scientific Advice as a Case Study

Aisling Murphy[1,2†], Nathalie Bere[1†], Spiros Vamvakas[1] and Maria Mavris[1]*

[1] *European Medicines Agency, Amsterdam, Netherlands,* [2] *GlaxoSmithKline, London, United Kingdom*

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TYPE Review
PUBLISHED 12 August 2022
DOI 10.3389/fmed.2022.968272

Check for updates

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

RECEIVED 13 June 2022

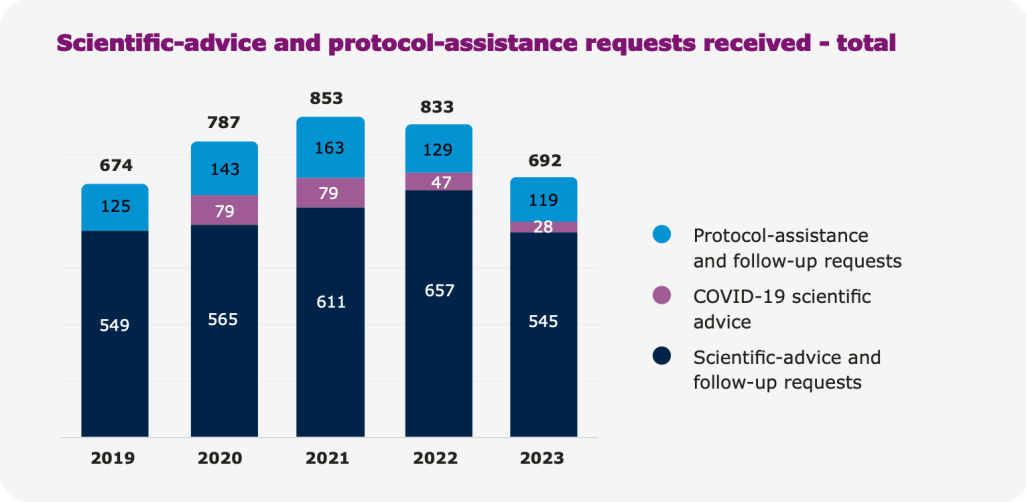
A review of patient-reported outcomes used for regulatory approval of oncology medicinal products in the European Union between 2017 and 2020

Maria Manuel Teixeira[1*], Fábio Cardoso Borges[2], Paula Sousa Ferreira[1,3], João Rocha[1,3], Bruno Sepodes[1,3] and Carla Torre[1,3]

[1]Faculdade de Farmácia da Universidade de Lisboa, Lisbon, Portugal, [2]European Organization for Research and Treatment of Cancer (EORTC), Brussels, Belgium, [3]Laboratory of Systems Integration Pharmacology, Clinical and Regulatory Science, Research Institute for Medicines (iMED.ULisboa), Lisbon, Portugal

Research questions drive the choice of evidence generation

- Strengthening clinical evidence generation through optimal study design
- Supported by Scientific Advice
- Research questions best answered by:
  - Experimental approach (clinical trials)
  - Observations (non-interventional studies)
- Building on existing clinical research frameworks

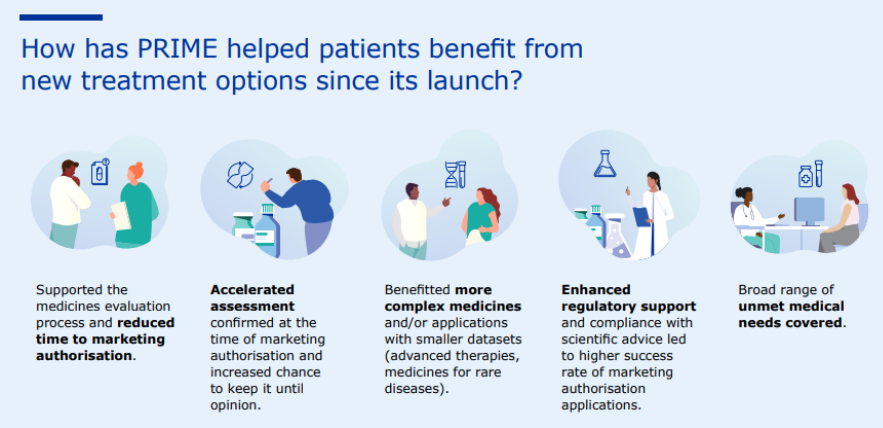


Scientific Advice and R&D support

At the heart of better evidence generation

- Build on PRIME
- Strengthen
- Rationalize and simplify

Key learnings from the PRIME analysis - 5-year experience



Clinical Trials

- Ensuring effective implementation of the Clinical Trials Regulation (including improved CTIS)
- Aligning CT approval with scientific advice
- Multistakeholder platform, with an advisory group of stakeholder representatives
- Supporting non-commercial sponsors
- Enabling innovative approaches
- Establishing place of novel methods including RWE
- Delivering training
- Aligning internationally (including GCP)

Aiming to accelerate change and innovation in clinical trials

The continuum of evidence generation in regulatory decision making

RCTs mainstay of drug efficacy and safety information for regulators/HTAs

Value of RWD is increasingly acknowledged

- Transform, accelerate and de-risk decision making
- Improve efficiency in design and conduct of trials
- Increase public health impact

Marketing Authorisation

- Contextualize study results
- Ensure generalisability of results to target population

Post-Authorisation

- Appreciate real-world value
- Long-term B/R balance

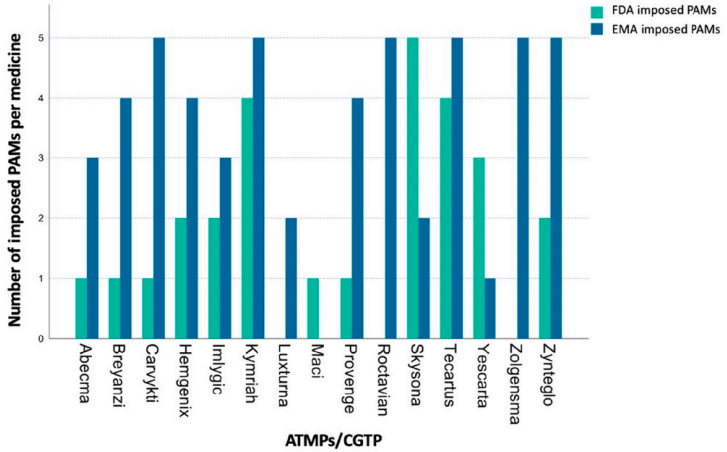
Source:https://copperbowl.de/Chess-Pieces-Tier-List-Cape-Fear-Games-61289.html

Use case example

Comparative Analysis of Post-Authorization Measures for Advanced Medicinal Products Authorized in the European Union and in the United States of America Between 2009 and 2023

Diana Mandslay[1], Diogo Almeida[1,2], Adriana Marques[1,2], João Rocha[1,2], Frantisek Drafi[3,4], Bruno Sepodes[1,2,†] and Carla Torre[1,2,*,†]

In the current landscape, regulatory agencies face the challenge of reconciling timely authorizations for novel medicines addressing life-threatening conditions with thorough evaluations of their benefits and risks. This challenge is pronounced with advanced therapy medicinal products (ATMPs), where expedited approval mechanisms and orphan drug designations are often applied, making post-authorization measures a crucial mechanism to address uncertainties. We compared post-authorization measures imposed by the U.S. Food and Drug Administration and the European Medicines Agency on ATMPs approvals, from 2009 to 2023. A systematic extraction of FDA postmarketing requirements (PMRs) and EMA-imposed post-authorization measures (PAMs) from publicly available regulatory documents was conducted. Descriptive analysis focused on post-authorization measure categories, objectives, study designs, and their status and registration rates. A total of 15 ATMPs were approved in both jurisdictions over the study period. For these products, the EMA imposed 53 PAMs (34 Annex II conditions and 19 Specific Obligations), whereas the FDA imposed 27 PMRs. As of December 2023, 15 EMA-imposed PAMs were fulfilled, with no explicit fulfilments indicated for FDA PMRs. Both agencies promoted real-world data use in around half of the imposed PAMs



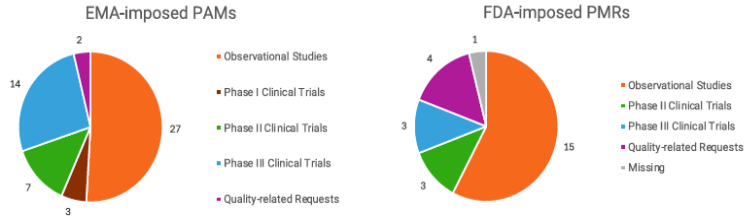
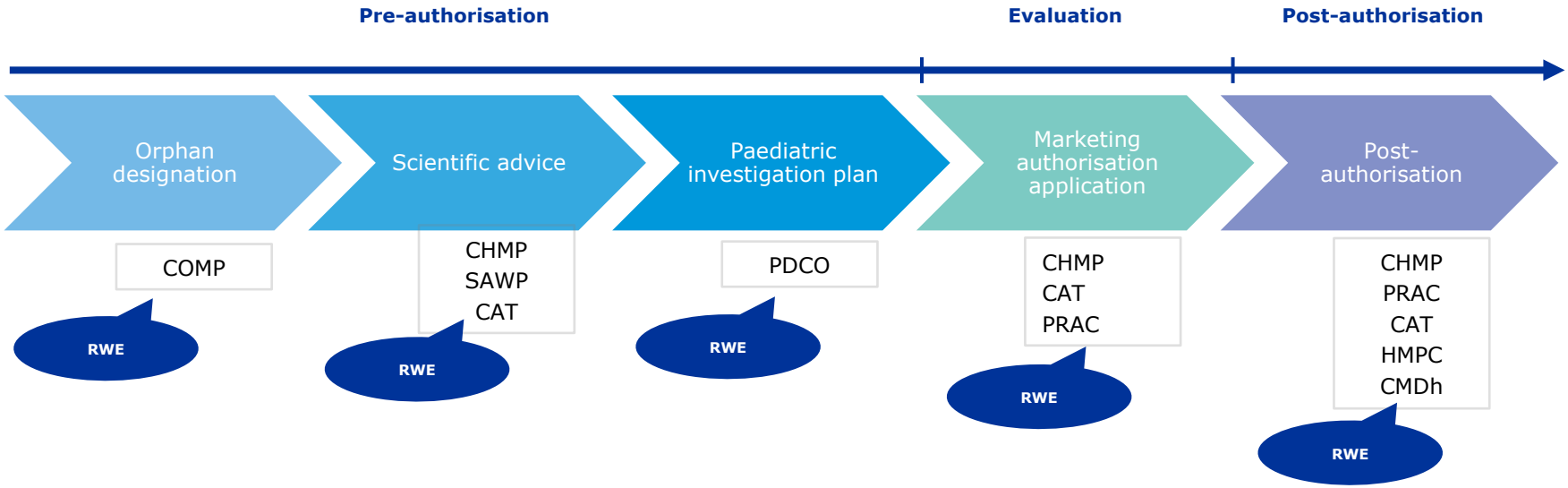


Figure 3 Study design for each PAM imposed by the EMA vs. the FDA. EMA, European Medicines Agency; FDA, Food and Drug Administration; PAM, Post-authorization Measure; PMR, Postmarket Requirement.

Mandslay D et al. Comparative Analysis of Post-Authorization Measures for Advanced Medicinal Products Authorized in the European Union and in the United States of America Between 2009 and 2023. Clin Pharmacol Ther. 2024

RWE use across the medicinal product lifecycle

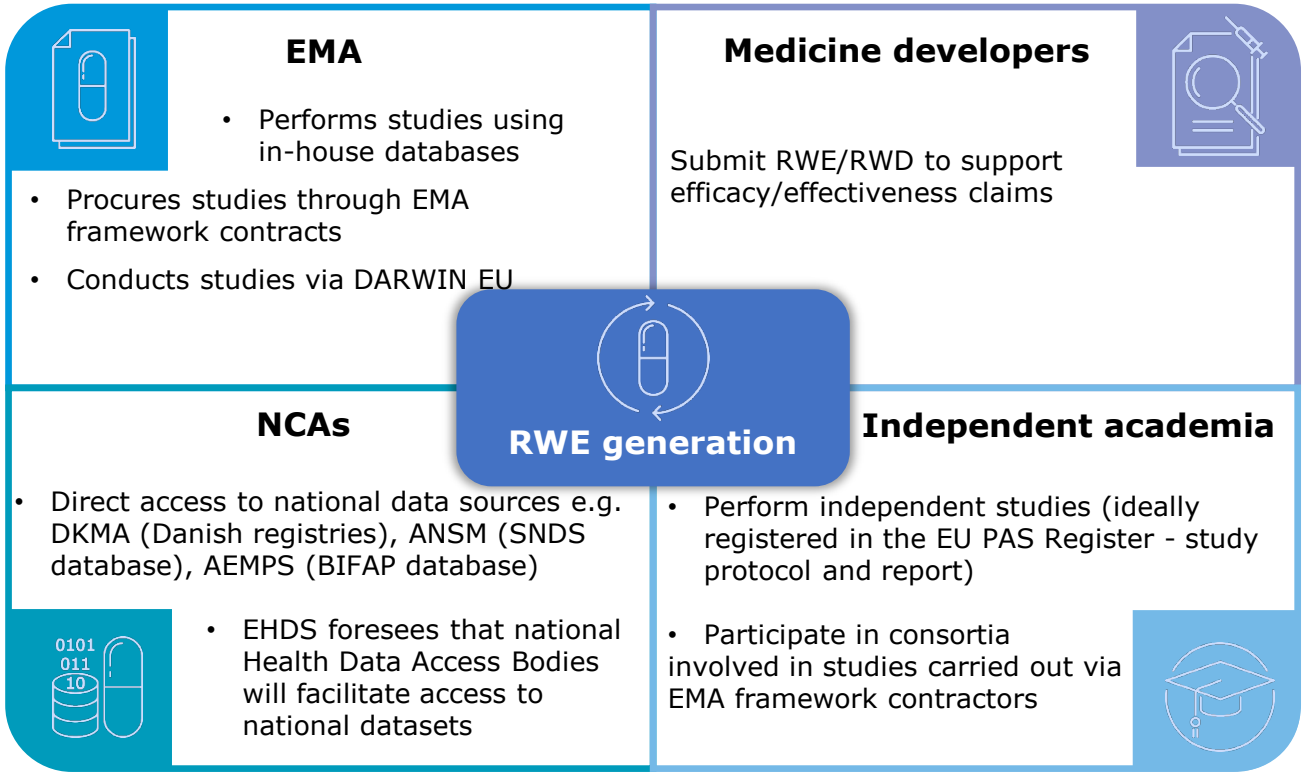


Understand the clinical context

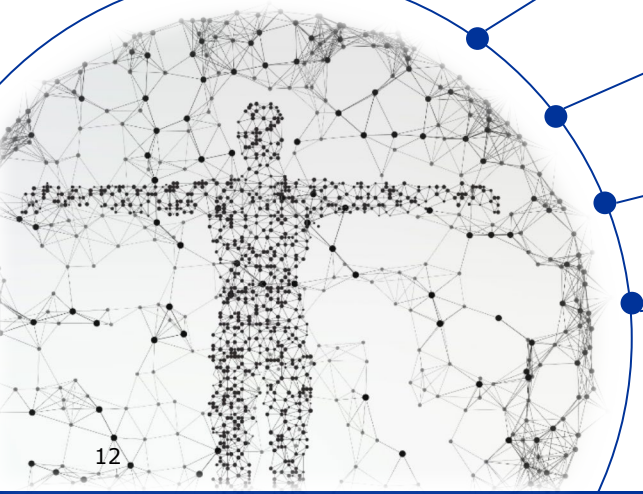
Support the planning and validity

Investigate associations and impact

Real-world evidence generation



What will DARWIN EU® do?



Provide scientific expertise in formulating and executing studies and analyses

Maintain & expand the federated network of data partners, assisting new data holders in conforming with required standards for usage in regulatory context

Conduct scientific studies and analyses on behalf of the EMRN and EMA scientific committees

Deliver training, governance, support of business services

Enable the EMRN, EMA and the scientific committees to make use of the EHDS in the context of medicines regulation, acting as EHDS 'pathfinder'

In the next years, the **use of RWE** will have been **enabled,** and the **value** will have been **established** across the spectrum of regulatory use cases

Real World Evidence

- Establish value across use cases
- Build business processes
- Set standards
- Enable access
- Validate methods
- Train
- Internationalise (build on ICMRA and ICH)

By 2025 DARWIN EU will deliver
More than 100 RWE studies annually

PERSPECTIVES

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]

We outline our vision that by 2025 the use of real-world evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases. We are working to deliver this vision through collaboration where we leverage the best that different stakeholders can bring. This vision will support the development and use of better medicines for patients.

Real-world data (RWD) and real-world evidence (RWE) are already used in the regulation of the development, authorization, and supervision of medicines in the European Union. Their place in safety monitoring and disease epidemiology are well-established while their evidentiary value for additional use cases, notably for demonstrating efficacy, requires further evaluation.[1] During the coronavirus disease 2019 (COVID-19) pandemic, RWE rapidly provided impactful evidence on drug safety, vaccine safety, and effectiveness and we were reminded of the importance of robust study methods and transparency.[2] Our vision, anchored in the European Medicines Regulatory Network (EMRN) strategy to 2025, is that by 2025 the use of RWE will have been enabled and the value will have been established across the spectrum of regulatory use cases.[3] Delivering this vision will support the development and use of better medicines for patients.

In December 2018, the US Food and Drug Administration (FDA) published its framework for RWE underpinned by three pillars: whether RWD are fit for use, whether the study design can provide adequate evidence, and whether the study conduct meets regulatory requirements.[4] In 2019 in the European Union, we published the OPTIMAL framework for RWE also consisting of three pillars: operational, technical, and methodological.[5] More recently, the EU approach places RWE in the wider context of big data and is guided by the priority recommendations of the Big Data Task Force. These recommendations are being implemented through the Big Data Steering Group and the second multi-annual work plan was published in August 2021.[6] Figure 1 represents the workplan with its 11 workstreams which will deliver our vision for RWE by 2025. The workplan places emphasis on collaboration across stakeholders and with international 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 through a collaborative approach where we leverage the best that different stakeholders can bring, and where those stakeholders can complement the central role of industry in generating evidence.

ENABLING USE

To enable use, we are working on multiple fronts with our stakeholders, including patients, healthcare professionals, industry, regulatory and public health agencies, health technology assessment bodies, payers, and academia. We are initiating work to establish a data quality framework, not just for RWD but for all data used in regulatory decision making. We are striving to improve the discoverability (findability) of RWD through agreement of metadata for RWD and through a public catalogue of RWD sources[8] that builds on the early work of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Guide on Methodological Standards in Pharmacoepidemiology,[9] extensively updated in 2021, is the core of our efforts to drive up the standards of study methods for RWE, and this is complemented by recently published guidance on conducting studies based on patient registries.[10]

The European Medicines Agency (EMA) and some national medicines agencies

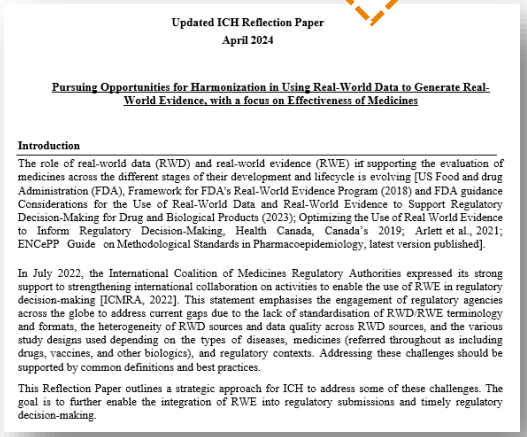
[1]European Medicines Agency, Amsterdam, Netherlands; [2]Danish Medicines Agency, Copenhagen, Denmark; [3]BfArM, Bonn, Germany. *Correspondence: Peter Arlett (Peter.Arlett@ema.europa.eu)

Received March 1, 2021; accepted November 1, 2021. doi:10.1002/cpt.2479

International collaboration and convergence

2022 ICMRA RWE statement

ICH Reflection Paper for convergence on RWE terminology, format of study protocols and reports, and study transparency



Updated ICH Reflection Paper
April 2024

Pursuing Opportunities for Harmonization in Using Real-World Data to Generate Real-World Evidence, with a focus on Effectiveness of Medicines

Introduction

The role of real-world data (RWD) and real-world evidence (RWE) in supporting the evaluation of medicines across the different stages of their development and lifecycle is evolving [US Food and drug Administration (FDA), Framework for FDA's Real-World Evidence Program (2018) and FDA guidance Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (2023); Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making, Health Canada, Canada's 2019; Arlett et al., 2021; ENCePP Guide on Methodological Standards in Pharmacoepidemiology, latest version published].

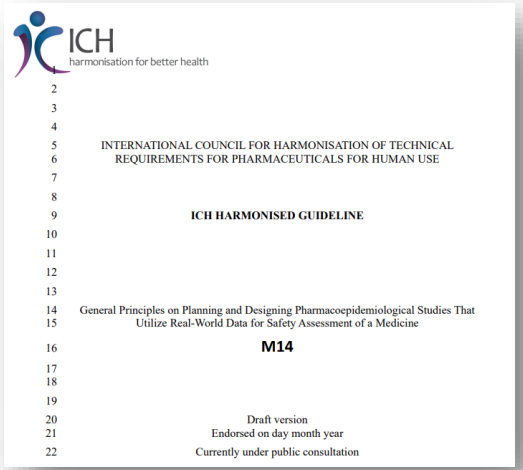
In July 2022, the International Coalition of Medicines Regulatory Authorities expressed its strong support to strengthening international collaboration on activities to enable the use of RWE in regulatory decision-making [ICMRA, 2022]. This statement emphasises the engagement of regulatory agencies across the globe to address current gaps due to the lack of standardisation of RWD/RWE terminology and formats, the heterogeneity of RWD sources and data quality across RWD sources, and the various study designs used depending on the types of diseases, medicines (referred throughout as including drugs, vaccines, and other biologics), and regulatory contexts. Addressing these challenges should be supported by common definitions and best practices.

This Reflection Paper outlines a strategic approach for ICH to address some of these challenges. The goal is to further enable the integration of RWE into regulatory submissions and timely regulatory decision-making.

ICMRA COVID-19 Real-World Evidence (RWE) and Observational Studies Working Group

ICMRA Working Group on Real-World Evidence for Public Health Emergencies co-chaired by EMA & Health Canada, to facilitate international collaborations between interested regulatory agencies to proactively enhance the efficiency of critical responses in case of new PHEs through collaborative studies

ICH M14 Guideline on non-interventional pharmacoepidemiological studies for safety assessment of medicines → Public consultation on draft guideline (Step 2) on-going, establishment Jan 2025



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

General Principles on Planning and Designing Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of a Medicine

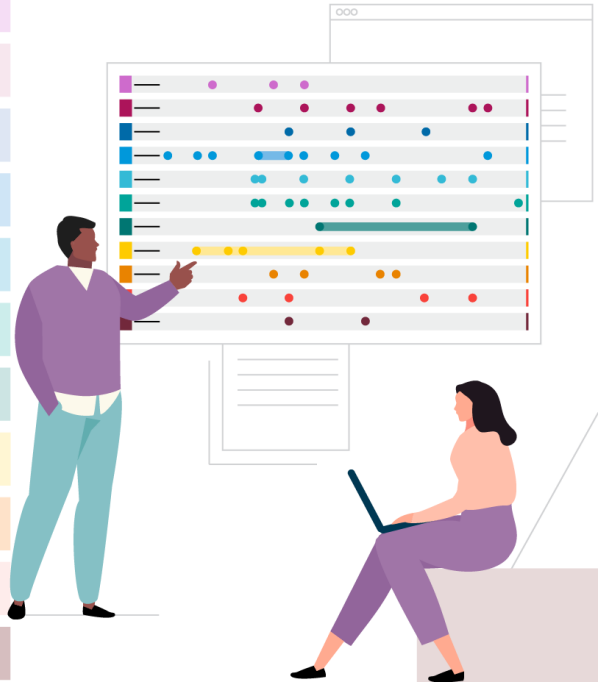
M14

Draft version
Endorsed on day month year
Currently under public consultation

Big Data Steering Group Workplan 2023-2025

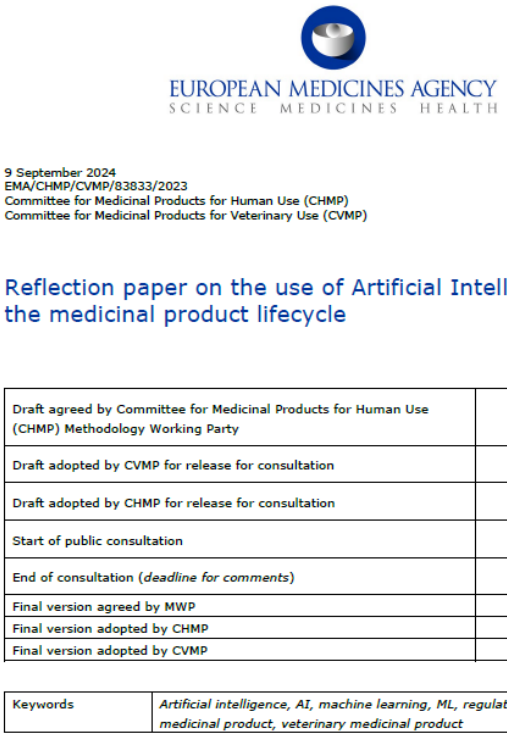
Framework - to enable use of data and facilitate its integration into regulatory decision making

- DARWIN EU
- Data quality & representativeness
- Data discoverability
- EU Network skills
- EU Network processes
- Network capability to analyse
- Delivery of expert advice
- Governance framework
- International initiatives
- Stakeholder engagement
- Veterinary recommendations



Artificial Intelligence

- In regulatory processes
- In clinical research
- In devices used in clinical practice
- Validate algorithms
- Establish processes
- Train
- Align internationally



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 September 2024
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Draft agreed by Committee for Medicinal Products for Human Use (CHMP) Methodology Working Party	July 2023
Draft adopted by CVMP for release for consultation	13 July 2023
Draft adopted by CHMP for release for consultation	10 July 2023
Start of public consultation	19 July 2023
End of consultation (*deadline for comments*)	31 December 2023
Final version agreed by MWP	6 September 2024
Final version adopted by CHMP	9 September 2024
Final version adopted by CVMP	11 September 2024

Keywords	*Artificial intelligence, AI, machine learning, ML, regulatory, medicine, human medicinal product, veterinary medicinal product*

Working with HTA and Payers

- Pre-approval joint advice procedures are successful and highly valued by all stakeholders
- Information exchange at the time of regulatory decision is coming together: the EPAR can be further optimised
- Collaboration on post-licensing evidence generation requirements shows potential – pilots through DARWIN EU in 2023/4

Jansen et al. (valueinhealthjournal.com)

ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

Strengthening the Interface of Evidence-Based Decision Making Across European Regulators and Health Technology Assessment Bodies

Ella Jansen, MSc, Philip A. Hines, MSc, Michael Berntgen, PhD, Angela Brand, PhD

Table 3. Pairwise comparison of clinical evidence use between 8 EPARs and corresponding rapid REAs.

	EPAR (8)	Rapid REA (8)
Active comparator used	2	6
Active comparator and placebo used	0	0
Surrogate endpoint as primary endpoint in efficacy/effectiveness domain	4	1
QOL measurement present	6	5
Perceived importance of QOL measurement	2 secondary endpoint, 5 exploratory endpoint, 1 not mentioned	6 critical endpoint, 1 secondary endpoint, 1 not mentioned
Subgroup analysis present	8	7
Discussion on reasons to include certain subgroup analyses	2 and 4 only partially	5
Assessment of risk of bias/strength of evidence reported	2	8
Requests for additional information fulfilled by the developer	7 and 1 not applicable	3

EPAR indicates European Public Assessment Report; QOL, quality of life; REA, relative effectiveness assessment.

Pharmacovigilance

- Smarter collection and reporting of safety reports of suspected adverse reactions
- Measurement of on-market performance of key new medicines using RWE
- Improved engagement between regulators, patients and healthcare professionals to optimise risk minimisation

PERSPECTIVES

PERSPECTIVE

Pharmacovigilance 2030 Invited Commentary for the January 2020 "Futures" Edition of *Clinical Pharmacology and Therapeutics*

Peter Arlett[1]*, Sabine Straus[2] and Guido Rasi[1]

A new healthcare system is emerging that encompasses systems approaches to biology and medicine, radically enhanced capabilities for collecting, integrating, storing, analyzing, and communicating data and information, and increasing numbers of networked and activated patients and consumers.

Pharmacovigilance systems around the world have come a long way in the last 60 years. Systems have evolved from reliance on the individual case safety report (ICSR) of suspected adverse drug reactions (ADRs), through addition of the periodic safety update report, and risk management plan, to the current era where many stringent regulators have a pallet of regulatory tools and access to an ever increasing spectrum of data sources, real-world or otherwise. Modern systems also leverage the collaborative efforts of multiple stakeholders, notably the biopharmaceutical industry, regulators, healthcare professionals, patients, and academia.

Pharmacovigilance is well stocked with clairvoyants who have made many claims, sometimes wild, for the future, including that we will rely on artificial intelligence and robotics, that the ICSR is dead (or should be dead), or that mobile health holds the ultimate promise for increasing engagement and impact.[1] There is no doubt that technology is advancing rapidly, that the accumulation of data is increasing logarithmically, and that society is changing, particularly the engagement of patients in healthcare decision making. However, some things stay the same. The ultimate goal remains to optimize the safe and effective use of medicines so patients can benefit in terms of health and quality of life while suffering the minimum of side-effects. The challenges to optimizing safe and effective use of medicines are common to all regulatory and healthcare systems: how to influence the behavior of patients and healthcare professionals based on robust evidence and sound decision making.

We make three predictions for pharmacovigilance in 2030. (1) Collection and reporting of ICSRs will be smarter. (2) Measurement of on-market performance of medicines will inform decision makers and users of medicines. (3) Improved engagement of patients and healthcare professionals will increase the impact of pharmacovigilance.

PREDICTION 1: SMARTER COLLECTION AND REPORTING OF ICSRS

By the end of 2018 EudraVigilance, the European database of ICSRs held over 14 million case reports and VigiBase, the World Health Organization (WHO) database held over 20 million. Although only representing a snapshot in time, these are electronic health records and have the huge value of capturing a suspicion of a patient or health care professional that a medicine may have caused an adverse reaction. With the onset of the digitalization of health care, there is the opportunity to access more and better data and provide alternative approaches in pharmacovigilance, including both the detection and evaluation of ADRs. This means that we need to design our systems based on an abundance of data rather than a scarcity.[2] However, over recent years, the proportion of new drug safety issues detected from ICSRs has been high at around 55%,[3] and the number of product withdrawals based partly or wholly on ICSRs has also remained high.[4] These observations have occurred despite the increasing interest in other data sources for signal detection. The evidence suggests that ICSRs remain a very useful data source for detecting potential new safety issues, whereas electronic health records (EHRs) are more useful for evaluating the issues already detected. This is in line with the principle of hypothesis testing in a dataset separate from that in which the hypothesis was generated.

We do not question that there are opportunities to improve the collection and management of ICSRs,[5] and in the way such reports are submitted to regulators. We also acknowledge that the investment in the collection and management of ICSRs has been and continues to be high. However, we believe that by 2030 ICSR reporting

[1]European Medicines Agency, Amsterdam, The Netherlands; [2]Medicines Evaluation Board, Utrecht, The Netherlands. *Correspondence: Peter Arlett (Peter.Arlett@ema.europa.eu)

Received August 14, 2019; accepted October 15, 2019. doi:10.1002/cpt.1689

Special Populations

- Neonates
- Children
- Pregnant women
- Breast feeding women
- Frail and very elderly
- Very small populations

Source: bigstock 139255382 scaled

Planned, inclusive and expert use of the spectrum of data and methods can generate evidence for decision-making across populations

Summary

We must seize the opportunity to get better medicines to patients faster

- Slow speed and high cost of product development leave unmet medical need
- Mandate for change from Network and Pharma strategies
- We are on a journey, <u>together</u> with interested parties and guided by patients
- The big picture of evidence generation:
  - planned based on knowledge and expertise
  - embracing the spectrum of data and methods
  - New approaches enabled and validated

At the core of a successful MA dossier is always **<u>excellent</u>** clinical evidence

Thank you for listening

Further information

See websites for contact details

Heads of Medicines Agencies www.hma.eu
European Medicines Agency www.ema.europa.eu

The European Medicines Agency is an agency of the European Union

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