Session IV: Health Technology Assessment, Real World Data

How can academia build capacity to optimise RWD collection in order to support health technology assessment in paediatrics

Enpr-EMA – October 2nd 2024.

Presented by Denise Umuhire, Kelly Plueschke
Data Analytics and Methods taskforce, Real World Evidence Workstream

Disclaimer

The presenter does not have any conflict of interest.

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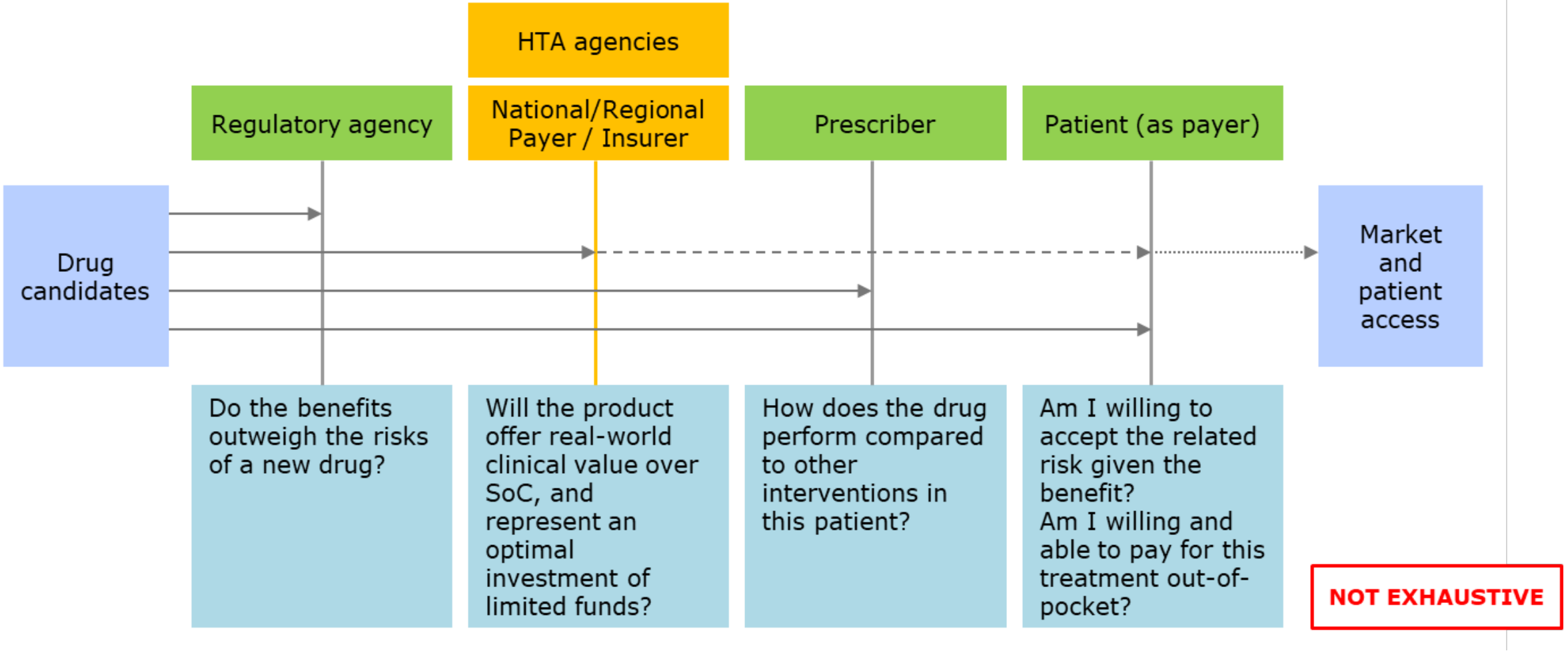
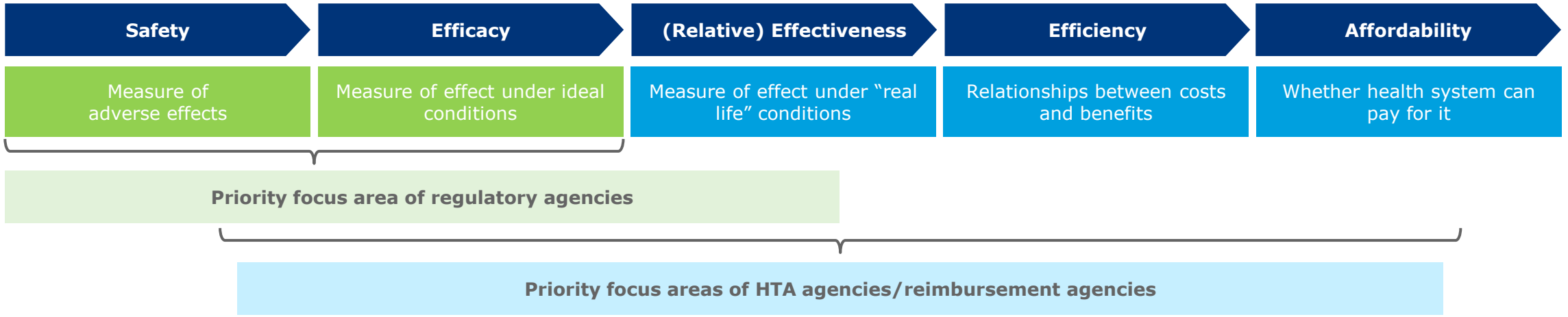
HTAs & Regulators – different questions, different but integrated evidence needs

Different (core) questions for different decision-makers



Eichler HG et al. Nat Rev Drug Disc 2010

“Traditional” priority assessment focus between regulatory and HTA/payers



HTA regulation

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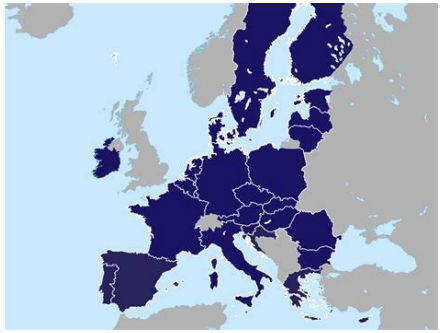
Health Technology Assessment (HTA)



HTA regulation

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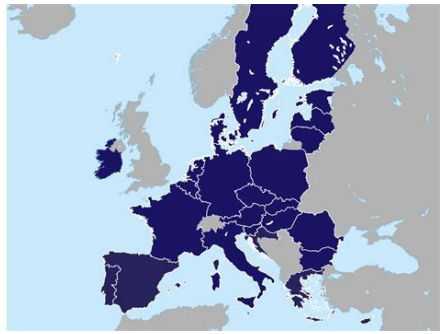
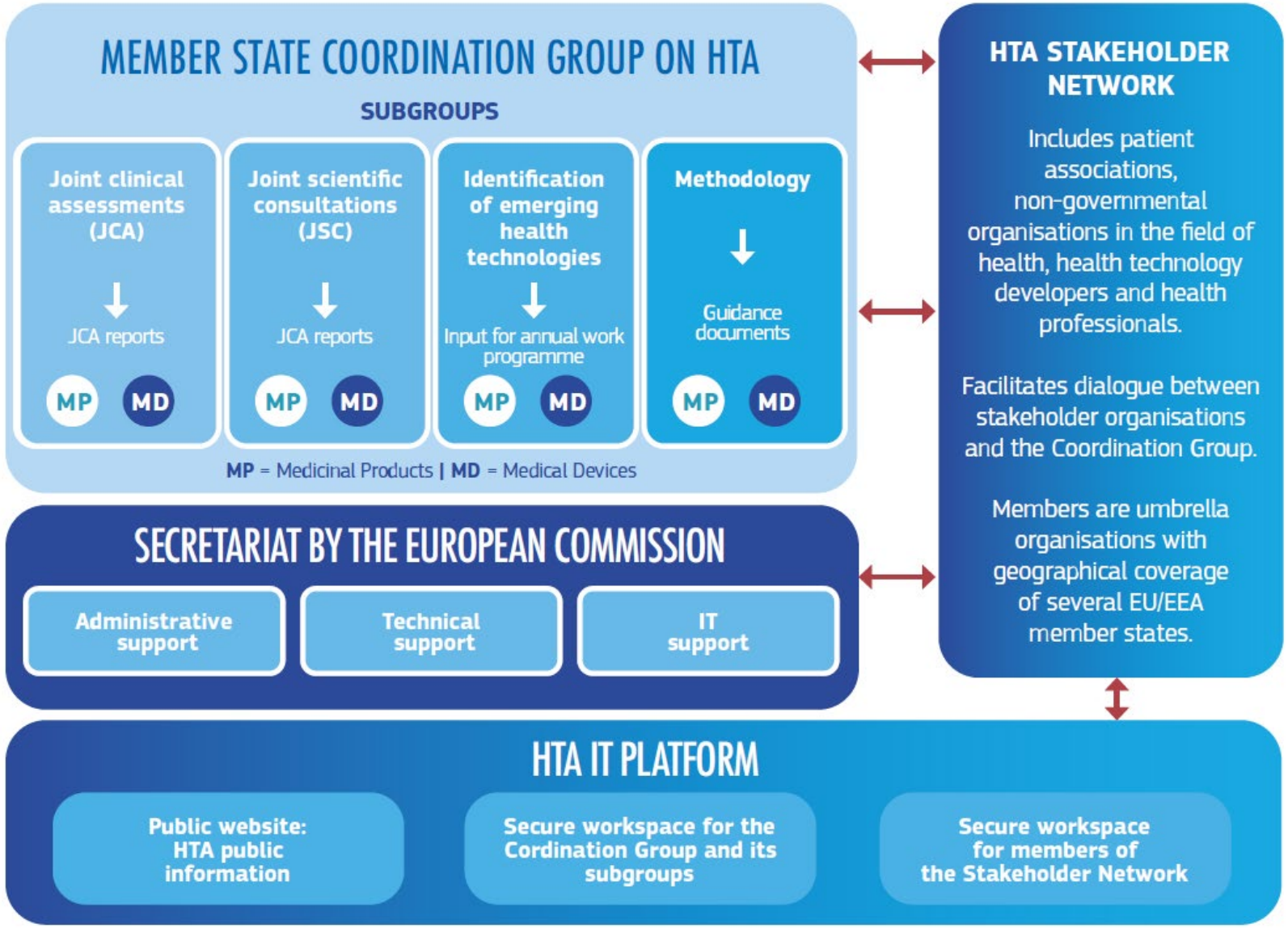


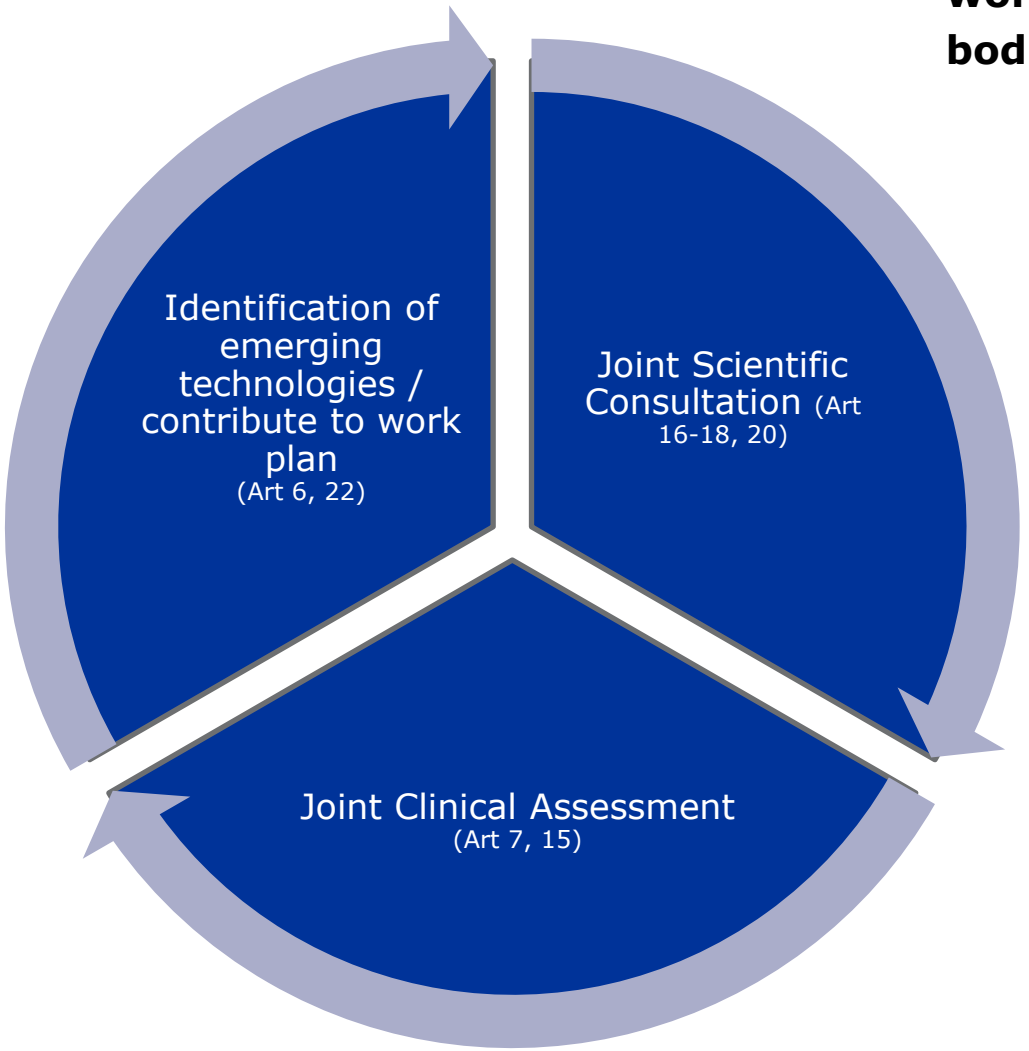
GOVERNANCE STRUCTURE



https://health.ec.europa.eu/latest-updates/factsheet-implementation-hta-regulation-2023-10-05_en

Collaboration with EMA under the HTA Regulation*

Note: "Joint" refers to collaborative work amongst HTA bodies



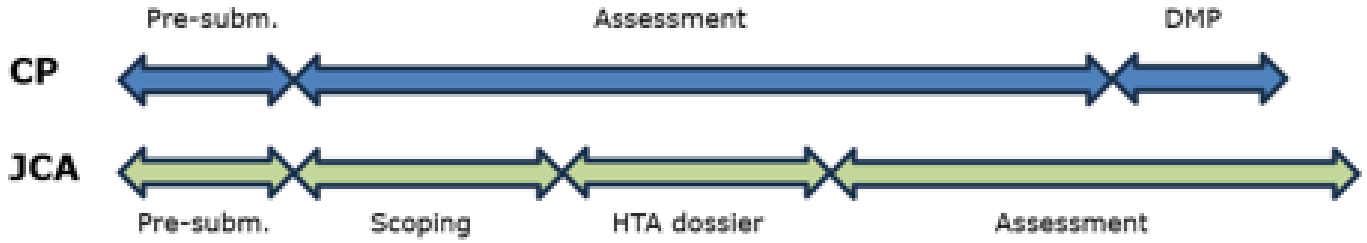
Further details through Implementing Acts

to be adopted by the EC (Art 15, 20)

* Regulation (EU) 2021/2282, entered into force in Jan 2022 and applies as of Jan 2025

Working at the HTA/regulatory interface: Joint Clinical Assessment for medicinal products

➔ **Core process under the HTAR starting from January 2025**



CHMP: data driven decision making → leading to indication

HTAs: defining scope first via PICO exercise – which then defines the evidence to be submitted for assessment by HTAs

Collaboration under HTA Regulation

Regulatory/HTA collaboration:

on a **scientific/technical** level (i.e. **not policy/economics**))

Guided by:

Ambition to enable the generation of evidence that can answer different questions for **benefit/risk assessment** and **relative effectiveness** assessment, respectively.

Regulator's role is to providing choices to health care systems

Synergy through alignment of evidence generation plans

Starting point: Regulators and HTAs

- answer different questions
- have different requirements in terms of evidence

Regulators are providing choices to healthcare systems

Aim: decision makers come together early to discuss

- the planned development including populations / comparators / design of trial / endpoints
- the requirements for post-licensing evidence generation

Expectation: Optimised evidence generation plan → improve access for patients

3 areas where RWE can support regulatory decision-making

1 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

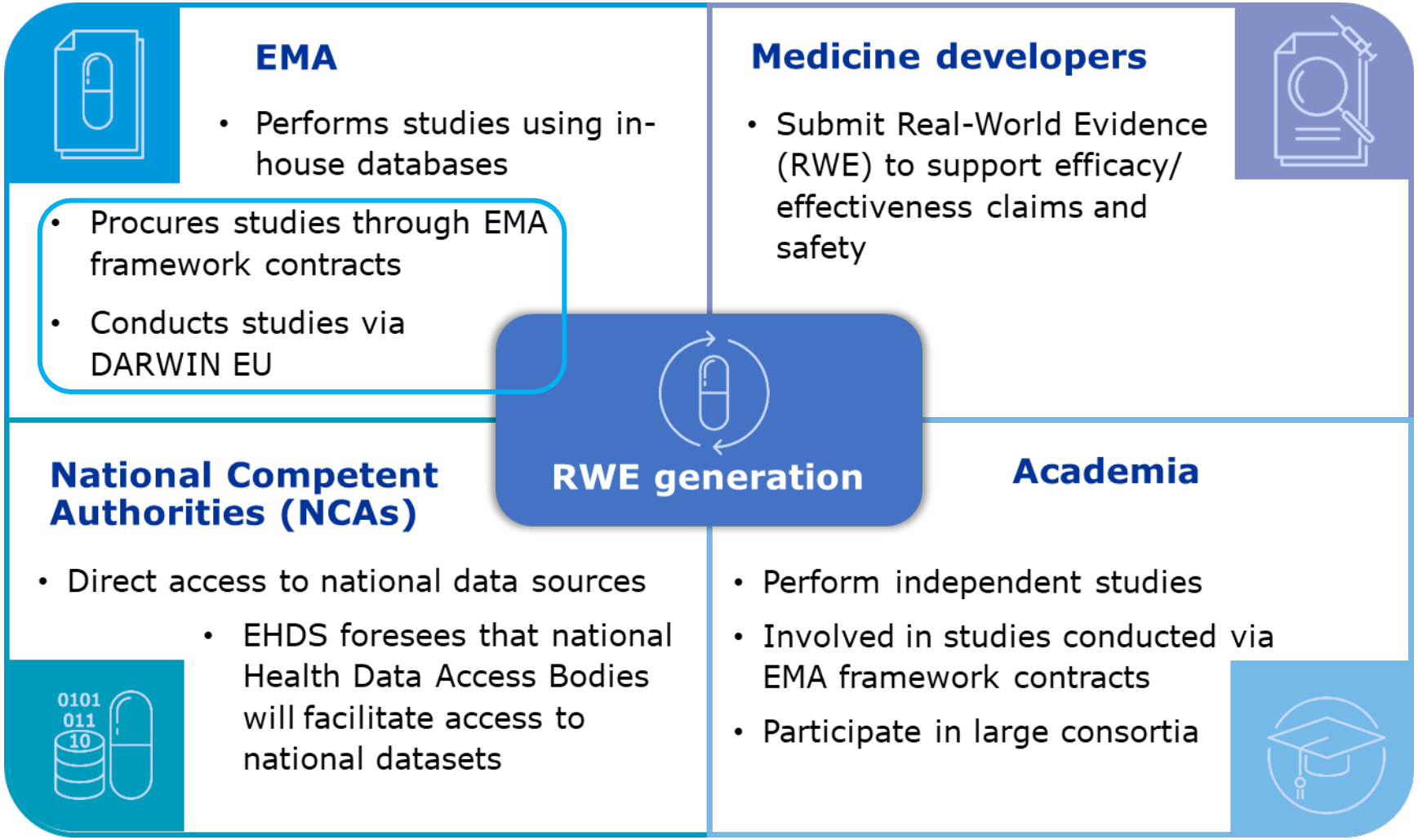
2 Support the planning and validity

- Design and feasibility of planned studies
- Representativeness and validity of completed studies

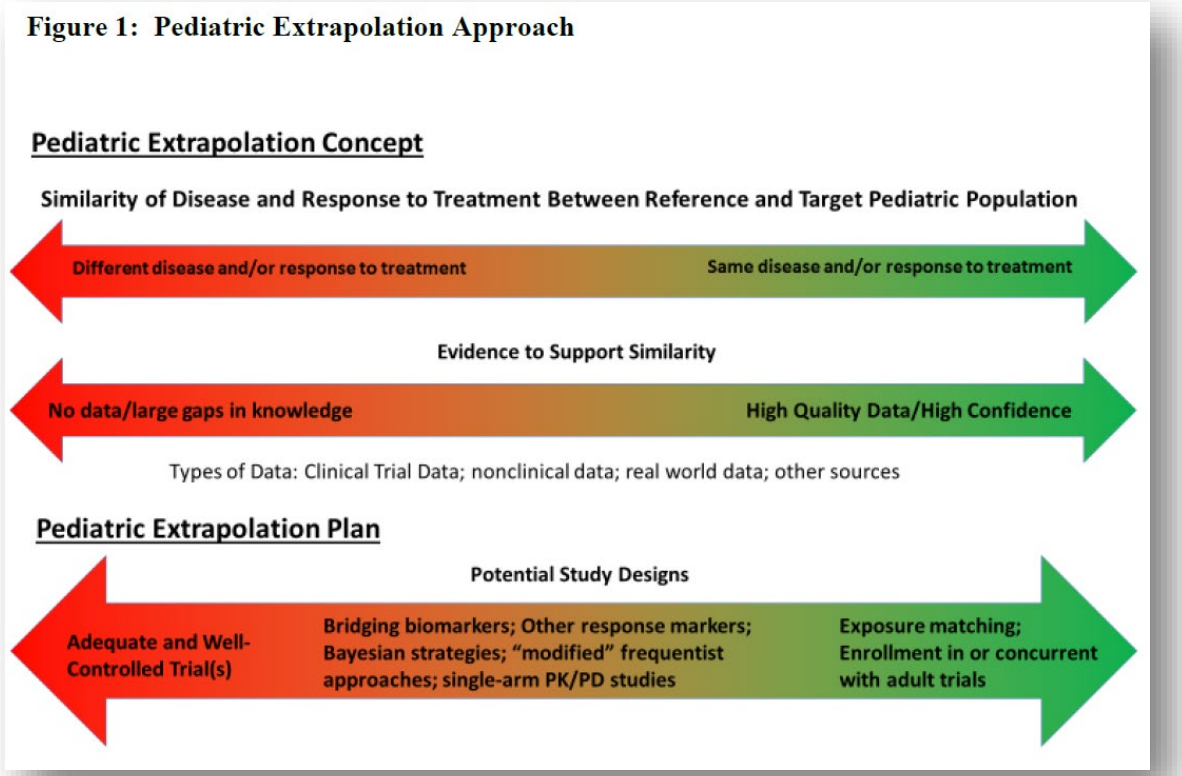
3 Investigate associations and impact

- Effectiveness and safety studies
- Impact of regulatory actions

Who delivers RWE for regulatory purposes in the EU?



Use-case - **Paediatric extrapolation** framework & how RWE could support



1. Key areas of paediatric extrapolation and how they might map to RWE research questions
   - **Disease similarity**
   - **Response to treatment**
   - **Pharmacology**

2. The type of evidence that could be generated

1) Disease similarity

- Do patients present in the same way?

  ➔*RQ: What are the demographic **characteristics** of children and adult patient populations at the point of diagnosis with (unresectable or metastatic) melanoma? What is the incidence/prevalence of disease? (by age, gender, clinical setting, stage)*

- Do patients have the same phenotype?

  ➔*RQ: What are the clinical **characteristics** of children and adult patient populations at the time of diagnosis with (unresectable or metastatic) melanoma? (by disease stage/severity, comorbidities, +/- prior prescriptions)*

- Do patients have the same/similar endpoints?

  ➔*RQ: What are the clinical **endpoints** used to measure disease course and progression among children and adult patient populations diagnosed with (unresectable or metastatic) melanoma? Are these endpoints measured in the same way between children and adults? How aligned are the phenotypes of endpoints in RWD?*

- Do patients have the same disease course?

  ➔*RQ: How do **mortality and other endpoints compare** among children and adults diagnosed with (unresectable or metastatic) melanoma? (mortality, treatment initiation approaches, stratified by age categories)* [Note: data source limitations]

- Other age-related differences?

  ➔*RQ: What are **other age-related differences** among patients diagnosed with (unresectable or metastatic) melanoma? [Needs specialised input to define]*

2) Treatment response

- Do children and adult patients have the **same/similar treatment strategies**?

  ➔*RQ: Are treatment strategies the same among children and adults diagnosed with melanoma (e.g. induction/consolidation/maintenance/bridging therapies)?*

  ➔*RQ: Are there difference in dose and duration of treatment among children and adults diagnosed with melanoma?*

  (Overall + stratified by age, gender, by disease stage)

- **Is response to treatment the same** among children and adult patients for safety and efficacy?

  ➔*RQ: What are the disease outcomes and response to treatment among patients diagnosed with (unresectable or metastatic) melanoma in terms of?*

  - *Mortality (OS), disease complications and disease progression (PFS)*
  - *Treatment complications and time to next line of treatment*
  - *RWE historic controls to support single arm studies*

  (Overall + stratified by age, disease stage, treatment strategy)

3) Pharmacology

- Are there **pharmacokinetic/pharmacodynamic differences**?
- Are there **ADME/genetic differences**?

➔*RQ: Do (off/on label) prescriptions in young(er) age groups use authorised posology/ or a weight/ surface area scaled approach?*

[Note: formal PK/PD genetic studies are potentially out of scope and requests would need to be considered on a case-by-case basis as to their feasibility due to limitation of data captured within databases]

1) Disease similarity

Population level analysis
(e.g. prevalence, incidence)

2) Response to treatment

Patient level analysis
(e.g. characterisation, natural history studies)

Complex studies
(e.g. aetiological/RWE controls)

3) Pharmacology

A challenging area currently

Occurrence of biomarkers assessment

- ! Recording of occurrence of biomarker assessment and NOT the actual value/result of the biomarker test
- Occurrence assessed before, on and after diagnosis (index date)
  - Antinuclear antibodies (ANA)
  - aspartate aminotransferase (AST)
  - Cancer Ag 125
  - C-reactive protein (CRP)
  - Creatine kinase (CK)
  - Erythrocyte sedimentation rate (ESR)
  - Lactate dehydrogenase (LDH)
  - Mi-2 antibody
  - Myoglobin
  - PL-12 antibody
  - PL-7 antibody
  - Polymyositis-scleroderma antibody
  - Ribonucleoprotein extractable nuclear antibody (ENA)
  - Signal Recognition Particle (SRP) antibody
  - SUMO-activating enzyme subunit 1 (SAE) antibody

- High variability across DBs and settings
- **Higher occurrence of CRP, AST, CK and ESR tests** in the months before and after diagnosis of DM and PM across DBs
- For JDM and JPM, the same biomarkers were observed but with **much lower percentages**

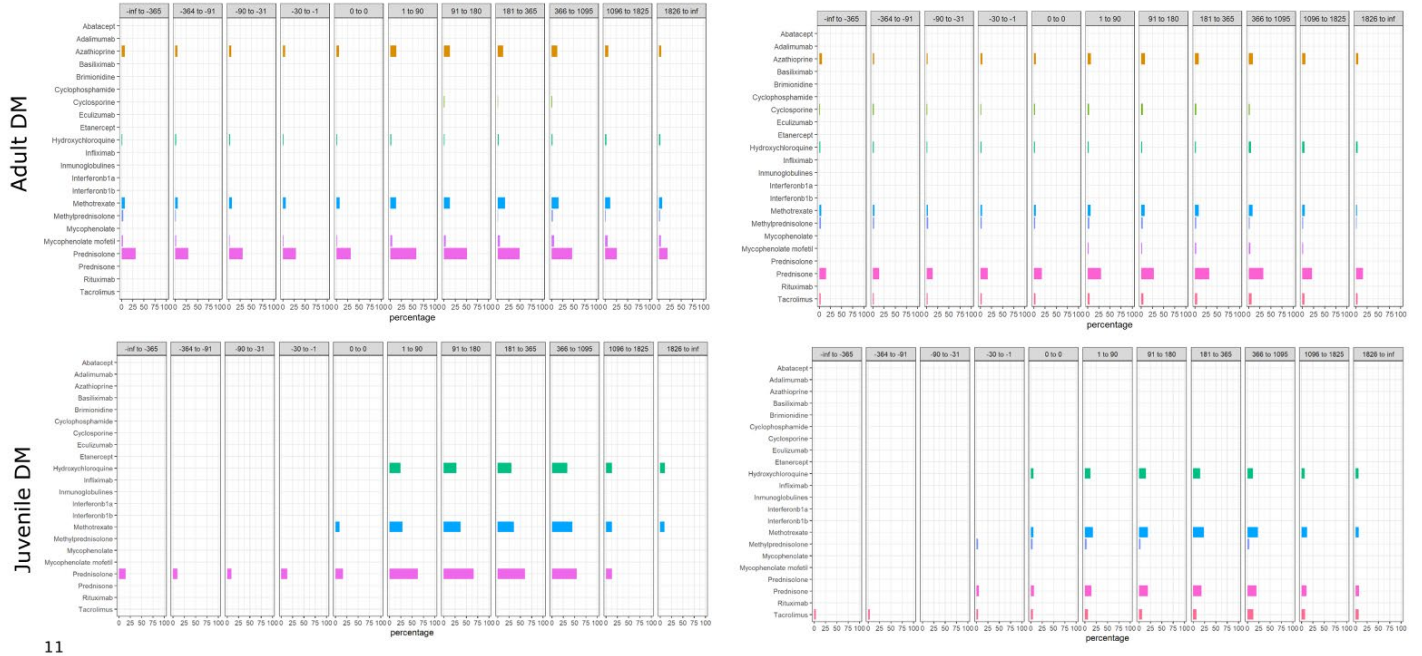
Table 12.9Biomarkeroccurring before, on, and after the diagnosis of Adult Dermatomyositis on 2006-2022

	outcome	anytime to 1y before	1 year to 3 months before	3 to 1 months before	1 month before	index date	3 months after	3 to 6 months after	6 to 12 months after	1 to 3 years after	3 to 5 years after	>5 years after
COMBinations	Antinuclear antibodies (ANA)	11 (6%)	7 (3%)	0 (0%)	6 (3%)	5 (3%)	17 (7%)	<5	<5	14 (6%)	13 (6%)	28 (13%)
	aspartate aminotransferase (AST)	141 (61%)	108 (47%)	63 (27%)	42 (18%)	128 (55%)	200 (87%)	101 (44%)	111 (48%)	144 (62%)	82 (36%)	68 (29%)
	Cancer Ag 125	0 (0%)	<5	0 (0%)	0 (0%)	0 (0%)	<5	<5	<5	<5	<5	0 (0%)
	C-reactive protein	142 (61%)	106 (46%)	58 (25%)	38 (16%)	129 (56%)	203 (88%)	95 (41%)	113 (49%)	146 (63%)	83 (36%)	69 (30%)
	Creatine kinase (CK)	107 (46%)	88 (38%)	50 (22%)	42 (18%)	103 (45%)	172 (74%)	87 (38%)	95 (41%)	113 (49%)	67 (29%)	62 (27%)
	Erythrocyte sedimentation rate (ESR)	<5	<5	<5	<5	<5	<5	<5	<5	<5	0 (0%)	5 (2%)
	Lactate dehydrogenase (LDH)	12 (5%)	11 (5%)	10 (4%)	7 (3%)	10 (4%)	24 (10%)	5 (2%)	8 (3%)	20 (9%)	9 (4%)	22 (10%)
	Mi-2 antibody	6 (3%)	5 (2%)	0 (0%)	6 (3%)	5 (2%)	10 (4%)	<5	<5	8 (3%)	<5	16 (7%)
	Myoglobin	5 (2%)	9 (4%)	0 (0%)	<5	7 (3%)	7 (3%)	<5	<5	<5	<5	7 (3%)
	PL-12 antibody	6 (3%)	5 (2%)	0 (0%)	6 (3%)	5 (2%)	10 (4%)	<5	<5	8 (3%)	<5	16 (7%)
	PL-7 antibody	6 (3%)	5 (2%)	0 (0%)	6 (3%)	5 (2%)	10 (4%)	<5	<5	8 (3%)	<5	16 (7%)
	Polymyositis-scleroderma antibody	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Ribonucleoprotein extractable nuclear antibody (ENA)	0 (0%)	0 (0%)									
	Signal Recognition Particle (SRP) antibody	6 (3%)	5 (2%)									
	SUMO-activating enzyme subunit 1 (SAE) antibody	6 (3%)	5 (2%)									
ERB	Antinuclear antibodies (ANA)	<5	<5									
	aspartate aminotransferase (AST)	19 (29%)	16 (24%)									
	Cancer Ag 125	<5	5 (8%)									
	C-reactive protein	53 (80%)	38 (58%)									
	Creatine kinase (CK)	21 (32%)	13 (20%)									
	Erythrocyte sedimentation rate (ESR)	12 (46%)	20 (30%)									
	Lactate dehydrogenase (LDH)	13 (20%)	6 (9%)									
	Mi-2 antibody	0 (0%)	<5									
	Myoglobin	<5	5 (8%)									
	PL-12 antibody	0 (0%)	<5									
	PL-7 antibody	0 (0%)	<5									
	Signal Recognition Particle (SRP) antibody	0 (0%)	<5									
	SUMO-activating enzyme subunit 1 (SAE) antibody	0 (0%)	<5									

Treatment prescriptions

CPRD Gold

SIDIAP



Impact and Limitations

Limitations

- Considerable variability across DBs and settings in occurrence of biomarker assessments, treatment prescriptions and clinical symptoms
- Only biomarker testing occurrence and not their results could be extracted
- Low numbers in juvenile forms

➔ Limited conclusions on disease similarity and response to treatment between paediatric and adult populations

Strengths & Usefulness (clearer once procedure closed)

- Largest and only international European study on the prevalence of DM or PM to date & the increasing trends in are in line with recent literature review on the epidemiology of IIMs
- The observed clinical manifestations are in line with the most recent clinical criteria (EULAR/ACR)
- Data to support contextualise evidence plan from the applicant

UNDER REVIEW

Evidence generation throughout paediatric medicines lifecycle -- learnings from collaborative work between EMA and EUnetHTA on use of extrapolation

CLINICAL PHARMACOLOGY | PHARMACODYNAMICS | PHARMACOKINETICS | TRANSLATIONAL PHARMACOLOGY

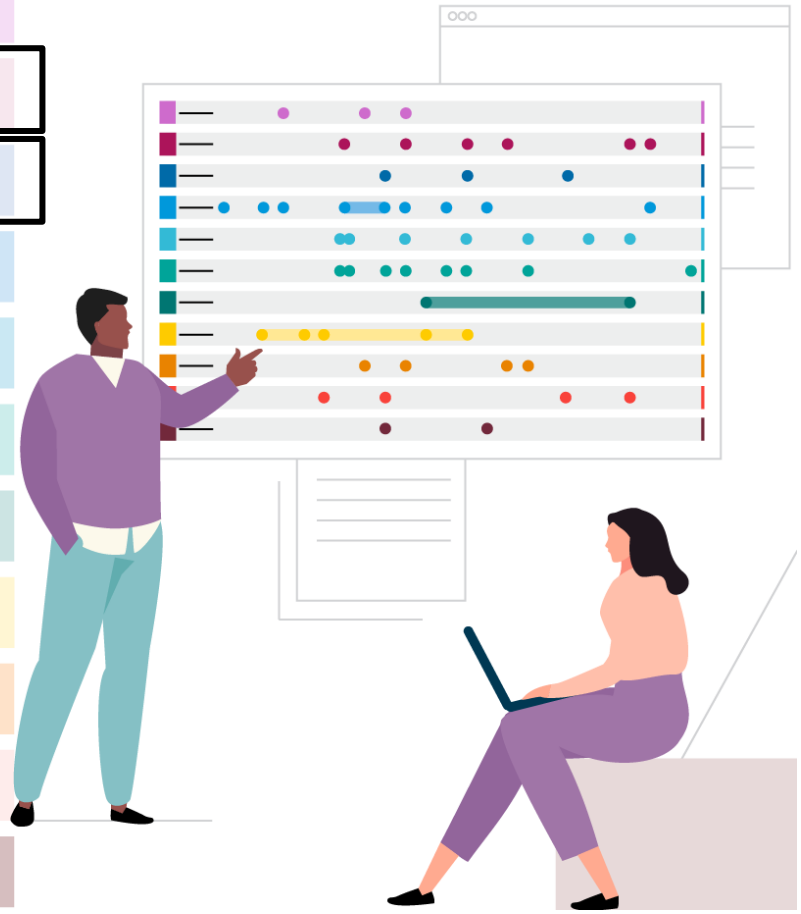
Dominik Karres, Marie Jose del Pino, Sylvie Benchetrit, Norbert Benda, Pierre Cochat, Sara Galluzzo, Alejandro García-Solís , Sara Gonzalez , Roberto de Lisa, David Kahn, Rita Lankester, Frederike Lentz, Pilar Angustias Martínez-Ortega , Simona Montilla , Daniel Morales, Flora Musuamba Tshinanu , Sonia Pulido Sánchez , Ana Rossignoli Montero , Sabine Scherer, Andrew Thomson, Belén Torres Garrido , Denise Umuhire, Siri Wang, Ralph Bax, Niklas Hedberg

Tools to optimise data quality, discoverability and assessment of relevance

EMA/HMA Big Data Initiative

EU's current framework to unlock value, enable use of Real-World Data (RWD) and facilitate 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



Big Data Steering Group workplan (BDSG)

Data Quality Framework for EU Medicines regulation


HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 October 2023
Data Analytics and Methods Task Force
EMA/326985/2023

Data Quality Framework for EU medicines regulation

- Provides **general considerations** for describing, characterising and assessing data quality for decision-making
- Outlines data (sub-)dimensions and metrics

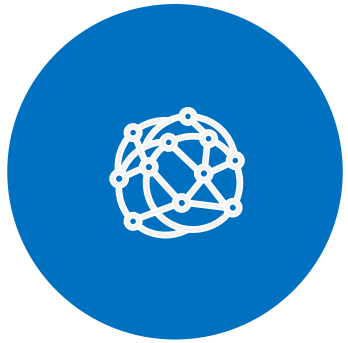
Objectives (publication link here)

- Enables **standardised approach** for DQ across all data sources
- Improves **consistency** in the evaluation of the quality of data used
- Supports **trust of stakeholders** in the data underpinning regulatory decisions
- Facilitates a more **systematic use of data** for decision-making on medicines

Watch out !

Imminent public consultation on a Chapter dedicated to RWD

Data Quality Framework: Main dimensions

				
Are data correct and representing what is meant to represent?	**How much data are there?**	**Can data be analysed as a whole?**	**Are data available at the right time, and acceptable up to date?**	**Is this the kind of data I need?**
RELIABILITY	**EXTENSIVENESS**	**COHERENCE**	**TIMELINESS**	**RELEVANCE***

*Suitability to a research question

Data quality is assessed from the angle of ***fitness for purpose*** for users' needs

Example of metrics

Dimension	Metric category	Example metrics	Example
Reliability	Plausibility checks	% of records where logical constraints between values is in line with expectations	For X% of records, discharge date happens before admission date
	Checks on dataset descriptors	% of variables/datasets that are based on imputation or derivation	End of treatment date is derived for X% of patients from treatment start date and treatment cycle length
Extensiveness	Comparison to other datasets	Relative percentage of records for which a variable is missing with respect to a trusted source of knowledge	X% of patients with missing date of diagnosis in a diabetes database, compared to a National and institutionally validated diabetes registry
Coherence	Conformance check	For relevant variables, % of records where data values conform to allowable values or ranges	X% of records have sex with one of the 3 allowable values “M”, “F”, or “U”.
Timeliness	Objective dataset assessment	Average time of updates in a database	Timestamps indicate patient records are updated on average every 3 months (after hospital visit)

Assessment of **relevance** of RWD sources

- Difficult to pre-specify thresholds or minimum criteria for data acceptance → depends on the type of study, disease-dependent / analysis-dependent factors, and other factors e.g., lack of other RWD sources impacting on setting acceptability thresholds

Planning to conduct a study

What do I want to study?

First: **identify the scientific question(s)**

Then: **Feasibility assessment** → evaluation of the **fitness for purpose** of the dataset for a **specific question**

Very important: ***Early dialogue*** *with* ***all relevant*** *stakeholders*

Does the dataset capture **key data elements** to address a research question in a **reliable, coherent and timely** way; are the **number of patients** and **follow-up time** sufficient to demonstrate the impact of the intervention/determinant under investigation

Various tools exist to assess relevance

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Vision paper on the sustainable availability of the proposed Registry Evaluation and Quality Standards (REQueST)

Report produced as part of EUnetHTA Joint Action 3 Work Package 5B (Post-Launch Evidence Generation and Registries

LINK

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Guideline on registry-based studies

LINK

And others….

Clinical Pharmacology & Therapeutics

Review | Open Access

The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework

Nicolle M. Gatto ✉ Ulka B. Campbell, Emily Rubinstein, Ashley Jaksa, Pattra Mattox, Jingping Mo, Robert F. Reynolds

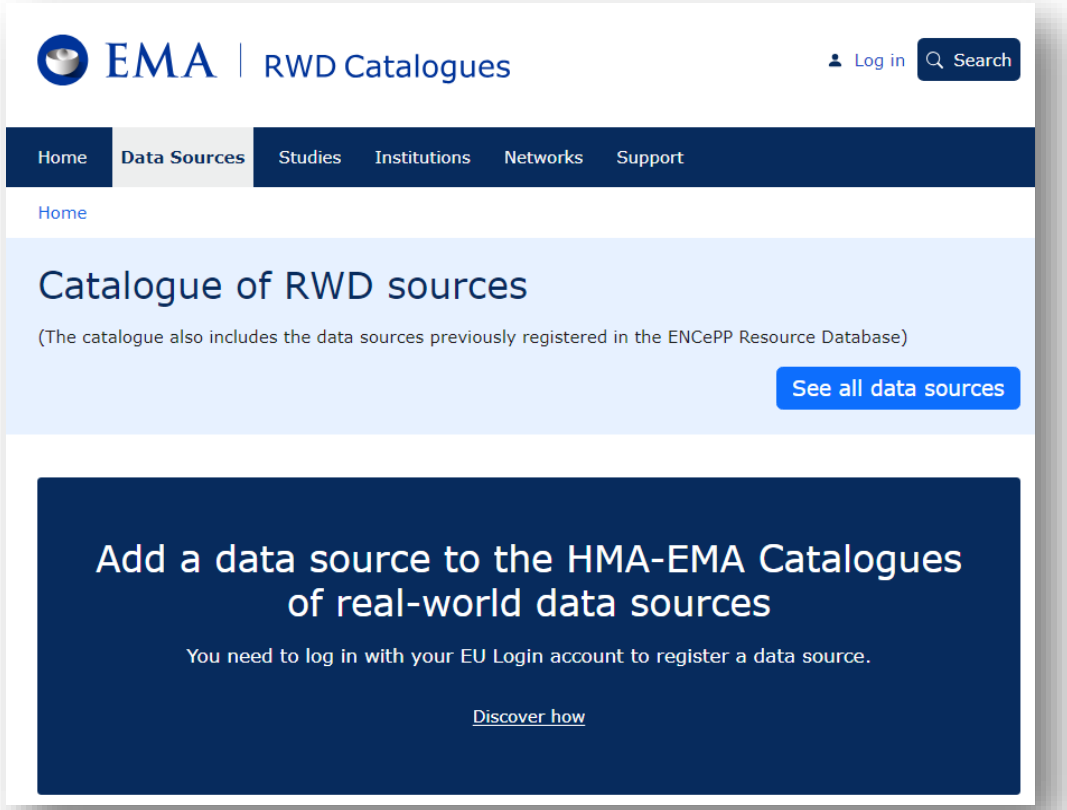
First published: 30 October 2021 | https://doi.org/10.1002/cpt.2466 | Citations: 19

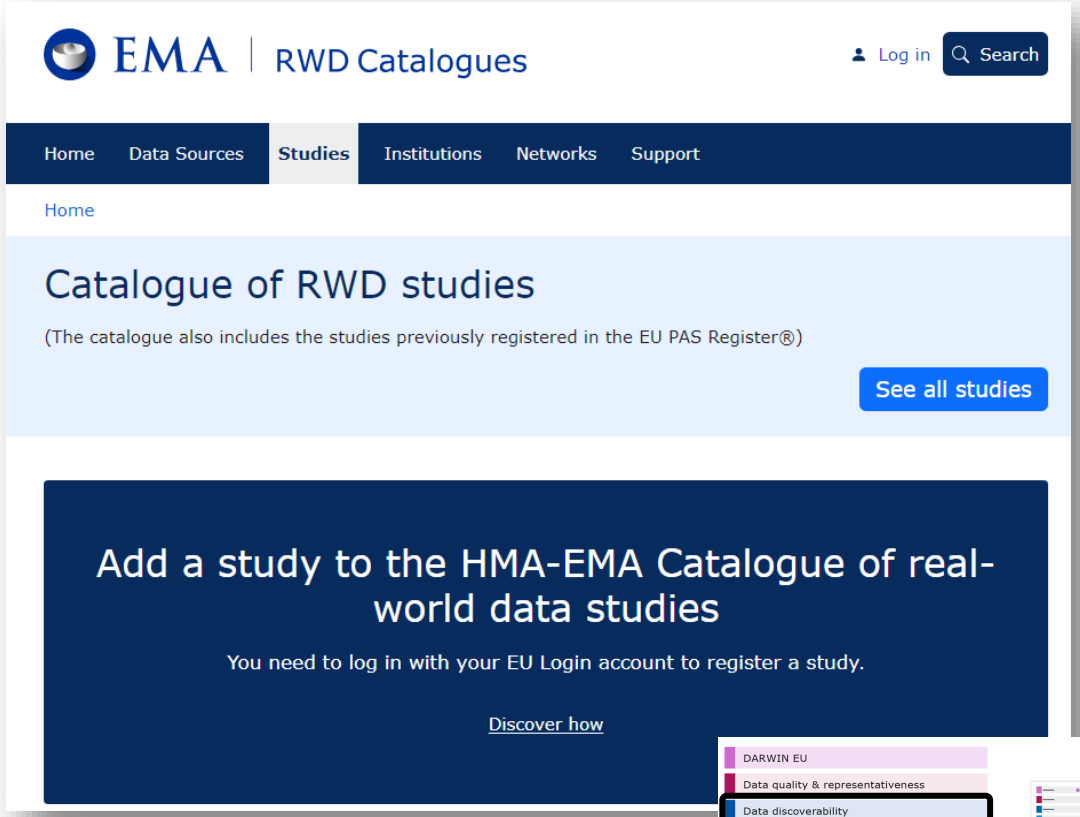
An earlier version of this work was presented at the 36th International Conference on Pharmacoepidemiology & Therapeutic Risk Management in, ICPE All Access Virtual Event, September 16–17, 2020 and the 37th International Conference on Pharmacoepidemiology & Therapeutic Risk Management in, ICPE All Access Virtual Event, August 23–25, 2021.

SPIFD1, SPIFD2

But how can we identify RWD sources?

EMA | RWD Catalogues **Launched 15th February 2024**





https://catalogues.ema.europa.eu/

HMA-EMA Catalogues of real-world data sources & studies

- Enhance **discoverability and evaluation of data sources and studies** -> facilitating the use of RWD sources, ultimately supporting evidence-based regulatory decision-making
- **Link RWD sources and studies** which can support study design, protocol evaluation, and results interpretation
- Facilitate **collaboration and research**
- Promote **transparency** in observational research and **reduce publication bias** by making publicly available metadata on non-interventional studies
- Promotion of good practices aligning with **'FAIR' data principles** for **F**indable, **A**ccessible, **I**nteroperable, and **R**eusable data
- Respond to the **DARWIN EU open call** to become a DARWIN data partner via the Catalogues
- **Free access** via the Catalogues webpage, hosted on EMA public website

List of metadata for Real World Data catalogues defining:

Data Sources

Studies

Institutions

Networks

Example

Currently 3 medicinal products authorised for the treatment of SMA

- Zolgensma (onasemnogene abeparvovec)
- Spinraza (nusinersen)
- Evrysdi (risdiplam)

https://catalogues.ema.europa.eu/node/3582/administrative-details

As diagnosis and treatments are changing quickly, we need to better understand

- The **natural history** and **progression** of SMA disease
- Standards of **diagnosis** and **clinical care**
- The **impact** of the disease modifying therapies

Study design: **Non-interventional retrospective** cohort study using European **registries of TREAT-NMD**

Identification of fit-for-purpose registries for the SMA study

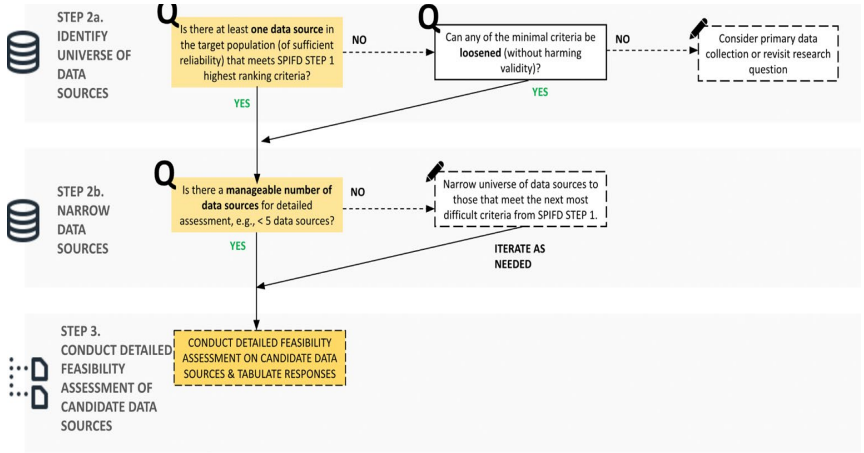
(1) Study concept -> operationalize minimal criteria and rank data

Research question:				
Row	**Design element**	**Minimal criteria for valid capture**	**Operational definition**	**Rank for uniqueness or importance**
1	Study population (inclusion and exclusion criteria)			
2	Treatment group			
3	Comparator group			
4	Primary outcome(s) (definition & ascertainment)			
5	Key secondary outcome(s) (definition & ascertainment			
6	Length and frequency of follow-up			
7	Confounding variable 1			
. . . N	. . . Confounding variable N			

SPACE Step 3

Questionnaire with a medical leader in SMA to define key variables needed (age, type of SMA, medications, disease characteristics, disease outcomes, …)

(2) Identify and narrow down registries options



Pre-feasibility: Contact of European SMA registries identified through TREAT-NMD network.

Feasibility : Preselected registries received the feasibility questionnaire.

Guidelines used for questionnaire construction:

- EMA Guideline on registry-based studies (2021)
- EUnetHTA - REQueST tool (2019)
- FAIR Guiding Principles (Wilkinson et al, 2016)

(3) Conduct feasibility assessment *

Row	Design element	Requested information	Data source 1	Data source 2	Data source 3	Data source 4
1	Study population (Inclusion/ Exclusion criteria)	• Availability of needed data types for each I/E • Cohort size				
2	Treatment group	• Availability of needed data types • Number of newly treated				
3	Comparator group	• Availability of needed data types • Number in comparator				
4	Primary outcome(s) (definition & ascertainment)	• Availability of needed data types • Risk of outcome in comparator				
5	Key secondary outcome(s) (definition & ascertainment)	• Availability of needed data types • Risk of outcome in comparator				
6	Length and frequency of follow-up	• Min, max, median follow-up time • Data lag time				
7	Confounding variable 1	• Availability of needed data types				
. . . N	. . . Confounding variable N	• Availability of needed data types				

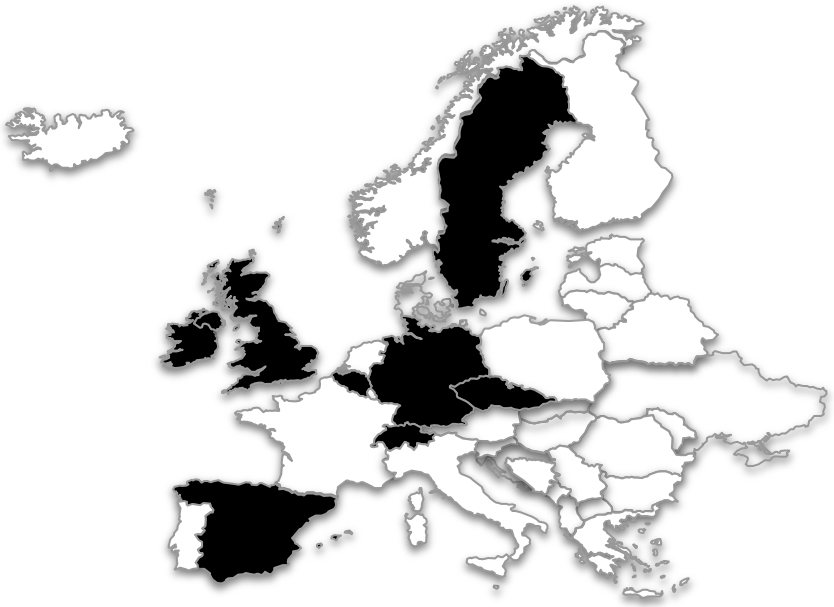
Quantitative and qualitative assessment:

- Qualitative: administrative info, quality requirements (SOP, data cleaning, audit…)
- Quantitative : completeness of variables

Design Element	Data Source A	Data Source B	Data Source C	Data Source D
Database size	5	4	2	2
Lab results	5	3	2	5
Microbiology data	4	5	5	1
Covariates	4	4	4	4
Procedural endpoints	5	5	5	5
Clinical endpoints	4	4	4	4
Contracting time	low	low	medium	high

***SPIFD**: Structured process for identifying fit-for-purpose data (Gatto et al., 2022)

Countries contacted for feasibility versus final selection



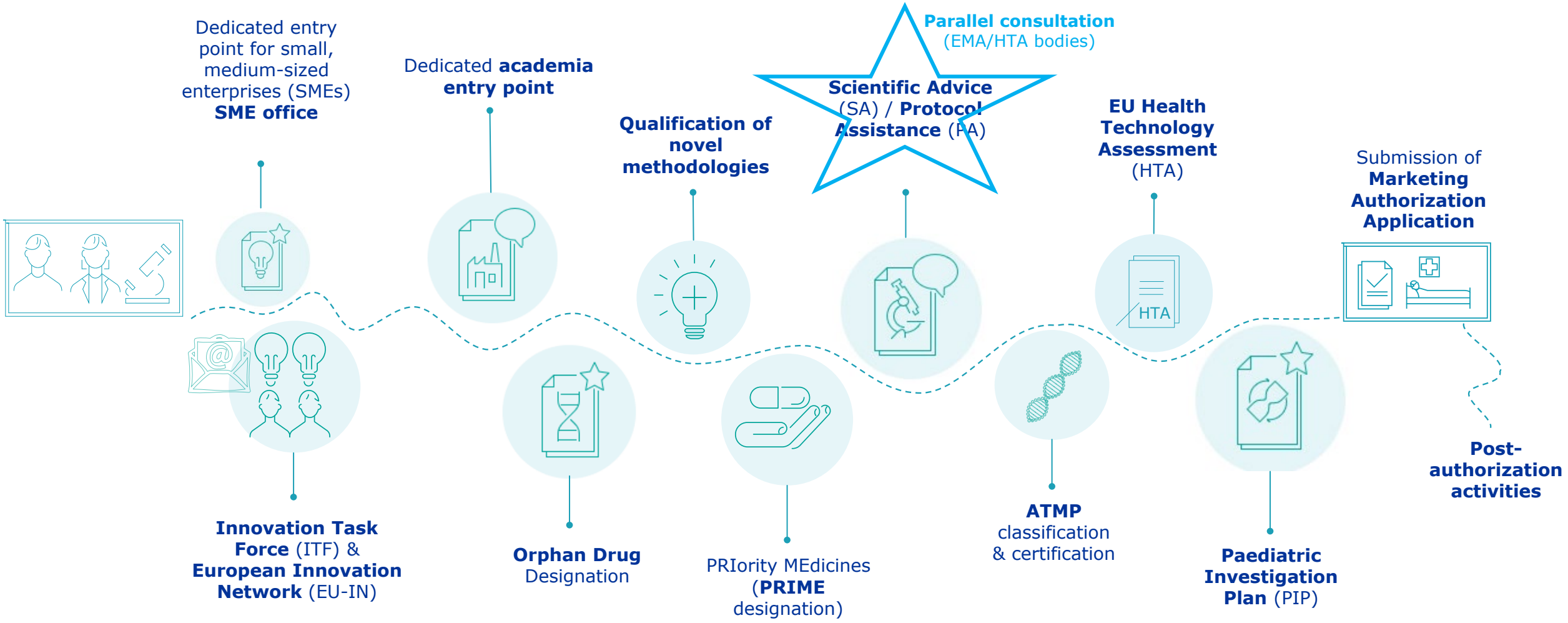
- **Across** the Treat-NMD network, all active registries within the EEA region were contacted for **pre-feasibility assessment (17 registries):** Belgium, Bulgaria, Croatia, Poland, Denmark, Hungary, Latvia, Slovenia, Turkey, Georgia, Ukraine, Spain, Switzerland, UK & Ireland, Czech Republic & Slovakia, Germany & Austria, Sweden

- **Outside the TREAT-NMD network:** France and Italy registries were contacted

Registries selected after feasibility assessment (7 registries including 3 clinicians and 4 patients led across 9 countries): Belgium, Spain, Switzerland*, UK & Ireland, Czech Republic & Slovakia, Germany & Austria, Sweden

** Switzerland was finally not included in the study due to lag time in contracting process and data sharing.*

EMA interactions across the medicine life cycle



Reference: *Supporting innovation | European Medicines Agency (EMA) (europa.eu)*

Conclusion

- HTA and regulators have different roles/mandates, different research questions, but still require the same high quality of data to generate evidence needed to inform decision-making
- RWD/RWE are valuable and have a crucial role in bridging the gap between clinical research and practice
- There are challenges, but tools exist to help address them (e.g., DQF, constellation of guidance documents, planning phase: catalogues, feasibility assessment)
- Early dialogues with all relevant stakeholders - to be continued throughout lifecycle of medicines (e.g. JSC, JCA, different interaction pathways with EMA/HTA…)

Thank you!

Further information

us denise.umuhire@ema.europa.eu & kelly.plueschke@ema.Europa.eu

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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