Patient registry data for decision-making on medicines

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Conflicts of interest

- I am participating in IMI-EPND, and receive unrestricted research grants from CBG-MEB, HORIZON EUROPE (PRIME-CKD, More-EUROPA) and IHI (BRIDGE)
- All my views presented today are my own, and may not necessarily reflect the opinion of the CBG-MEB, the EMA or one of its committees or working parties

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RCTs and RWD

- RCTs mainstay of drug efficacy and safety information for regulators & HTA bodies
- Value of RWD increasingly acknowledged
  - transform, accelerate and de-risk decision making
  - improve efficiency in design and conduct of trials
  - increase public health
- Around licensing: contextualize study results, ensure generalisability of results to target population
  - E.g., Yescarta SmPC (Crump et al. 2017 https://doi.org/10.1182/blood-2017-03-769620)
- Post-licensing: appreciate real-world value, long-term B/R

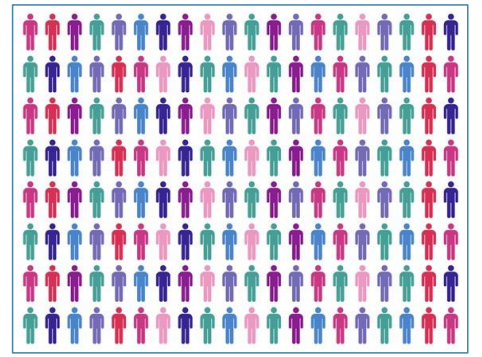
Patients in randomized trials

In- and exclusion criteria!

Exclusion for melanoma trials:

- Brain metastases
- ECOG score ≥2
- Auto-immune disease
- Immunosuppression
- Other malignancies
- Not Recist evaluable
- Etc.

Patients in daily practice



The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials

Marco Donia [a,b,*], Marie Louise Kimper-Karl [c], Katrine Lundby Høyer [d], Lars Bastholt [c], Henrik Schmidt [d], Inge Marie Svane [a,b]

Donia et al. EJC, 2017

Areas of decision-making for which registries can be useful

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	

Throughout the entire drug development life cycle

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European Commission

Aims:

- 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

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. Arlett p. et al. CPT 2021
https://doi.org/10.1002/cpt.2479

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The More-EUROPA team

Kick-off Groningen
30-31 May 2023

More-EUROPA: 15 partners, started January 2023

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EURORDIS
RARE DISEASES EUROPE

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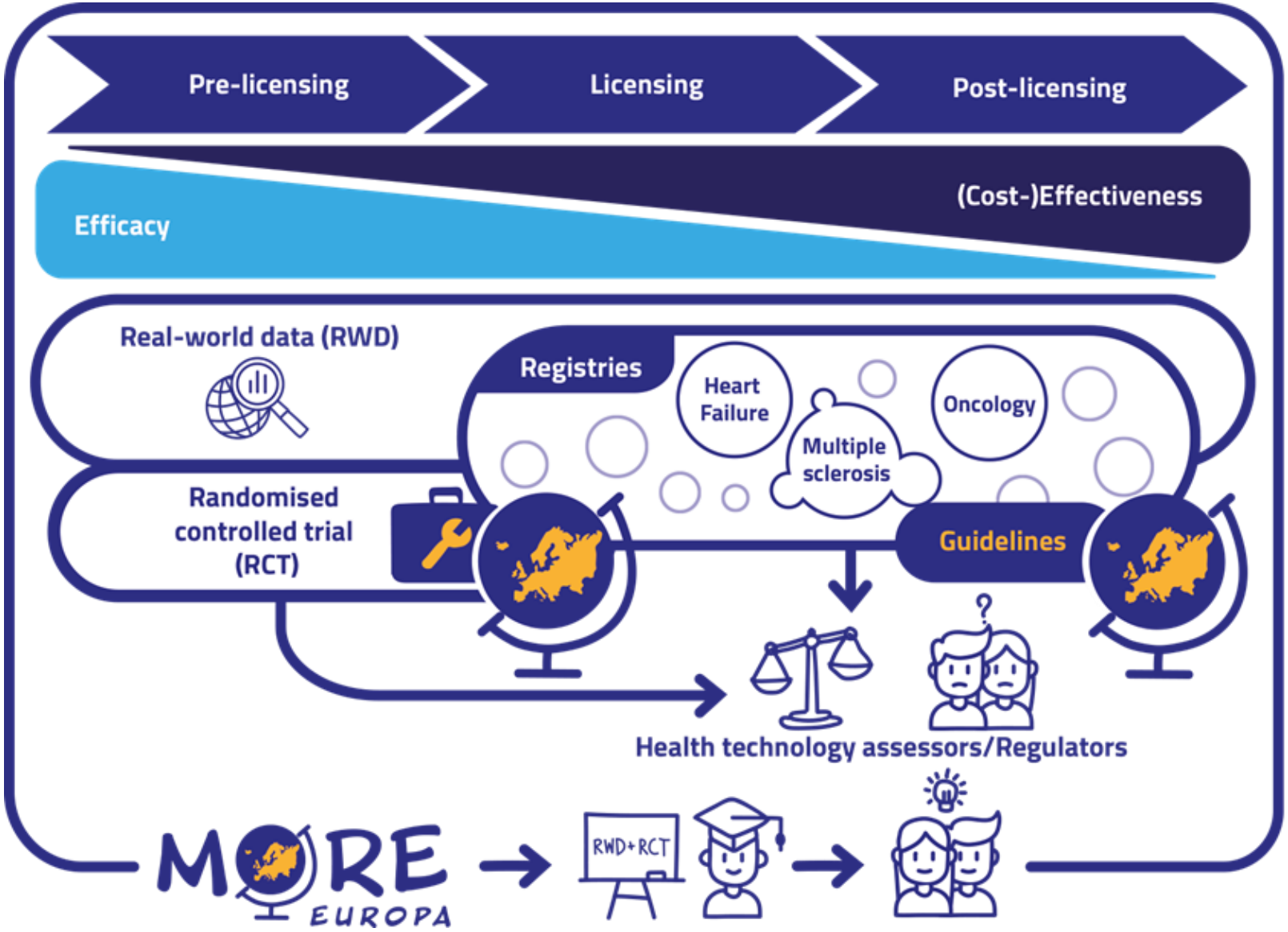
More-EUROPA Summary

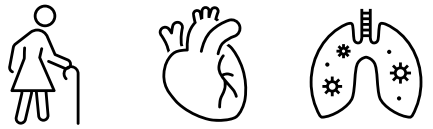


Priorization of registries as RWD source

- Quality standards already available
- Data immediately available for analyses case studies

→ Outcomes practical, implementable and adopted

Focus on 3 registries



	Swedish Multiple Sclerosis registry (SMSreg)	Swedish Heart Failure Registry (SwedeHF)	Dutch Institute for Clinical Auditing (DICA)‡
Disease	Multiple sclerosis	Heart failure	Cancer (lung cancer)
Established since	1997	2000	2010
# patients captured in the registry	20,000	Till 2018, 156.000 registrations from 90.000 patients	In the pilot DICA-medicines: 10,000 patients (2018-2022)§
Data linkage	Cause of Death Registry National Patient Registry Statistics Sweden Prescribed Drug Registry		Hospital database (possible to scale up to nation-wide participation) PALGA (pathology) Vektis (claim database)
Age range	12-96 years	18-106 years	19-104 years
Sex	70% females	39% females	54% females
Registry-based RCT	**RIFUND-MS (EudraCT 2015-004116-38)**	**SPIRRIT-HFpEF (clinicaltrial.gov NCT02901184)**	N/A

Walhalla – Swedish registries

SwedeHF registry

Socialstyrelsen
THE NATIONAL BOARD OF HEALTH AND WELFARE

National Patient Registry
- Additional comorbidities
- Outcomes
  - Cause specific hospitalization
  - Incident comorbidity

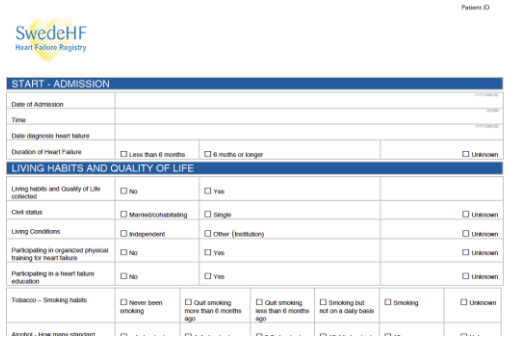
Dispensed drug registry

Cause of death registry

Personal number (Tax number)

RiksSvikt
nationellt hjärtsviktsregister

- Demographics
- Comorbidity
- Clinical (**Ejection fraction** ,x-ray, ECG, BP, HR)
- Laboratory (creatinine, K, Hb, NT-proBNP)
- Medications and doses
- PRO
- Biobank (ongoing)
- Planned follow-up


SwedeHF
Heart Failure Registry

START - ADMISSION

Date of Admission			
Time			
Date diagnosis heart failure			
Duration of Heart Failure	☐ Less than 6 months	☐ 6 moths or longer	☐ Unknown

LIVING HABITS AND QUALITY OF LIFE

Living habits and Quality of Life collected	☐ No	☐ Yes	
Civil status	☐ Married/cohabitating	☐ Single	☐ Unknown
Living Conditions	☐ Independent	☐ Other (institution)	☐ Unknown
Participating in organized physical training for heart failure	☐ No	☐ Yes	☐ Unknown
Participating in a heart failure education	☐ No	☐ Yes	☐ Unknown

Tobacco – Smoking habits	☐ Never been smoking	☐ Quit smoking more than 6 months ago	☐ Quit smoking less than 6 months ago	☐ Smoking but not on a daily basis	☐ Smoking	☐ Unknown

UCR

Inclusion criterion:
Clinician judged HF

Personal number (Tax number)

SCB

Statistics Sweden
- Socioeconomic characteristics (income, civil status, n. children, education)
- Matched control population (e.g. without HF)

National Diabetes Registry NDR NATIONELLA DIABETESREGISTRET

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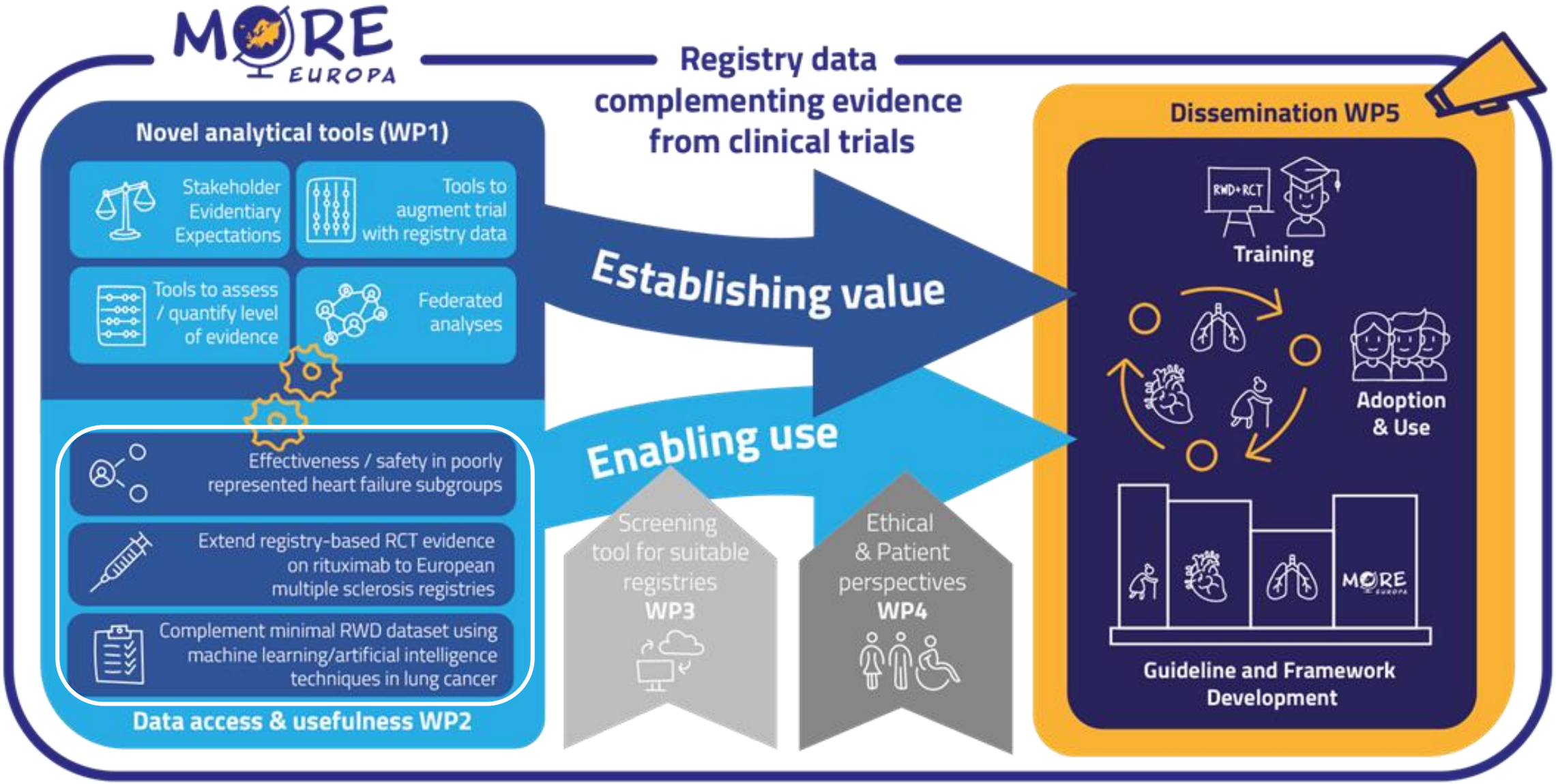
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Registry data complementing evidence from clinical trials
Novel analytical tools (WP1)
Stakeholder Evidentiary Expectations
Tools to augment trial with registry data
Tools to assess / quantify level of evidence
Federated analyses
Effectiveness / safety in poorly represented heart failure subgroups
Extend registry-based RCT evidence on rituximab to European multiple sclerosis registries
Complement minimal RWD dataset using machine learning/artificial intelligence techniques in lung cancer
Data access & usefulness WP2
Establishing value
Enabling use
Screening tool for suitable registries WP3
Ethical & Patient perspectives WP4
Dissemination WP5
RWD+RCT
Training
Adoption & Use
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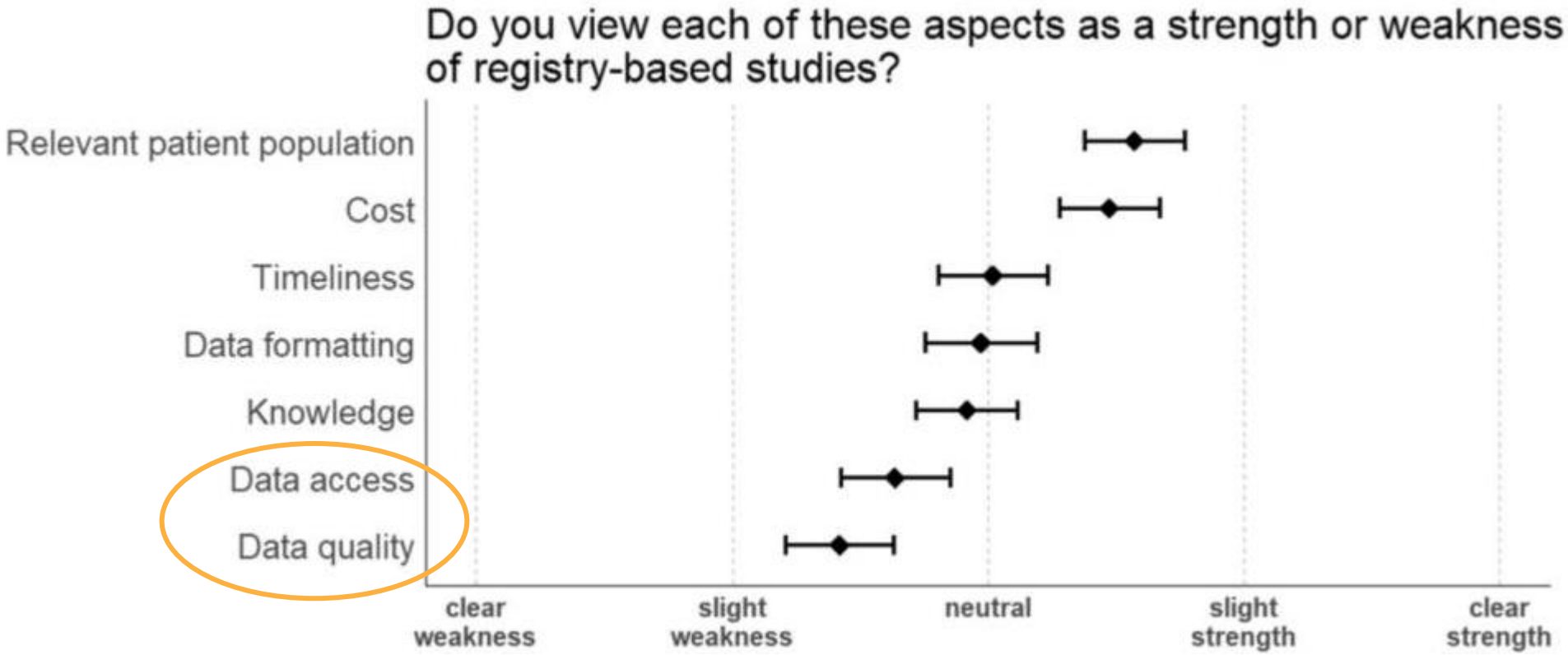
Guideline and Framework Development

Strengths and weaknesses of registry-based studies

- b)



https://doi.org/10.1007/s40264-025-01528-7

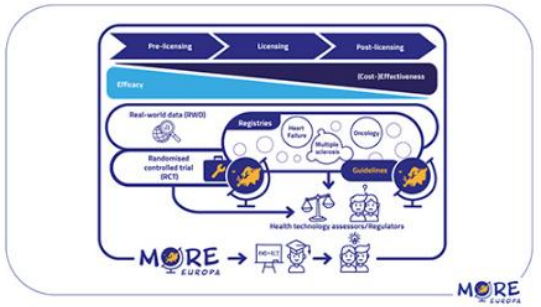
More-EUROPA webinars & patient trainings

Webinars

November 2025

Understanding real world drug effects by performing federated analyses

February 2025



How can real-world registry data be used to augment clinical trial data

July 2024

AI and ML approaches to identify and appraise registries and relevant data

November 2023

Use of Registries in Regulatory Decision Making

More-EUROPA webinars & patient trainings

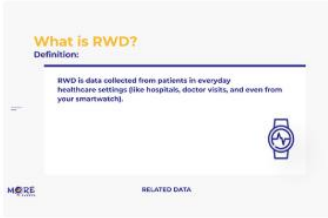
Session 1

Understanding Real-World Data (RWD) and Registries

Session 2

Registries and Real-World Data in Healthcare

Session 3



RWD vs Clinical Trials

Session 4

Data Analysis in the Context of Registries

Session 5

Ethical Considerations in Real-World Data (RWD)

Session 6

Examples of Real-World Data (RWD) Studies and the impact of it

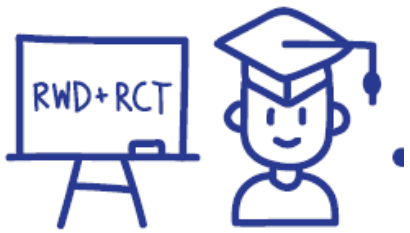
Session 7

Creating a Data Union with the European Health Data Space

Take aways

- Regulators & HTAb decision-making remains to be primarily informed by RCTs
- RWE can inform drug development across life cycle
- Data quality & pre planning – Key!
- More-EUROPA focuses on disease registries
  - Curated data sets & proven data collection
  - Activities centered around complementing trial data
- Activities around implementation
  - Long term survey
  - Guidance development
  - Interactions / network building

Questions



Patient registry RWD for decision-making on medicines in rare diseases

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Rare tumour

The ***comparisons*** of XXXXX efficacy endpoints to ***external control data*** were ***not pre-specified*** in the study protocol. They were entirely defined in a SAP addendum, finalised after the data cut-off date of the pivotal single-arm trial. In this situation, it cannot be excluded that several aspects of planned analyses (historical data sets and selection criteria, endpoint selection and definition, propensity score weighting/matching methods and associated covariates, planned statistical models and adjustment…) ***could be at least partially data-driven***. The ***lack of pre-specification is a clear limitation of these external control comparisons***. Moreover, it is highly likely that relevant prognostic factors (known or unknown) were not accounted for and may have biased the estimates of external control comparisons.

Rare tumour

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Cystic fibrosis

Kaftrio

ivacaftor / tezacaftor / elexacaftor

On 27 February 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending a change to the terms of the marketing authorisation for the medicinal product Kaftrio. The marketing authorisation holder for this medicinal product is Vertex Pharmaceuticals (Ireland) Limited.

The CHMP adopted extensions to the existing indications for Kaftrio film-coated tablets and granules in sachets to extend their use to patients with at least one non-class I *CFTR* mutation. The full indications for Kaftrio will therefore be as follows:[2]

> Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one **non-class I** ~~*F508del*~~ mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see sections **4.2 and** 5.1).

The CHMP based its recommendation on the assessment of efficacy and safety data from ***clinical*** and ***in vitro*** (laboratory) studies, including one randomised placebo-controlled ***trial***, an open-label study, data from a ***real-world evidence study*** conducted by the United States Cystic Fibrosis Foundation as well as bibliographical data obtained through a ***French compassionate use*** programme.

Expanded French Compassionate Use Programme

- Real word data: observational data set of non-F508del pwCF
- 4–6-week trial for all-comers CF population with lung disease in France
- Clinical response: an increase in ppFEV1 ≥5% and/or a decrease in SwCl ≥20 mmol/L

479 pwCF enrolled

114 with FDA-approved variant
365 without FDA-approved variant

290 (61%) responsive

109 with FDA-approved variant: 96%
181 without FDA-approved variant: 51%

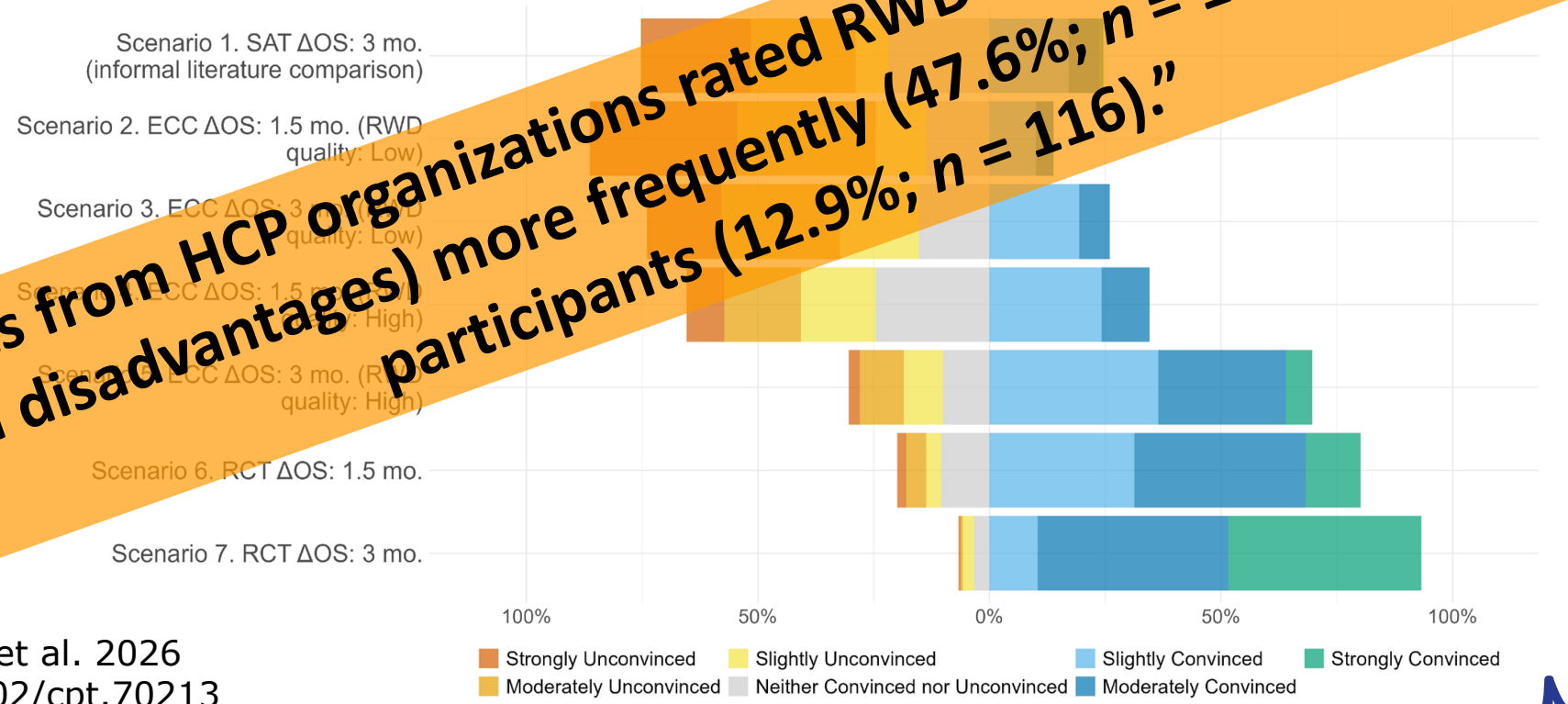
- Responsiveness of a mutation assigned in pwCF:
  - Homozygous for a specific mutation (two similar alleles)
  - Heterozygous for a specific mutation and a known non-responsive mutation in trans (e.g. MF mutation)
  - In pwCF without clinical response, both mutations were considered non-responsive

Five categories:
Responsive: ≥3 pwCF with clinical response
Probably responsive: 1-2 pwCF with clinical response
Probably non-responsive: 1-2 pwCF without clinical response
Non-responsive: ≥3 pwCF without clinical response
Inconclusive: without sufficient data

Assessing Overall Survival Benefits in Advanced Cancers: The Role of External Comparator Cohort Studies with Real-World Data

- Distribution of strength of evidence ratings that the new treatment has a favorable effect on OS in the studied population.

"Participants from HCP organizations rated RWD studies favorably (advantages outweigh disadvantages) more frequently (47.6%; *n* = 103) compared to RA participants (12.9%; *n* = 116)."

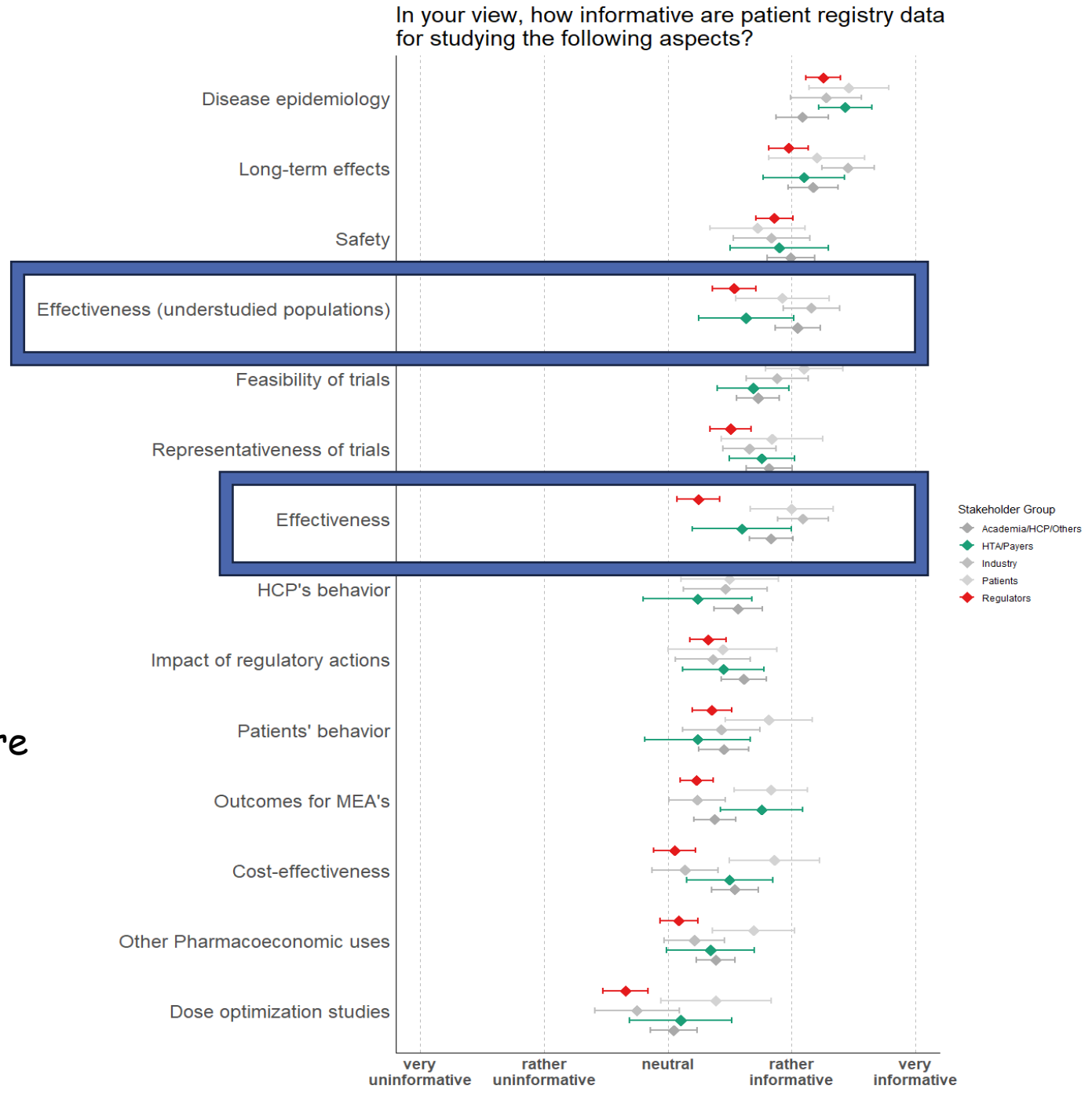


Pignatti, F et al. 2026
doi:10.1002/cpt.70213

In your view, how informative are patient registry data for studying the following aspects?

N=382
December ' 24 – feb "25

Results similar to last year, but some more Granularity due to increased numbers

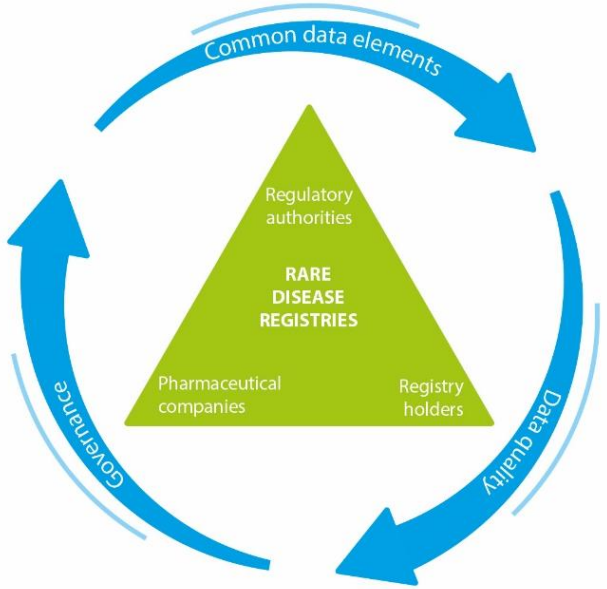


EMA Patient Registry Initiative

- ***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

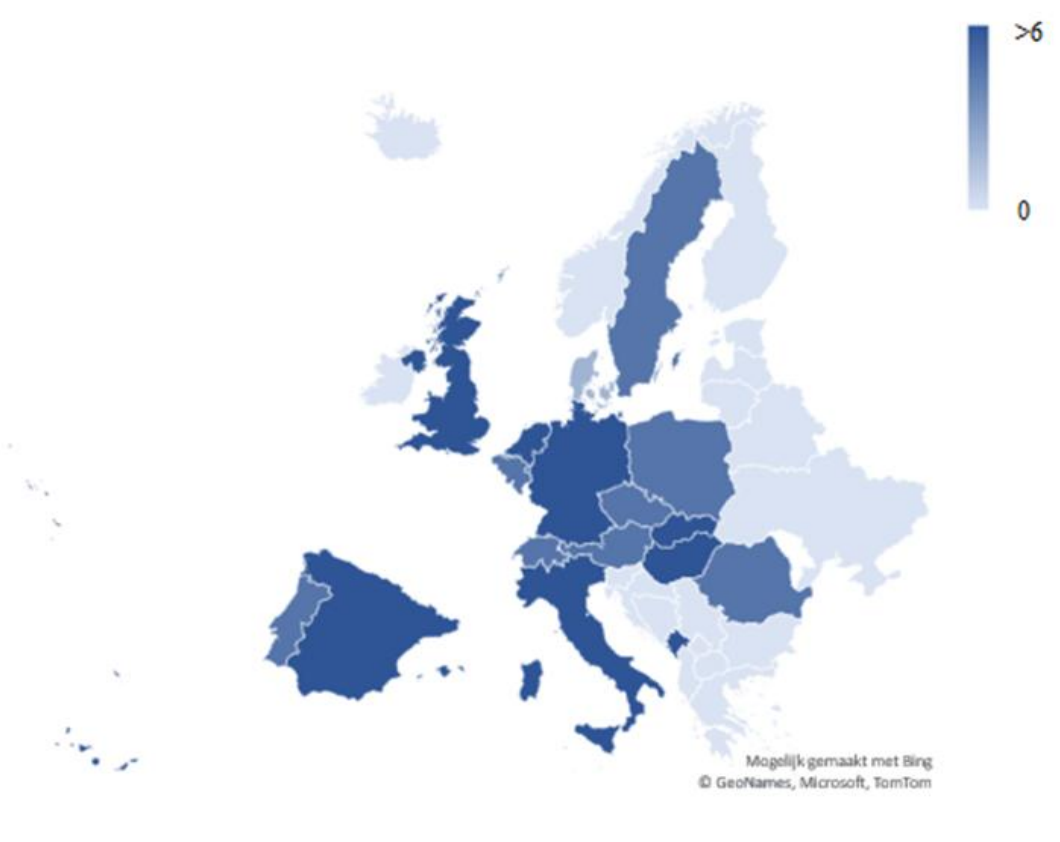
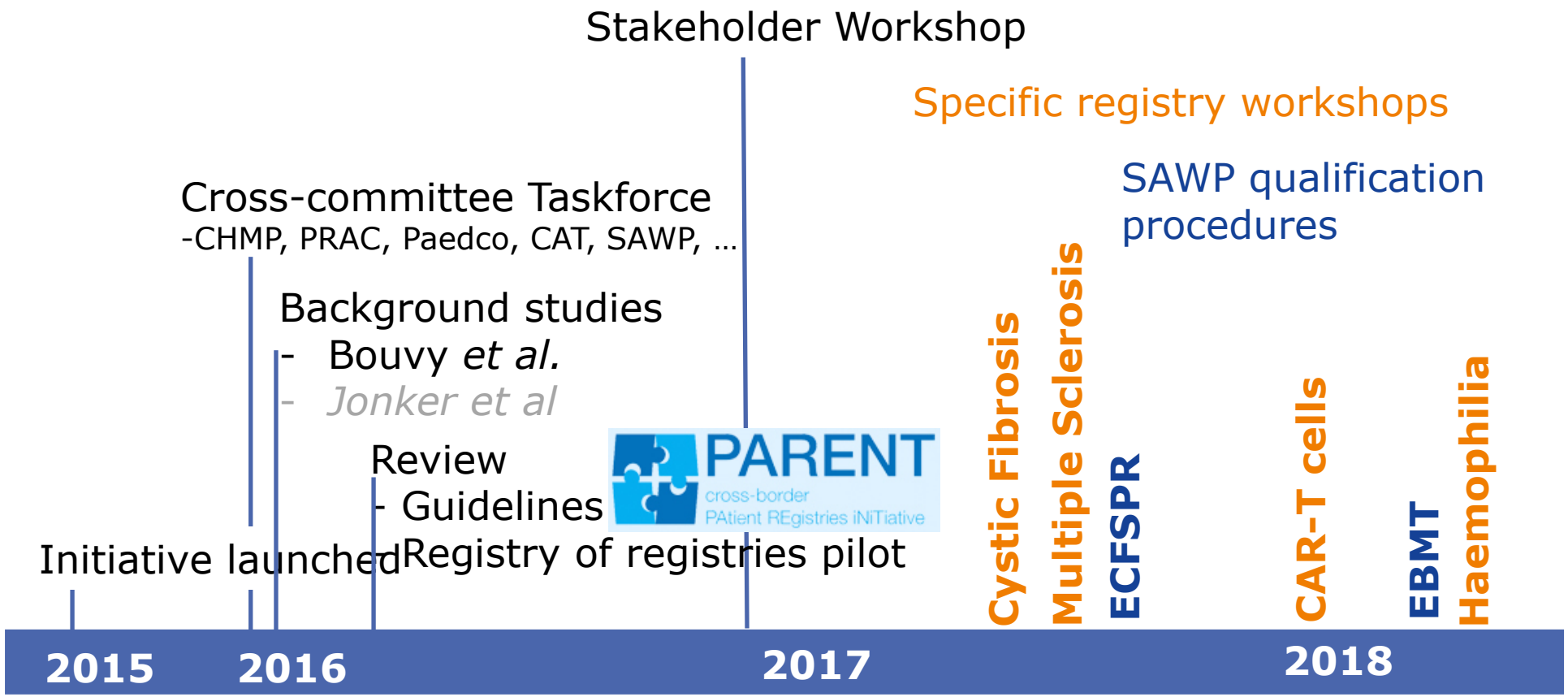


Figure. *Geographical distribution of heart failure data sources in Europe, with darker shades of colour representing more data sources. Adapted from Studer et al., 2022.*

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

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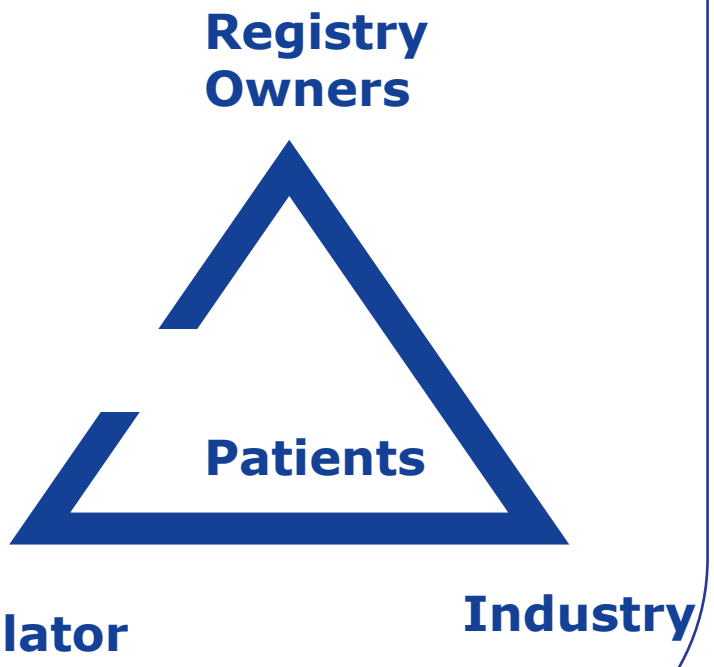
How can regulators support use of disease registries?

- **Methodological guidance** on use of disease registries from a regulatory perspective
- **Scientific Advice** on PASS/PAES study protocol using registries, e.g. joint collaborative studies
- **Inventory of disease registries : EMA RWD catalogue**
- **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!



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

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Procedure No.: EMEA/H/SAB/080/1/QA/2017
EMA/CHMP/SAWP/802259/2017
Product Development and Scientific Support Department

Qualification Opinion

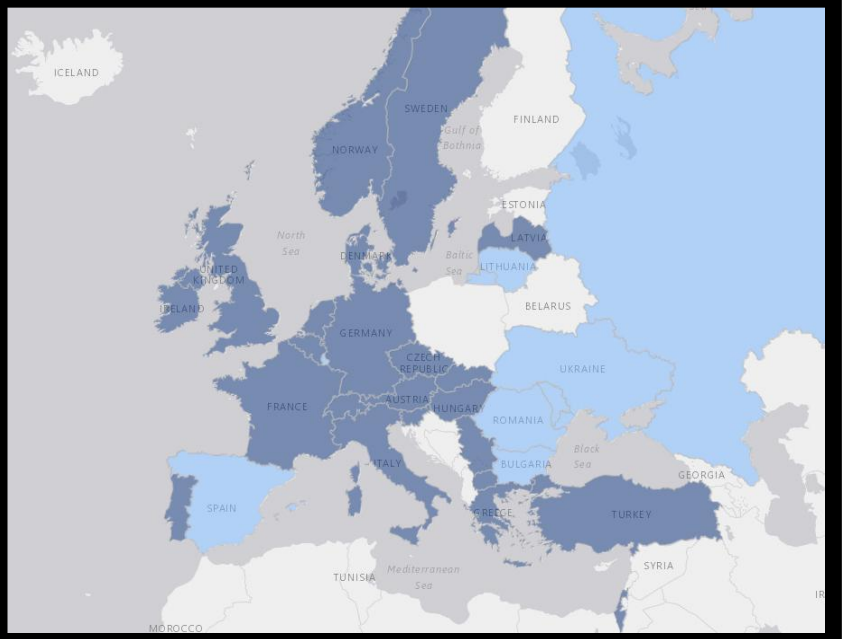
The European Cystic Fibrosis Society Patient Registry (ECFSPR)

Context of Use

- ***Drug utilisation studies***
  - - For total recorded population and by subgroup such as CF complications, age, gender, FEV1 status, genotype, etc.
- ***Drug efficacy/effectiveness studies***
  - - For concurrent assessment of post authorisation efficacy/effectiveness using annual best FEV1, mortality, pulmonary exacerbations using the ECFSPR working definition or CF complications;
  - - As a source of historical control data ..for contextualization, e.g. for comparative purposes in the context of non-randomized clinical trials (i.e. when this would be the only reasonable option).
- ***Drug safety evaluation***
  - - As a tool to collect safety data with a particular focus on important identified and potential risks. *{and some fine print qualifications}*

General Queries: Coverage of ECFS Registries

- 31 Countries
- **>42,000 patients**
- 17 National Registries
  - 12 Upload
- 85 centres use ECFS Registry Software*
- GPP not currently required
- Broad coverage

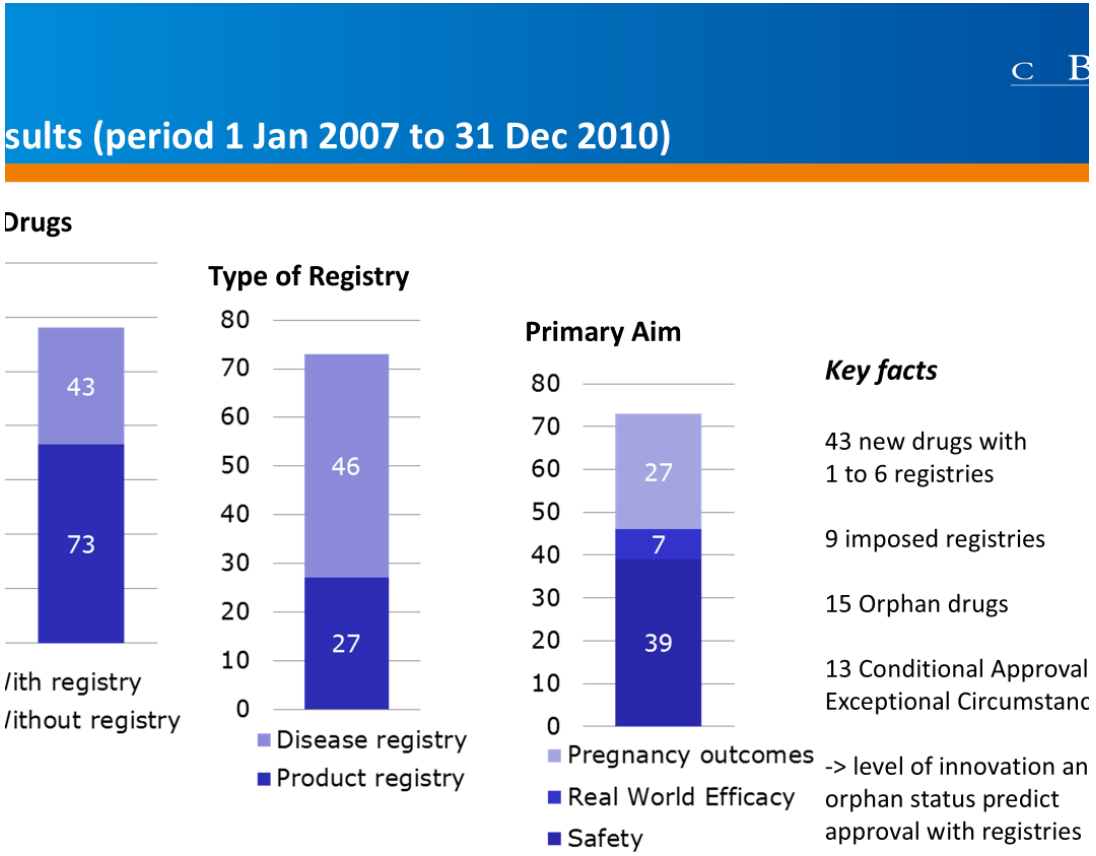


* + 13 centres of the CF Registry Ireland

Presented ECFS 2017

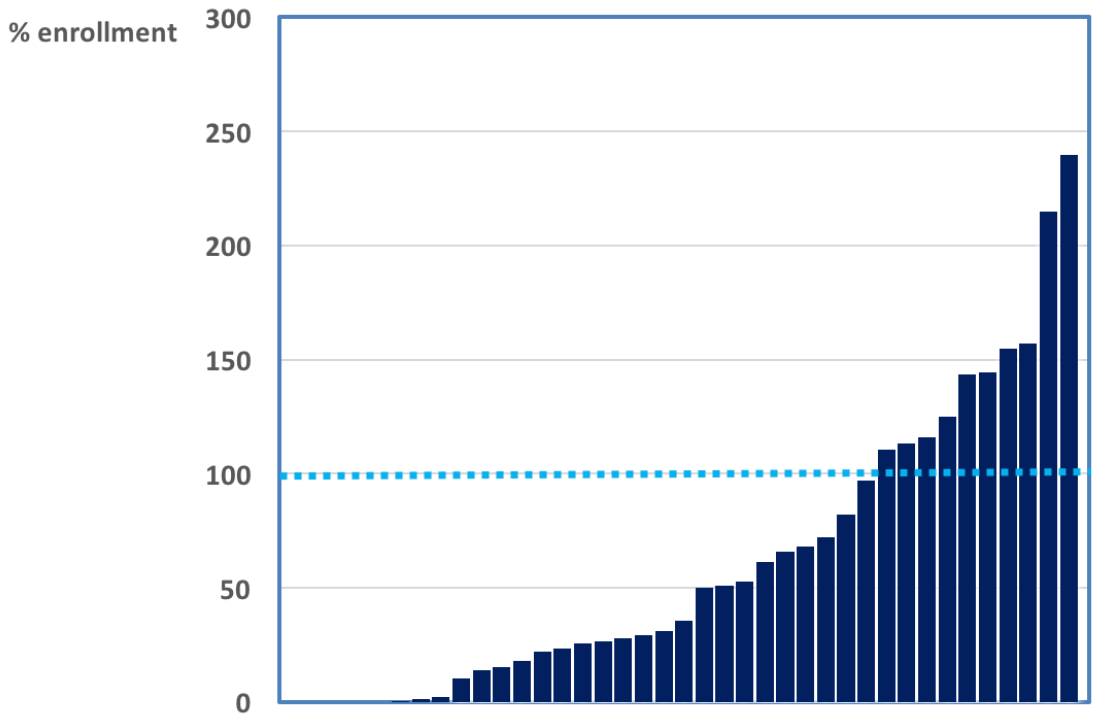
But,'Drug Registries and Approval of Drugs: Promises, Placebo, or a Real Success?'

- Regulatory authorities often require post-authorization studies that involve patient registries.
- It is unknown, however, whether such registry studies are adequately completed.
- We investigated whether registry studies for new drugs were performed as agreed at time of approval.



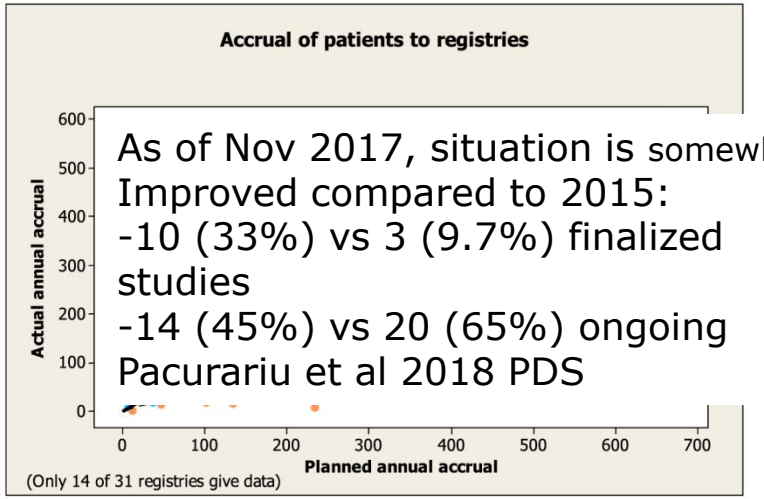
C. Jonker et al. Pharmacoepidemiol Drug Saf. 2017;1–7

Enrolment, however is/was problematic…



Enrolment in 41 of 73 registries (registry studies) with predefined sample sizes (a median of) 5 years after approval

Jonker C et al. Clinical Therapeutics 2018



As of Nov 2017, situation is somewhat Improved compared to 2015:
-10 (33%) vs 3 (9.7%) finalized studies
-14 (45%) vs 20 (65%) ongoing
Pacurariu et al 2018 PDS

Bouvy J et al. Pharmacoepidemiol Drug Saf. 2017;1-8

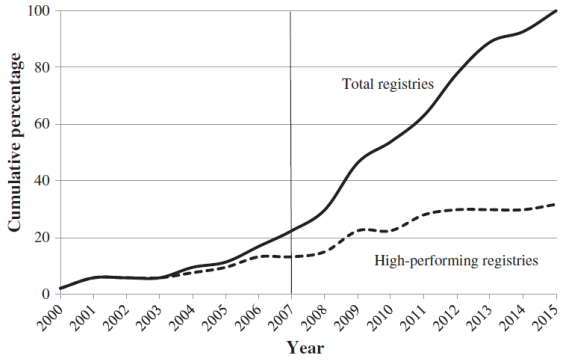


FIGURE 1 Cumulative distribution of postmarket product registries. Total registries represent the 54 registries identified that have initiated (nonpending status)

Zhao Y et al. Pharmacoepidemiol Drug Saf. 2018;1-8

Many developments

- Multiple workshops, guidance (DQF)
- Qualification procedure registries: EBMT, ECFSPR, ...
  - But be careful: SMA – registries: data linkage vs. too detailed data collection!?
    - Jonker et al., 2026, Neuromuscular Disorders
  - Patient involvement in data collection, harmonisation, PRO
  - Data linkage ☺ , … still unstructured data ☹
- Delphi approaches what to collect
  - Lung cancer registries – minimal data set (Grit et al, 2026, unpublished)
  - Metachromatic leukodystrophy (Schoenmakers et al., 2022, Orphanet J Rare Dis)
  - Primary Biliary Cholest… (EASL-AASLD, 2026 unpublished)
- Long term safety of gene therapies (Haart et al, 2025, Drug Disc Today)

2026 Regulatory Thinking

- Plethora of Guidances, a.o.
  - Registry-based study guideline
  - Data Quality Framework
  - ICH E23 Considerations for the use of RWE to inform regulatory decision making with a focus on effectiveness of medicines
- DARWIN EU
- Interactions with stakeholders, e.g., Duchenne, Alzheimer (not rare), and regular support in medicines applications
- Supportive role in addition to trial data
  - Sometimes Compassionate Use
- BUT; data quality, pre-planning and bias!

Thank you for your attention!

How are we gonna make it work?

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