How can Real World Registry Data be used to augment clinical trial data to improve drug development and regulatory decision making

13th February 2025

Housekeeping

All participants will automatically be muted.

The chat box is disabled.

Please add your questions in the Q&A box. They will be answered either during the webinar or at the Q&A session at the end.

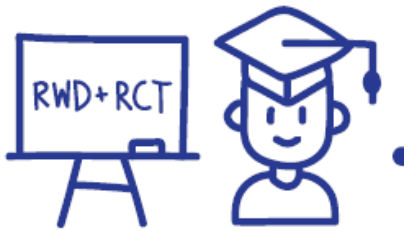
This webinar is being recorded; we will share the recording with all registrants after the webinar.

Agenda

Topic	Speaker(s)	Time Duration
Welcome and introduction	Carla Torre (University of Lisbon)	10 min
MAA Made to the European Medicines Agency: What was the Contribution of Real-World Evidence?	Kelly Plueschke (EMA)	30 min
Patients' perspective on RWD	François Houÿez (EURORDIS)	30 min
Registry data for early development decision making	Kit Roes (Radboud University Medical Center)	30 min
Q&A session **Panelists:**	Moderator: Kit Roes (Radboud University Medical Center)	30 min
Wrap-up and conclusion	Kit Roes (Radboud University Medical Center) and Peter Mol (University of Groningen)	5 min

1. Welcome and introduction

Carla Torre, FFUL



More-EUROPA

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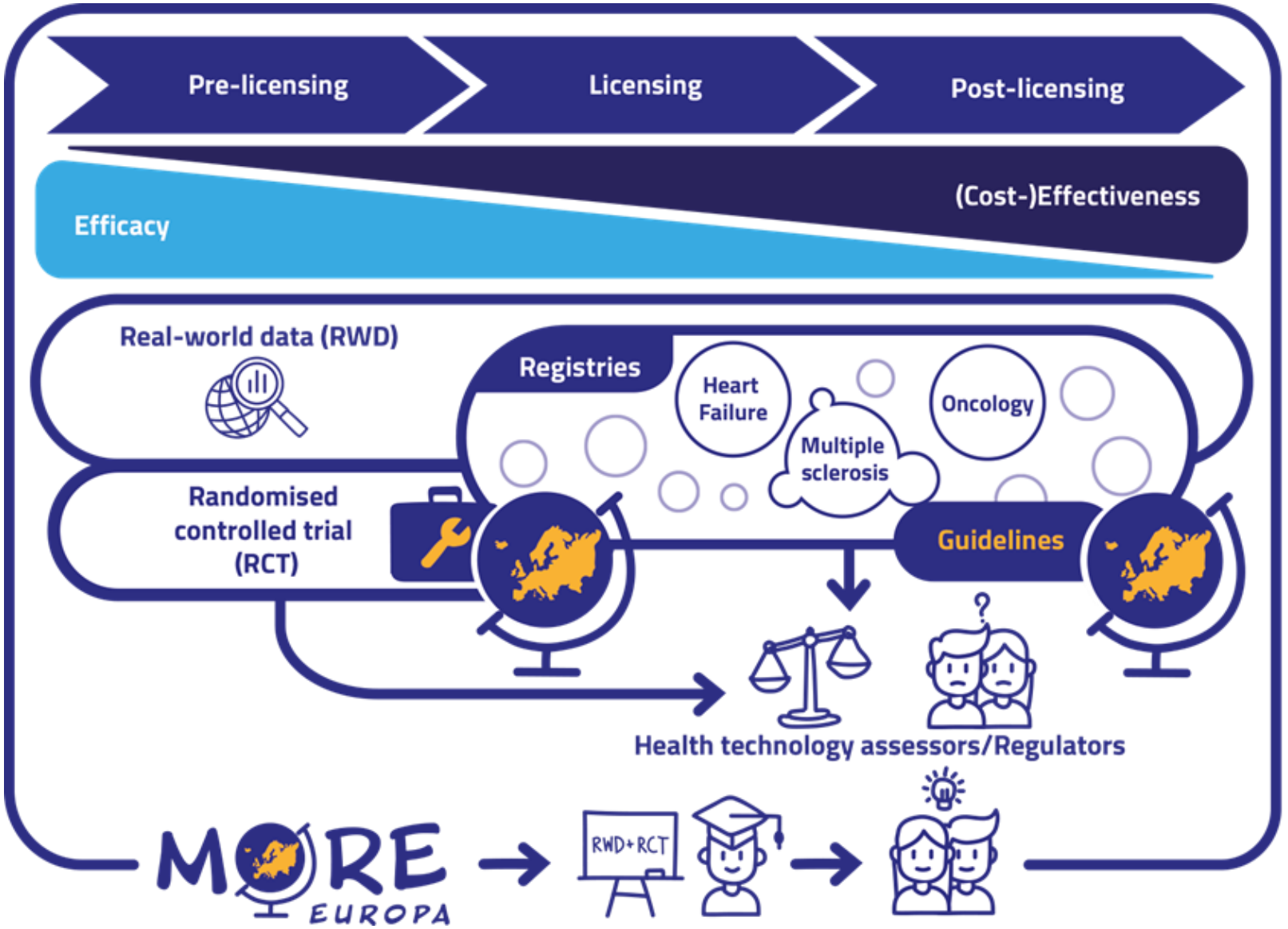
- Horizon-HLTH-2022-TOOL-11-02

Aims

- Establish value of registry-based RWD in augmenting RCTs
- Enable **more** **e**ffective and ethical **u**se of **r**egistry data to supp**o**rt **pa**tient-centered regulatory and health technology assessment decision-making


Pre-licensing
Licensing
Post-licensing
Efficacy
(Cost-)Effectiveness
Real-world data (RWD)
Registries
Heart Failure
Multiple sclerosis
Oncology
Randomised controlled trial (RCT)
Guidelines
Health technology assessors/Regulators
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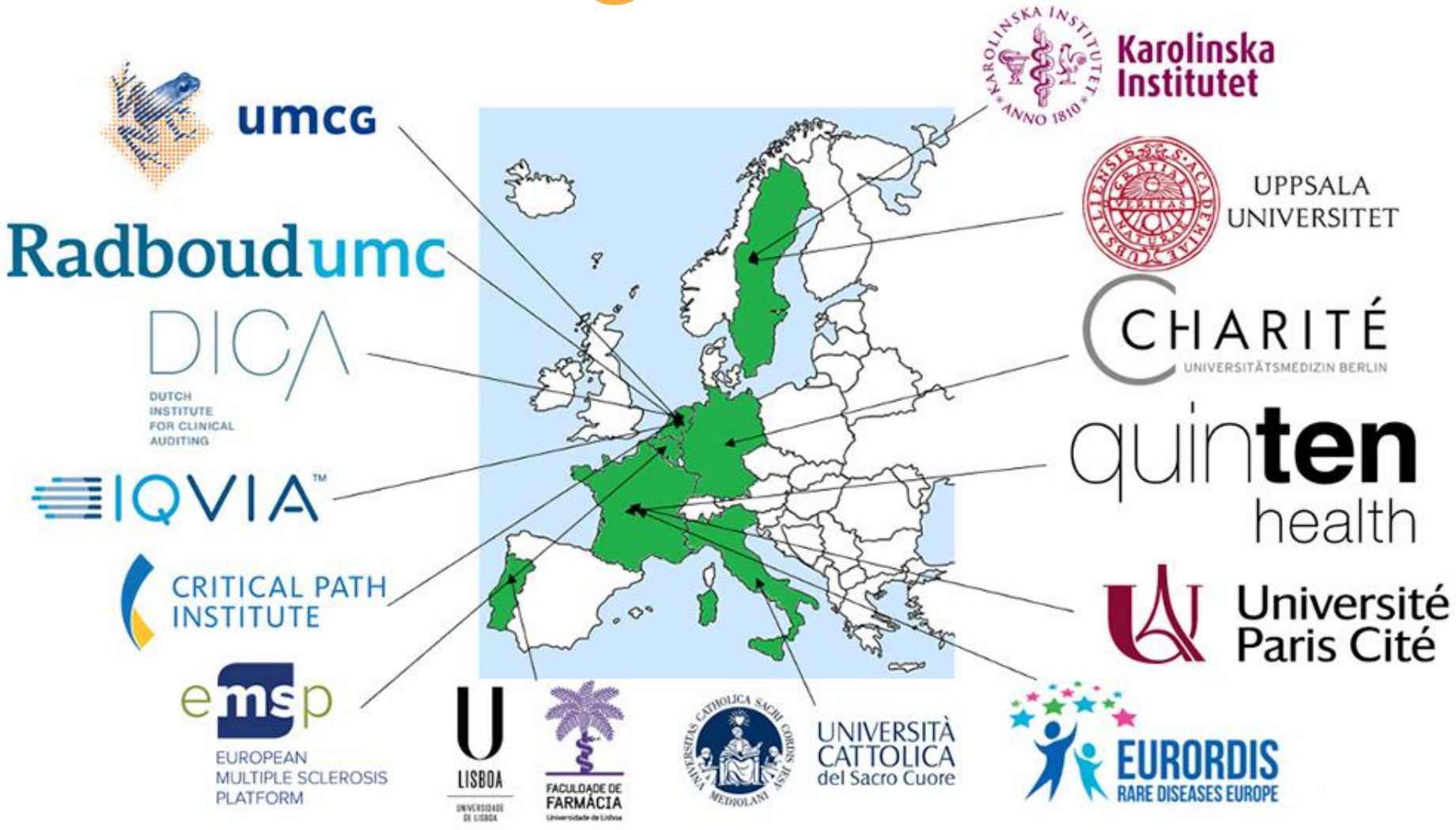
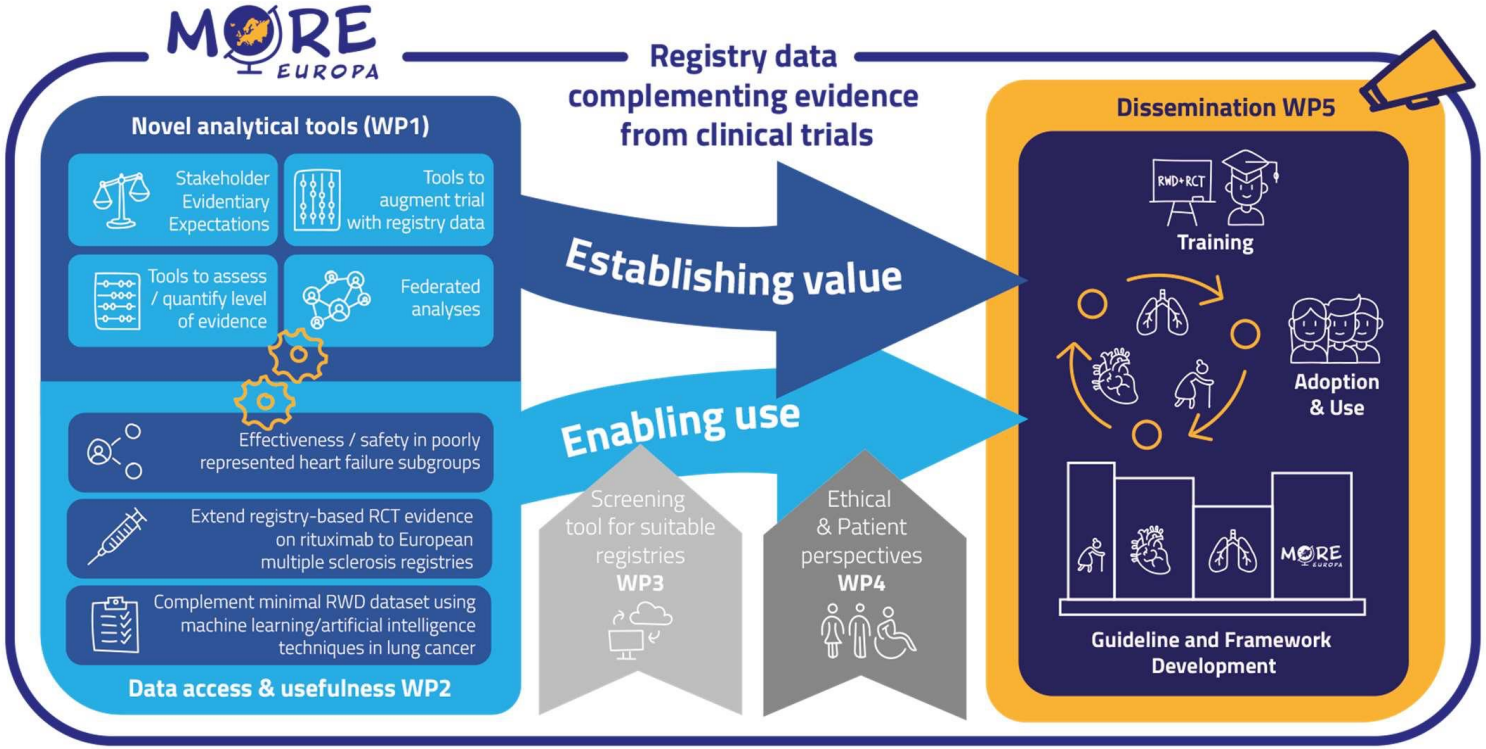
RWD+RCT

15 Organisations





Early development

- Biomarker & to support **probability of success** & clinical outcome associations full development decisions

Full development & decision making

- **Contextualisation**
- Direct augmentation of clinical trial data (hybrid)
- Modeling efficacy / effectiveness in broad population based on clinical trial data

Beyond Full development

- Target trial emulation for observational studies
- Registry-based clinical trials
- Modelling for **HTA support**, including external controls

Using mutiple registries
Federated inference

Scientific publications

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2023) 9, 343–352
https://doi.org/10.1093/ehjcvp/pvad012
ORIGINAL ARTICLE
Heart failure/cardiomyopathy

Eligibility for sotagliflozin in a real-world heart failure population based on the SOLOIST-WHF trial enrolment criteria: data from the Swedish heart failure registry

Peter Moritz Becher[1,2,†], Gianluigi Savarese[1,3,†], Lina Benson[1], Ulf Dahlström[4], Patric Karlström[5,6], Peter G.M. Mol[7], Marco Metra[8], Deepak L. Bhatt[9], Bertram Pitt[10] and Lars H. Lund[1,3,*]

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2024) 10, 296–306
https://doi.org/10.1093/ehjcvp/pvae026
ORIGINAL ARTICLE
Heart failure/cardiomyopathy

Glucagon-like peptide-1 receptor agonists use and associations with outcomes in heart failure and type 2 diabetes: data from the Swedish Heart Failure and Swedish National Diabetes Registries

Markus Wallner[1,†], Mattia Emanuele Biber[2,3,†], Davide Stolfo[2,4], Gianfranco Sinagra[4], Lina Benson[2], Ulf Dahlström[5], Soffia Gudbjörnsdottir[6,7], Francesco Cosentino[2,8], Peter G. M. Mol[9], Giuseppe M. C. Rosano[10], Javed Butler[11,12], Marco Metra[13], Lars H. Lund[2,8], Giulia Ferrannini[2,‡] and Gianluigi Savarese[2,8,*,‡]

PLOS ONE

RESEARCH ARTICLE

Eligibility for omecamtiv mecarbil in a real-world heart failure population: Data from the Swedish Heart Failure Registry

Felix Lindberg[1‡], Natanael Øigaard[1‡], Marco Metra[2], Giuseppe M. C. Rosano[3,4], Ulf Dahlström[5], Peter Mol[6], Camilla Hage[1,7], Lars H. Lund[1,7], Gianluigi Savarese[1,7*]

ESC European Society of Cardiology
European Journal of Heart Failure (2023) 25, 1418–1428
doi:10.1002/ejhf.2939
RESEARCH ARTICLE

Eligibility for vericiguat in a real-world heart failure population according to trial, guideline and label criteria: Data from the Swedish Heart Failure Registry

Ngoc V. Nguyen[1], Felix Lindberg[2], Lina Benson[2], Giulia Ferrannini[2], Egidio Imbalzano[3], Peter G.M. Mol[4], Ulf Dahlström[5], Giuseppe M.C. Rosano[6], Justin Ezekowitz[7], Javed Butler[8,9], Lars H. Lund[2,10], and Gianluigi Savarese[2,10*]

ESC European Society of Cardiology
European Journal of Heart Failure (2023) 25, 2164–2173
doi:10.1002/ejhf.3049
RESEARCH ARTICLE

Safety of continuing mineralocorticoid receptor antagonist treatment in patients with heart failure with reduced ejection fraction and severe kidney disease: Data from Swedish Heart Failure Registry

Federica Guidetti[1], Lars H. Lund[1,2], Lina Benson[1], Camilla Hage[1], Francesca Musella[1,3], Davide Stolfo[1,4], Peter G.M. Mol[5], Andreas J. Flammer[6], Frank Ruschitzka[6], Ulf Dahlstrom[7], Giuseppe M.C. Rosano[8], Oscar Ö. Braun[9], and Gianluigi Savarese[1,2*]

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Scientific publications

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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Frits Lekkerkerker,
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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*†]

ESC European Society of Cardiology

European Journal of Heart Failure (2024) **26**, 1101–1110
doi:10.1002/ejhf.3272

RESEARCH ARTICLE

Sex differences in the prognostic role of achieving target doses of heart failure medications: Data from the Swedish Heart Failure Registry

Amerigo Ferrari[1,2†], Davide Stolfo[1,3†], Alicia Uijl[1,4], Nicola Orsini[5], Lina Benson[1], Gianfranco Sinagra[3], Peter Mol[6], Sieta T. de Vries[6], Ulf Dahlström[7], Giuseppe Rosano[8,9], Lars H. Lund[1,10], and Gianluigi Savarese[1,10*]

van den Akker *et al. BMC Medicine* (2024) 22:577
https://doi.org/10.1186/s12916-024-03799-w

BMC Medicine

RESEARCH Open Access

Check for updates

Ethics practices associated with reusing health data: an assessment of patient registries

Olmo R. van den Akker[1*], Susanne Stark[1] and Daniel Strech[1]

SYSTEMATIC REVIEW

On the Concepts, Methods, and Use of "Probability of Success" for Drug Development Decision-Making: A Scoping Review

Aysun Cetinyurek Yavuz[1,*], Muhammad Bergas Nur Fayyad[1], Ce Jiang[2], Florie Brion Bouvier[3], Celine Beji[3], Sonia Zebachi[2], Ghinwa Y. Hayek[2], Billy Amzal[2], Raphael Porcher[3], Julien Tanniou[2], Kit Roes[1] and Laura Rodwell[1]

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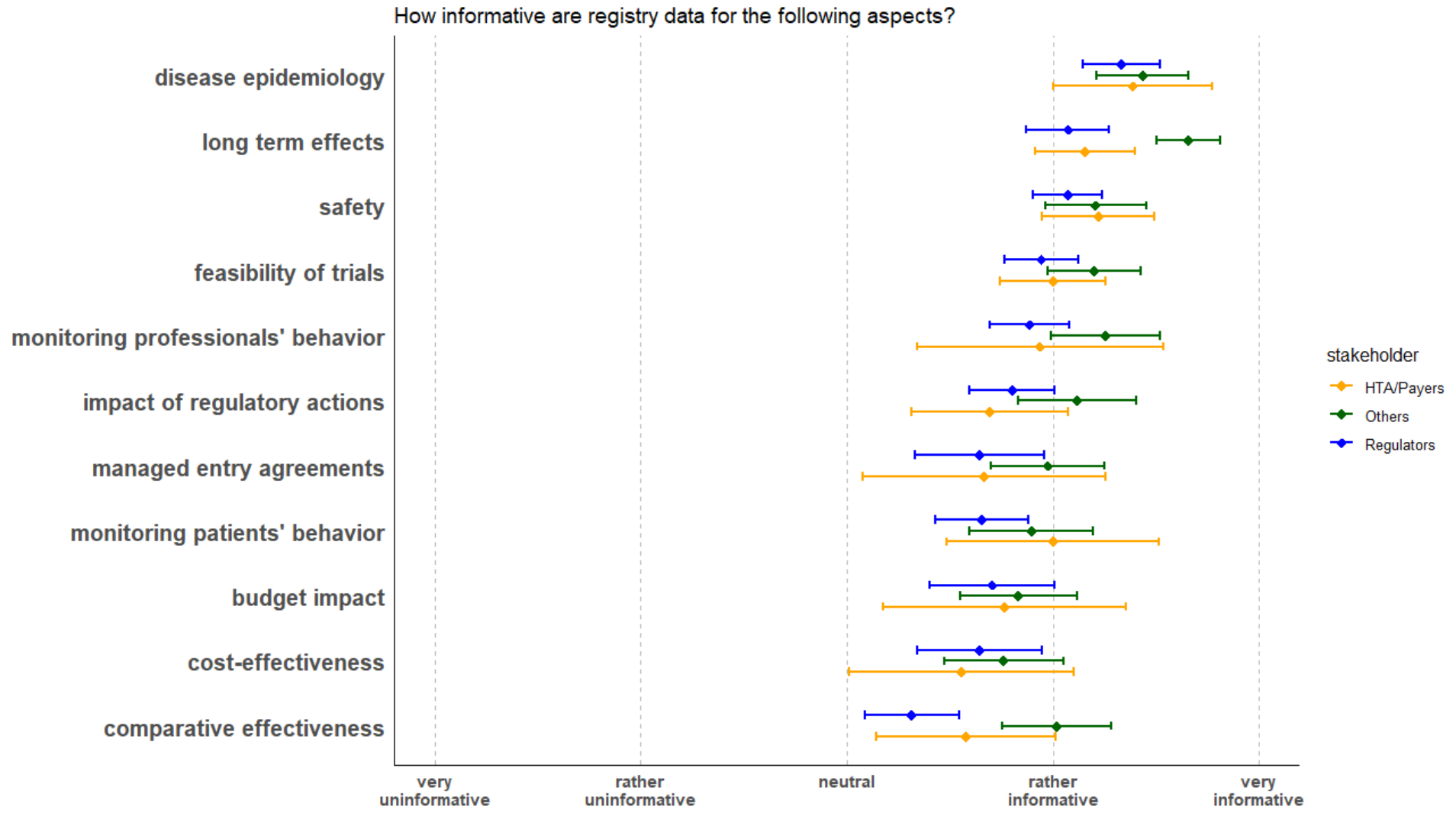
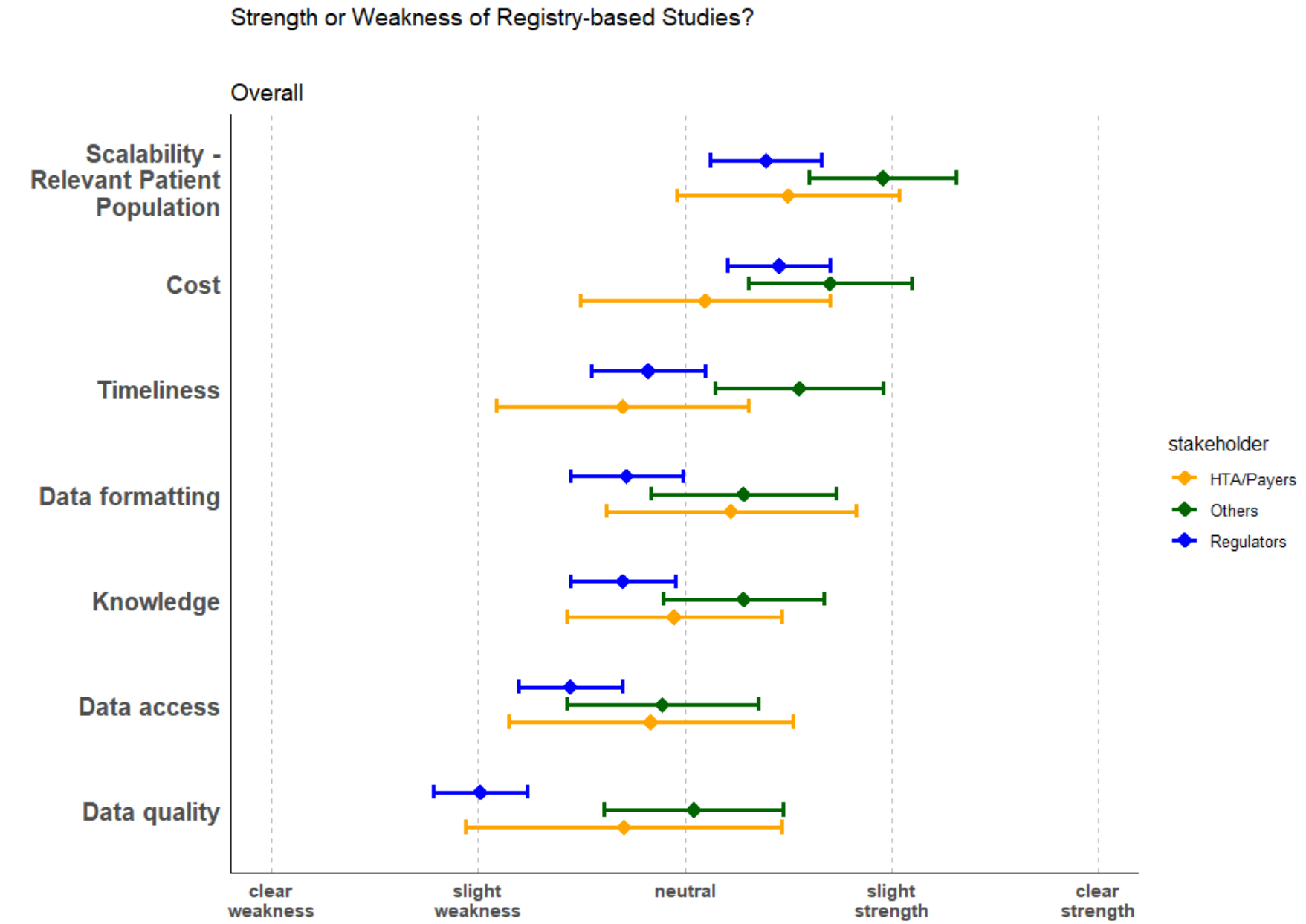
Some results survey study

N = 191 (regulators: 110, HTA/payers: 24, Other 57)

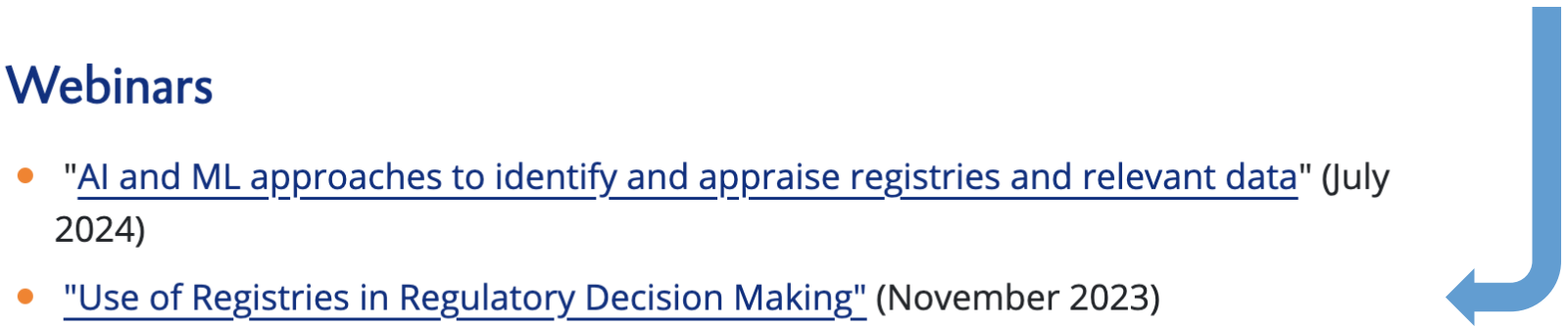



Strength or Weakness of Registry-based Studies?
Overall
Scalability - Relevant Patient Population
Cost
Timeliness
Data formatting
Knowledge
Data access
Data quality
clear weakness
slight weakness
neutral
slight strength
clear strength
stakeholder
HTA/Payers
Others
Regulators

Previous webinars

- AI and ML approaches to identify and appraise registries and relevant data
- Use of Registries in Regulatory Decision Making

Access recordings: **https://umcgresearch.org/more-europa-news-events**



MAA submitted to the European Medicines Agency: What was the Contribution of Real-World Evidence?

MORE EUROPA webinar – 13 February 2025

Presented by:

Kelly Plueschke, Data Analytics and Methods taskforce, Real World Evidence Workstream, EMA

Anna Rasokat, Epidemiology – Data Science, University Clinic Köln, Germany

Disclaimer

The presenters do not have any conflict of interest.

The views expressed in this presentation are personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Table of content

- Background
- Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making (2018-2019)
- Follow-up study covering 2020-2023
- Key messages for the future

Background

"***Promote use*** *of* ***high-quality*** *real-world data (RWD) in decision-making."*

[…]

"Real world data is currently used predominantly in the post-authorisation phase but there are ***opportunities for further application*** *throughout the medicines lifecycle to help* ***address some of the limitations of clinical trials****."*

What RWE is submitted to EMA? At which occasion? With what level of quality? How has is been used in decision-making?

Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making 2018-2019

Clinical Pharmacology & Therapeutics

Flynn R. et al. (2022)

Review | Open Access

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Robert Flynn, Kelly Plueschke, Chantal Quinten, Valerie Strassmann, Ruben G. Duijnhoven, Maria Gordillo-Marañon, Marcia Rueckbeil, Catherine Cohet, Xavier Kurz

First published: 24 October 2021 | https://doi.org/10.1002/cpt.2461 | Citations: 5

Clinical Pharmacology & Therapeutics

Bakker E. et al. (2022)

Article | Open Access

Contribution of Real-World Evidence in European Medicines Agency's 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 | Citations: 2

1. To **characterise RWD/RWE** submitted to EMA included in centralised marketing authorisation applications (MAA) and extensions of indications (EoI) submitted to EMA in 2018-2019 *(exclusion: generic, informed consent, well established use products + ongoing evaluations)*
2. To **analyse their contribution to the assessment and decision-making** by the Committee for Medicinal Products for Human Use (CHMP) *(note: focus was on pre-authorisation RWE)*
3. To **identify gaps in guidance** on the use, and evaluation of RWD/RWE

Working definitions at the time of the study (2020/2021)

- **Real-World Data (RWD):** "*routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials*" (→ includes patient registries)
- **Real-world evidence (RWE):** "*information derived from analysis of real-world data*"

INCLUDED AS RWD/RWE

- Non-interventional studies conducted pre- or post-authorisation, for example:
  - Use of real-world data to contextualise the submissions (e.g. disease epidemiology, drug utilisation, patient characteristics, effects)
  - Use of real-world data source as external control groups in clinical trials
  - Surveys addressed to patients

NOT INCLUDED AS RWD/RWE

- Clinical trials without use of RWD/RWE (Phase I - IV), pre-clinical studies, toxicological studies, dose-response studies, drug-drug interaction studies
- Open-label follow-up studies of clinical trial
- Routine pharmacovigilance activities in RMP
- Surveys addressed to HCPs

Study 1 methods

Clinical Pharmacology & Therapeutics

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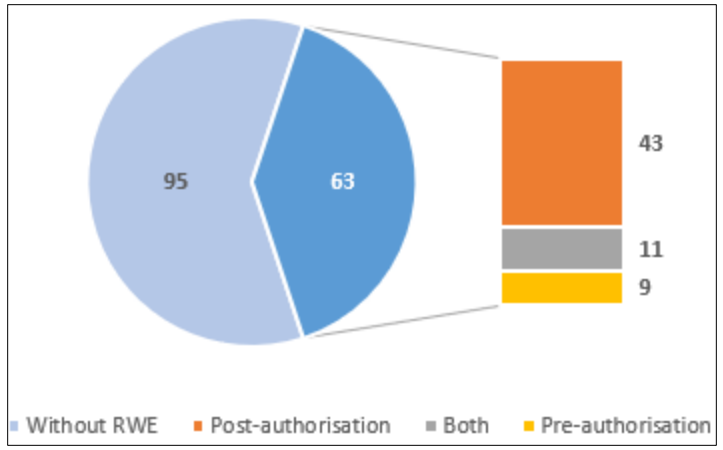
First published: 24 October 2021 | https://doi.org/10.1002/cpt.2461 | Citations: 5

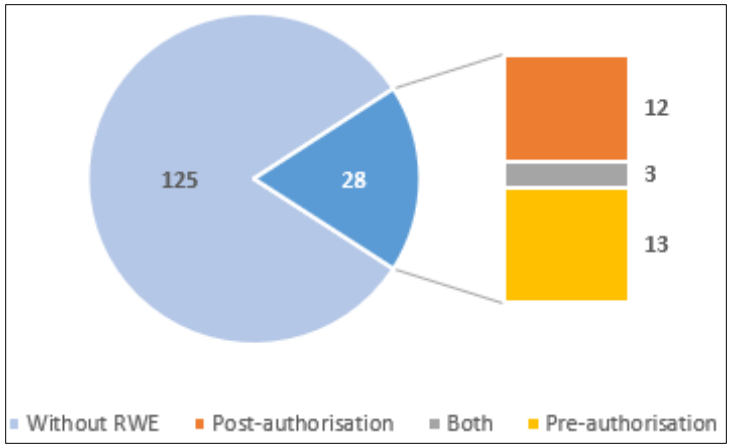
- Manual review of final version of CHMP assessment reports, risk management plans, protocols to identify and characterise RWD/RWE
- Data extraction using standard form
- Verification of samples of products by 2 independent reviewers

Study 1 results

Initial MAAs (N = 158)



EoIs (N = 153)



- MAAs: RWE **in 40%** of the applications (63/158), mostly post-A
- EoIs: RWE in **18%** (28/153)
- Majority of products: **Antineoplastic** and **Immunosuppressants** (35% MAA and 42% EoI)

Study 1 results

Characteristics of RWD/RWE studies used	Initial MAAs n (%) total MAAs = 63	EoI n (%) total EoI = 28
Data sources		
Electronic health care records from primary care	8 / 63 (12.7)	2 / 28 (7.1)
Electronic health care records from secondary care	8 / 63 (12.7)	0 / 28 (0.0)
Medical records from primary care *	8 / 63 (12.7)	5 / 28 (17.9)
Hospital data	20 / 63 (31.7)	7 / 28 (27.0)
Claims data	5 / 63 (7.9)	2 / 28 (7.1)
Prescription data	6 / 63 (9.5)	3 / 28 (10.7)
Dispensing data	5 / 63 (7.9)	1 / 28 (3.6)
All registries †	38 / 63 (60.3)	13 / 28 (46.4)
Disease registry	21 / 63 (33.3)	9 / 28 (32.1)
Product registry	9 / 63 (14.3)	3 / 28 (10.7)
Other registries ‡	13 / 63 (20.6)	2 / 28 (7.1)
Data from compassionate use programme	2 / 63 (3.2)	1 / 28 (3.5)
Spontaneous reports §	4 / 63 (6.3)	3 / 28 (10.7)
Re-use of data from observational studies	4 / 63 (6.3)	1 / 28 (3.6)
Linked data sources	3 / 63 (4.7)	1 / 28 (3.6)
Other data sources ‖	18 / 63 (28.6)	5 / 28 (17.9)

RWE Real world evidence; MA Marketing authorisation; MAAs Marketing Authorisation Applications; EoI Extensions of Indication

* Primary care medical records were not always identified as electronic or paper based

† Products might be associated with registries of multiple different types

‡ Other registries: pregnancy registry, birth defect registry, population registries, other patient registries (unspecified)

§ Use of spontaneous reports for purposes other than routine pharmacovigilance: typically, these were included as part of wider safety databases incorporating data from multiple sources

‖ Example of other data sources: medical charts or combination of different data sources

Registries used as source of RWE for 24% of products with new MAA

For **60% of MAAs** and **46% of EoI**: Registry data submitted in applications, or proposed to be submitted post-approval (mostly the latter)

Study 2 methods

Clinical Pharmacology & Therapeutics

Bakker E. et al. (2022)

Article | Open Access

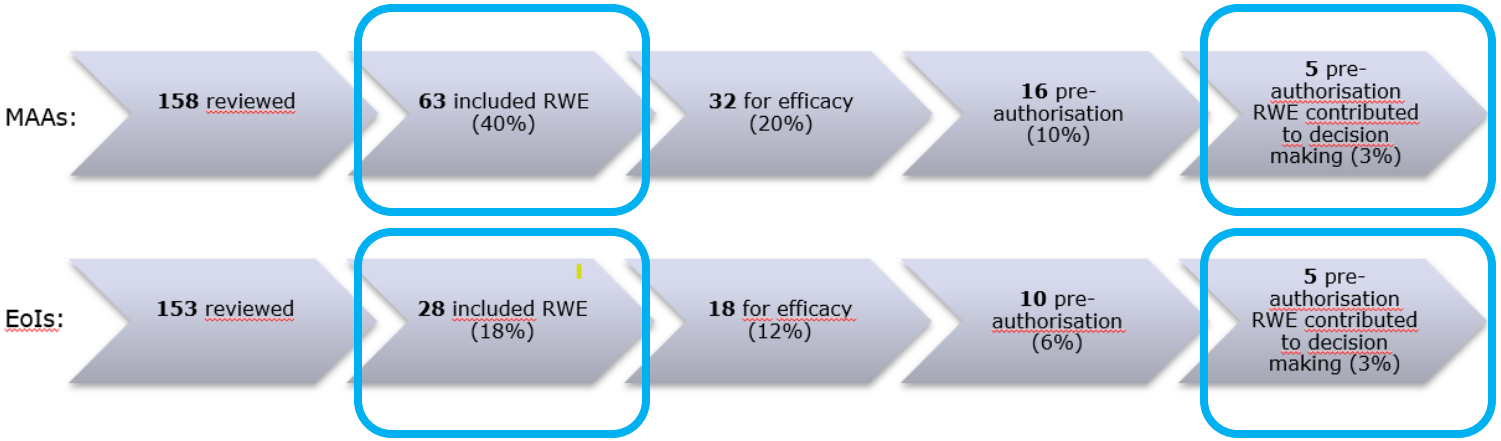
Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making

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 | Citations: 2

- In depth manual review of Study 1 products with pre-authorisation RWE to support efficacy claims
- Data extraction of CHMP appraisal of RWD/RWE (strengths, limitations, relevance for decision-making)
- Verification of samples of products by 2 reviewers

Final results (2018-2019)



Pre-authorisation RWE	MAA (n=16)	EoI (n=10)
Evidence brought by RWE to the application		
Efficacy data	13	8
External comparator	5	3
Contextualisation data (natural history, standard of care)	3	1
Safety data	6	5
Drug utilisation data	1	1
Data source		
Literature	7	4
Medical records	5	3
Registry	5	3
Other (compassionate use programme, drug utilisation studies, survey)	3	0

Final results (2018-2019)

In efficacy evidence considered by CHMP:

- No MA initial application was supported by registry data
- 3 EoIs were supported by registry data - rare haematological conditions
    - Eptacog alfa (activated) for Glanzmann's thrombasthenia (effectiveness and safety data, natural history)
    - Catridecacog and congenital FXIII A-subunit deficiency (effectiveness and safety data, use patterns)
    - Ivacaftor and cystic fibrosis with specific gene mutations (effectiveness data and external comparator)

- In general, appraisal of strengths were mentioned less often than limitations, e.g.:
    - Missing data
    - Lack of representativeness of e.g.: study population, study period, measuring time points
    - Small sample size
    - Lack of an adequate or pre-specified analysis plan
    - Risk of several types of confounding and bias, e.g.: selection bias, publication bias

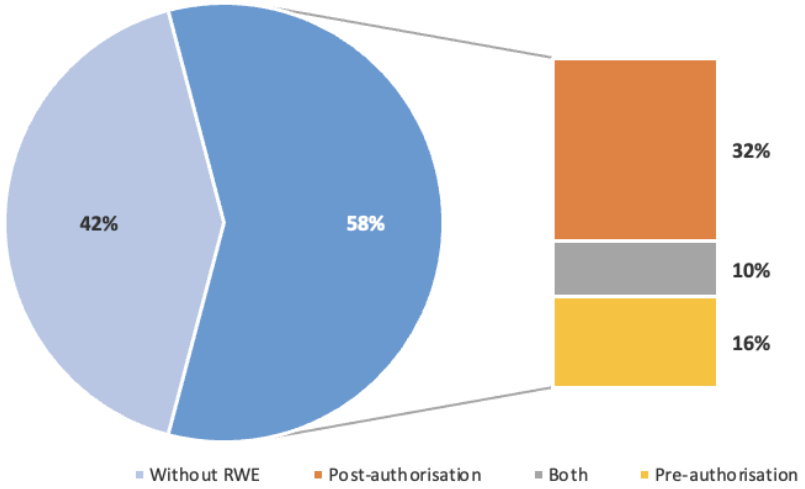
Follow-up Study: Preliminary results

RWE contributing to EMA's Regulatory Decision Making 2020-23

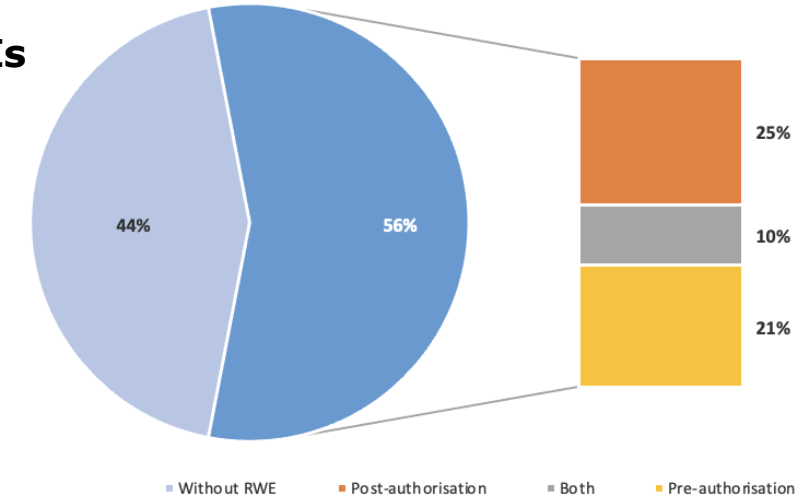
Automated Search and Data Extraction	Quality Checks 1st and 2nd Reviewer	Manual Data Extraction
Key Terms as wildcards external control, external comparator, historical control, retrospective, observational, cohort study, registry, claims based, health records, real world, routinely collected, survey, matched controls, matching, propensity	• removal of mere citations of RWE • RWE for pre-authorization vs post-authorization • disambiguation	• CHMP appraisal of RWD/RWE • strength and limitations • relevance
744 applications for MAA and EoI **318** Initial Marketing Authorization **426** Extension of indication **42** no assessment report available yet		ongoing

Follow-up Study 2020-23: **Preliminary Results**

Initial MAAs



EoIs



The use of RWE in applications made to EMA has significantly increased compared to the previous study period (2018-19)

- MAAs: RWE in 58% (vs. 40% 2018-19) of the applications, mostly post-A
- EoIs: RWE in 56 % (vs. 18%) of the applications
- Therapeutic indication of the majority of products with RWE pre-authorization: **Antineoplastic** and **Immunosuppressants** (39% MAA and 56% EoI)

N.b. Results will be updated once outstanding assessment reports for products submitted during the study period become available

Follow-up Study 2020-23: Strengths and Limitations of RWE

Name	Indication	RWE purpose	Data sources	CHMP appraisal:
Teysuno tegafur / gimeracil / oteracil	Extension of indication to include treatment of metastatic colorectal cancer in adult patients where treatment with another fluoropyrimidine is not possible due to intolerability.	efficacy / effectiveness	1. Meta-analysis 2. Retrospective cohort study: CardioSwitch 2. Prospective Dutch Colorectal Cancer (PLCRC) cohort, linked to the Netherlands Cancer Registry (Switch Cohort Study)	• Acknowledgement that RCT not possible due to lack of proper control and unmet medical need • Meta-analysis + exploratory RWE suggest that EoI is a "valuable treatment option" • Limitations: retrospective and uncontrollled nature of data, limited sample size, heterogeneity re tumor types and treatments received
Livmarli maralixibat	Treatment of Progressive Familial Intrahepatic Cholestasis Type 2 (PFIC2) in patients aged ≥ 1 year	External control	NAPPED (NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion Study Group) registry, a non-interventional, multi-national, multi-center longitudinal registry study of approximately 700 PFIC patients of different etiologies	• Additional information is required to address concerns regarding the NAPPED registry and to allow a better understanding of the analyses • Fundamental limitations of indirect comparisons: Residual bias cannot be excluded / quantified, therefore RWE not pivotal evidence for efficacy, **but supportive**
Enhertu trastuzumab	Treatment of unresectable or metastatic HER2-positive breast cancer and HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma	External control arm (ECA)	Historical controls from matched Unicancer cohort	Matching was considered **inadequate** regarding • comparison of baseline characteristics between trial and ECA, • information on timing and follow-up scans with assessing tumor status • Information PFS definition / censoring of PFS.

Follow-up Study 2020-23: Strengths and Limitations of RWE

Name	Indication	RWE purpose	Data sources	CHMP appraisal:
Ceprotin human protein C	Treatment of congenital protein C deficiency	efficacy	Prospective, international, multi-center, noninterventional, observational post-authorization registry	• RWE was Supportive: pivotal study has limitations re small uncontrolled sample size but efficacy is supported by publications, registry data and retrospective data. • Short exposure time of pivotal trial: only retrospective data from the RDC and registry study with longer treatment length (up to 8 years) revealed common cause of drug discontinuation (catheter thrombosis).
Apretude cabotegravir	Pre-exposure prophylaxis of HIV-1 infection	safety	Antiretroviral Pregnancy Registry	• No new safety concerns • Post-Authorization: Prospective monitoring of birth defects in a registry (collaboration of several companies).

Acknowledgement of the Value of RWE in CHMP's Appraisal

Febseltiq (Infigratinib)

RWE would have been needed for contextualization to show unmet medical need

"Of note, the applicant did not make an attempt to contextualise the results, e.g. by comparing to external data, although some approaches for contextualisation were discussed during CHMP scientific advice. A retrospective, observational, natural history study […] was conducted but not directly used for contextualisation. [… I]n the context of a conditional marketing authorisation with another product conditionally authorised for the same indication, demonstration that infigratinib fulfils the unmet medical needs to a similar or greater extent than what is understood for the already conditionally authorised product is required such that contextualisation is needed."

Breyanzi (Lisocabtagene maraleucel)

Encouragement of an infrastructure for RWD collection: long-term follow-up in a technology-specific registry for regulatory purposes

"The Rapporteur recommended a common platform to be used by all CAR-T products that will be marketed to collect as much safety as possible and avoid loss of patient follow-up.

EMA would like CAR-T sponsors to work together, and may host a joint meeting with sponsors in the future."

Key messages

- **RWE, including from patient registries, can contribute to medicines BR decision-making**
- Data are **part of the overall evidence package:** Difficult to isolate the exact impact, acceptability influenced by main or supportive studies, their characteristics, and disease
- Appraisal of RWE requires **case-by-case analysis** to ensure it is **fit-for-purpose** in the specific settings:

❖ Prior **Feasibility assessment** is key to understand RWD opportunities and limitations (several guidelines available: CHMP Guideline on registry-based studies, ICH M14, HMA/EMA Data Quality Framework, GVP Module VIII, Reflection paper on use of RWD in non-interventional studies)

❖ Importance of **early interaction with regulators :** various interaction pathways

- **Roadmap of Guidance documents** to enable the use and facilitate RWE integration in regulatory decision making: HMA/EMA Big Data + Methodology Working Party workplan

EMA interaction pathways for regulatory and scientific support

- To **foster development** of new and innovative medicines, from the early phases in the laboratory all the way to the patient.
  - EU Innovation Task Force
  - Academia
  - SME Office
  - PRIME scheme
  - Qualification advice on novel methodologies
  - Scientific advice / protocol assistance

- Protocol assistance free of charge to academic organisations developing orphan medicines

EMA Qualification of patient registries

Name	Output	Disease	Launch date	Geographical coverage	Nb of patients	Purpose for qualification
ECFSPR	Opinion (2018)	Cystic fibrosis	2008	Europe (WHO-region)	54 546 (2022)	PAES, PASS
EBMT	Opinion (2019)	Blood-related disorders	1974	Worldwide	+700 000 (2023)	Drug utilisation, PAES, PASS
Interna-tional Niemann-Pick Registry	Advice (2021)	Niemann-Pick disease	2013	Europe, North America, South America	500+ (2024)	PAES, PASS, NH data
Big MS Data Network of registries	Advice (2022)	Multiple sclerosis	2014	Europe + Worldwide	+250 000	PASS
Enroll-HD	Opinion (2022)	Huntington's disease	2012	Europe, North America, Australasia, Latin America	21 561 (2024)	PAES, PASS
TREAT-NMD	Advice (2022)	Neuromus-cular diseases	2007	Worldwide (centres in each continent)	65 750	PAES, NH data, Clinical trial control arm data, outcome measures validation
WFH GTR	Advice (2023)	Haemo-philia	2023	Worldwide	N/A	PAES, PASS
HARMONY BD platform	Advice (2023)	Blood cancers	2017	Worldwide (centres in each continent)	122 450 (2024)	External control arms, PAES, PASS, surrogate endpoints validation, NH data

- Qualification is based on (a) specific **context(s) of use**
- **Does not replace** the feasibility assessment linked to a research question
- No qualification **does not mean** data are not good enough for regulatory purposes
- Qualification Guidance currently **under review**

See more details here:
Report - Joint HMA/EMA multi-stakeholder workshop on Patient Registries

Thank you

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Anna.rasokat@uk-koeln.de

[Big Data Highlights]


December 2024

Big Data Highlights

Quarterly update on implementing the joint HMA-EMA Big Data workplan

EMA EUROPEAN MEDICINES AGENCY

Follow us

HMA EMA

The Heads of Medicines Agencies and the European Medicines Agency set up a joint Big Data Steering Group to implement the European medicines regulatory network's Big Data workplan. The aim of the plan is to help prioritise and prepare concrete actions to make best use of big data in support of innovation and public health in the European Union.

Featured topics

Routine clinical study data submission holds promise of faster medicine authorisation

Patients' interest for clinical trials and/or registries

More-Europa

3rd Webinar "How can real world registry data be used to augment clinical trial data to improve drug development and regulatory decision-making"

13 February 2025

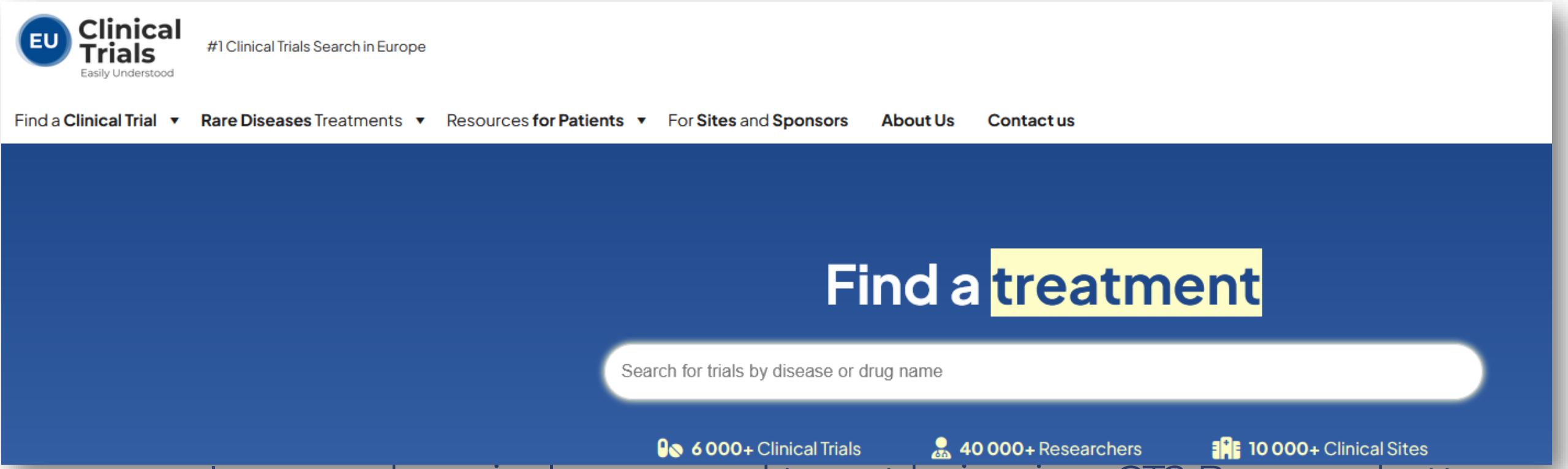
disclosure

Founder of EuroCAB, European network of Community Advisory Boards

partnership EURORDIS / EUPATI-Spain

- Member of the Executive Board, GetReal Institute
- Member of the ACT EU Multistakeholder Platform Advisory Group
- Member of the DCT implementation working group

Introductory remarks

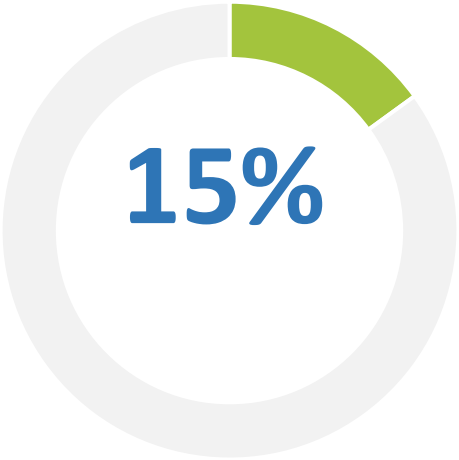


- Improved survival compared to not being in a CT? Because better taken care of? Or recruitment bias?

1. Wendler D, Krohmal B, Emanuel EJ, Grady C; ESPRIT Group. Why patients continue to participate in clinical research. Arch Intern Med. 2008 Jun 23;168(12):1294-9. doi: 10.1001/archinte.168.12.1294. PMID: 18574086.

Rare diseases: what are the chances of joining a new medicine clinical trial?

- *US FDA: Since 1983, **11 to 15%** of rare diseases have at least one drug that has been developed and shown promise (1,079 out of 6,000-7,000 RD)*



- Fermaglich LJ, Miller KL. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet J Rare Dis. 2023 Jun 23;18(1):163.

= 27 rare diseases see a R&D for the first time each year

The offer for research projects needs to be enlarged

Clinical trials and difficult decisions

Amyotrophic lateral sclerosis: 2 to 3 years life expectancy from diagnosis

- Would you join a RCT with 50% risk of receiving a placebo? And then die?
- Platform trials reduce the risk of being in control arm, making it even more difficult for those in the control arm

Wiskott Aldrych syndrome: 10 first treated children positive to coronavirus SARs-CoV2 after gene therapy and yet asymptomatic

- Alternative treatment: bone marrow transplant with survival <50%
- Would you accept a confirmatory trial gene therapy versus bone marrow transplant?

EURORDIS
RARE DISEASES EUROPE

So, when there isn’t a trial?

2003: a mother who lost her two children from neuronal ceroid lipofuscinosis

Losing our children was devastating

They had suffered for 15 years with us taking care of them 24/7

My husband and I are now too old to envisage a new life with children again

And then we learned no data had been recorded, no tissues had been stored, no registry, nothing: no research can be done to benefit children in the future

“They died for nothing”

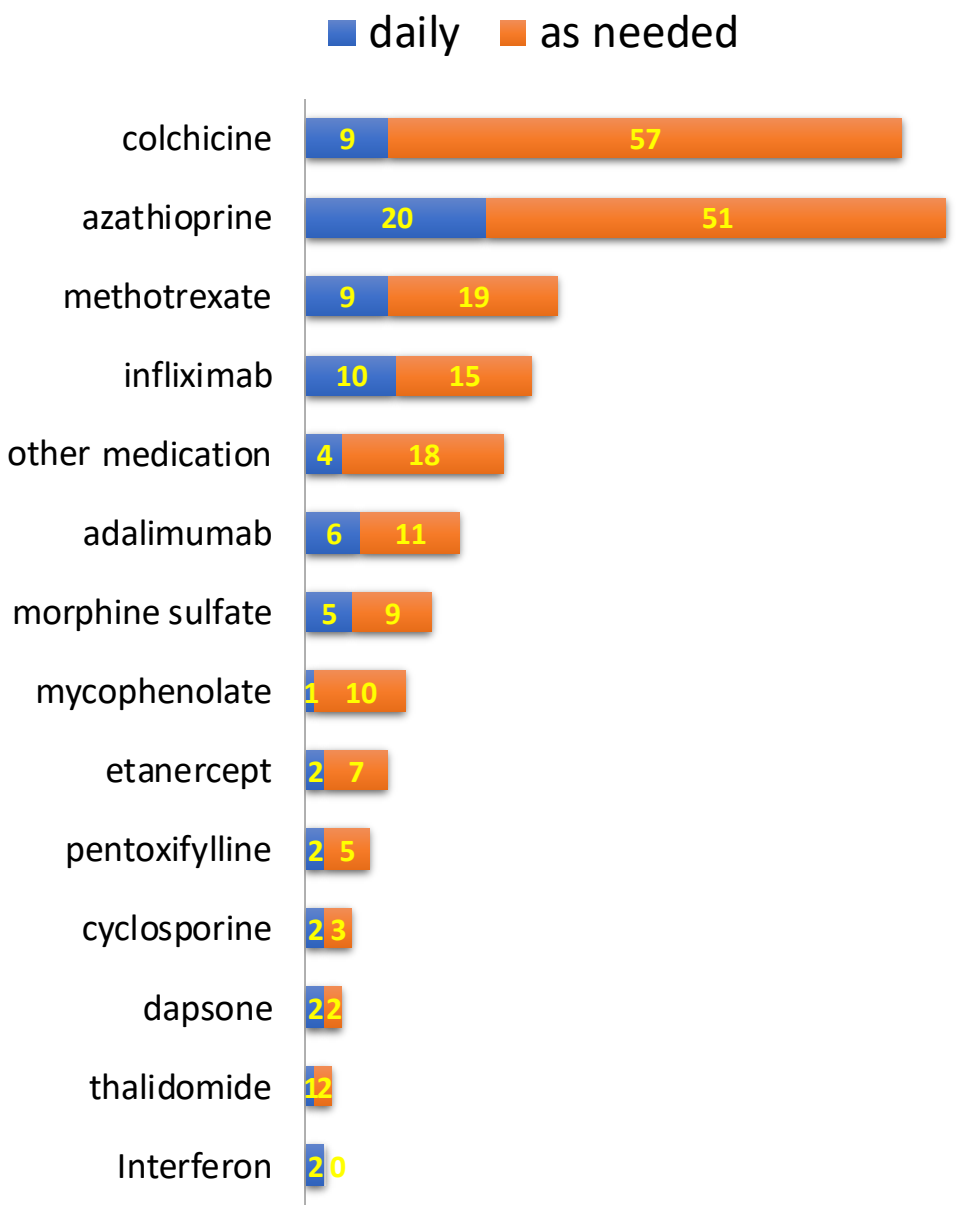
Behcet's syndrome

No clinical research for 20 years, then four at a time (infliximab, canakinumab, apremilast, gevokizumab)

- European groups: 300 patients
- May 2011: online community created
- Map @ 3 months: 900/1,348 patients indicated their location

- Highly medicated patient population
- All off-label
- No data collected

Patient groups decided to support the creation of international registry for Behcet



https://www.rareconnect.org/en/community/behcet-s-syndrome/article/behcet-s-syndrome-community-poll-results
http://eurordiscloud.s3.amazonaws.com/treatments.pdf

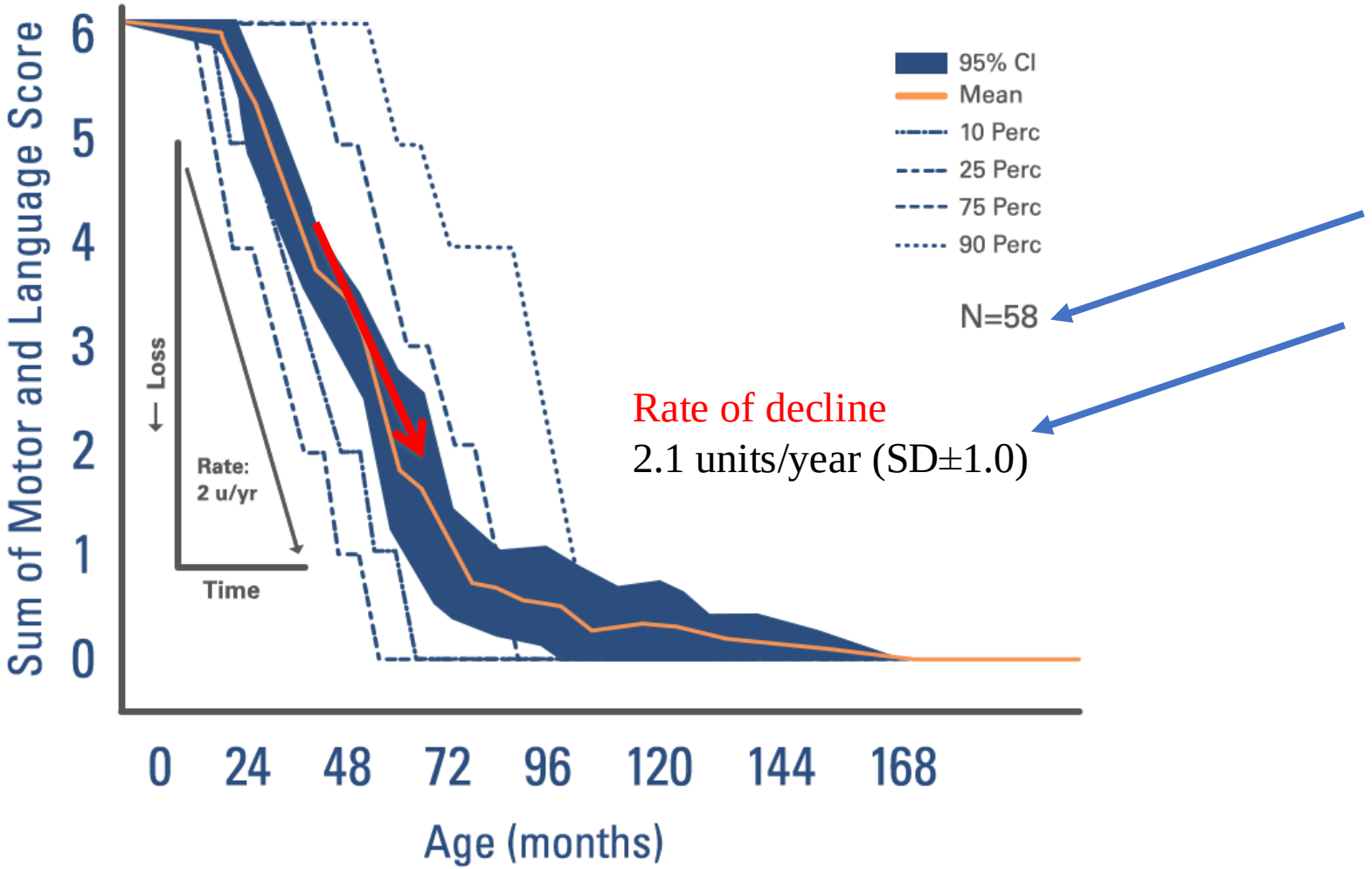
When several CTs compete to recruit patients: a global registry? Or each company its own?

Sanfilippo type A (5,000 patients in the EU, incidence 1 / 100 000, treatment needed within 2 years after onset)
Audit by parents in October 2005: no product in R&D

Difficult decisions for parents: which R&D to opt for?

Designation		Technology
2008	Shire	Recombinant enzyme
2010	Lysogene	Gene therapy 1
2011	Esteve	Gene therapy
2014	Lysogene	Gene therapy 2
2014	Orchard	Gene therapy
2016	SOBI	Recombinant enzyme
2016	Abeona	Gene therapy

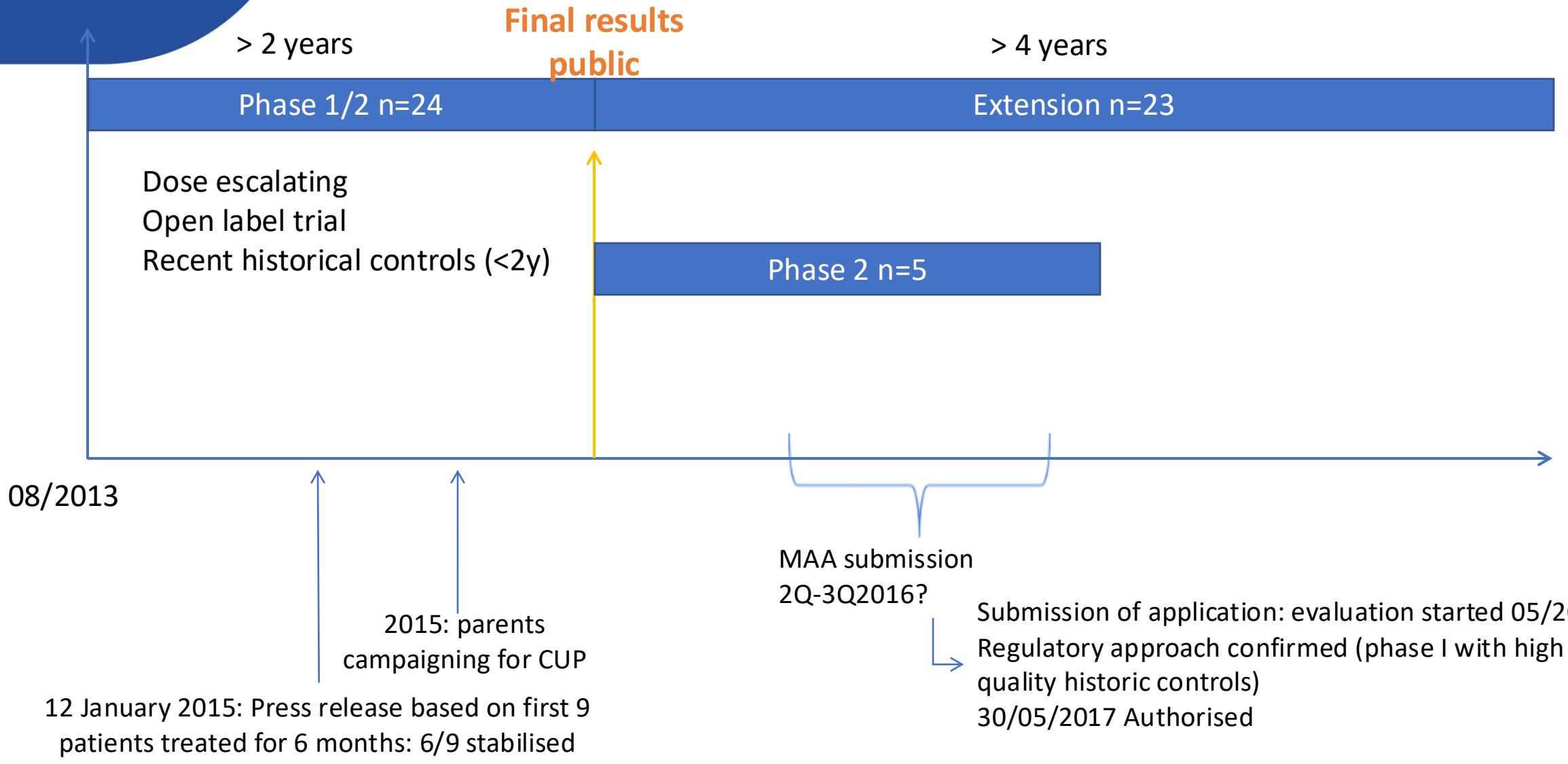
Natural History of CLN2 Disease (Batten disease): recent data (less than 2 year-old)



Credits: Dr Angela Schulz, University Hospital Hamburg, Germany

CLN2 Disease, Brineura

Value of information. Can we decide, or do we need more? At what cost?



What do patients like about registries?

• Natural disease

- A pre-requisite for any R&D
- Prognostic factors and biomarkers
- Impact of the disease

• Counting patients

- Epidemiology studies
- Pharmaco-epidemiology (confirming effectiveness, reducing uncertainty)

• Comparing care

- Standard of care in different settings, and their outcomes
- Evolution of survival in different countries

• Organisation

- In theory, no additional consultations, visits or exams
- No need to travel to (remote) clinical trial site
- How to reach 95% exhaustivity?

• Different purposes

- The purposes of registries vary
- Which data need to be collected? Don't need be?
- Data entered by patients? Wearables etc.

Patients don’t fully realise it yet

Target Trial Emulation (TTE) for real world data analyses to support HTA decisions

Alastair Bennett, Andrea Manca, Noemi Krief
Centre for Health Economics, University of York, UK
alastair.bennett@york.ac.uk

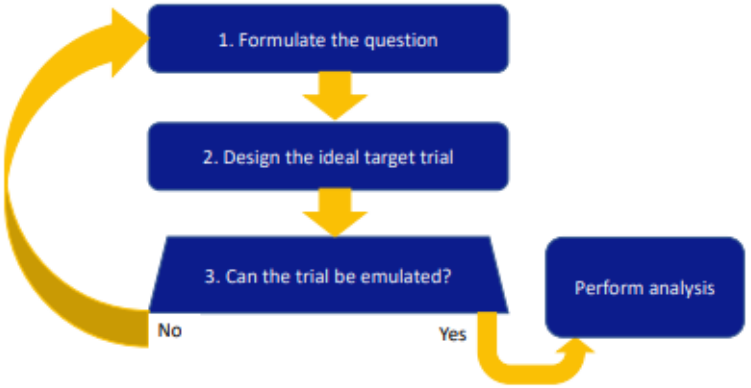
Background

risk Myelodysplastic syndrome (LR-MDS) is a chronic
e marrow malignancy most prevalent in the elderly,
an average age at diagnosis of 75 years.

prognosis of patients with LR-MDS varies considerably
it is mostly affected by the lower than normal number
lood cells.[1]

blood cell transfusions can alleviate the anaemia

Target Trial methodology is an iterative process.



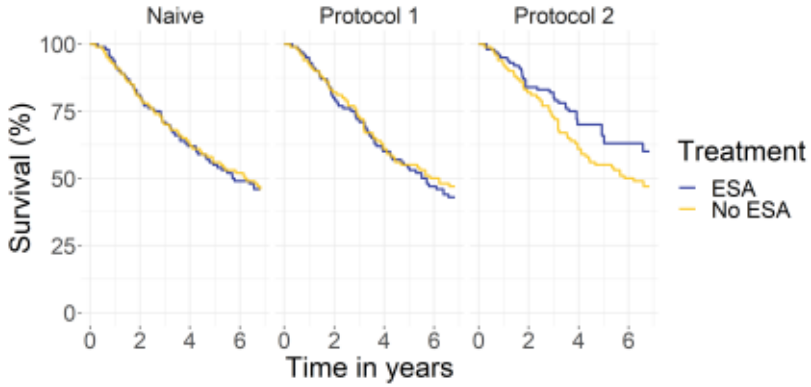


Figure 1: Displays Kaplan Meier curves for naïve analysis (left) and weighted Kaplan Meier curves protocol 1 (middle) and protocol 2

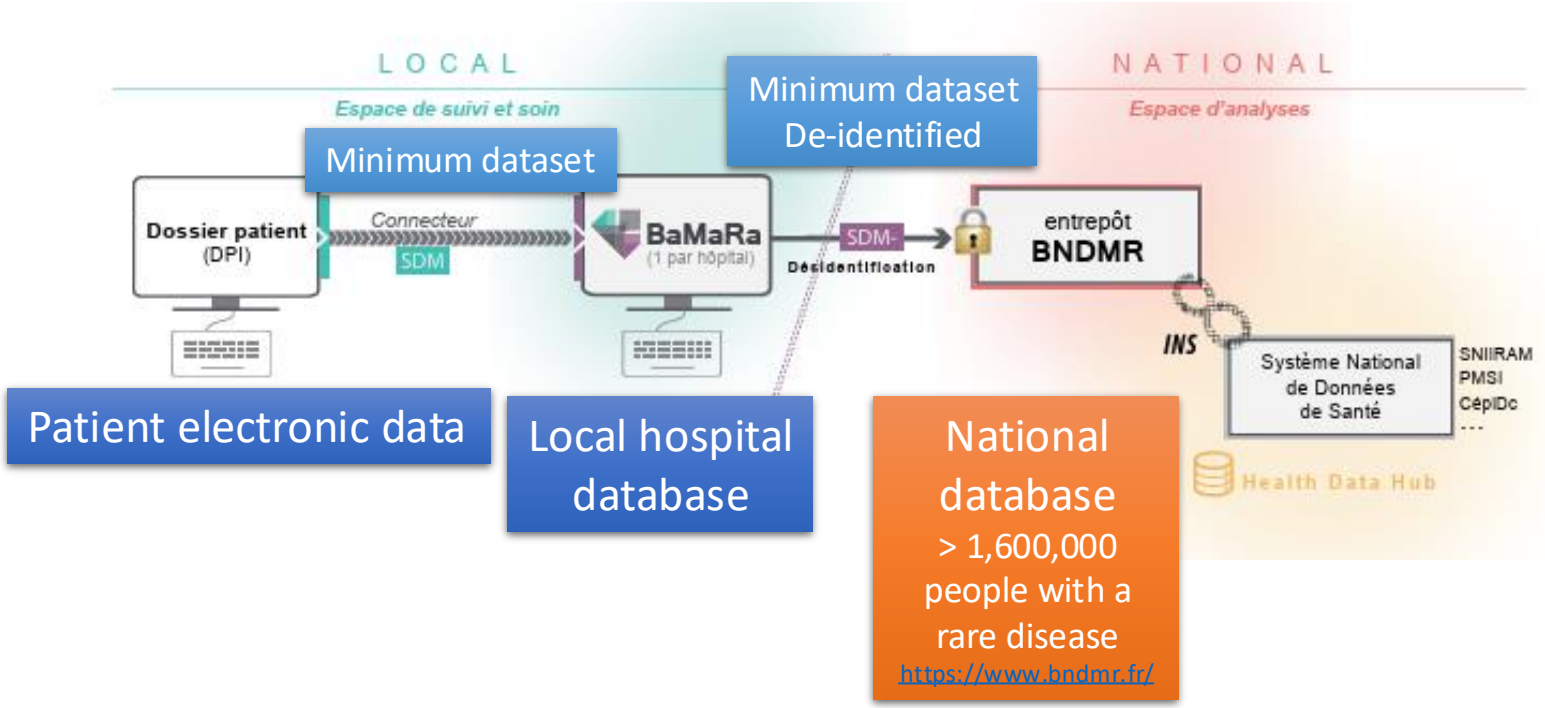
Focus on rare diseases database in France & pharmaco-epidemiology

Minimum dataset, including treatment

BNDMR (National Databank for Rare Diseases) is an outcome of the 2nd plan for rare diseases.

Patients' organisations were involved in all aspects of its development

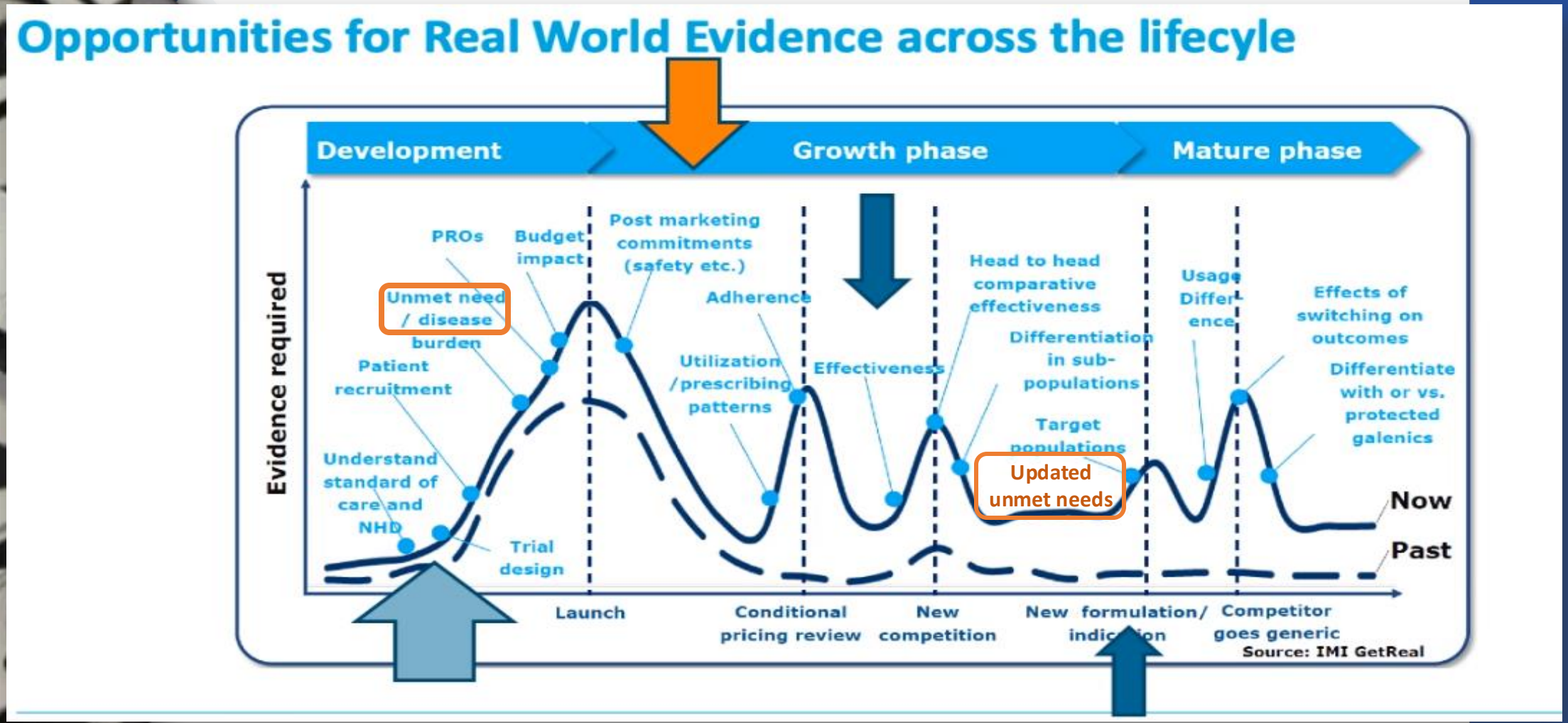
https://www.bndmr.fr/wp-content/uploads/2022/06/AFCRO_juin2022.pdf



- Name of the product
- Dosage
- Route of administration
- Duration of treatment
- Efficacy and safety

Purposes
- Off-label medicines in rare diseases (96 as of 2024)
- Real-life pharmaco-epidemiological studies
- Therapeutic use protocol in the context of early and compassionate access.

Final considerations



Thank you for your attention!

Director of Treatment Information and Access

francois.houyez@eurordis.org

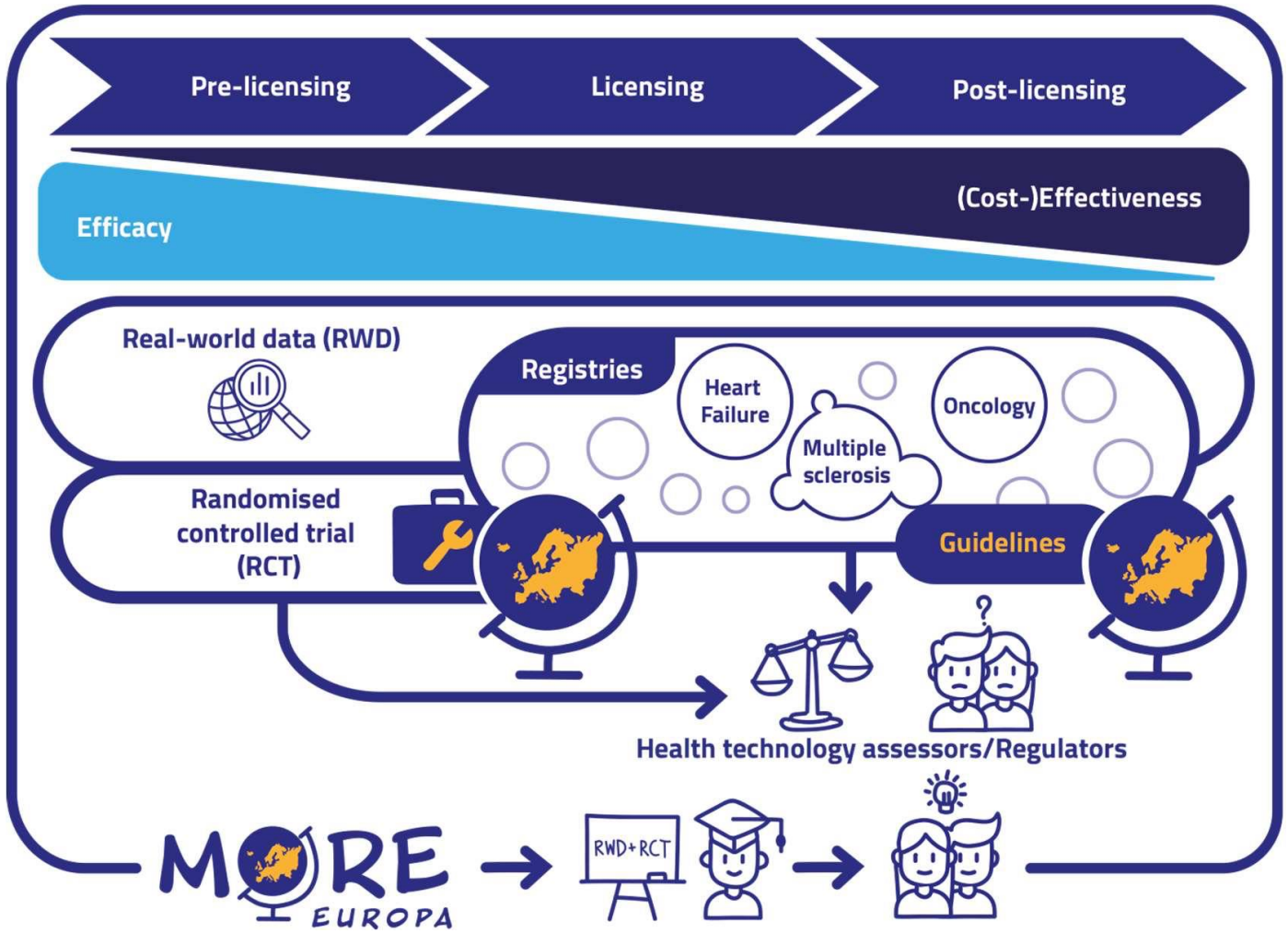
Registry data for early development decision making

More-EUROPA 3rd webinar

13 February 2025

Kit Roes & Bergas Fayyad

Registries & drug development life cycle



Leverage registry data

1. Support the planning and validity of applicant studies
2. Understand the clinical context
3. Investigate associations and impact

Substantial attention for use of Real-World Data with challenging objectives.

- To augment RCTs and Single Arm Trials with external data for primary efficacy assessment.
- To rely on Real World Data (only) for some primary decisions.

Improvement in decision making throughout the drug development life cycle possible.

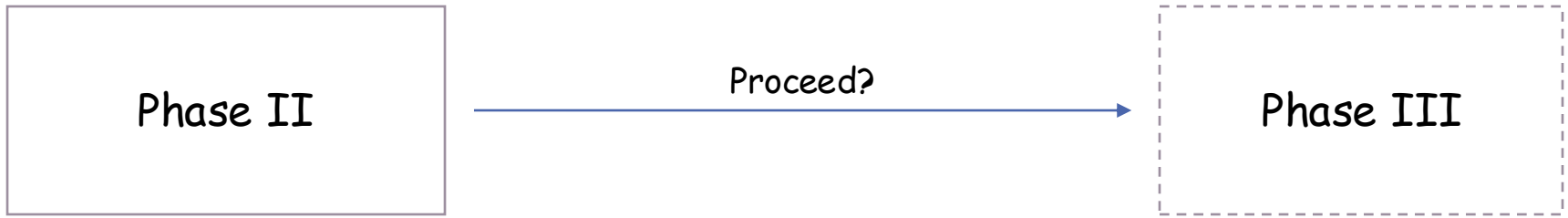
- Including registry data in assessment of probability of success during drug development.
- Leverage registry data & modeling to transport treatment effects observed in RCTs to broader populations.

MORE EUROPA

Registries in pre-licensing decisions

- Decision to enter Phase III development: Use of Probability of Success
- Leveraging registry data for assessment of Probability of Success
- Example: Swedish Heart Failure Registry (SwedeHF)
- Key learning and take aways

Clinical drug development: Decision to move to Phase III

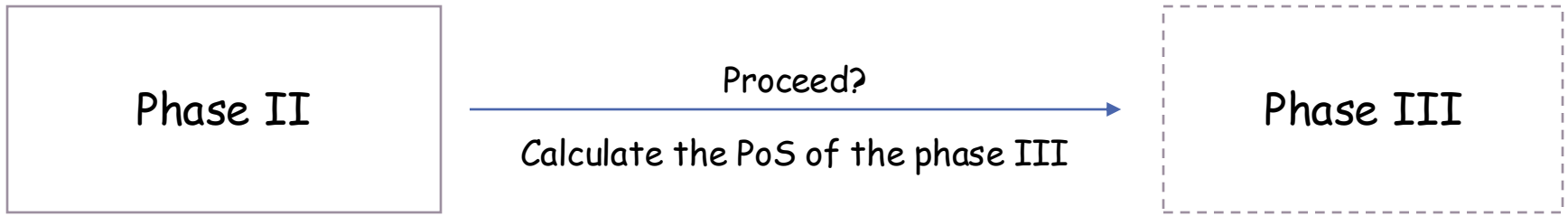


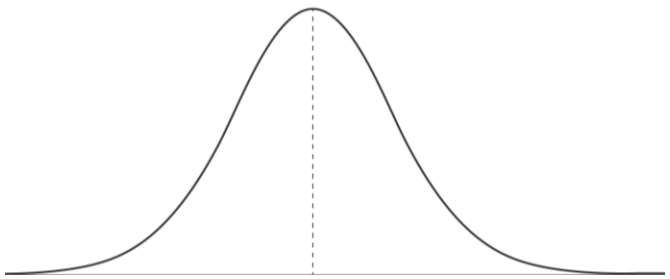
Quanitative method to assess the uncertainty

-> Probability of Success (PoS)

Probability of Success (PoS)

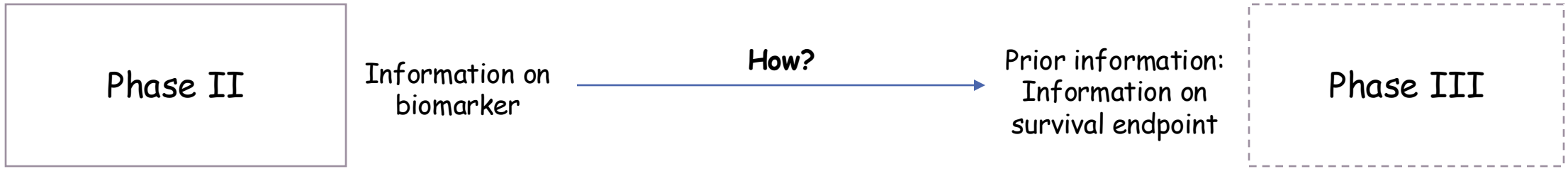
Probability that the trial will show a significant treatment effect given a prior belief/information on the possible treatment effect





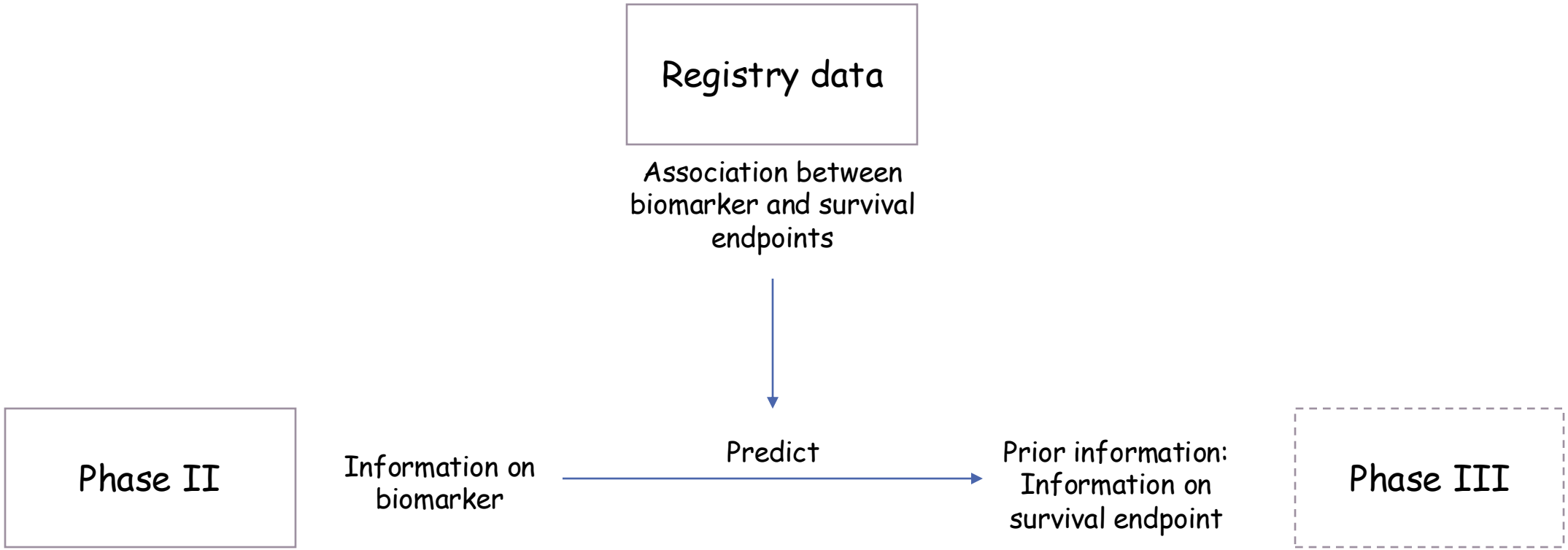
Calculating PoS

- Use the estimate from phase II as the prior belief
- Straightforward if the endpoint used in phase II and phase III trials are the same
- **Challenge**: Phase II trial uses biomarker endpoint while phase III trial uses survival endpoint



How can we use the information on biomarker from phase II to get the information on survival endpoint for PoS calculation?

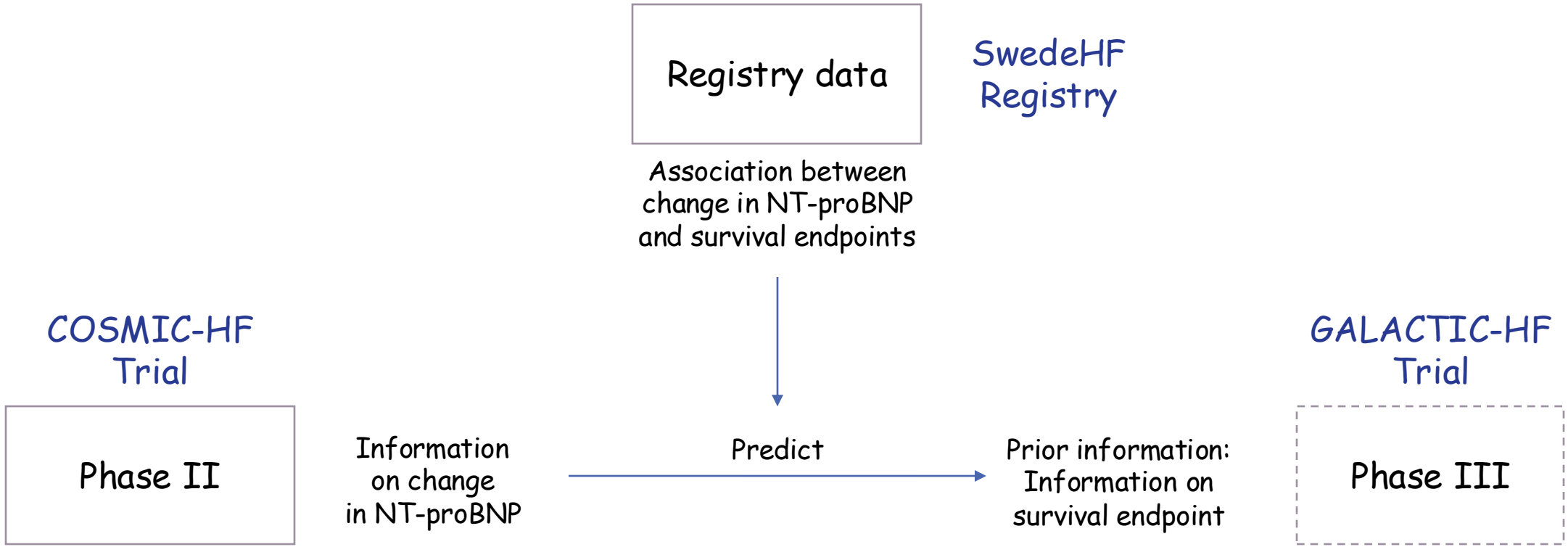
Incorporating registry data



Modelling using registry data

- to obtain the association between biomarker and hard clinical survival endpoint
- E.g. with cox proportional hazard model

Example

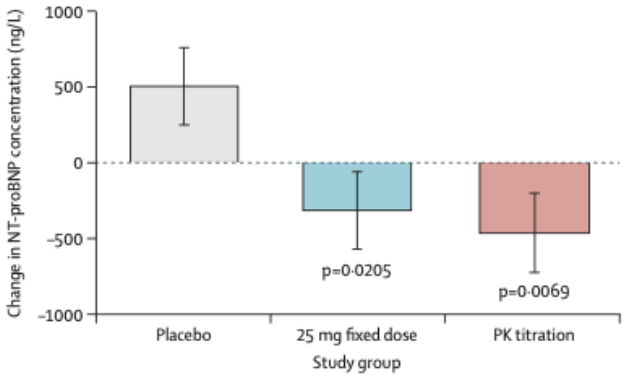


- Using SwedeHF registry to calculate PoS of a planned GALACTIC-HF from a biomarker estimate in COSMIC-HF
- Biomarker: changes from baseline of NT-proBNP at week 20

Example

COSMIC-HF Trial (February 2013 – August 2015)

- Randomised, double blind study. 87 sites in 13 countries
- Patients with symptomatic chronic heart failure and reduced ejection fraction (left ventricular ejection fraction 40% or lower)
- Arm0 (149 patients): placebo
  Arm1 (150 patients): omecamtiv mecarbil 25 mg twice daily (fixed-dose)
  Arm2 (149 patients): omecamtiv mecarbil 25 mg twice daily titrated to 50 mg (pharmacokinetic-titration)
- Primary: maximum concentration of omecamtiv mecarbil in plasma
  Secondary: changes from baseline in NTproBNP at week 20



➢ Changes from baseline in NTproBNP at week 20

PK titration vs placebo:
-970 pg/mL with 95% CI (-1772;-268)

Modelling using registry data

Important decisions required in using registry data:

1. Timing of the follow-up and biomarker measurement
2. Patient populations
3. Data availability and missing data
4. Additional: Type of endpoint

Timing of the follow-up & biomarker measurement

- Period of the study

- Duration of the follow-up for each patient
  - Similar to phase II study
  - Similar to phase III study
  - Other

- Biomarker measurement
  - Similar to phase II study
  - Similar to phase III study
  - Other

Example

Timing of the follow-up & biomarker measurement

SwedeHF example:

- Using the data from January 2000 until August 2015 (the end of COSMIC-HF)
- 3 year follow-up time
- Changes from baseline in NTproBNP at week 20

Patient populations

- In registry data: broader population characteristics

  It includes patients with extreme condition (more severe condition than in RCT)

  - In general: match the population characteristics in phase II or phase III study?
    Broader range of characteristics -> more reliable correlation

- Possible subgroup of population?

SwedeHF example:

- Patient with heart failure and reduced ejection fraction (HFrEF)

- Exploration of subgroup:
  patients with HFrEF in general VS patients with HFrEF that received optimal treatments

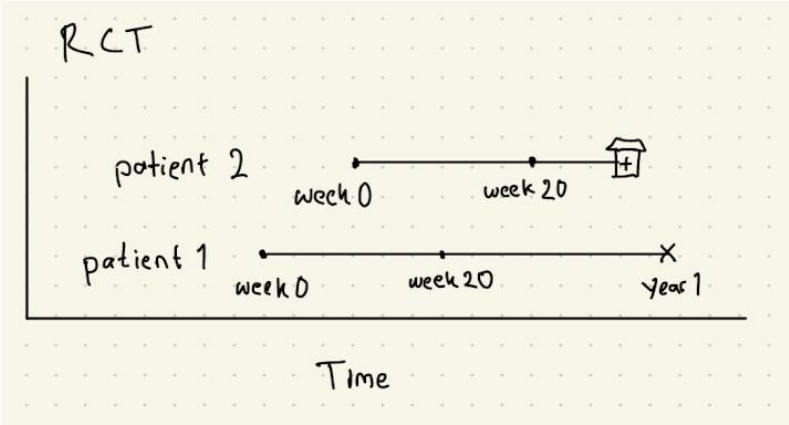
Data availability and missing data

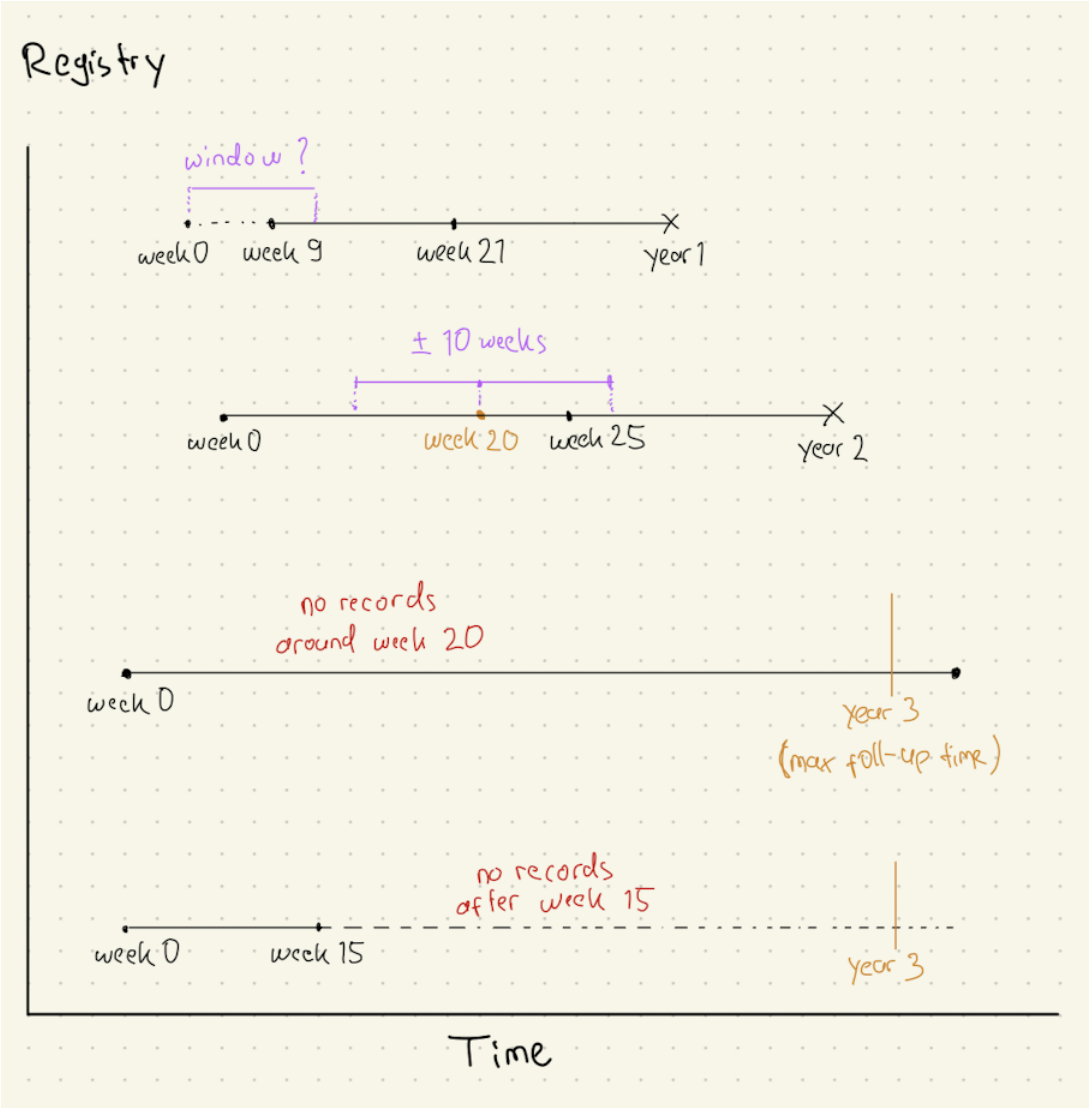
- In registry: data are collected much more irregularly than in RCT
  - Different follow-up time among patients
  - Affects other important aspects (timing of follow-up and biomarker measurement)
    - Window of measurements
- Dealing with missing data
  - Multiple imputation?

SwedeHF example

- COSMIC-HF measures the change from baseline of NT-proBNP at week 20
- In SwedeHF, not all patients had exactly NT-proBNP record at week 20
  - Window of ± 10 week

Data availability and missing data





Type of endpoint

- Generally, use the endpoint planned for phase III study

- For survival outcome:
  death, hospitalisation, composite, etc.

SwedeHF example:

- Cardiovascular death
- Composite outcome of cardiovascular death and heart failure hospitalisation

Recap

Important decisions required in using registry data:

1. Timing of the follow-up and biomarker measurement
   - Determine the period in registry data
   - Determine follow-up time for each patients
   - Determine the timing of the biomarker measurement

2. Patient populations
   - Generally, match the characteristics of patients in phase II and phase III study
   - Consider subgroup of population

3. Data availability and missing data
   - The data in registry are more irregularly collected than RCT
   - Determine and apply windows of measurements

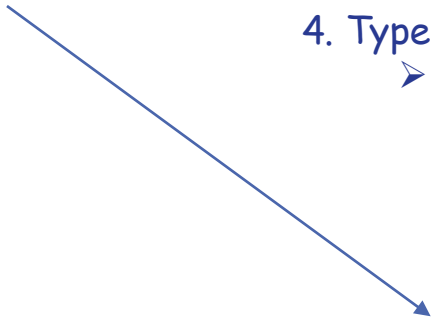
4. Type of endpoint (exploration)
   - Generally, use the endpoint planned for phase III study
   - Consider other endpoints

Example result

SwedeHF

Association between change in NTproBNP and survival endpoints

1. Timing of the follow-up and biomarker measurement
   - January 2000 until August 2015
   - 3 year follow-up time
   - Change from baseline in NTproBNP at week 20
2. Patient populations
   - Heart failure patients with reduced ejaction fraction
   - General VS Optimally treated patients
3. Data availability and missing data
   - Window of ± 10 weeks
4. Type of endpoint
   - Composite outcome and cardiovascular death



COSMIC-HF

Estimate on change in NTproBNP

-970 pg/mL
(95% CI -1672 to -268)

Predict

Prior information: Information on survival endpoint

GALACTIC-HF

PoS?

Example result

HFrEF patients from January 2000 until August 2015

Initial number of patients = 32725

patients	endpoint	n	n event	PoS
general	composite	1124	462	0.1058
	cvdeath		131	0.1142
optimal	composite	384	177	0.2728
	cvdeath		33	0.2765

Take away

- Discussion among the clinician, statistician, and expert on registry data is very important
- Match the settings with the ones used in RCT without losing data
- Use as much information as the data allow
- Consider different settings/scenarios (sensitivity analysis)

Thank you!

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