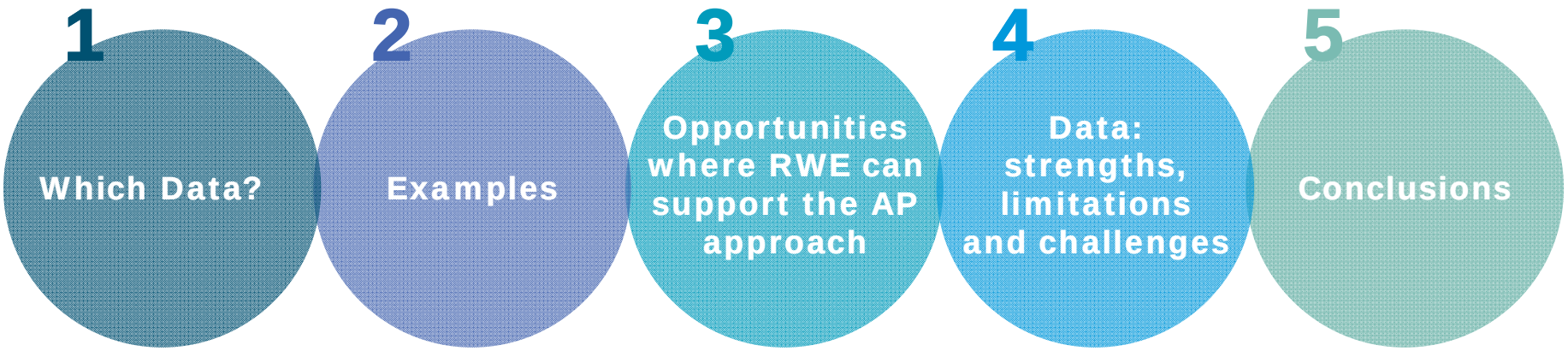
Objectives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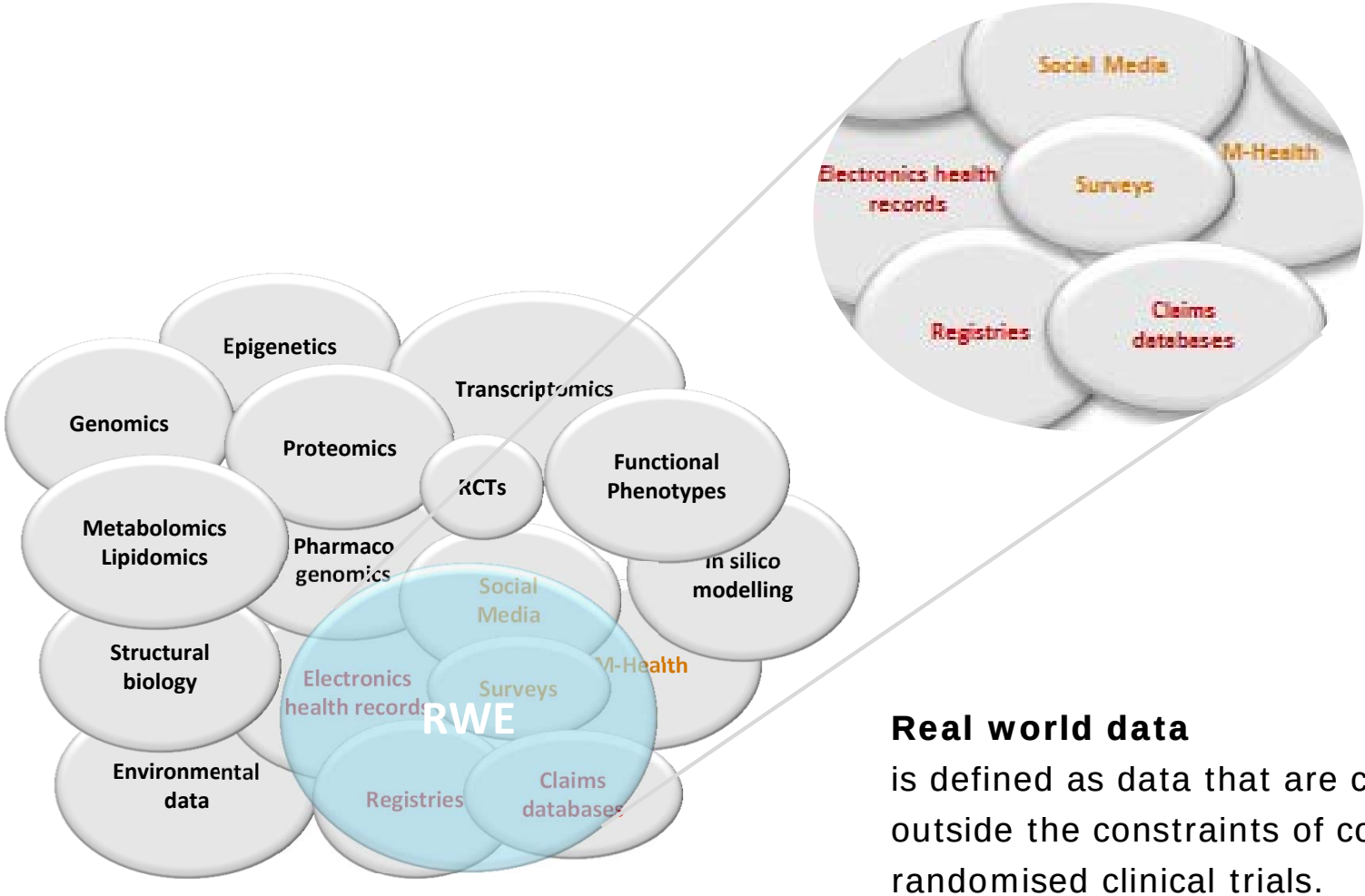
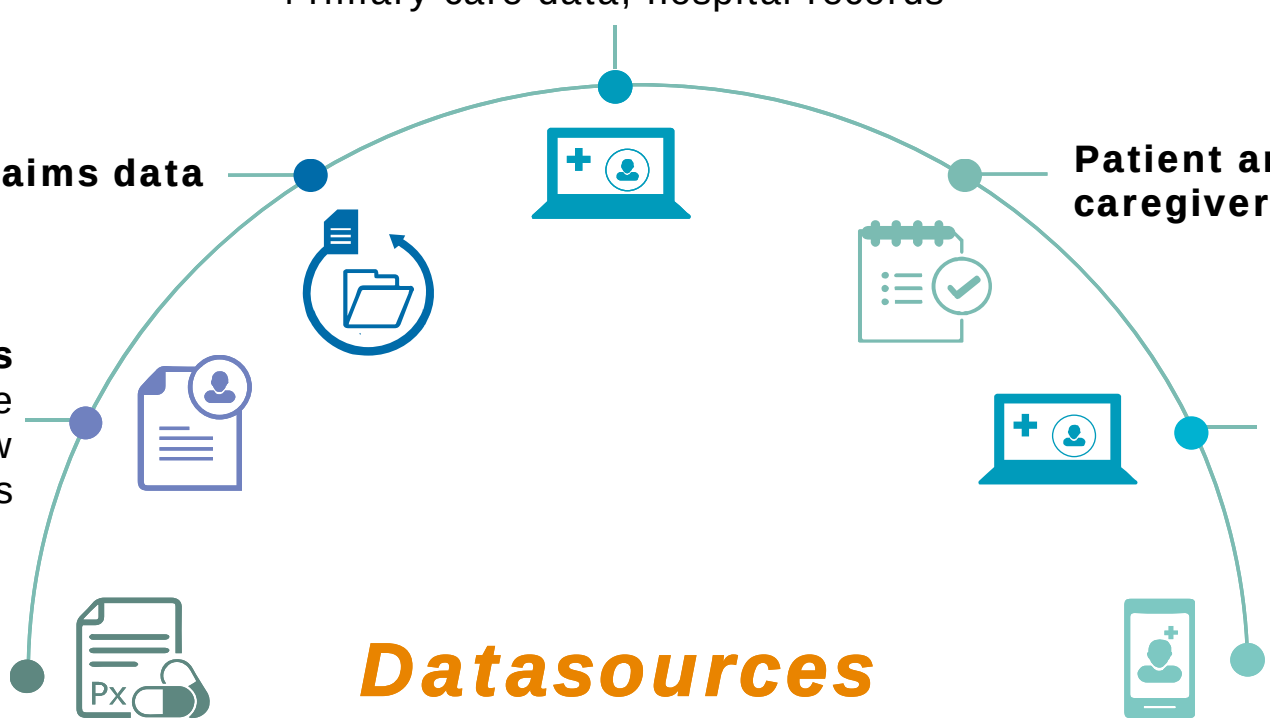
Which Data?



Real world data
is defined as data that are collected outside the constraints of conventional randomised clinical trials.

Which Data?



Electronic health records
Primary care data, hospital records

Claims data

Patient and caregiver surveys

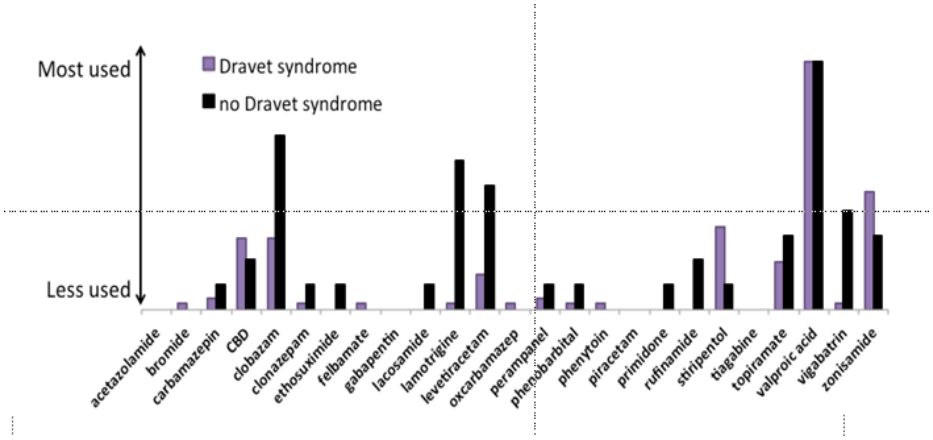
Registries
Existing disease Registries / new product registries

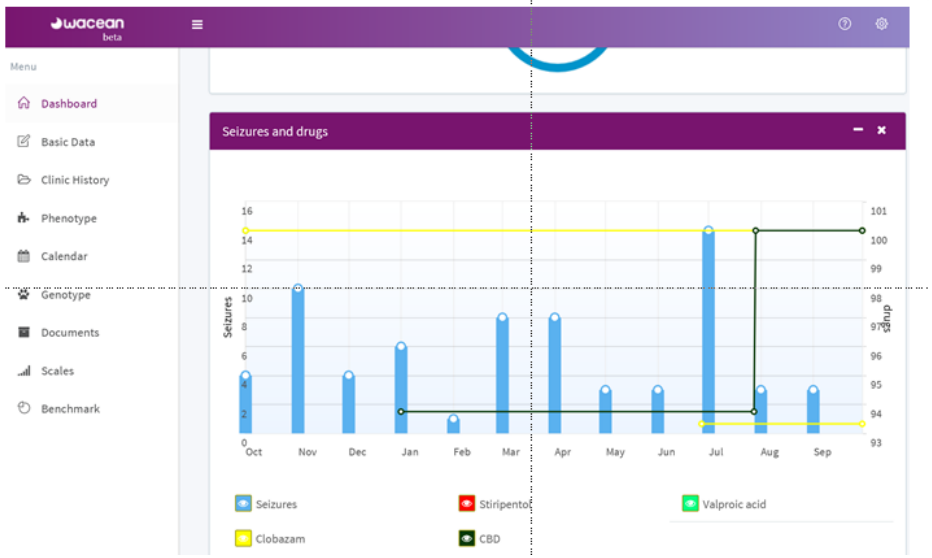
The Future
Social media data

Prescription databases
Drug utilisation

Patient derived data
(via smart phone or web based technologies)

Patient Driven Platform for RWE – the future

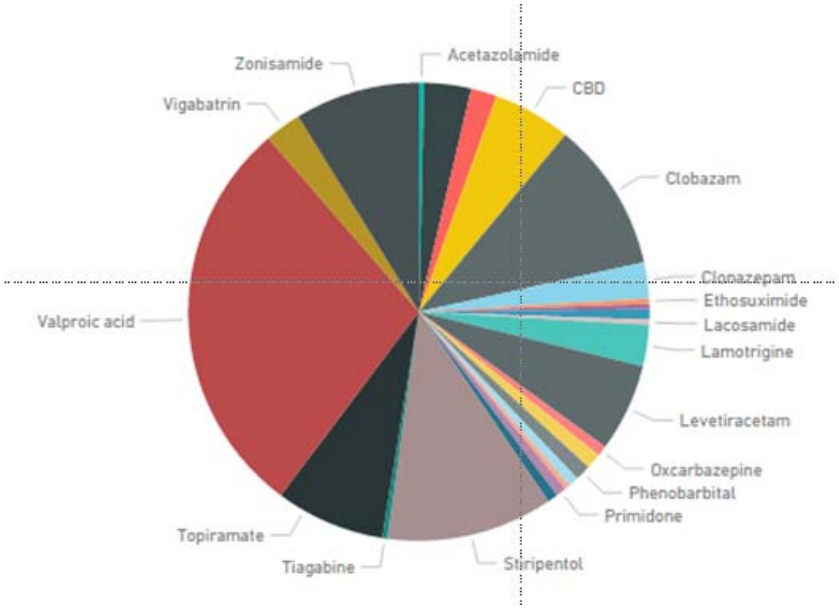




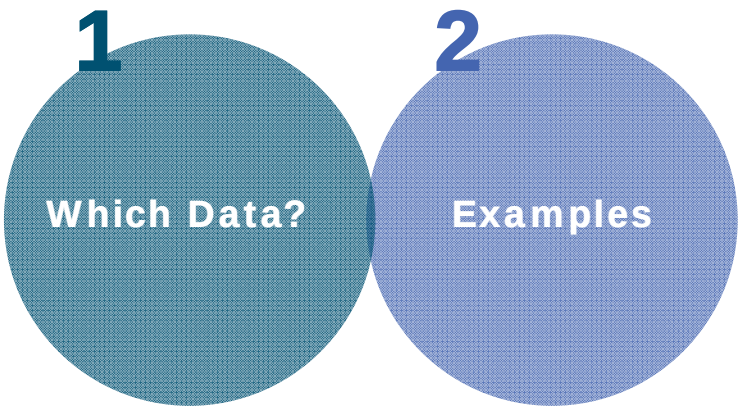
wacean

DRAVET SYNDROME FOUNDATION
DELEGACIÓN EN ESPAÑA
www.dravetfoundation.eu

Julian Isla



Objectives



RWE is already in routine use in the EU

Particularly true for marketed products - safety monitoring and drug utilisation.

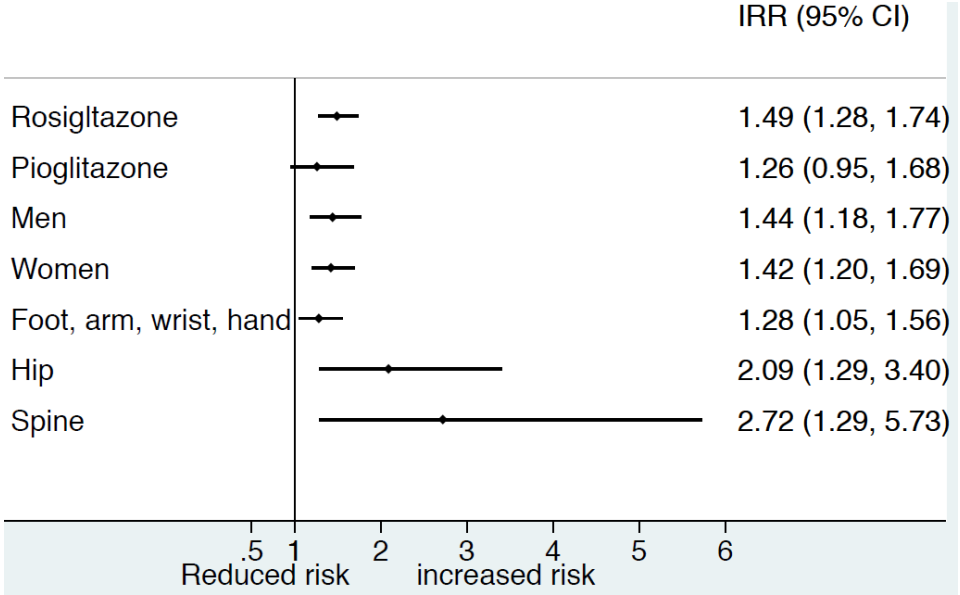
Post-authorisation safety

The Risk of Fractures Associated with Thiazolidinediones: A Self-controlled Case-Series Study

Ian J. Douglas[1]*, Stephen J. Evans[2], Stuart Pocock[2], Liam Smeeth[1]

1 Non Communicable Disease Unit, Department of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom, **2** Medical Statistics Unit, Department of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom

- **RCT suggested increased fracture risk in women at arm, wrist, hand & foot.**
- **Electronic health records – GPRD**
- **1819 patients were included with well defined exposure and a fracture.**
- **Increased fracture risk with exposure to rosiglitazone and pioglitazone, in both men and women and at a range of fracture sites.**



Post-authorisation safety

EARLY REPORT

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

ARTICLES

Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association

Brent Taylor, Elizabeth Miller, C Paddy Farrington, Maria-Christina Petropoulos, Isabelle Favot-Mayaud, Jun Li, Pauline A Waight

Special needs / disability registers linked to immunisation records

MMR and autism: further evidence against a causal association

C. Paddy Farrington [a,*], Elizabeth Miller [b], Brent Taylor [c]

[a] *Department of Statistics, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK*
[b] *Immunisation Division, Public Health Laboratory Service Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK*
[c] *Centre for Community Child Health, Royal Free Campus, Royal Free and University College Medical School, University College London, London NW3 2QG, UK*

Observational studies supporting withdrawals/restrictions

Table 2 List of evidence used to support medicinal product withdrawals in all EU member states between 2002 and 2011 derived from EMA reports, PubMed literature search and websites of competent authorities

Drug name	Case reports	Animal studies	Case–control	Cohort	RCTs	Meta-analysis	*Others
Rofecoxib	X		x	x	x	X	
Thioridazine	X	X	x		x	X	
Valdecoxib	X				x	X	
Rosiglitazone	X		x	x	x	X	
Sibutramine	X				x		x
Orciprenaline	X				x		
Benfluorex	X		x	x	x		
Clobutinol	X	X			x		
Buflomedil	X	X					
Veralipride	X						
Rimonabant	X				x	X	
Carisoprodol	X	X		x	x		x
Aceprometazine+Acepromazine +Clorazepate	X						x
Dextropropoxyphene	X						x
Nefazodone	X						x
Ximelagatran/melag							
Lumiracoxib							
Sitaxentan							
Bufexamac							

*Other studies include
EMA, European Medic

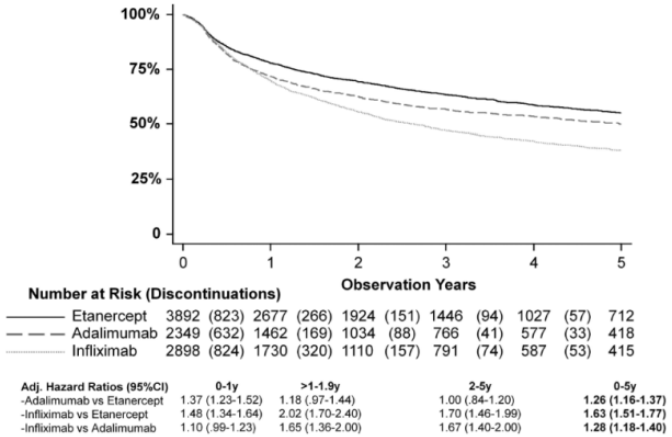
A population-based study of the drug interaction between proton pump inhibitors and clopidogrel

David N. Juurlink
Peter C. Austin P
Muhammad M. I

Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study

OPEN ACCESS

Increasing use of RWE for understanding the prescribing landscape, effectiveness studies, delivering outcomes for HTA, and rapid cycle evaluation of medicines.



Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab

M Neovius,[1] E V Arkema,[1] H Olsson,[1] J K Eriksson,[1] L E Kristensen,[2] J F Simard,[1] J Askling,[1,3] for the ARTIS Study Group

Swedish Biologics Registry (Artis)

Medicare Claims Data
Directly compared risk of stroke, bleeding or death in patients with nonvalvular AF

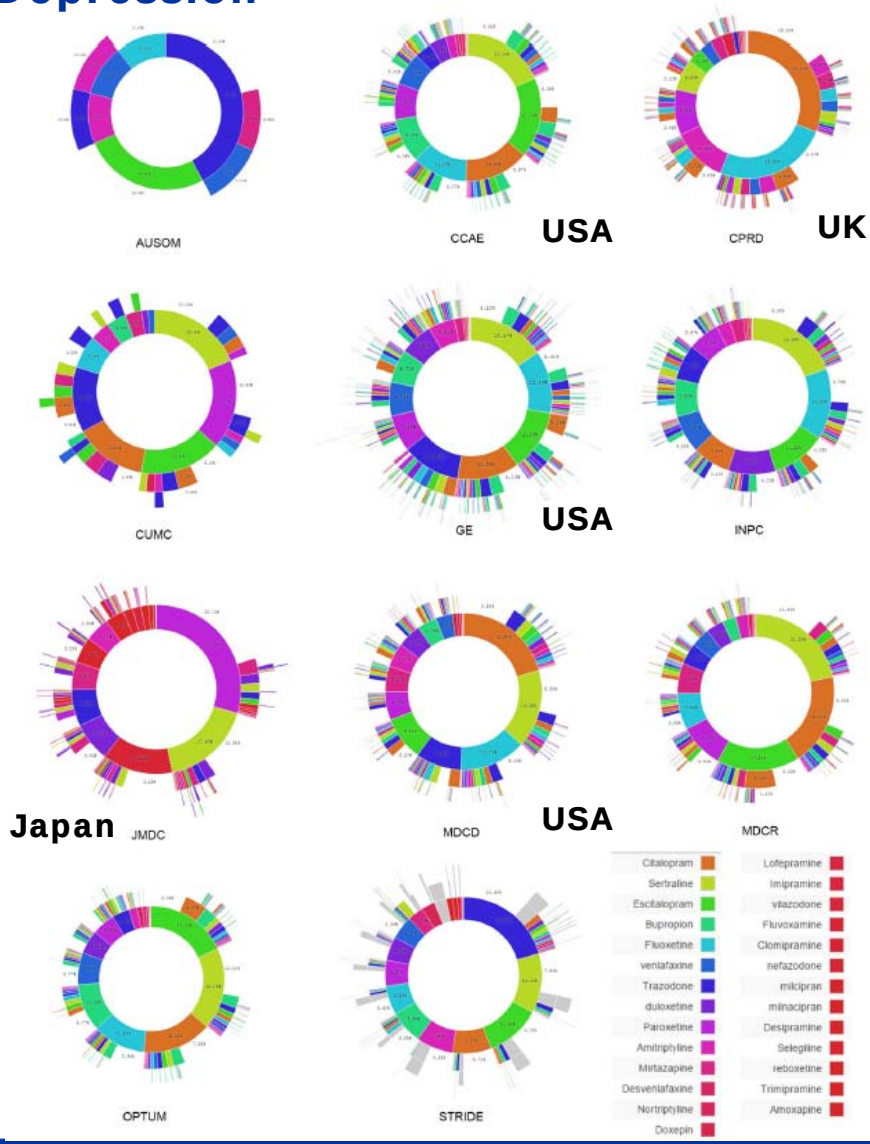
JAMA Internal Medicine | Original Investigation

Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Ya-Hui Hsueh, PhD; Rima Izem, PhD; Mary Ross Southworth, PharmD; Yuqin Wei, MS; Jiemin Liao, MA; Margie R. Goulding, PhD; Katrina Mott, MHS; Yoganand Chillarige, MPA; Thomas E. MaCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc

Understanding the Landscape

Depression



Observational Health Data Science and Informatics (OHDSI)

Substantial variation in treatment practice for depression across data sources, health systems, geographies, and over time

Consistent heterogeneity in treatment choice as no source showed one preferred first-line treatment

11% of depressed patients followed a treatment pathway that was shared with no one else in any of the databases

Use of RWE can help identify the most appropriate comparator group

Hripcsak et al, PNAS, 2016

Use of Registry Data to support an extension of an Indication

- Soliris (eculizumab), a C5 inhibitor was approved in June 2007 for paroxysomal nocturnal haemoglobinuria (PNH) in a restricted patient population with a prior history of transfusions

- At authorisation a PNH disease registry was agreed which ultimately recruited approximately 2000 patients and included PNH patients treated and not treated with eculizumab across all stages of disease severity

However these examples were not prospectively planned studies……..

- The use of registry data to extend the indication to patients without a prior history of infusions was discussed with CHMP via the Scientific Advice process. It was agreed that depending on patient numbers, the registry may allow for some assessment of the benefit of treatment in this patient population.

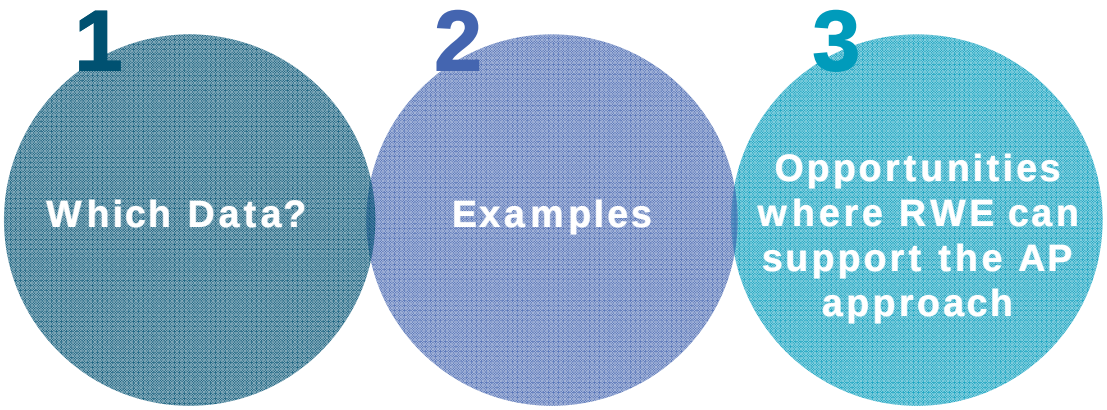
- Given the challenges of the disease and the efficacy of eculizumab, a prospective randomised study requiring a non treatment group was not possible

- A comparison of outcome recorded by the registry in patients with no transfusion history treated or not with eculizumab enabled a extension of the indication to **patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history.**

Adaptive pathways

- A prospectively designed iterative, developmental plan
- Incorporation of real world evidence to complement RCTs in the post authorisation phase
- Early involvement of HTA and other downstream decision makers

Objectives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Opportunities of Real World Data

Development

- Characterisation of disease progression and unmet need
- Identification of the target population
- Understanding current clinical care practices (resource utilisation)
- Drug utilisation
- Registry data for historical controls in rare / orphan diseases
- Validation of surrogate endpoints

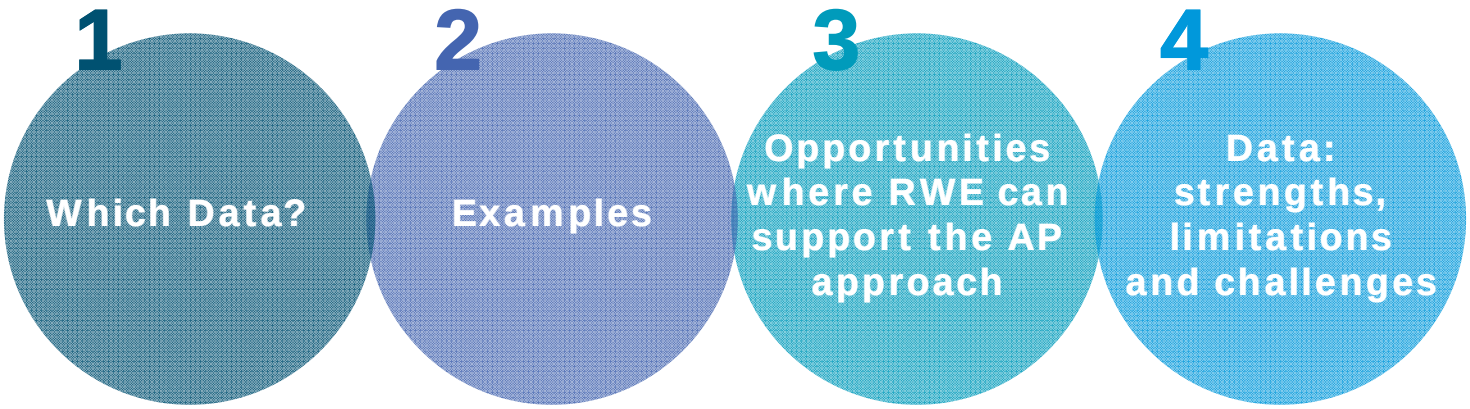
Authorisation

- Open label extension studies in a registry
- Drug utilisation studies to monitor use
- Confirming long term safety
- Risk management activities to address uncertainties
- Comparative effectiveness studies

Post - authorisation

- Quality of life metrics
- Pragmatic clinical trials / registry studies
- Understanding subgroups
- Assessing long term safety
- Collecting patient reported outcomes

Objectives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Data: strengths, limitations and challenges

Claims Data

Electronic Health Records

Patient Registries

Claims Data

Strengths

- Quality of recording may be better as link to payment
- Auditable
- More consistent terminology
- Large data sets
- Relatively low cost
- Good for resource utilisation studies

Limitations

- Structural limitations
- Bias due to reporting and coding
- Bias due to differential follow up
- Often short term follow up
- May not have full medical history
- Inability to assess appropriateness of care
- Benefits of treatment may be missing
- Absence of diagnosis, data on life time factors and PROS
- Medical records needed for in depth analysis
- Mother/child linkage difficult
- Non-reimbursed products/services missing

Electronic Health Records

Strengths

- Longitudinal record – cradle to grave (with unique patient identifier)
- Full patient history
- Linkage may be possible
- Large data sets
- Relatively low cost
- Good for resource utilisation studies
- Possibility of capturing off label use

Limitations

- Variable quality
- Hospital prescribing not recorded
- Variability in care delivery impacts on datasets
- Variation in diagnosis/coding across GPs
- No over the counter information
- Frequently missing data
- Limited PROs
- Challenge to monitor drug use in children as the number of drugs with sufficient exposure to detect rare adverse events in children and adolescents is limited.

Patient Registries

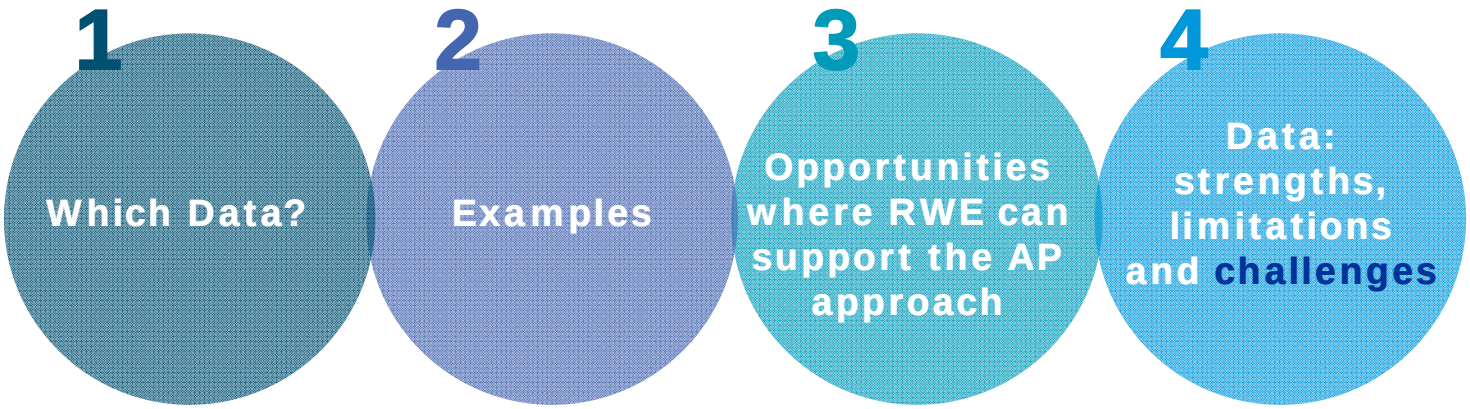
Strengths

- Systematic assessment of investigator designed measurements of relevant clinical parameters
- Natural history of disease
- Disease burden
- Standard of care
- Patient stratification
- RCTs
- Open label studies possible
- Capture off label use
- Captures information on high risk groups and rare diseases
- Patient reported outcomes

Limitations

- Substantial set up and running costs (sustainability)
- Time consuming to initiate
- Medications commonly missing
- ADRS not routinely recorded
- Co-morbidities missing
- Data ownership/governance challenges
- Data Quality - absence of clear benefit for clinical practice limits HCP commitment
- If no comparator will limit utility

Objectives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Data: strengths, limitations and challenges

What is the current European landscape?

….fragmentation,
……lack of interoperability,
……..increased cross border collaborations are required to leverage existing data and knowledge

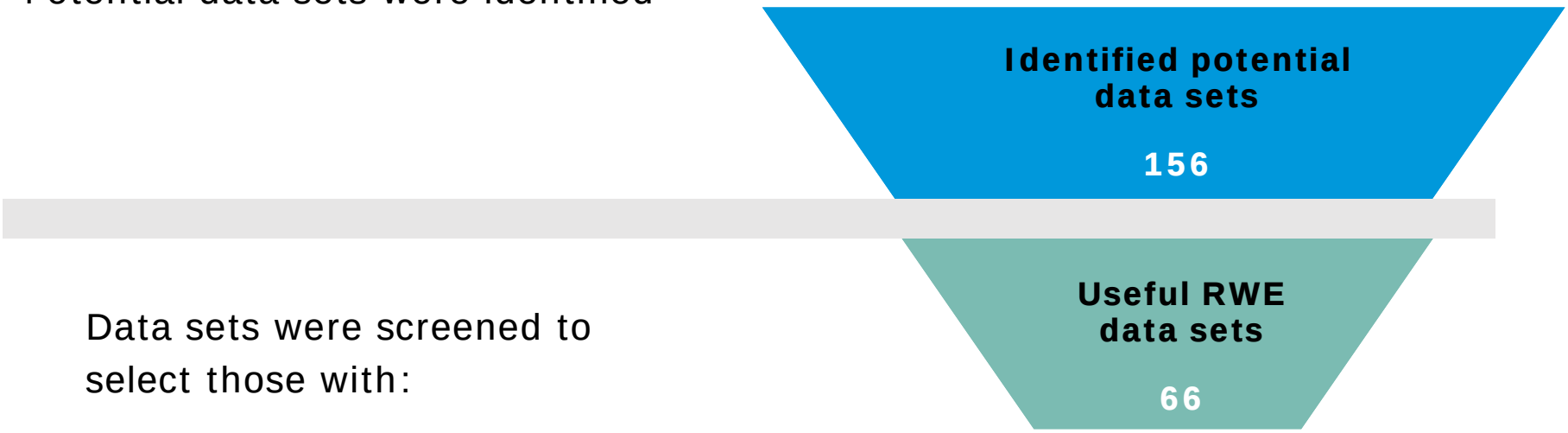
Analysis of EU Wide Datasets

Potential data sets were identified

- ENCePP Resource Database
- PROTECT
- ADVANCE
- EU-ADR
- FRAMEWORK CONTRACTS

Analysis of EU Wide Datasets

Potential data sets were identified



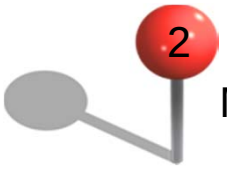
Data sets were screened to select those with:

- Longitudinal data
- National representation
- Linked exposure to outcome data
- Quality/validity/scientific publications

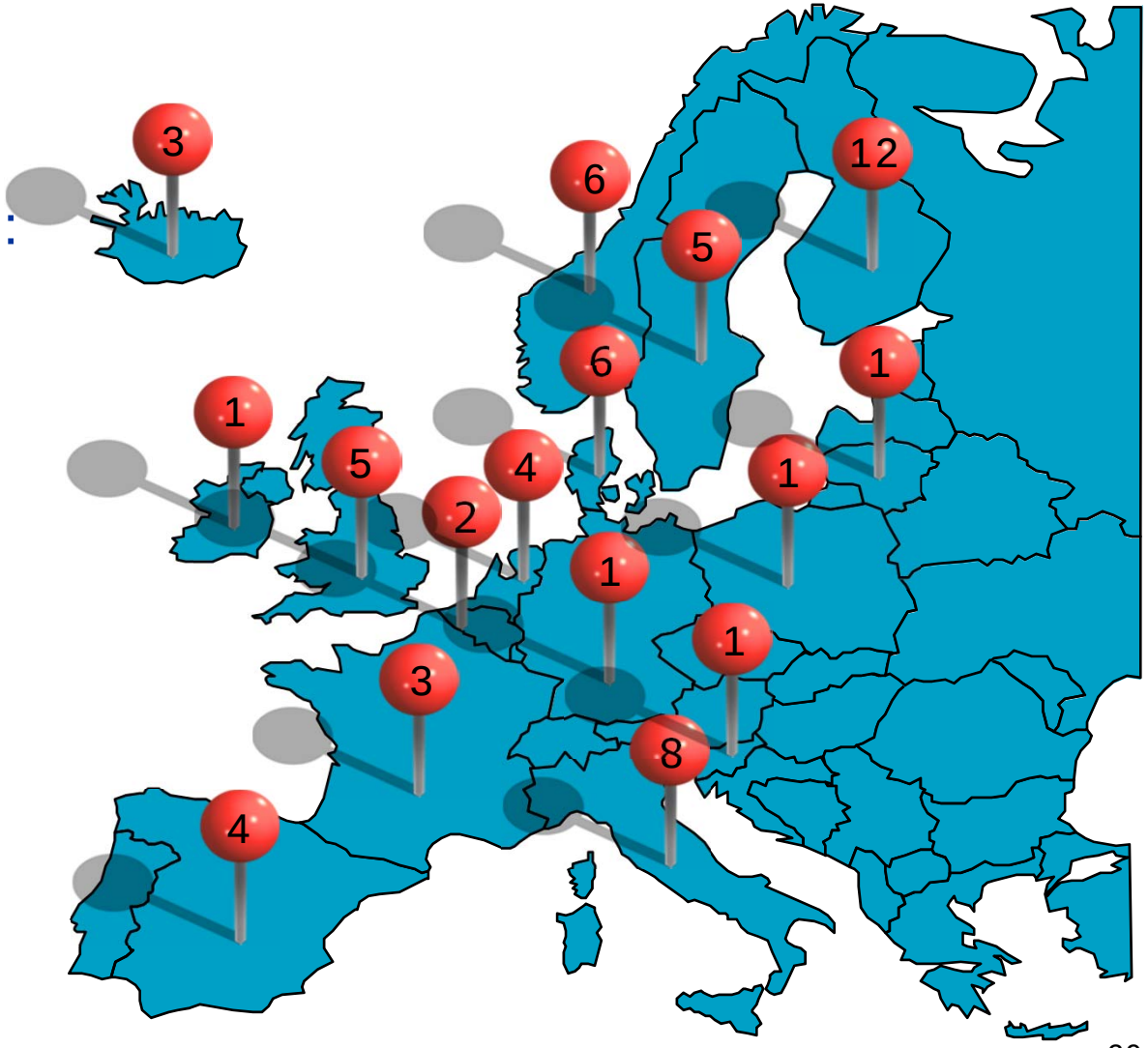
Analysis of EU Wide Datasets

Data source verification:

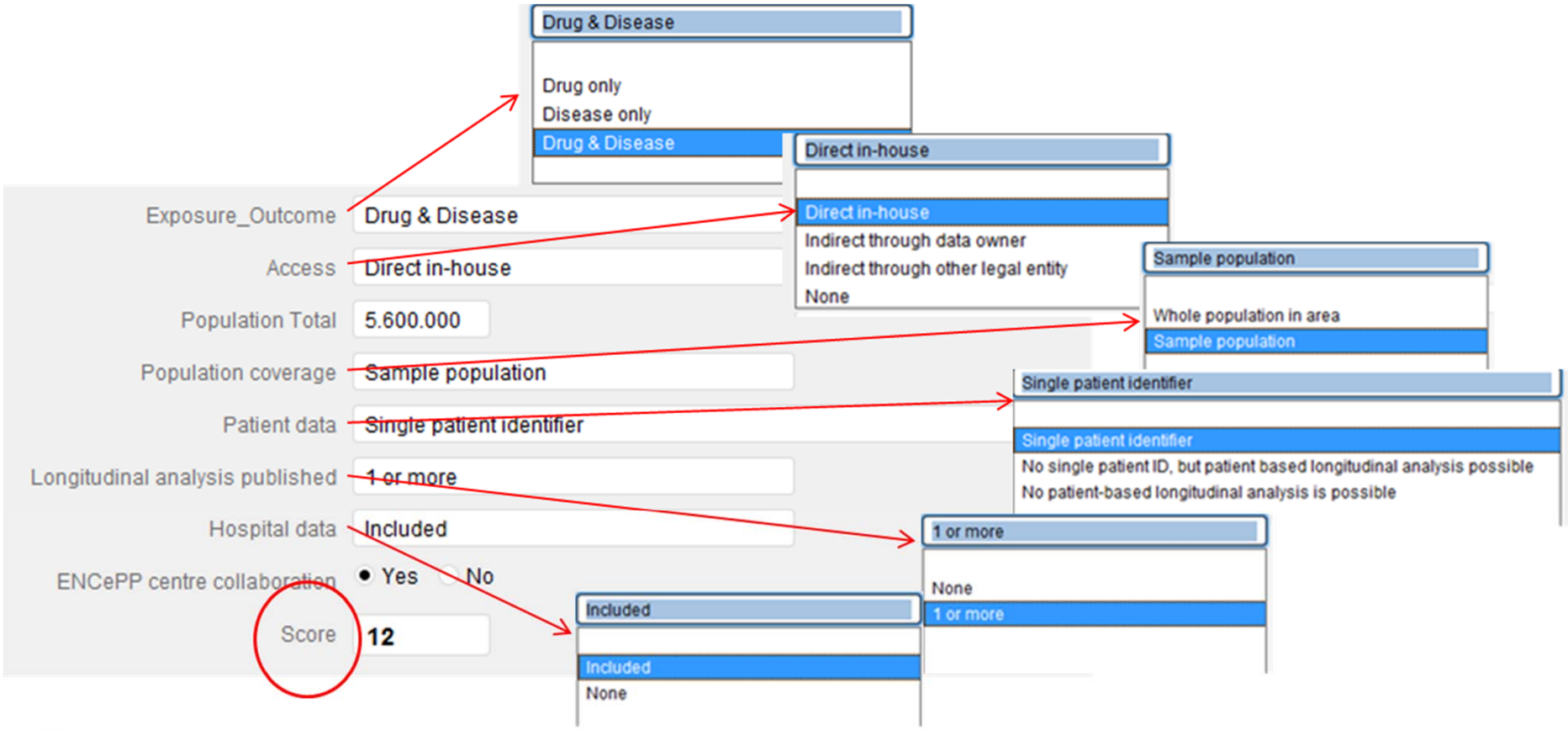
66 in total



Multi-national



Analysis of EU Wide Datasets



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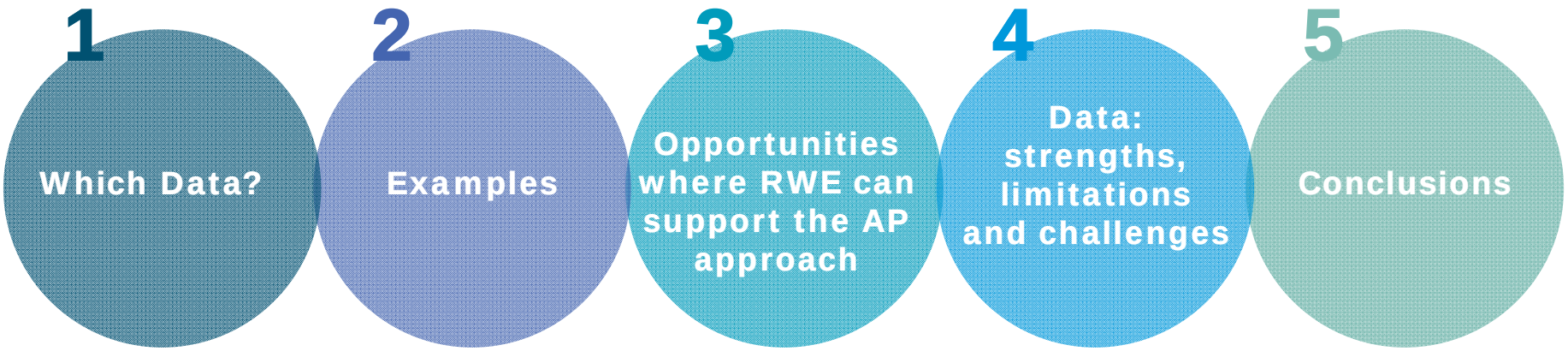
Objectives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Conclusions

RWE is already in routine use in Europe

This is particularly true in the post authorisation stage

Europe is rich in datasets but there are multiple challenges in their exploitation

Integration of multiple databases may be needed to increase power in order to study rare exposures or outcomes or diverse populations.

Conclusions

While RCTs will remain central to decision making at authorisation, there are multiple opportunities for RWE to add to the evidence base to support the adaptive pathways process

A clear understanding of the strengths and limitations of the available datasets and of where they can add the most value will be essential in the design of RWE studies to complement RCTs in the post authorisation phase

Early and frequent engagement between all stakeholders will be key for success.

EUROPEAN MEDICINES AGENCY

Thank you

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#AdaptivePathways