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SCIENCE MEDICINES HEALTH

The Challenges of Real World Data for Regulatory Decision Making

MRCT Annual Meeting 2017

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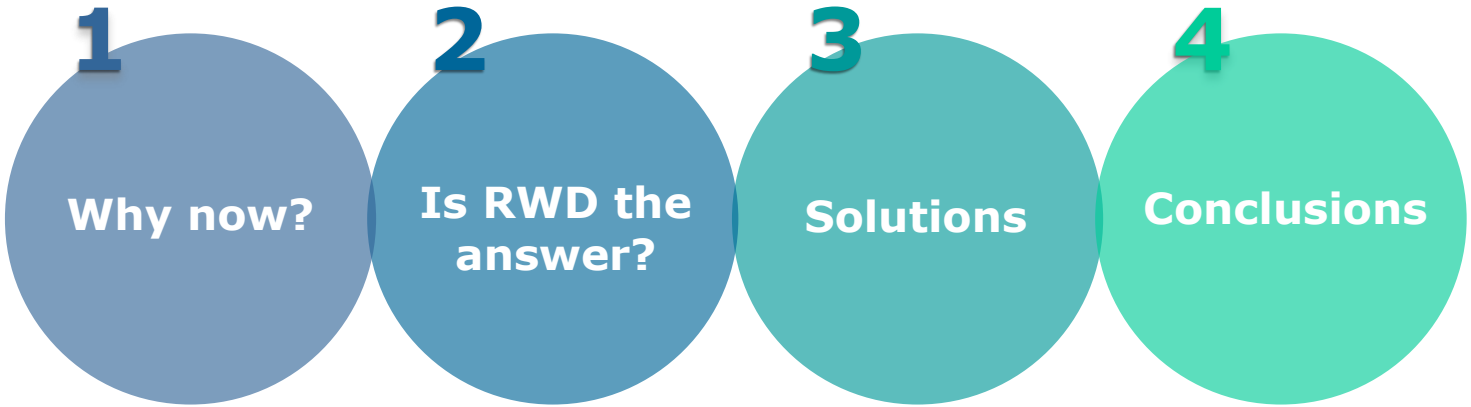
Disclaimer

The views expressed in this presentation are my 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.

Objectives



Objectives

1

Why now?

Why Now?

An increasing number of medicines with genomic mechanism of action and/or genomic biomarkers enabling smaller, focused RCTs but creates other challenges.

Genomic Based Mechanism of Action

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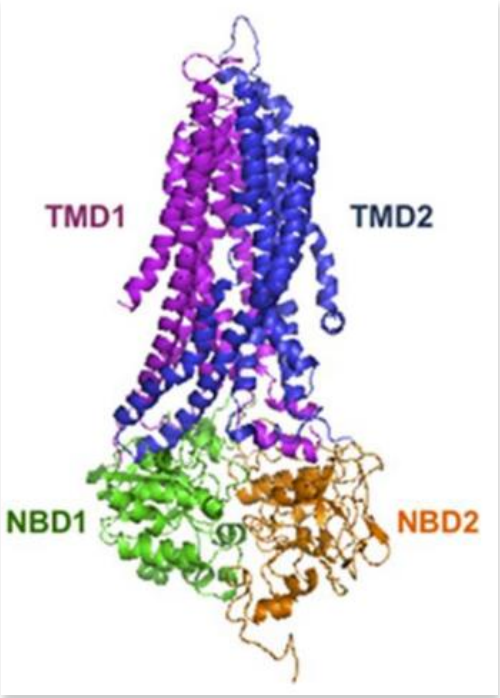
- Cystic fibrosis is caused by one of nearly 2000 mutations.
- CF drug, ivacaftor which targets *G551D* mutation in the *CFTR* gene (4% of CF population).
- Delivers increases in FEV_1 ~10%.

Indication gradually expanded to covers further mutations



The future

Challenge of determining the level of evidence required to extend indications when further mutations are identified.

Kim and Skach, Front Pharmacol. 2012 Dec 13;3:201

Genetic Biomarkers

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The Opinion Pages | OP-ED CONTRIBUTOR

Angelina Jolie Pitt: Diary of a Surgery

By ANGELINA JOLIE PITT MARCH 24, 2015

Michela Buttignol

LOS ANGELES — TWO years ago I wrote about my choice to have a preventive double mastectomy. A simple blood test had revealed that I carried a mutation in the BRCA1 gene. It gave me an estimated 87 percent risk of breast cancer and a 50 percent risk of ovarian cancer. I lost my mother, grandmother and aunt to cancer.

I wanted other women at risk to know about the options. I promised to follow up with any information that could be useful, including about my next preventive surgery, the removal of my ovaries and fallopian tubes.

I had been planning this for some time. It is a less complex surgery than the mastectomy, but its effects are more severe. It puts a woman into forced menopause. So I was readying myself physically and emotionally,

Review

Genetics of dementia

Clement T Loy, Peter R Schofield, Anne M Turner, John B J Kwok

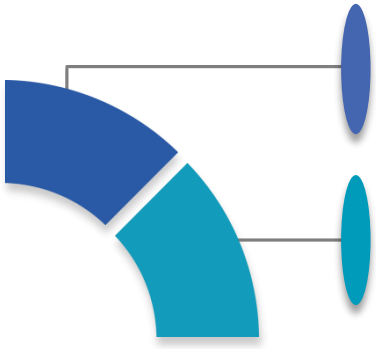
Lancet 2014; 383: 828–40
Published Online August 6, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60630-3

School of Public Health, University of Sydney, Sydney, NSW, Australia (C T Loy FRACP); Neuroscience Research Australia, Randwick, NSW, Australia (C T Loy, P R Schofield PhD, A M Turner PhD, J B J Kwok PhD)

25% of all people aged 55 years and older have a family history of dementia. For most, the family history is due to genetically complex disease, where many genetic variations of small effect interact to increase risk of dementia. The lifetime risk of dementia for these families is about 20%, compared with 10% in the general population. A small proportion of families have an autosomal dominant family history of early-onset dementia, which is often due to mendelian disease, caused by a mutation in one of the dementia genes. Each family member has a 50% chance of inheriting the mutation, which confers a lifetime dementia risk of over 95%. In this Review, we focus on the evidence for, and the approach to, genetic testing in Alzheimer's disease (*APP*, *PSEN1*, and *PSEN2* genes), frontotemporal dementia (*MAPT*, *GRN*, *C9ORF72*, and other genes), and other familial dementias. We conclude by discussing the practical aspects of genetic counselling.

But for other diseases the genetic risk is less predictive e.g. Alzheimer's, Parkinson's

How do you identify patients to be treated prophylactically and how do you assess the benefit-risk profile?



An increasing number of medicines with genomic mechanism and/or genomic biomarkers enabling smaller, focused RCTs but increasing uncertainties

Innovative medicines and personalised prescribing creates regulatory challenges.

Zalmoxis - Adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies.

Pivotal trial – single arm Phase I/II study with an endpoint of immune reconstitution defined as CD3+ cells>100/μL + an on-going Phase III trial.

A comparison of the treated patients (from both studies) with suitable historical controls was requested.

The EBMT patient registry was used to compile an appropriate control group selected on same criteria as the control arm of the on-going Phase III trial and a specific set of matching parameters.

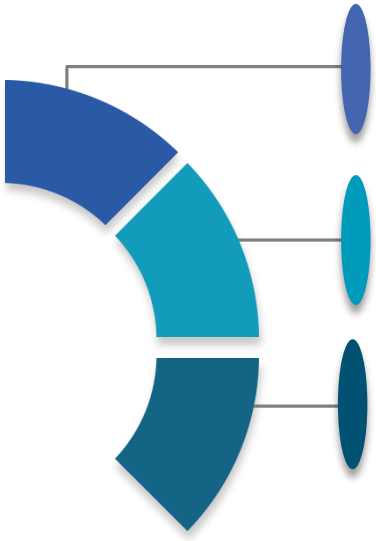
Conditional MA

Uncertainties

Impact of differences in baseline characteristics (historical controls)
Long term relevance of immune reconstitution as an early surrogate marker for efficacy
Long term safety and effectiveness

Post Authorisation

A non-interventional study to determine long term safety and efficacy study in real clinical practice by collecting data about the disease status and outcome for all treated patients using the EBMT registry.



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Innovative medicines and personalised prescribing creates regulatory challenges.

Rare diseases may be associated with more limited information at authorisation

Strimvelis - Corrective gene therapy for children with SCID-ADH (Severe Combined Immunodeficiency due to adenosine deaminase deficiency).
Occurrence: 0.22-0.68 per 100,000 population

- 12-patient pivotal study; Open label
- Primary outcome: 3-year survival
- Secondary outcome: severe infections

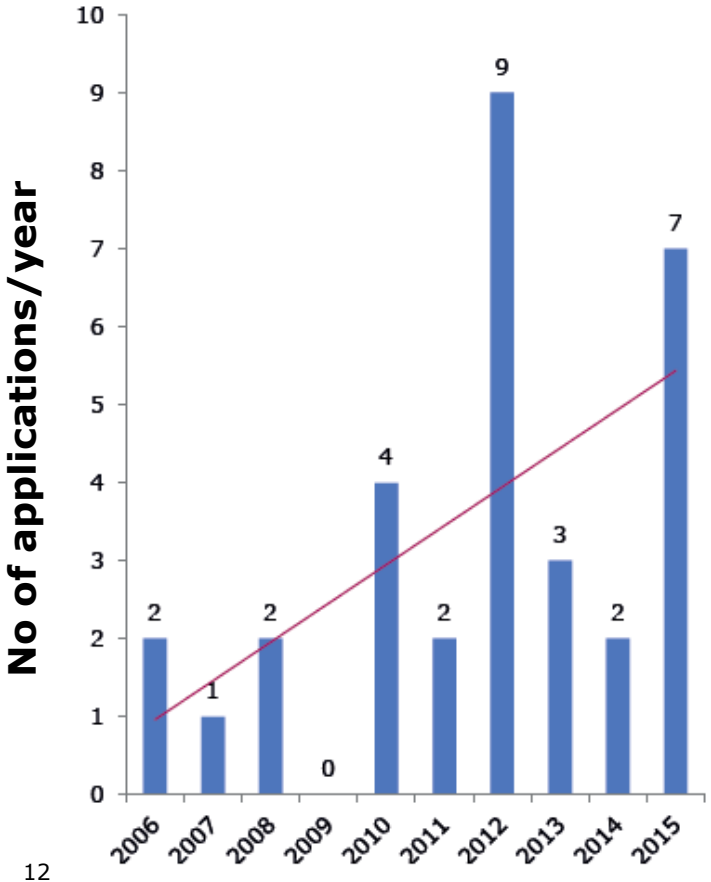
- 3-year survival: 12/12
- 9/12 successful response
- 12/18 auto-immune AEs

Uncertainties

- Long term durability of benefit (comparison with stem cell transplant)
- Late failure – need for further treatment eg stem cell transplant
- Late toxicity
- Long-term immunogenicity

Conditional MA

Number of applications requesting conditional marketing authorisation at submission, by year of submission



107 post-authorisation obligations

(of these, 57 obligations were fulfilled before June 2016)

Categories of specific obligations imposed to companies

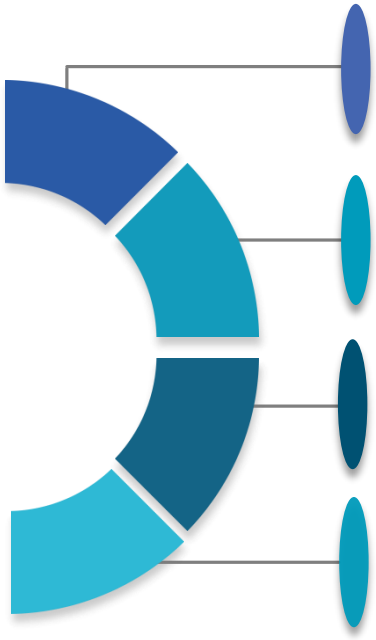
78	Final results from clinical studies or pool of studies
9	Interim results of a clinical trial
8	Additional analysis
3	Quality data
9	Other measures

How timely was the submission of specific obligation results?

33	Due date +/- 1 month
15	Early (1-6 months)
4	Early (6-12 months)
1	>1 year early
2	Late (1-6 months)
2	Late (6-12 months)

>90% of completed specific obligations did not have major changes to their scope

≈70% of specific obligations were completed within specified timelines



An increasing number of medicines with genomic mechanism and/or genomic biomarkers enabling smaller, focused RCTs but increases uncertainties

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Rare diseases to may be associated with more limited information at authorisation

Unknown generalisability of RCT results to normal clinical practice: Need for new approaches to gather complementary evidence

Unknown generalisability of RCTs

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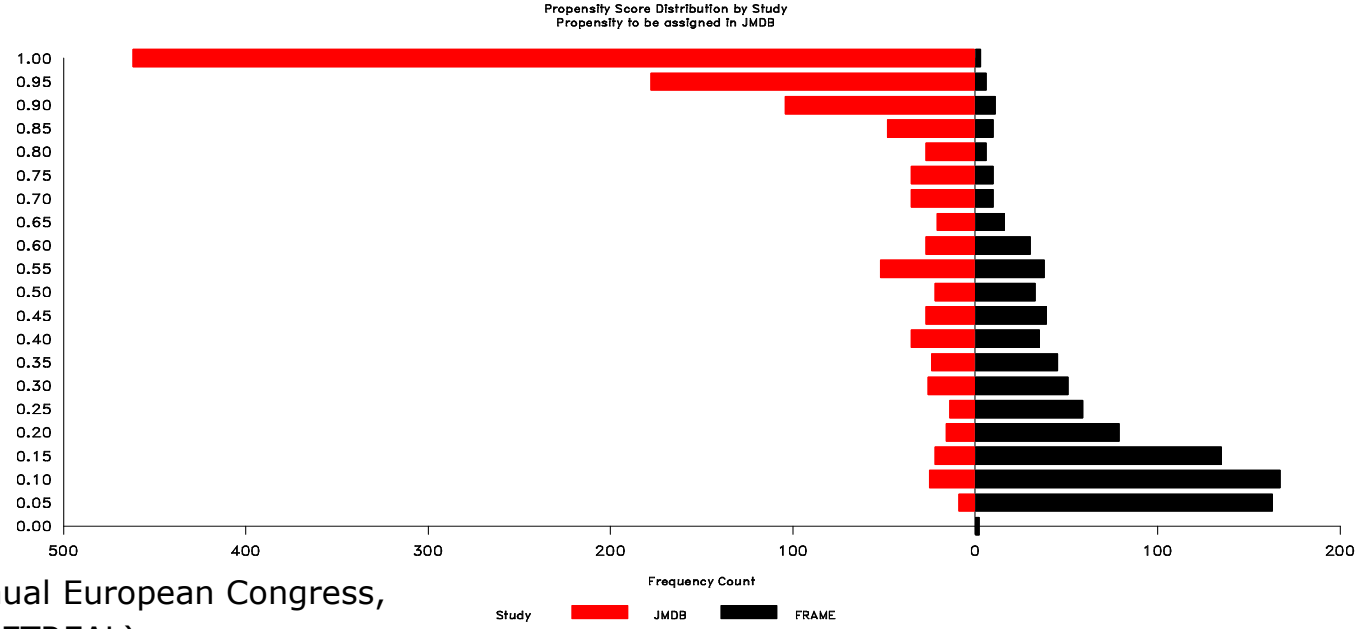
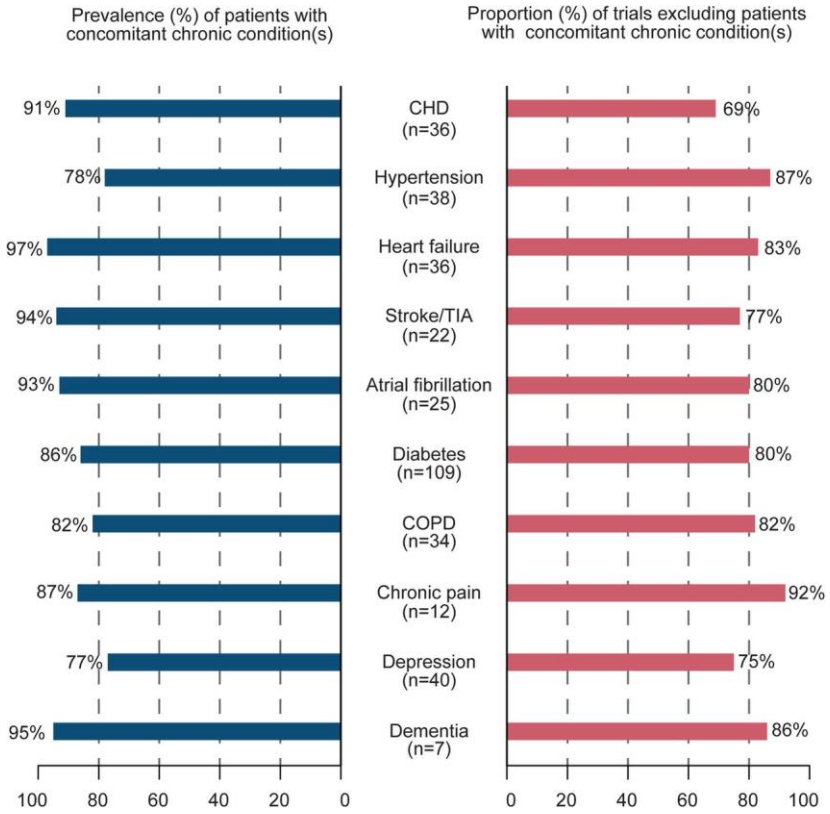
Happich *et al* developed a propensity score model that predicts participation in either a RCT (JMDB) or the real world (FRAME), given a set of common total baseline characteristics. Resulting propensity scores were used to assess the overlap between the two cohorts.



(ISPOR 19th Annual European Congress, GETREAL)



Proportion of trials excluding patients with concomitant chronic condition(s)

For example, 91% of patients with coronary heart disease (CHD) had a concomitant chronic condition, but 25 trials (69%) targeting patients with CHD excluded patients with concomitant chronic condition(s).

Buffel du Vaure *et al*, BMJ Open, 2016

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Additional data sources are needed to better monitor risk/benefit in high risk groups often excluded from clinical trials

Geriatric Population – Underrepresentation in clinical trials

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CLINICAL INVESTIGATION

Exclusion of Elderly People from Randomized Clinical Trials of Drugs for Ischemic Heart Disease

Florence T. Bourgeois, MD, MPH,†‡ Liat Orenstein, MSc,‡ Sarita Ballakur,§ Kenneth D. Mandl, MD, MPH,*†‡ and John P. A. Ioannidis, MD, DSc¶***

OBJECTIVES: To measure exclusion of elderly adults from randomized trials studying drug interventions for ischemic heart disease (IHD) and describe the characteristics of these trials.

DESIGN: Cross-sectional analysis.

SETTING: Interventional clinical trials studying a drug intervention for IHD that started in 2006 and after were identified in ClinicalTrials.gov. Data were extracted on study features, including age-based inclusion criteria. Data on participants and their age distribution were collected from trial publications, investigator inquiry, and result data in ClinicalTrials.gov.

PARTICIPANTS: Individuals aged 65 and older.

MEASUREMENTS: Proportion of trials excluding individuals based on age, mean age of trial participants, and proportion of enrolled participants aged 65 and older and 75 and older.

RESULTS: Of 839 identified trials, 446 (53%) explicitly excluded elderly adults. The most-frequent upper age limits were 80 (n = 164) and 75 (n = 114), with a median upper age limit of 80 (interquartile range 75–80). Trials with upper age limit exclusions tended to be smaller (median number of participants 100 vs 201, $P < .001$) and were more likely to be funded primarily by nonindustry sources (78.3% vs 70.0%, $P = .006$). The overall mean age of trial participants was 62.7 (mean maximum age 74). The estimated proportion of participants aged 65 and

CONCLUSION: Despite the high burden of IHD in elderly adults, the majority of drug trials do not enroll participants reflective of age-related prevalence of the disease. **J Am Geriatr Soc 2017.**

Key words: ischemic heart disease; evidence-based medicine; research methodology

Individuals age 65 and older account for 14% of the U.S. population, but bear a large and disproportionate amount of the healthcare burden.[1,2] More than 60% of individuals with cancer, for example, and nearly 65% of those hospitalized with heart disease are age 65 and older.[3,4] Overall, this age group consumes more than one-third of total U.S. personal healthcare expenses every year and 30% of all prescription drug costs,[2] but there is strong evidence that elderly adults are persistently excluded from or underrepresented in clinical trials for a range of conditions, including osteoarthritis, diabetes mellitus, and various types of cancer.[5–7] As many as half of all clinical trials have explicit upper age limitations, and others limit participation of older adults based on indirect exclusion criteria

Of 839 identified trials, 446 (53%) explicitly excluded elderly adults.

Other exclusion criteria included comorbid conditions, cognitive impairment and polypharmacy

Increasing incidence of polypharmacy.

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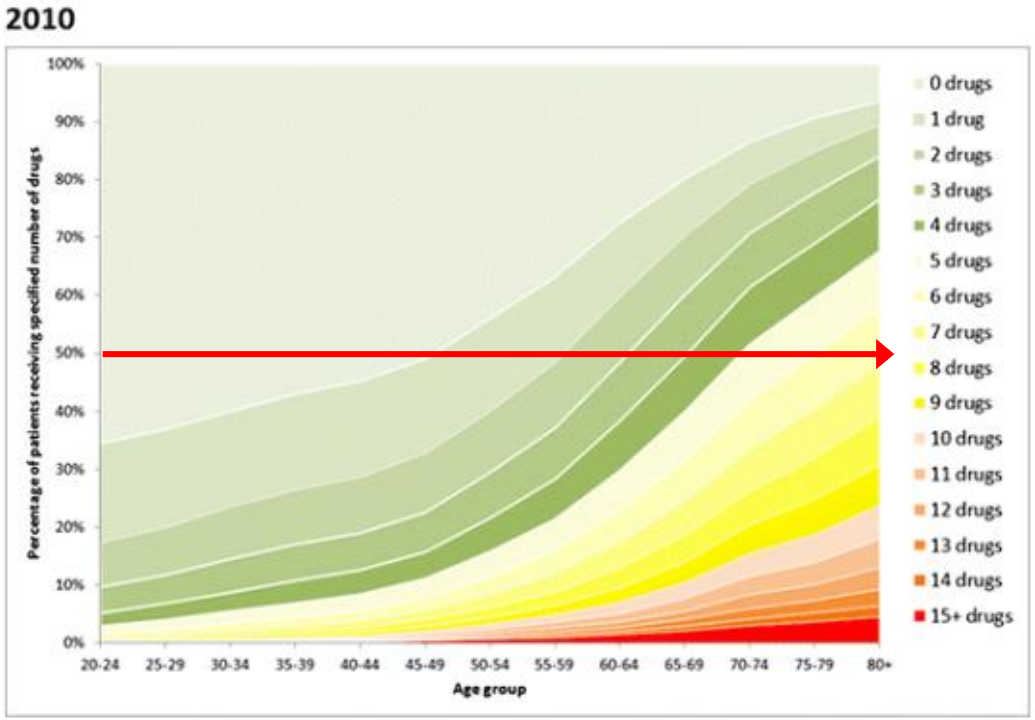
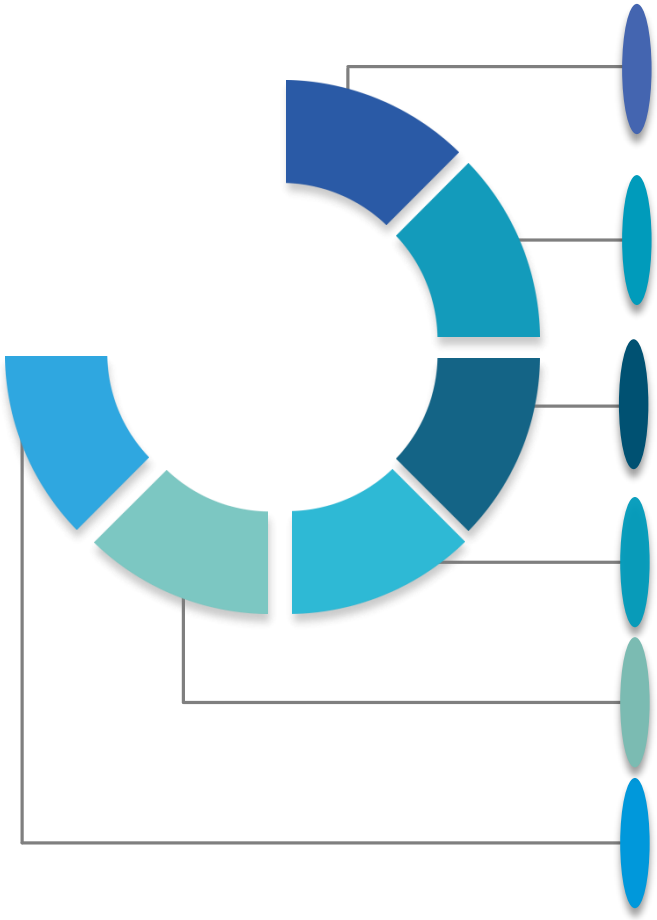


Guthrie et al. BMC Medicine (2015) 13:74

Receipt of ≥10 drugs was very strongly associated with increasing age

- 50% of those aged 70yrs received 6 or more medicines.
- 24% of aged >80 received 10 or more medicines

Significant increase in polypharmacy over last decade.



An increasing number of medicines with genomic mechanism and/or genomic biomarkers enabling smaller, focused RCTs but increases uncertainty.

New innovative medicines and personalised prescribing creates regulatory challenges.

Welcome activity in the rare disease area to meet unmet medical needs is associated with more limited information at authorisation

The high internal validity of clinical trials at the expense of external validity demands new approaches to gather complementary evidence

Additional data sources are needed to appropriately monitor risk/benefit in high risk groups often excluded from clinical trials

Increasing interest in combination therapies to treat complex diseases creates regulatory challenges

Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor

Clinical Pharmacist | 10 MAY 2017 | By Sharanie V. Sims CA, Elizabeth A. Neuner, Robert A. Bonomo

Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality

Jan W. Eriksson, Johan Bodegard, David Nathanson, Marcus Thuresson, Thomas Nyström, Anna Norhammar

RHEUMATOID ARTHRITIS

Comparing durability of combination therapies

According to observations from a follow-up study of the RACAT trial looking at patients with rheumatoid arthritis who have suboptimal responses to methotrexate, triple therapy with methotrexate, sulfasalazine and hydroxychloroquine is more durable than combined methotrexate–etanercept therapy. Of the 289 patients followed up, 78% remained on triple therapy at 1 year compared with 63% who remained on methotrexate– etanercept therapy; significantly more patients changed from methotrexate–etanercept therapy to triple therapy than vice versa ($P = 0.005$).

ORIGINAL ARTICLE Peper, S. M. *et al.* Rheumatoid arthritis treatment after methotrexate: triple therapy is more durable than etanercept. *Arthritis Care Res. (Hoboken)* http://dx.doi.org/10.1002/acr.23255 (2017)

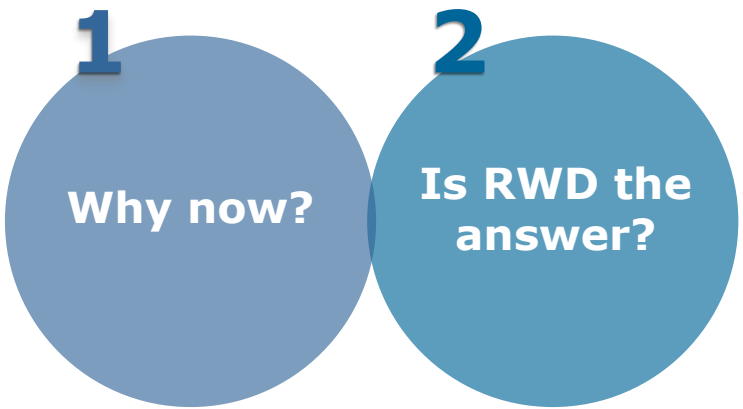
Challenges

Understanding ADRS which only arise in the combination product

Monitor changes in efficacy or development of resistance?

We need to capture the entire picture not just simply isolated snapshots

Objectives



Electronic health records
Primary care data, hospital records

Patient and caregiver surveys

Claims data

Patient Disease Registries

Datasources

Spontaneous ADRS

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

Prescription databases
Drug utilisation data sources

The future
- patient derived data (via smart phone or web based technologies), Patient reported outcomes

RWD is already in used routinely for regulatory decision making

Predominantly for marketed products - safety monitoring and drug utilisation.

Post-authorisation safety

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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

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

David N. Juurlink MD PhD, Ta
Peter C. Austin PhD, Jack V. T
Muhammad M. Mamdani Pha

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

OPEN ACCESS

ARTICLES

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

Brent Taylor, Elizabeth Miller, C Paddy Farrington, Maria-Christina Petropoulos, Is
Pauline A Waight

Open Access Research

BMJ Open

Metformin initiation and renal impairment: a cohort study in Denmark and the UK

Christian Fynbo Christiansen,[1] Vera Ehrenstein,[1] Uffe Heide-Jørgensen,[1] Stine Skovbo,[1] Helene Nørrelund,[1] Henrik Toft Sørensen,[1] Lin Li,[2] Susan Jick[2]

But pharmacovigilance is not an exact science

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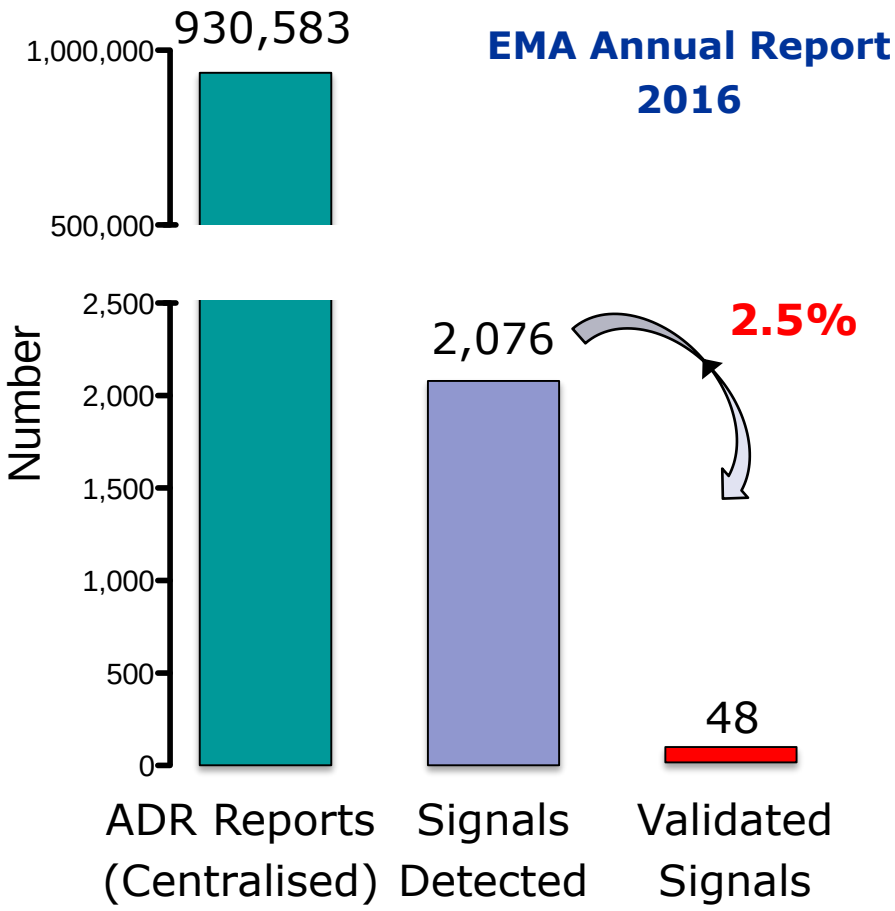
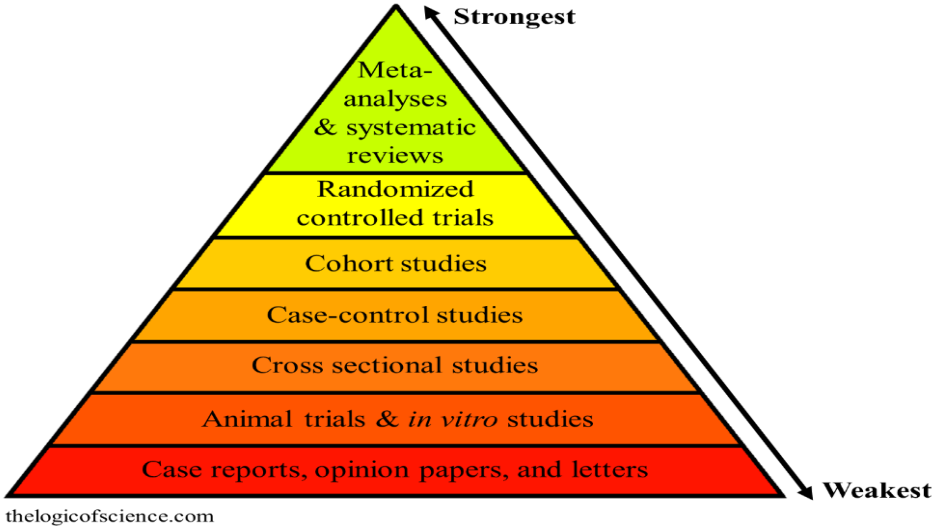
Multiple sources of evidence of **varying quality** from **multiple stakeholders** are balanced to inform decision making.

Many validated signals required further evidence to define and understand.

RWD forms part of this jigsaw.

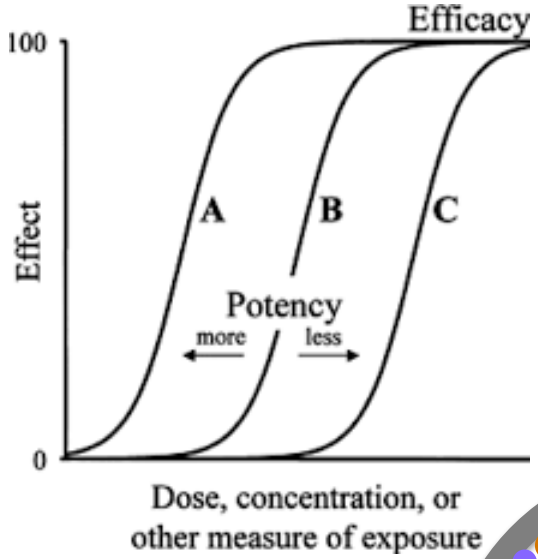


Evidence Hierarchy varies according to context of use



What is "acceptable" varies according to the **decision being made**, the **unmet need** and the **opportunity to capture** other data.

What about effectiveness?



Changes in the Traditional Regulatory Paradigm

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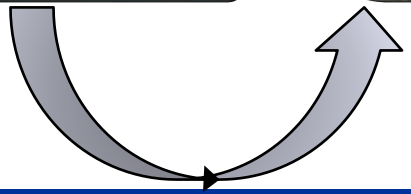
- Structured data (RCT) generated in accordance with strict guidelines and known provenance
- High certainty

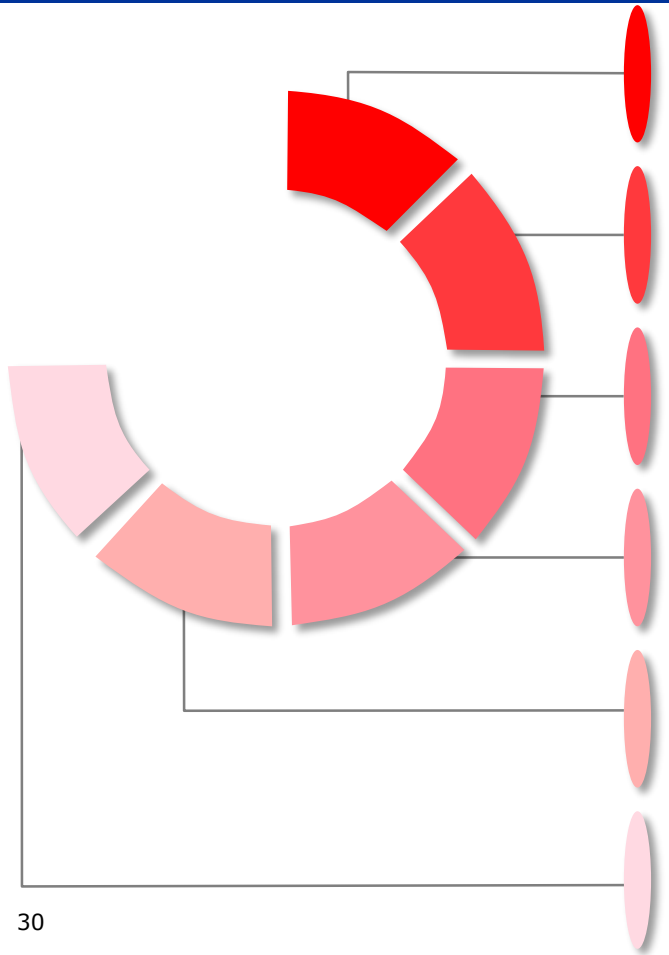
Currently

Challenge

- Unstructured, unvalidated data of unknown provenance
- Turning data into knowledge
- More uncertainty



Multiple Uncertainties



Real world data is produced for clinical care delivery not for research - records are subject to systematic and random error

Unknowns around the consistency, accuracy, completeness, and representativeness of the data – influenced by the clinical care setting

The capture of lifestyle factors is variable among databases

Characterising the patient population, identifying and measuring exposure and outcomes with sufficient sensitivity and specificity is difficult

Challenges in integration of data across multiple datasets and across the whole hierarchy of evidence (from RCTS to spontaneous reports)

Multiple examples where observational studies on the same safety issue produce disparate results

Conflicting results creates Uncertainties

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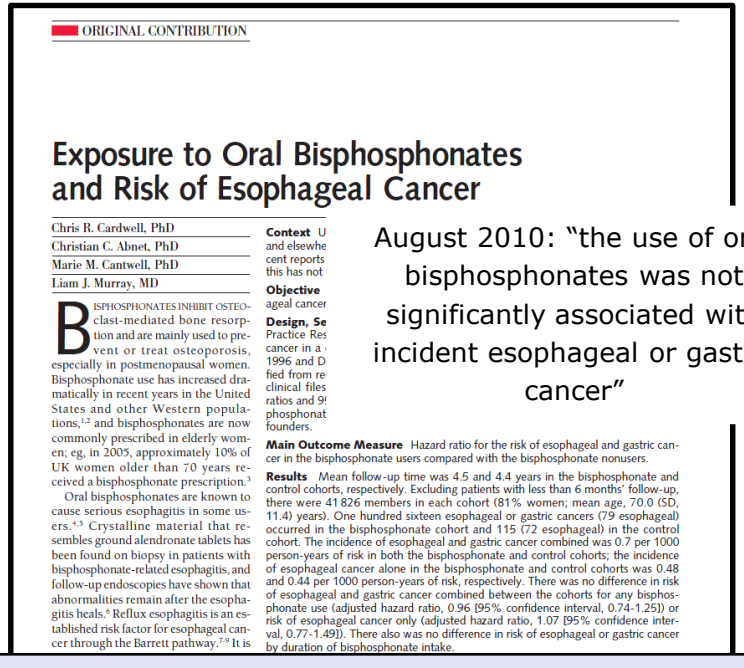

ORIGINAL CONTRIBUTION

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Chris R. Cardwell, PhD
Christian C. Abnet, PhD
Marie M. Cantwell, PhD
Liam J. Murray, MD

BISPHOSPHONATES INHIBIT OSTEOclast-mediated bone resorption and are mainly used to prevent or treat osteoporosis, especially in postmenopausal women. Bisphosphonate use has increased dramatically in recent years in the United States and other Western populations,[1,2] and bisphosphonates are now commonly prescribed in elderly women; eg, in 2005, approximately 10% of UK women older than 70 years received a bisphosphonate prescription.[3]

Oral bisphosphonates are known to cause serious esophagitis in some users.[4,5] Crystalline material that resembles ground alendronate tablets has been found on biopsy in patients with bisphosphonate-related esophagitis, and follow-up endoscopies have shown that abnormalities remain after the esophagitis heals.[6] Reflux esophagitis is an established risk factor for esophageal cancer through the Barrett pathway.[7-9] It is

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Objective
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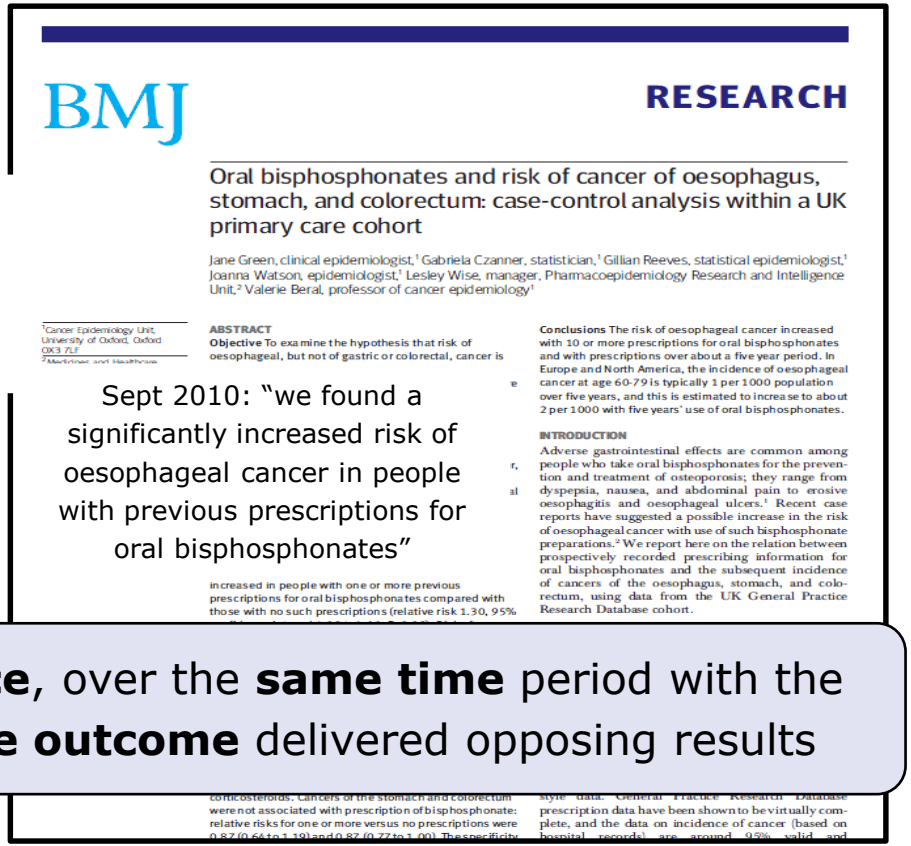
Main Outcome Measure Hazard ratio for the risk of esophageal and gastric cancer in the bisphosphonate users compared with the bisphosphonate nonusers.

Results Mean follow-up time was 4.5 and 4.4 years in the bisphosphonate and control cohorts, respectively. Excluding patients with less than 6 months' follow-up, there were 41 826 members in each cohort (81% women; mean age, 70.0 (SD, 11.4) years). One hundred sixteen esophageal or gastric cancers (79 esophageal) occurred in the bisphosphonate cohort and 115 (72 esophageal) in the control cohort. The incidence of esophageal and gastric cancer combined was 0.7 per 1000 person-years of risk in both the bisphosphonate and control cohorts; the incidence of esophageal cancer alone in the bisphosphonate and control cohorts was 0.48 and 0.44 per 1000 person-years of risk, respectively. There was no difference in risk of esophageal and gastric cancer combined between the cohorts for any bisphosphonate use (adjusted hazard ratio, 0.96 [95% confidence interval, 0.74-1.25]) or risk of esophageal cancer only (adjusted hazard ratio, 1.07 [95% confidence interval, 0.77-1.49]). There also was no difference in risk of esophageal or gastric cancer by duration of bisphosphonate intake.

August 2010: "the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer"



BMJ

RESEARCH

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,[1] Gabriela Czanner, statistician,[1] Gillian Reeves, statistical epidemiologist,[1] Joanna Watson, epidemiologist,[1] Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,[2] Valerie Beral, professor of cancer epidemiology[1]

[1]Cancer Epidemiology Unit, University of Oxford, Oxford OX3 7LF
[2]Medicines and Healthcare

ABSTRACT

Objective To examine the hypothesis that risk of oesophageal, but not of gastric or colorectal, cancer is

increased in people with one or more previous prescriptions for oral bisphosphonates compared with those with no such prescriptions (relative risk 1.30, 95%

corticosteroids. Cancers of the stomach and colorectum were not associated with prescription of bisphosphonate: relative risks for one or more versus no prescriptions were 0.87 (0.64 to 1.19) and 0.87 (0.77 to 1.00). The specificity

Conclusions The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period. In Europe and North America, the incidence of oesophageal cancer at age 60-79 is typically 1 per 1000 population over five years, and this is estimated to increase to about 2 per 1000 with five years' use of oral bisphosphonates.

INTRODUCTION

Adverse gastrointestinal effects are common among people who take oral bisphosphonates for the prevention and treatment of osteoporosis; they range from dyspepsia, nausea, and abdominal pain to erosive oesophagitis and oesophageal ulcers.[1] Recent case reports have suggested a possible increase in the risk of oesophageal cancer with use of such bisphosphonate preparations.[2] We report here on the relation between prospectively recorded prescribing information for oral bisphosphonates and the subsequent incidence of cancers of the oesophagus, stomach, and colorectum, using data from the UK General Practice Research Database cohort.

style data. General Practice Research Database prescription data have been shown to be virtually complete, and the data on incidence of cancer (based on hospital records) are around 95% valid and

Sept 2010: "we found a significantly increased risk of oesophageal cancer in people with previous prescriptions for oral bisphosphonates"

Studies utilising the **same datasource**, over the **same time** period with the **same drug** of interest and the **same outcome** delivered opposing results

Sources of Variability in Multiple Database Studies

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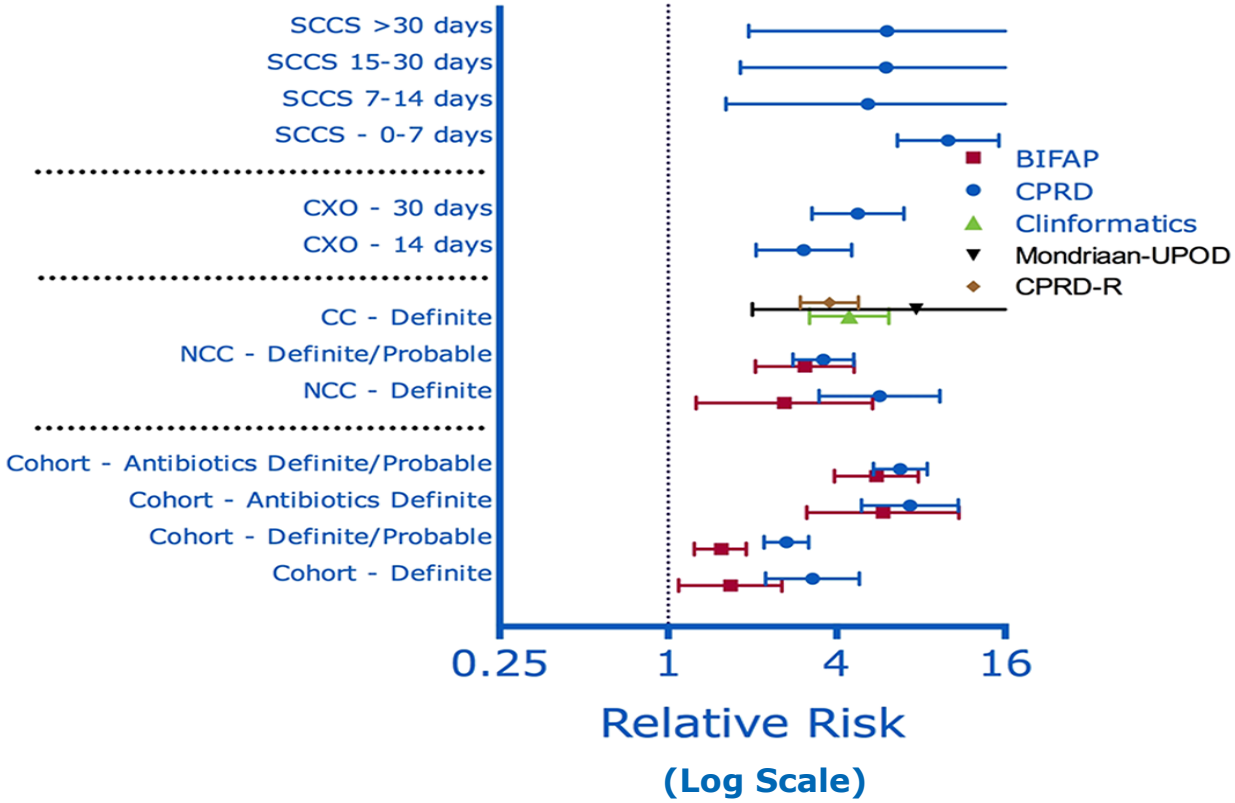

PROTECT
Antibiotics and the risk of acute liver injury

Joint development of Common protocol

Independent conduct in different databases

Pharmacoepidemiology and Drug Safety
2016;156-165. DOI: 10.1002/pds.3968

SCCS: self-controlled case series, CXO: case cross-over, CC: case–control, NCC: nested case–control

Sources of Variability in Multiple Database Studies

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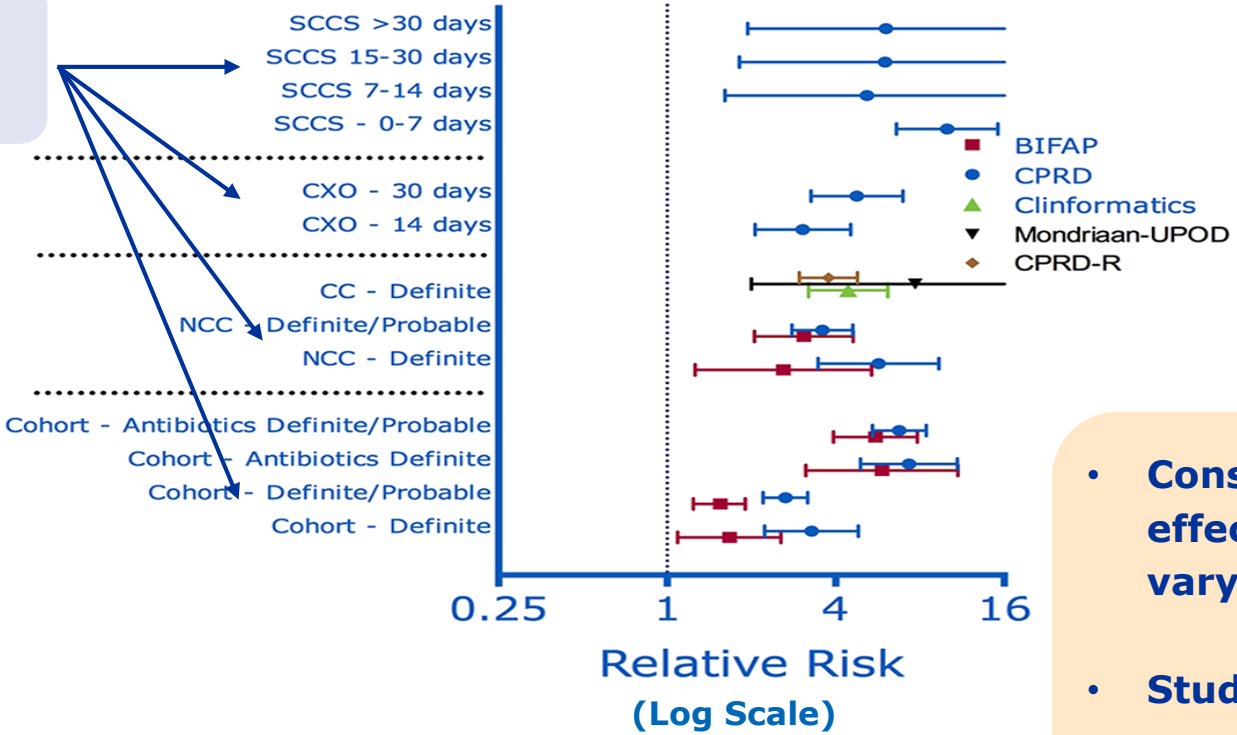
Study design



- **Consistent direction of effect estimate but of varying magnitude**
- **Study design should be a conscious decision**

Sources of Variability in Multiple Database Studies

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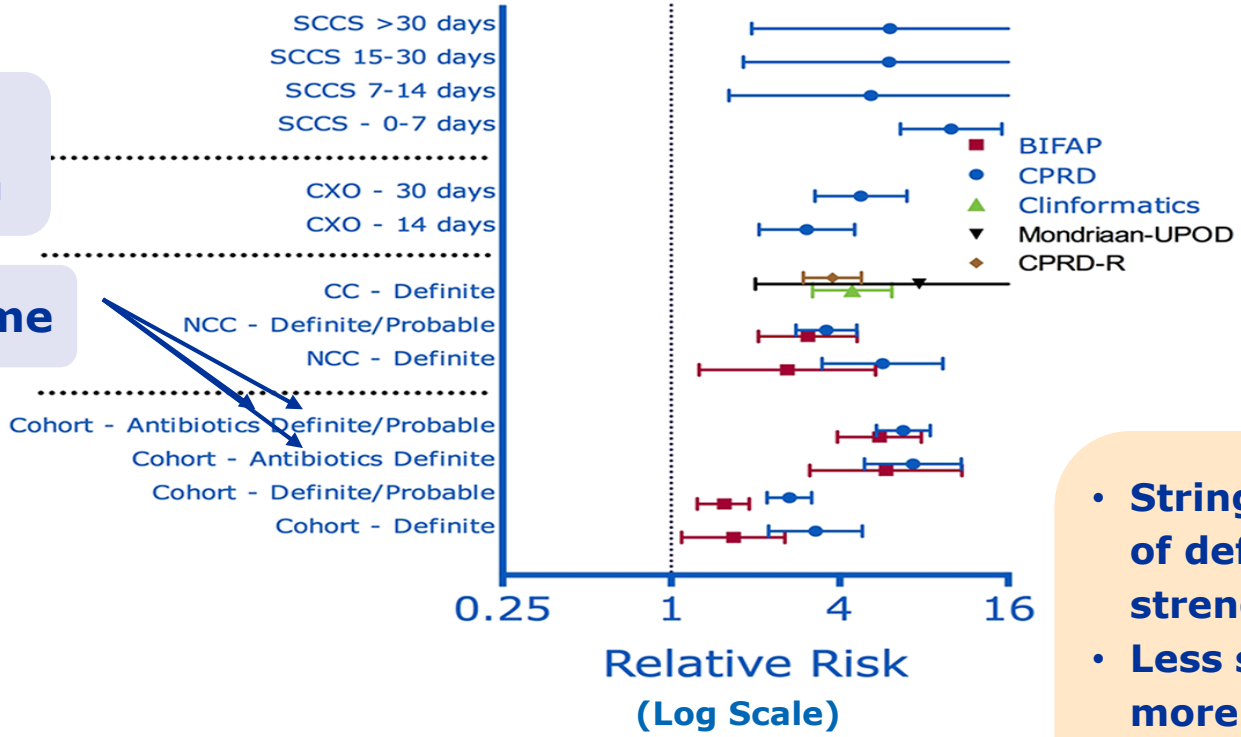
Study design

Outcome



- **Stringency and accuracy of definition increased strength of association**
- **Less stringency led to more false positives**
- **Outcome needs to be carefully defined.**

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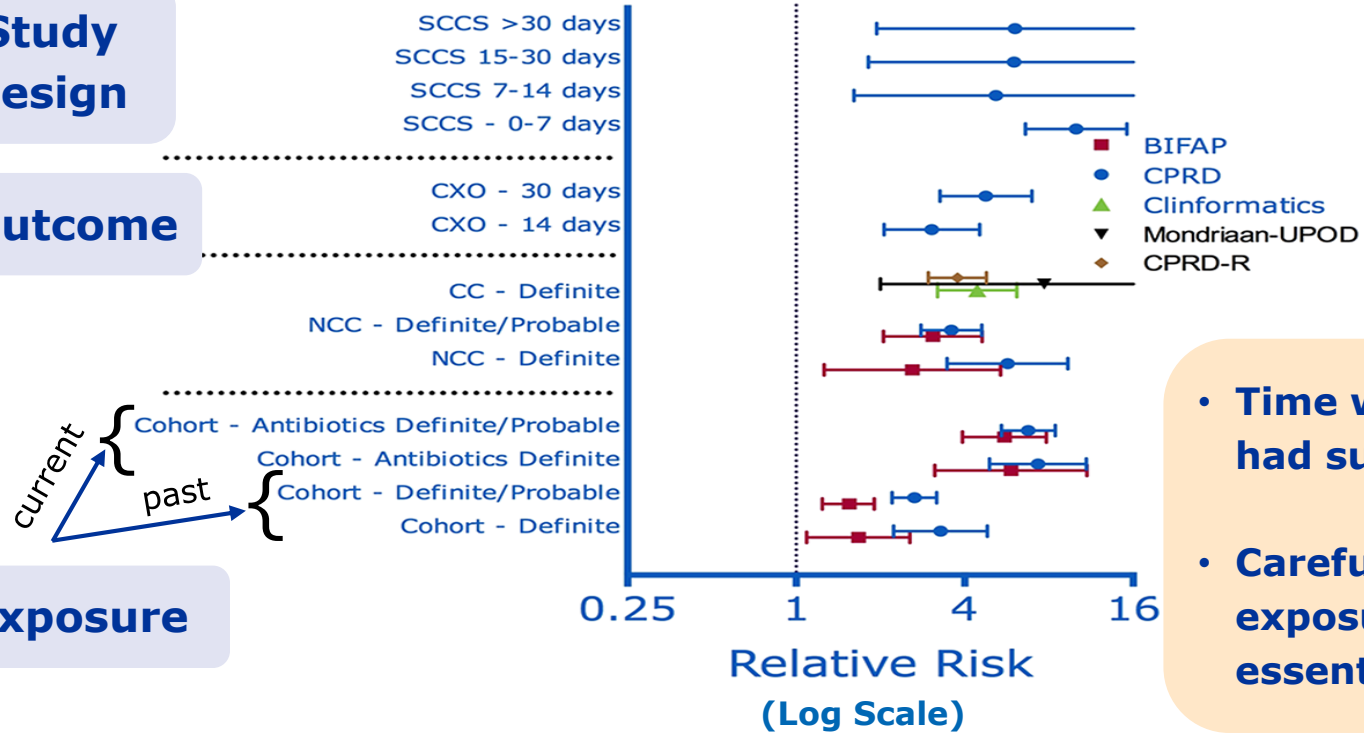
Exposure



- **Time window of exposure had substantial impact**
- **Careful definition of exposure window is essential**

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Top 20 of 5561 descriptions of codeine product dose

doscode	Frequency	Description	Standard recoding
0000047	2492510	TAKE 1 OR 2 4 TIMES/DAY	6.00
0021825	494909	TAKE 1 OR 2 FOUR TIMES DAILY	6.00
0000126	421667	1-2 FOUR TIMES A DAY WHEN REQUIRED	-1.00
0000098	246520	2 FOUR TIMES A DAY WHEN REQUIRED	-1.00
0000185	237956	TAKE TWO 4 TIMES/DAY	8.00
0000201	206628	1 OR 2 FOUR TIMES A DAY WHEN REQUIRED	-1.00
0000227	171983	1-2 FOUR TIMES A DAY	6.00
0000048	139230	TAKE ONE 4 TIMES/DAY	4.00
0000114	138386	2 FOUR TIMES A DAY	8.00
0000034	116813	ONE OR TWO FOUR TIMES A DAY WHEN REQUIRED	-1.00
0016164	114705	2 TABS 4 TIMES DAILY	8.00
0000003	108314	AS DIRECTED	-1.00
0000496	92268	TAKE 1 OR 2 4 TIMES/DAY WHEN REQUIRED	-1.00
0000257	92250	TAKE 1 OR 2 3 TIMES/DAY	4.50
0007812	78018	TAKE ONE OR TWO FOUR TIMES/DAY	6.00
0001588	76761	TAKE 1 OR 2 EVERY 4-6 HRS	6.00
0010666	76284	ONE OR TWO TO BE TAKEN UP TO FOUR TIMES A DAY WHEN REQUIRED FOR 'PAIN	-1.00
0000026	65854	TWO FOUR TIMES A DAY WHEN REQUIRED	-1.00
0000021	65460	TAKE ONE TWICE DAILY	2.00

Identical

Yes. 6 is between 4 and 8. But how useful is this!

Uncodable

25,911 dose descriptors overall in the THIN dataset.

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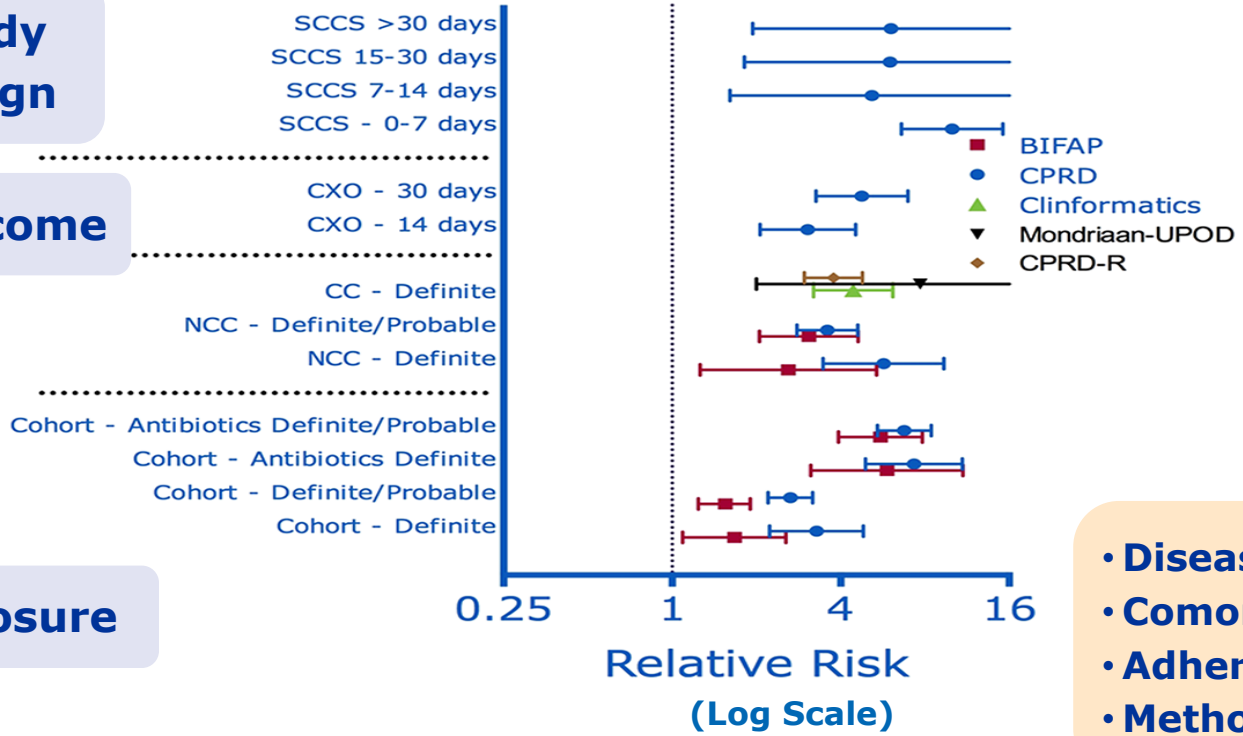
Exposure

Study population



- **Disease stratification**
- **Comorbidities/medications**
- **Adherence**
- **Methodology for matching**

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Study design

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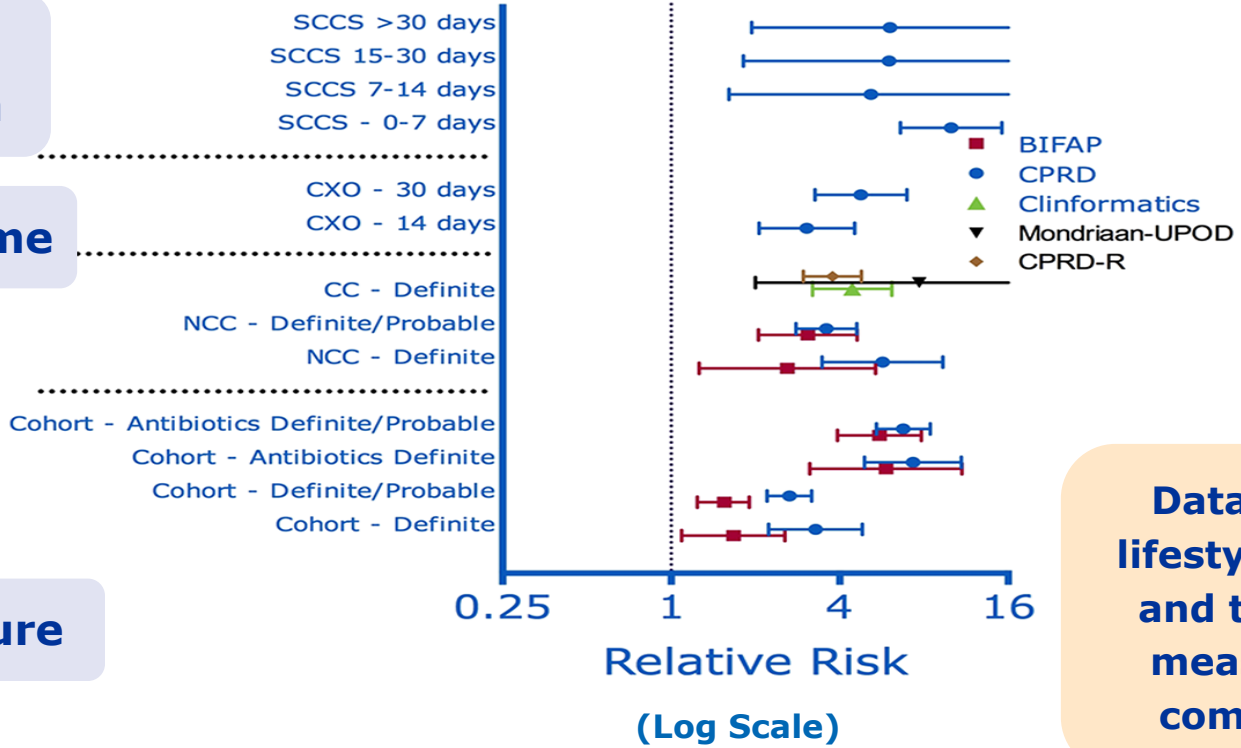
Exposure



Study population

Confounding adjustment

Databases vary in the lifestyle factors recorded and the quality of their measurement making comparisons difficult

Different Prescribing Rates and Practices Across Europe

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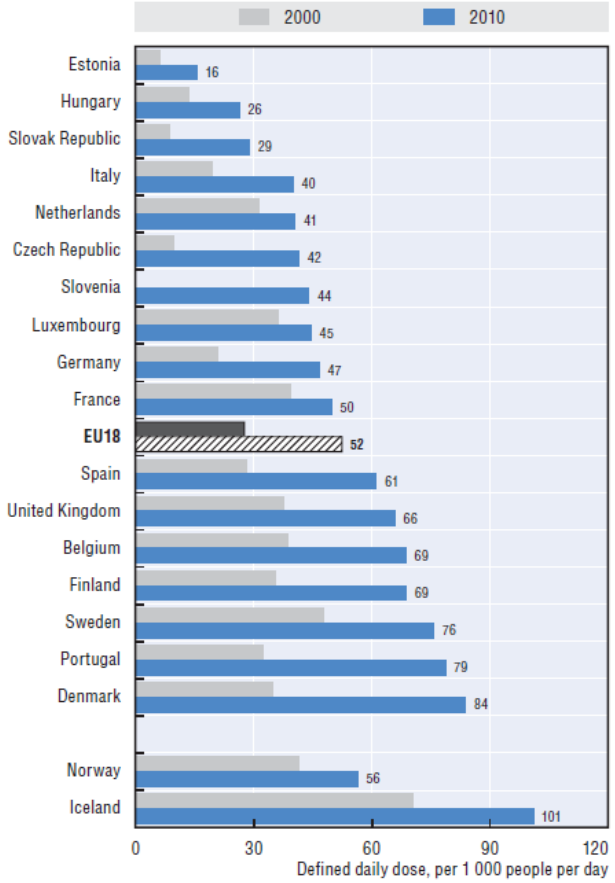
Antidepressants consumption 2000 and 2010



Source: OECD Health Data 2012.

Prescribing of antidepressants **varies widely** between European countries despite **no evidence of difference in the prevalence** of affective disorders.

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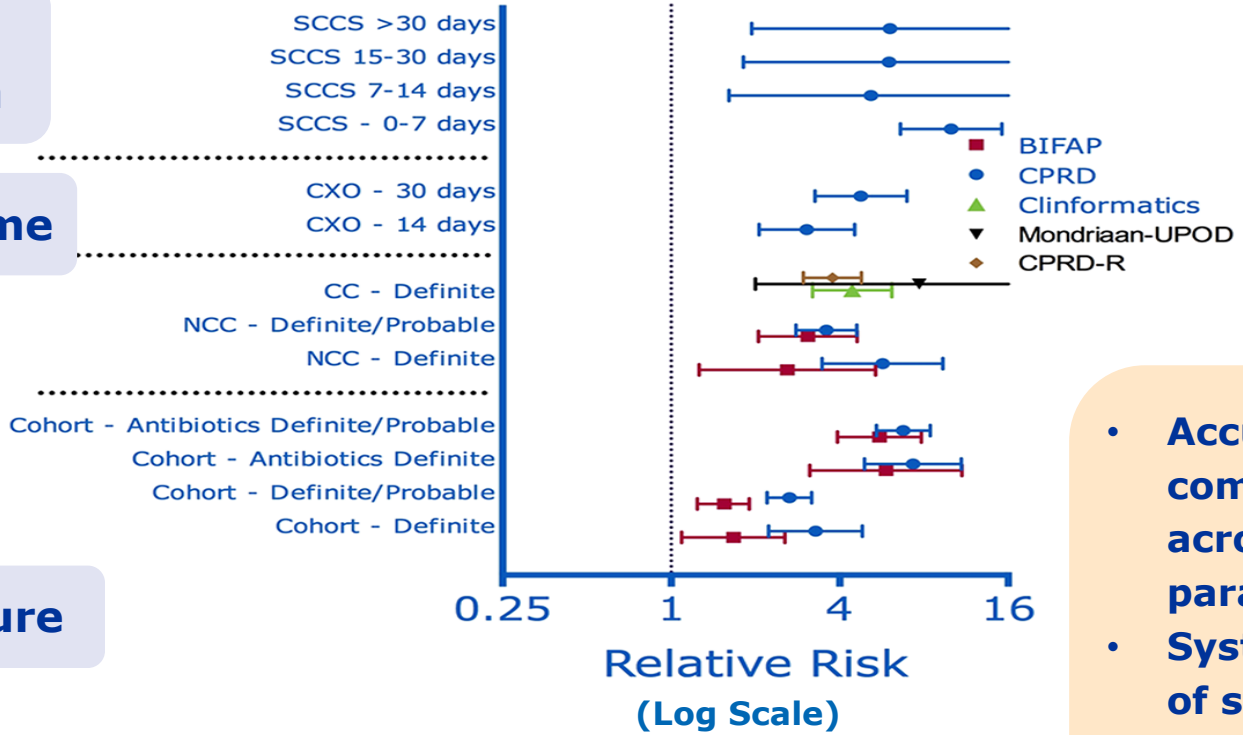
Study design

Outcome

Exposure



Study population

Confounding adjustment

Database

- **Accuracy and completeness data across different parameters is variable**
- **Systematic evaluation of strengths and limitations is essential**

Database heterogeneity

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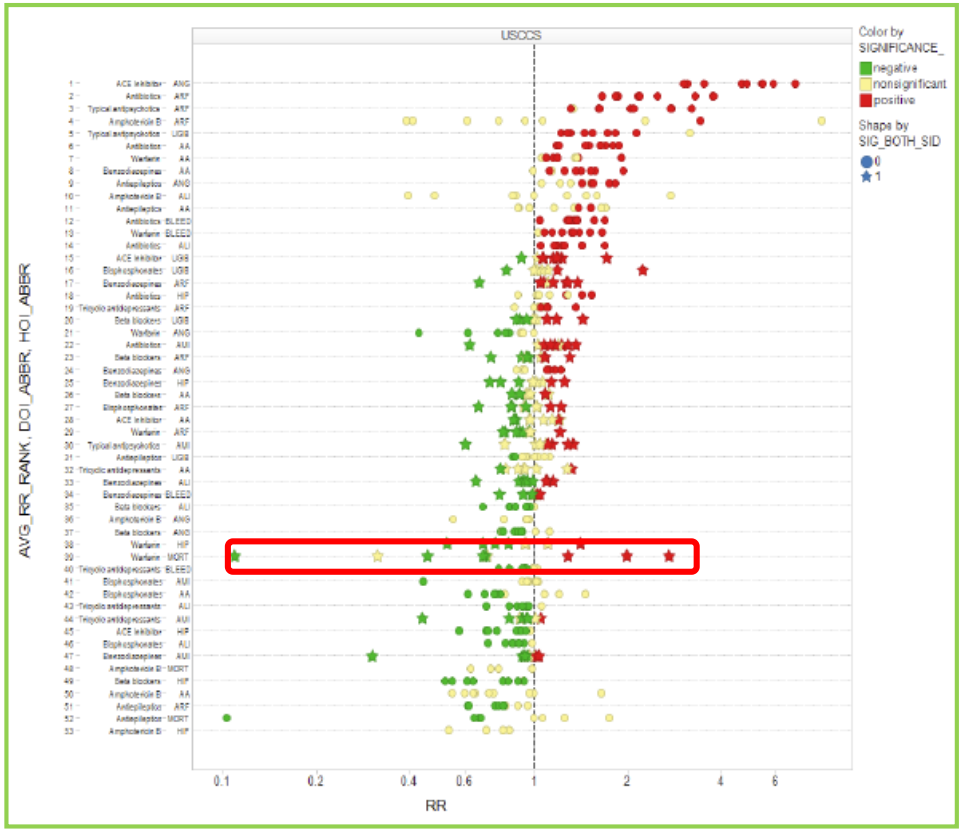
Estimated Relative Risks From the Self-Controlled Case Series Design.



Madigan et al,
Am J Epidemiol. 2013;178(4):645–651 2013

Systematically studied **heterogeneity** across **10 databases** and 53 drug outcome pairs and 2 widely used study designs (cohort and self controlled case series)

Despite holding study design constant, **20%–40%** of observational database studies can swing from statistically significant in 1 direction to statistically significant in the opposite direction depending on the choice of database,

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Fluoroquinolones + Retinal Detachment

Study name	Rate ratio	Lower limit	Upper limit	p-Value
Etminan et al, 2012 (case-control)	4.50	3.56	5.69	0.00
Fife et al, 2014 (case-control_CCAE)	1.39	1.01	1.91	0.04
Fife et al, 2014 (case-control_Optum)	1.19	0.68	2.07	0.54
Kapoor et al, 2014 (cohort)	1.82	0.26	12.89	0.55
Eftekhari et al, 2014 (cohort)	0.56	0.08	4.03	0.56
Pasternak et al, 2013 (cohort)	1.29	0.53	3.13	0.57
Kuo et al, 2014 (cohort)	2.07	1.45	2.96	0.00
Chui et al, 2014 (case series)	1.26	0.65	2.46	0.50
Fife et al, 2014 (case series_CCAE)	1.13	0.99	1.29	0.07
Fife et al, 2014 (case series_Optum)	0.85	0.66	1.09	0.20
	1.47	0.95	2.27	0.09

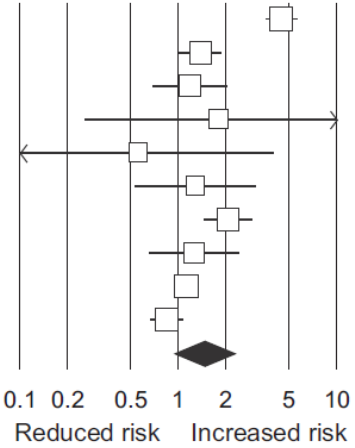


Fig. 2. Pooled rate ratio and 95% CI of retinal detachment associated with fluoroquinolones.

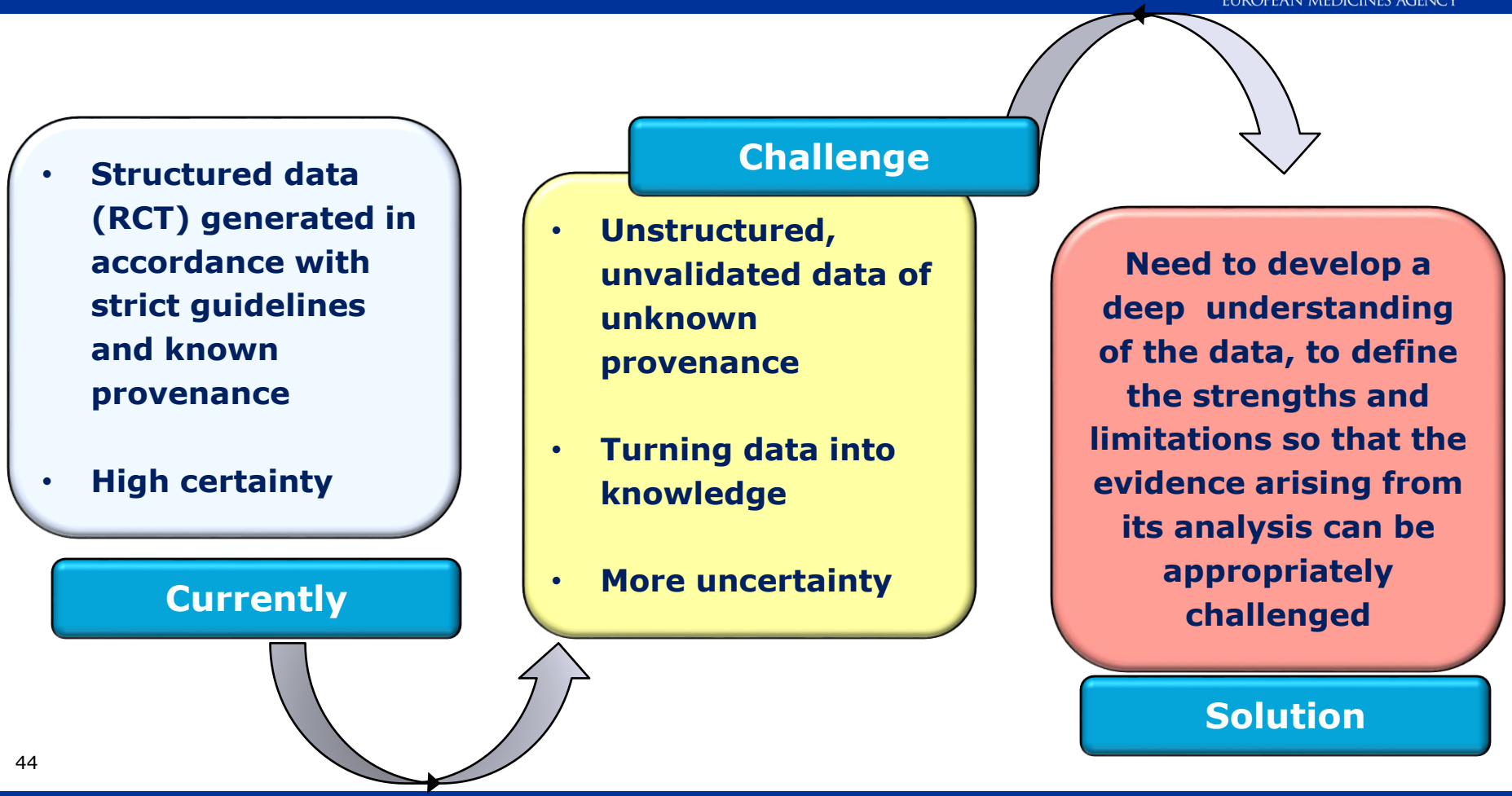
Reassurance is built from multiple studies reporting similar results.

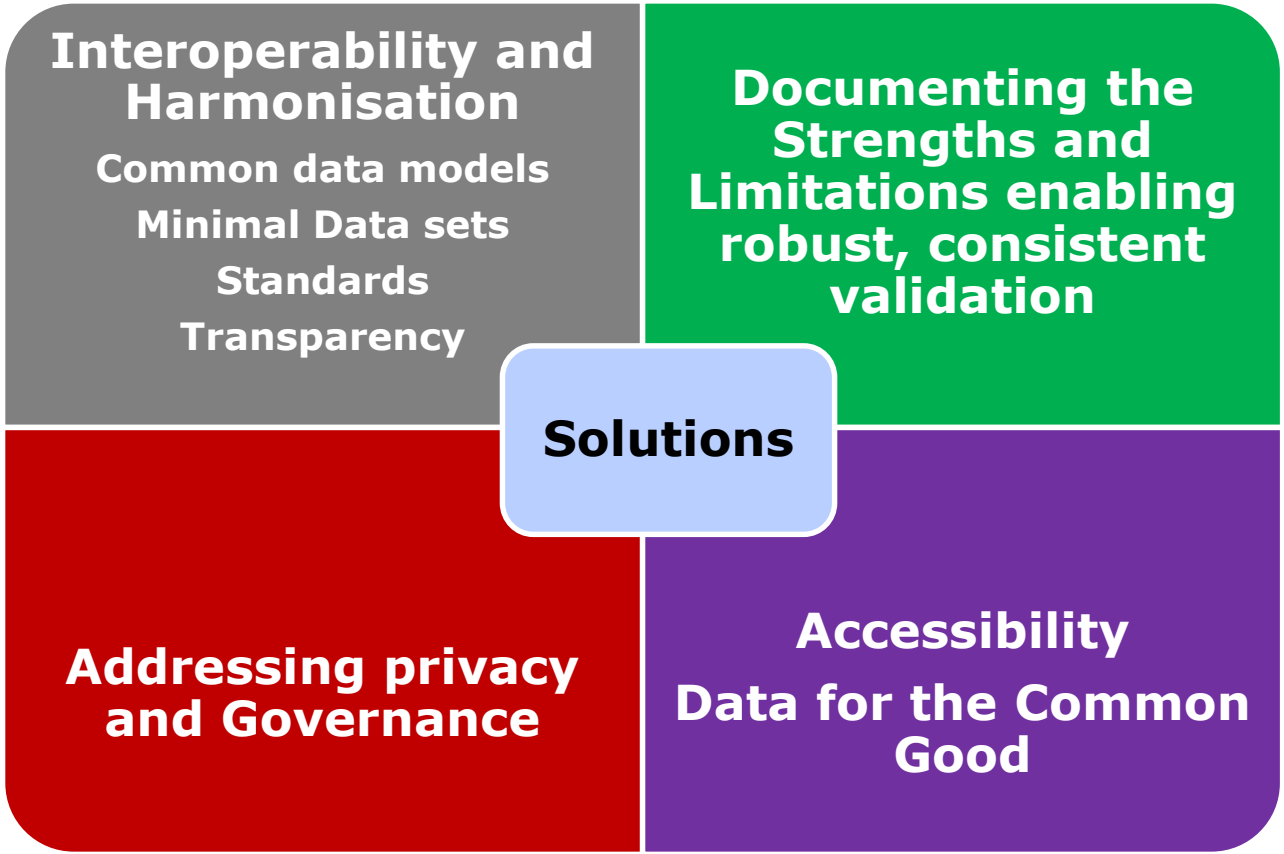
However this is at the expense of time.

Alves C, Penedones A, Mendes D, Marques F. A systematic review and meta-analysis of the association between system fluoroquinolones and retinal detachment. Acta Ophthalmol. 2016: 19: e251-e259

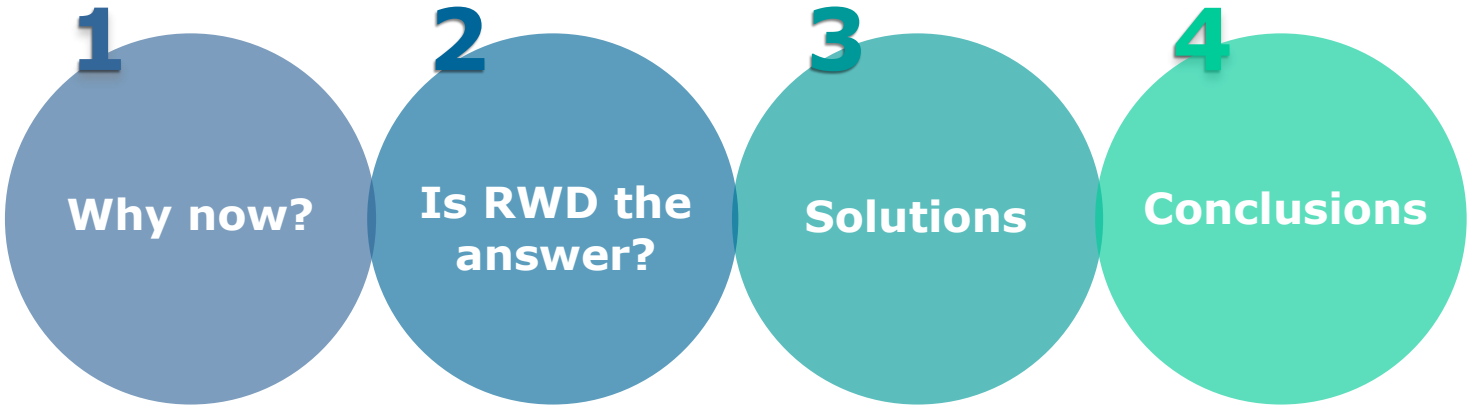
Objectives

Changes in the Traditional Regulatory Paradigm




Interoperability and Harmonisation
Common data models
Minimal Data sets
Standards
Transparency
Documenting the Strengths and Limitations enabling robust, consistent validation
Solutions
Addressing privacy and Governance
Accessibility
Data for the Common Good

Objectives



Conclusions

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- Randomised control trials remain the gold standard for unbiased estimates of efficacy.
- RWD does not necessarily equal RWE.
- Considerations around acceptability of RWD are not necessarily the same pre and post authorisation. Context of use, unmet need and alternative opportunities to capture data should be considered.
- The question should not be only about RCT vs RWD but on how the two may complement each other to provide additional insight – we need to consider the research question, the study design, the quality of the datasource and in particular its' ability to accurately record exposure and outcomes in the patient population of interest.
- Transparency in what drives the methodological choice will increase confidence and allow external verification

Thank you for your attention

Further information

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