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

1. Why now?
2. Is RWD the answer?
3. Solutions
4. Conclusions
Objectives

1. Why now?
An increasing number of medicines with genomic mechanism of action and/or genomic biomarkers enabling smaller, focused RCTs but creates other challenges.
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
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.
**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.
An increasing number of medicines with genomic mechanism and/or genomic biomarkers enabling smaller, focused RCTs but increasing uncertainty.

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

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<td>2014</td>
<td>2</td>
</tr>
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<td>2015</td>
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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?

- 78: Due date +/- 1 month
- 9: Early (1-6 months)
- 8: Early (6-12 months)
- 3: >1 year early
- 1: 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

Innovative medicines and personalised prescribing creates regulatory challenges.

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**
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.
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).

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

Innovative medicines and personalised prescribing creates regulatory challenges.

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

**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

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

Other exclusion criteria included comorbid conditions, cognitive impairment and polypharmacy.
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, 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 Bodagard, David Nathanson, Marcus Thuresson, Thomas Nyström, Anna Norhammar

**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

1. Why now?
2. Is RWD the answer?
Datasources

Electronic health records
Primary care data, hospital records

Patient and caregiver surveys

Patient Disease Registries

Prescription databases
Drug utilisation data sources

Claims data

Spontaneous ADRS

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

The future
- patient derived data (via smart phone or web based technologies), Patient reported outcomes
RWD is already in use routinely for regulatory decision making.

Predominantly for marketed products - safety monitoring and drug utilisation.
The Risk of Fractures Associated with Thiazolidinediones: A Self-controlled Case-Series Study

Ian J. Douglas¹*, Stephen J. Evans², Stuart Pocock², Liam Smeeth¹

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

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

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

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 Norrelund,¹ Henrik Toft Sørensen,¹ Lin Li,² Susan Jick²
But pharmacovigilance is not an exact science

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

Currently

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

Challenge

- Unstructured, unvalidated data of unknown provenance
- Turning data into knowledge
- More uncertainty
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
August 2010: “the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer”

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

Conflicting results creates Uncertainties

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

PROTECT
Antibiotics and the risk of acute liver injury
Joint development of Common protocol
Independent conduct in different databases

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

Pharmacoepidemiology and Drug Safety
2016;156-165. DOI: 10.1002/pds.3968
Sources of Variability in Multiple Database Studies

- Consistent direction of effect estimate but of varying magnitude
- Study design should be a conscious decision
• Stringency and accuracy of definition increased strength of association
• Less stringency led to more false positives
• Outcome needs to be carefully defined.
Sources of Variability in Multiple Database Studies

- Time window of exposure had substantial impact
- Careful definition of exposure window is essential
# The Challenge of Defining Dose

## Top 20 of 5561 descriptions of codeine product dose

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<thead>
<tr>
<th>doscode</th>
<th>Frequency</th>
<th>Description</th>
<th>Standard recoding</th>
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<td>2 FOUR TIMES A DAY WHEN REQUIRED</td>
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<td>0000114</td>
<td>138386</td>
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<td>8.00</td>
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- **Identical**: 6 is between 4 and 8. But how useful is this!
- **Uncodable**: 6 is between 4 and 8. But how useful is this!

25,911 dose descriptors overall in the THIN dataset.
Sources of Variability in Multiple Database Studies

- Study design
  - SCCS >30 days
  - SCCS 15-30 days
  - SCCS 7-14 days
  - SCCS - 0-7 days
  - CXO - 30 days
  - CXO - 14 days
  - CC - Definite
  - NCC - Definite/Probable
  - NCC - Definite
  - Cohort - Antibiotics Definite/Probable
  - Cohort - Antibiotics Definite
  - Cohort - Definite/Probable
  - Cohort - Definite

- Outcome

- Exposure

- Study population
  - BIFAP
  - CPRD
  - Clinformatics
  - Mondriaan-UPOD
  - CPRD-R

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

Relative Risk (Log Scale)
Databases vary in the lifestyle factors recorded and the quality of their measurement making comparisons difficult.
Prescribing of antidepressants **varies widely** between European countries despite **no evidence of difference in the prevalence** of affective disorders.
Sources of Variability in Multiple Database Studies

- **Study design**
  - SCCS >30 days
  - SCCS 15-30 days
  - SCCS 7-14 days
  - SCCS - 0-7 days

- **Outcome**
  - CXO - 30 days
  - CXO - 14 days
  - CC - Definite
  - NCC - Definite/Probable
  - NCC - Definite

- **Exposure**
  - Cohort - Antibiotics Definite/Probable
  - Cohort - Antibiotics Definite
  - Cohort - Definite/Probable
  - Cohort - Definite

- **Database**
  - BIFAP
  - CPRD
  - Clinformatics
  - Mondriaan-UPOD
  - CPRD-R

- **Study population**

- **Confounding adjustment**

- Accuracy and completeness data across different parameters is variable

- Systematic evaluation of strengths and limitations is essential
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,
Fluoroquinolones + Retinal Detachment

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Rate ratio and 95% CI</th>
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<tr>
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<td>Rate</td>
<td>Lower limit</td>
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<td>1.01</td>
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<td>Fife et al, 2014 (case-control_Optum)</td>
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<td>0.95</td>
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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.

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1. Why now?
2. Is RWD the answer?
3. Solutions?
Changes in the Traditional Regulatory Paradigm

Currently

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

- Unstructured, unvalidated data of unknown provenance
- Turning data into knowledge
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Need to develop a deep understanding of the data, to define the strengths and limitations so that the evidence arising from its analysis can be appropriately challenged

Solution
Interoperability and Harmonisation
Common data models
Minimal Data sets
Standards
Transparency

Documenting the Strengths and Limitations enabling robust, consistent validation

Addressing privacy and Governance

Solutions

Accessibility
Data for the Common Good
Objectives

1. Why now?
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Conclusions

• 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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