Realizing the potential of Real World Evidence

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IMS Health

Real World Evidence Workshop
The Academy of Medical Sciences, ABPI
Royal Academy of British Architects, London, September 17th, 2015
Stakeholders are split about the value of RWE

**Skeptic**

See RWE narrowly – supporting safety or mandatory submissions

**Evangelist**

See RWE as a broad lever to engage stakeholders and to help benefit-risk assessment
A paradigm change has just happened!

**Disease oriented care**
- EBM
- Clinical trials

**Patient oriented care**
- RWE
- Observational studies

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**Graphs showing interest over time**

**Clinical trial**
- Search term
- Evidence based medicine
- + Add term

**Observational study**
- Search term
- Real world evidence
- + Add term
Generating evidence from real world data

Data sources

Primary data collection

Consumer data

Social media

Claims databases

Test results, lab values, pathology results

Electronic medical and health records

Pharmacy data

Mortality, other registries

Hospital visits, service details

Meaningful questions

Fit for purpose data

Appropriate methods & analyses

REAL-WORLD EVIDENCE (RWE)
## Stakeholder requirements: Is there an overlap?

<table>
<thead>
<tr>
<th><strong>Regulatory</strong>*</th>
<th><strong>HTA</strong>**</th>
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<tbody>
<tr>
<td>Exposure</td>
<td>Burden of target disease (mortality, morbidity prevalence, incidence, DALYs, QALYs)</td>
</tr>
<tr>
<td>Epidemiology of the indication(s)</td>
<td>Conditions of use</td>
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<td>Prescribing conditions</td>
<td>Expected benefit of the technology</td>
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<td>Characteristics of patients who actually receive the drug</td>
<td>- On burden of disease</td>
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<td></td>
<td>- On management of disease</td>
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<td></td>
<td>- Economical</td>
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<tr>
<td>New safety concerns, known ones, risk factors</td>
<td>- Organisational</td>
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<td>- Social</td>
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<tr>
<td>Efficacy in real life / in specific populations</td>
<td>Confirmation of the expected benefit</td>
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<td>Effectiveness of risk minimization measures</td>
<td>Potential to cover unmet medical needs or to improve covered needs</td>
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<td>Signal detection</td>
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* European Medicines Agency (EMA)

** European Network of Health Technology Assessment Bodies (EUnetHTA)
<table>
<thead>
<tr>
<th>Research question, goals and design</th>
<th>Clinical trials</th>
<th>Real world studies</th>
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<tbody>
<tr>
<td></td>
<td>Predefined goals expressed in 3 sequential phases</td>
<td>Research questions still differ between regulatory and HTA bodies</td>
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<td></td>
<td>Predefined endpoints</td>
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<tr>
<th>Ethical considerations</th>
<th>Informed consent, IRB/IEC review</th>
<th>Different requirements for informed consent and IRB/IEC</th>
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<tr>
<th>Good practice</th>
<th>ICH GCP</th>
<th>EMA GVP, ISPE GPP, GRACE, ENCePP, ISPOR checklist for database studies, guidelines for database selection…</th>
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<tr>
<th>Obligation for Registration</th>
<th>Generally Yes</th>
<th>Generally No</th>
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<tr>
<th>Reporting</th>
<th>CONSORT statement</th>
<th>STROBE statement</th>
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RWD* supply is driven by the usefulness of electronic data and stakeholder ability for access for research purposes.

- **USEFUL data** has extensive coverage, illustrates the full patient journey and has clinical depth and quality.
- **ACCESSIBLE data** is available and transparent to all stakeholders.

Bubble size indicates total journal publication output.

* Real World Data
Increasing focus on RWE is associated with the greater supply of electronic patient-level data.

Cumulative publications; some of the research output is not related to medicines
Source: PubMed
The volume of « unused » data is massively growing.
RWD supply push may cause a seismic shift in the way we evaluate medicines.

**THE PAST**

- **RCT**
  - Controlled trials, manufacturer led
  - Few evaluators at launch, mostly regulators and large payers

- **Efficacy and Safety**
  - Initial view of benefit-risk

**THE PRESENT**

- **RCT and RWE**
  - Shift to secondary patient-level data across sources
  - Many groups over time including clinical and small payers

  - Almost everything
    - Insights on environment, outcomes, costs, comparative effectiveness
Data availability alone is insufficient; creating meaningful insight from data requires a framework.

Frameworks detail how decision-making includes RWE in the form of HTA, reimbursement process, clinical guideline development etc.
Drug evaluation is becoming progressively harmonised.

EMA is taking more space in the central evaluation of drugs.

- **2012**: ENCePP-HTA working group is launched
- **2013**: EMA releases Good Vigilance practice (GVP) and launches PRAC
- **2014**: EU Commission releases delegated act on post-authorisation studies
- **2015**: EUnetHTA releases position papers on Additional Evidence Generation And Core HTA pilot
- **2016**: EMA and EUnetHTA enhanced collaboration to pave the way for a coordinated benefit/risk evaluation process

Massoud Toussi (IMS Health), Realizing the Potential of Real World Evidence
The Academy of Medical Sciences - ABPI, London, 2015-09-17
A framework is being formed around the evaluation methods.

Rapid HTA assessment

Evidence synthesis and generation

Full HTA assessment

Data collection

ENCePP

PASS

Drug research & discovery

Clinical development

Marketing authorisation

Pharmacovigilance

Regulatory review

Health Technology Agencies

European Medicines Agency

Courtesy: Luis Prieto (EMA) with adaptation
We need a framework for data supply and governance.

- The best database is the one which is most fit-for-purpose.
- One potential solution could be considered as T-shaped framework
Conclusion

- Real world evidence (RWE) is a real trend.
  - It brings additional insights on the benefit-risk value of a drug as it is used in real life.
- There is need for harmonization and frameworks.
- European multi-stakeholder forums such as ENCePP can help bridging capacity and knowledge about how to address the requirements.
- There is need for harmonization on the supply capacity and governance of real world data, as well as the appreciation of its value.
Thank you!

Questions?
MHRA’s view on acceptability of real world evidence

Dr June Raine, Director of Vigilance and Risk Management
As UK’s regulatory authority, MHRA must…

• Assess changing risk benefit of medicines in clinical use

• Reach prompt decisions which take into account therapeutic context

• Implement proportionate risk minimising action

• Constantly seek to improve & strengthen methodologies
Knowledge of safety when medicine licensed
Pharmacovigilance cycle

- Better characterised risks of medicine
- Ongoing evaluation of benefit risk
- Monitor risk minimisation effectiveness
- Signal detection in real world use

Risk minimisation, communication, maintain favourable benefit risk
Real world evidence used by MHRA

Spontaneous reports of suspected adverse reactions
Longitudinal health record data – Clinical Practice Research Datalink
Prescription and sales data – IMS
Hospital episode statistics
Registries – prospective cohorts
Social media (under evaluation)
Yellow Card Scheme has established role in detecting safety signals esp rare and unusual

Widely acknowledged as an exemplar among surveillance schemes - but major limitations

– Differing levels of under-reporting and incomplete data
– Lack of exposure data
– Can be too easy to dismiss confounded signals
Detecting safety signals

Routine weekly analysis using statistical tools

Scientific review of data ‘signals’

Evaluation at multidisciplinary meeting

Detailed assessment in context of other evidence including exposure
IMI PROTECT project – multi-national public-private consortium carried out program of research to address limitations of current methods in pharmacoepidemiology and pharmacovigilance

Studies most relevant for statistical signal detection included:
1. Performance evaluation of different signal detection disproportionality algorithms
2. Impact investigation of stratified and subgroup analyses

Key findings:
• All disproportionality methods can achieve similar overall performance by choice of algorithm
• Subgroup analyses consistently perform better than stratified analyses

Seabroke S et al. Subgroup analyses outperform stratification for statistical signal detection in pharmacovigilance. In preparation
Populations with high(er) baseline risks

Examples of high baseline risk/low RR:
• Antidiabetics and cardiovascular risk
• Obesity drugs and psychiatric events
• MABs and PML
• Antidepressants and suicide risk

Ref Leufkens, BL 2012
Electronic healthcare record data

Electronic healthcare record data becoming increasing rich & available, increased computing capabilities

Used for drug utilisation studies, and formal pharmacoepidemiological studies to evaluate signals

Key Challenge: To optimise the use of electronic healthcare record data to routinely support and strengthen pharmacovigilance providing robust data on risks and benefits as quickly as possible
Proactive surveillance

In situation of rapid population exposure conduct observed versus expected analyses eg vaccine campaign
Yellow Card reports in context of age and gender specific background rates of events of interest
Assumptions based on different levels of under-reporting
Example: Observed vs expected Rotavirus and Intussusception

MaxSPRT for Intussusception with Rotarix - 1 week risk window (first vaccination only, assuming RR=6.8 based on Australian data)
Pertussis vaccine in pregnancy

Over 17,000 vaccinated women identified in 6m
6,000 with pregnancy outcome

12 stillbirths (~1/500 deliveries) RR = 0.85
(95% CI 0.45-1.62)

No other identified safety concerns
Strengthening signal assessment

- Chronographs to look at temporal pattern of event compared to exposure
- Strengthen the signal
- Software initially designed at Uppsala Monitoring Centre and further developed by:
  Ref: Noren et al. Data Min Knowl Disc 2010; 20: 361-387
Longitudinal Drug Exposure software

- Drug exposure over time and description of treated population
- Frequency of events in population
- Frequency of drug-event combination

Put signals into context
Registries

Specific medicines and classes of medicines

Depend on healthcare professionals and patients’ support

Regulatory utility (data at right time) and long term sustainability can be an issue
Signal analysis in social media?

Case recognition?

Signal detection?

Signal strengthening?

Duplicate detection?
WEB-RADR consortium conducting scientific investigation of utility of data from social media for signal detection

Will social media supplement evidence from spontaneous data?
Conclusions

• MHRA uses real world data to monitor changing benefit risk of medicines in clinical use using range of data sources
• Limitations of real world data in terms of establishing causal associations are appreciated – approaches depend on use of multiple sources to characterise and quantify risk
• Current opportunities relate to new data sources, methodologies and IT capabilities to use large datasets and to move to real-time monitoring
• Future challenges will arise from early access and adaptive pathways especially for medicines used in small populations
• Goal - more robust data sooner to better protect public health
European Medicine Agency’s perspectives on the acceptability of real world evidence

Workshop on Real World evidence

London, 17 September 2015

Presented by Xavier Kurz
Head of Monitoring and Incident Management, Pharmacovigilance Department
Disclaimer

The views expressed in this poster are the personal views of the authors 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.
In this presentation

• Concept of **information from clinical use** in regulatory decision making

• Use and acceptability of real-world data for
  - Safety
  - Efficacy: Results of an expert workshop on methods for efficacy studies in the everyday practice, 24-25 October 2013

• Conclusions
Information from clinical use in context

• EMA seeks to optimise the benefit/risk profile of medicines
• This involves many complementary initiatives to support decisions on benefit/risk
• Bottom line is ensuring we are effective in doing this and we are doing it as efficiently as possible
Decision cycle

Information from clinical use
Information from clinical use to support regulatory decision making

- The EU network manages or has direct or indirect access to potentially highly relevant data, information, or knowledge e.g.:
  - Safety data from clinical trials (SUSARs in EudraVigilance)
  - Suspected adverse reaction reports from marketed use (ADRs in EudraVigilance)
  - Published literature
  - Electronic healthcare records (e.g. EMA THIN/IMS, MS e.g. BIFAP, CPRD)
  - Access to networks that have data, and methodological expertise e.g. the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)
  - Patient registries
  - Existing authorisation applications including, potentially, patient level data
  - Previous authorisation assessments / Committees decisions

Regulatory science projects
Information from clinical use and knowledge management to support regulatory decision making

- The EU network manages or has direct or indirect access to potentially highly relevant data, information, or knowledge e.g.:
  - Safety data from clinical trials (SUSARs in EudraVigilance)
  - Suspected adverse reaction reports from marketed use (ADRs in EudraVigilance)
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  - Patient registries
  - Existing authorisation applications including, potentially, patient level data
  - Previous authorisation assessments / Committees decisions
  - Regulatory science projects
Data, information and knowledge: complementary strategies

EU Regulatory network studies using real-world data (in-house and commissioned)
ENCePP

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [www.encepp.eu]

- 152 Centres in 19 countries
- ENCePP Resources database
- EU Post-authorisation Studies (PAS) register
- The aim is to improve the quality, ease, speed, transparency and reliability of post-authorisation benefit:risk evidence feeding into regulatory decision making (PRAC/CHMP)

- Source of (pharmaco)epidemiology expertise for Ad-hoc expert groups.
- Provision of data in response to an invitation from EMA.
- Development of guidance
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<th>Status</th>
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<th>Last Updated</th>
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<td>Finalised</td>
<td>Validation of a US Health Care Claims Database for the Study of Cardiovascular</td>
<td>Dr Brandon Suehs</td>
<td>31/08/2015</td>
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<td>and Neoplasm Events Among Users of Treatments for Overactive Bladder</td>
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<td>Estimation of Background Incidence Rates of Guillain-Barré Syndrome in Germany</td>
<td>Dr Tania Schink</td>
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<td>Pharmacoepidemiological Safety Study of Neuroleptics and Antidepressants in the</td>
<td>Dr Tania Schink</td>
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<td>Risk of Venous Thromboembolism and All-Cause Mortality in Cancer Patients Treated</td>
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<td>with Epoetins either with or without Transfusions versus Cancer Patients Treated</td>
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<td>Effectiveness of prescribing similar vs dissimilar devices for COPD management</td>
<td>Dr Arjun Jain</td>
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<td>State of the Union: Current asthma morbidity in the UK</td>
<td>Dr Arjun Jain</td>
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<td>Observational Influenza vaccine active surveillance study: A Phase IV Prospective</td>
<td>Dr James Larcombe</td>
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<td>A Non-Interventional Study of Bosutinib In Patients With Previously Treated</td>
<td>Dr Jorge Cortes</td>
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<td>Dr Maryse Lapeyre-</td>
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<td>Professor Erland</td>
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<td>treatment with Ploglitzone or placebo In addition to existing antidiabetic</td>
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<td>Cohort Study of Ploglitzone and Cancer Incidence in Patients</td>
<td>Dr Assiamira Ferrara</td>
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Contribution of real-world data in decision making - safety

- Timely information about drug utilisation, including:
  - Dose, duration, co-medication, channelling
  - Switch between drugs
  - Determinants: age, gender, co-morbidity, others
  - Incident and prevalent drug use over time – impact of regulatory action on use of medicines

- Comparative data
  - Comparative safety studies within drug classes
  - Comparisons between indications and population groups
  - Others
What is needed from real-world data - safety

- **Data on usage**, while e.g. sales data has been used in the past for rough estimates of use, number of users is required for valid estimates.

- **Relevant data**, capturing drug use of interest, clinical outcomes, POR (if required), confounders, effect modifiers

- **Sufficient sample**, hundreds of thousands of patients; for drugs used to treat rare diseases: millions

- **Longitudinal data**, Data from cross sectional sources might be sufficient to determine prevalence, but for incidence longitudinal data are required.
Workshop with experts on methods for efficacy studies in the everyday practice  24-25 October 2013

Objectives

• to understand strengths and weaknesses of different design options to study efficacy in the conditions of the everyday medical practice
• to issue recommendations on best use of methods to account for bias and confounding
• to identify needs for improvement

Five topics discussed

• Pragmatic trials
• Observational studies
• Registries
• Use of electronic health records for pragmatic trials
• Methods to control for confounding

Pragmatic trials

• Attention to be given to external validity of results to real-world setting (need for consent has major impact on population enrolled)

• Lack of confirmatory diagnosis tests may be a limitation

• Different design options are not equal, e.g. for rare outcomes

• Quality metrics should be used and reported, i.e. measures quantifying to what extent and which control mechanisms from Phase III RCTs were relaxed

• Adherence to CONSORT statement
Observational studies

• Useful when efficacy has been demonstrated

• Aim is to study effect modifiers, e.g. drug doses, treatment schedules, patient sub-groups, factors related to country or health care system

• If historical data exist, observational studies may be useful when a rapid answer to an efficacy question is needed or when a comparator drug used as reference changes over time

• Confidence in reliability of results is increased when:
  • Exposures and outcomes measured objectively and with high specificity
  • Same outcomes as those used to prove efficacy in RCTs
  • Ability to measure relevant confounding factors and effect modifiers
  • Appropriateness of statistical methods
  • Documented use of strict standards of quality control.
Registries

• Existing patient registries can be used when data on exposure, outcomes and confounders are available, or can be collected, or if linkage to external data source is possible

• Patient registries may be used as source of subjects for RCTs on marketed medicines where infrastructure allows it, follow-up is adequate and there is interest in non-randomised comparator group

• Registries appropriate when events that would not come to the attention of traditional care providers or health care systems are collected, for patient-reported outcomes, rare conditions

• Limitations are lack of specificity in disease or exposure classification, inadequate follow-up, lack of reasonably unbiased comparators

• Data quality and representativeness/coverage are key to interpretation of results.
Conclusions

• Real-world data on clinical use of medicines are fully integrated in regulatory decision-making

• EU regulatory network’s strategy includes strengthening its capability to adequately assess and monitor the safety, efficacy and quality of authorised medicines; this requires:
  • access to real-world databases that have the potential to pick-up and analyse safety issues and efficacy in everyday medical practice and sub-populations
  • collaboration with academia, health care professionals and patients’ associations
  • identification/development and testing of methodologies for unbiased analyses of safety and efficacy in medical practice
    e.g. IMI projects: PROTECT, GetReal, ADVANCE, EHR4CR, ADAPT-SMART,…

• Increasing availability of electronic health records provides new opportunities

• Involvement of patient registries and other data sources to be further developed.
Thank you for your attention

Further information

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Regulatory Applications of Real World Evidence: US Food & Drug Administration:

Jonathan P Jarow, MD
Office of Medical Policy
CDER
Evidence from Clinical Experience

• Definition
  – Evidence obtained from observational studies or clinical experience
  – Patient registry’s, electronic health records, claims data

• Uses
  – Regulatory
    • Safety & Efficacy
  – Healthcare economic information
  – Research
FDA Regulatory Standards: Substantial Evidence

- Efficacy versus safety
- Drugs versus devices
Sentinel Partner Organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners
Sentinel

• Launched in 2008 (FDAAA)

• Improve FDA’s capability to rapidly identify and investigate safety issues in **near real time**
  - Monitor newly approved drugs
  - Evaluate post-market safety issues for drugs that have been on the market (e.g., new potential safety issue, known issue that re-emerges or changes character)

• Complement FDA’s existing postmarket safety surveillance capabilities
Sentinel

• > 30 Collaborating institutions (18 Data Partners)
• Common Data Model & Distributed data network
• Secure querying behind data partners’ firewall
• Access to quality checked, electronic healthcare data of > 178 million patients
Use of Registries for Rare Diseases

• Lumizyme for Pompe disease – survival data from an international Pompe disease registry in patients with infantile-onset disease

• Carbaglu for N-acetylglutamate synthase deficiency – data on plasma ammonia level reductions in a case series

• Cholbam for bile acid synthesis disorders – data on growth, survival, and reduction in laboratory parameters of cholestasis in a case series

• Glucarpidase for MTX toxicity - data on a ~20 patient subset within what was essentially a treatment protocol at NIH

• Metreleptin for Leptin deficiency/lipodystrophy - case series out of NIH, similar to glucarpidase, was essentially a treatment protocol
Vaccines and Real World Evidence

• High-dose influenza vaccine versus standard dose
  – Retrospective cohort study of Medicare claims
  – High-dose: 929,730
  – Standard dose: 1,615,545

• Rabies vaccine dose schedule
  – Standard five dose versus four dose used during drug shortage
  – Change in CDC recommendations
CURE-NTD
(Collaborative Use Repurposing Engine)

• Repurposing of drugs for neglected tropical diseases
• Website/mobile app
• Global reporting tool for cases
• Searchable curated database
• Fuel drug development for neglected tropical diseases
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<td>Leprosy</td>
<td>3 Thalidomide, Dapsone, Clofazamine</td>
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<td>Tuberculosis (TB)</td>
<td>11 Sirturo, Isoniazid, Rifampin, Ethambutol, Pyrazinamide, Rifapentine, Rifabutin, Capreomycin, Para-aminoosalicyclic acid (PAS), Cycloserine, Streptomycin</td>
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37 FDA approved drugs/combinations for HIV since 1987
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</tbody>
</table>
National Database

• FDA: Sentinel (claims)
• CDC: Vaccine safety database
• CMS: claims
• DoD: claims and medical records
• VA: claims and medical records
• PCORI: electronic medical records
Future

- Limited role in approvals of new molecular entities
- Potential role in supplements
- Safety surveillance
- Health care economic information
- Incorporation of real world evidence in cluster-randomized large practical trials
Health Technology Assessment and Real world evidence

Professor Sarah Garner
Associate Director NICE
Science Policy & Research
sarah.garner@nice.org.uk
Find guidance

Choose a category to find guidance in your area:

- Conditions and diseases
- Health protection
- Lifestyle and wellbeing
- Population groups
- Service delivery, organisation and staffing
- Settings

NICE guidance

Lists of NICE guidance, including published guidance, in development and consultations

- All NICE guidelines
  - Clinical guidelines
  - Public health guidelines
  - Social care guidelines
  - Safe staffing guidelines
  - Medicines practice guidelines
- Quality standards
  - Technology appraisal guidance
  - Interventional procedures guidance
  - Medical technologies guidance
  - Diagnostics guidance
  - Highly specialised technologies guidance
This is fine, I can see all the evidence I need from here.
Efficacy vs Effectiveness

- Patient benefit and harm in experimental and closely monitored research studies, normally RCTs.
- Design minimises bias - high internal validity
- Generalisability questionable
  - restricted entry criteria
  - unrepresentative settings

- Patient benefit and harm when the technology is actually applied in everyday practice.
  - pragmatic clinical trials
  - observational studies
  - synthesis

- ISPOR: “evidence used for decision-making that is not collected in conventional randomized controlled trials (RCTs)”

- “Dirty” - a lot of variability and biases
Guide to the methods of technology appraisal 2013

3.3 Types of evidence

Non-randomised and non-controlled evidence

3.3.4 The problems of confounding, lack of blinding, incomplete follow-up and lack of a clear denominator and end point occur more commonly in non-randomised studies and non-controlled trials than in RCTs.

3.3.5 Observational (or epidemiological) studies do not apply an intervention, but instead compare outcomes for people who use the technology under appraisal with outcomes for people who do not use the technology. These studies may be biased in that the people who use the technology may fundamentally differ in their risk of the outcome than the people who do not use the technology. Some observational studies lack a control group, and include only people who receive the technology.

3.3.6 Inferences will necessarily be more circumspect about relative treatment effects drawn from studies without randomisation or control than those from RCTs. The potential biases of observational studies should be identified, and ideally quantified and adjusted for. When possible, more than 1 independent source of such evidence should be examined to gain some insight into the validity of any conclusions.

3.3.7 Evidence from sources other than RCTs is also often used for parameters such as the valuation of health effects over time into QALYs, and for costs. Study quality can vary, and so systematic review methods, critical appraisal and sensitivity analyses are as important for review of these data as they are for reviews of data on relative treatment effects from RCTs.
# Review of HTA outputs

## Recent NICE appraisals

<table>
<thead>
<tr>
<th>TA</th>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA 232</td>
<td>Retigabine for the adjunctive treatment of partial onset seizures in epilepsy.</td>
<td>Clinical trials mandated forced (protocol-driven) titration rather than titration tailored to individual patient as is seen in practice.</td>
</tr>
<tr>
<td>TA278</td>
<td>Omalizumab for treating severe persistent allergic asthma (review of TA 133 and 201).</td>
<td>Observational data used for extrapolation of treatment effect and for HRQoL in children amongst other things.</td>
</tr>
<tr>
<td>TA279</td>
<td>Vertebral fractures – Vertebroplasty and kyphoplasty</td>
<td>Observational data used by committee to accept mortality benefit (however committee could not use the data to quantify it).</td>
</tr>
<tr>
<td>TA283</td>
<td>Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion</td>
<td>Observational data used by committee to assess safety compared with unlicensed bevacizumab, however committee stopped short of using it for cost-effectiveness analysis.</td>
</tr>
</tbody>
</table>
## Review of HTA outputs: NICE

### Use of non-RCT data for estimating clinical efficacy in modelling

<table>
<thead>
<tr>
<th>TA 151</th>
<th>Diabetes – Insulin pumps</th>
<th>Clinical efficacy from a registry – Insulin Pumps Clinical database - much larger, of longer duration and more representative of people likely to be considered for CSII therapy in routine clinical practice than the populations in the RCTs available</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA 165</td>
<td>Organ preservation (renal) - machine perfusion and static storage</td>
<td>Prospective cohort study and multi-national registry study used for efficacy in model</td>
</tr>
<tr>
<td>TA 166</td>
<td>Hearing impairment - cochlear implants</td>
<td>Baseline risk of operative mortality in model, other parameters in modelling as judged most appropriate source</td>
</tr>
<tr>
<td>TA 185</td>
<td>Soft tissue sarcoma – trabectedin</td>
<td>Three uncontrolled phase II trials of trabectedin</td>
</tr>
<tr>
<td>TA 188</td>
<td>Human growth hormone (somatropin) for the treatment of growth failure in children (review)</td>
<td>Kabi International Growth (KIGS) observational database</td>
</tr>
<tr>
<td>TA 202</td>
<td>Chronic lymphocytic leukaemia – ofatumumab</td>
<td>NO RCT- conditional license</td>
</tr>
<tr>
<td>TA 209</td>
<td>Gastrointestinal stromal tumours (unresectable/metastatic) – imatinib</td>
<td>One non-randomised retrospective cohort study</td>
</tr>
<tr>
<td>TA 241</td>
<td>Leukaemia (chronic myeloid) - dasatinib, nilotinib, imatinib (intolerant, resistant)</td>
<td>Twelve studies were observational (seven of dasatinib, four of nilotinib and one retrospective study of both) three single-arm studies of high-dose imatinib – available RCTs were of poor quality</td>
</tr>
</tbody>
</table>
# Review of HTA outputs: NICE

## Appraisals using non-RCT data for some parameters in model

<table>
<thead>
<tr>
<th>TA</th>
<th>Condition</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>167</td>
<td>Abdominal aortic aneurysm - endovascular stent-grafts</td>
<td>Large registries of relevance to UK practice - baseline risk of operative mortality in model, other parameters in modelling as judged most appropriate source</td>
</tr>
</tbody>
</table>

## Appraisals using non-RCT data for longer term effectiveness

| TA  | Condition                      | \n|-----|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 177 | Eczema (chronic) – alitretinoin |                                                                                                                                          |
| 211 | Constipation (women) – prucalopride |                                                                                                                                          |
| 221 | Thrombocytopenic purpura – romiplostim |                                                                                                                                          |
| 247 | Rheumatoid arthritis - tocilizumab (rapid review TA198) |                                                                                                                                          |
| 293 | Thrombocytopenic purpura – eltrombopag (review) |                                                                                                                                          |

## Other uses of non-RCT data in appraisal

<table>
<thead>
<tr>
<th>TA</th>
<th>Condition</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>238</td>
<td>Arthritis (juvenile idiopathic, systemic) – tocilizumab</td>
<td>observational study of 146 patients - adjustment factor - difference in the proportion of responders between the total population with JIA and the subpopulation with systemic JIA. Used to correct for ACR response rates in the indirect comparison</td>
</tr>
</tbody>
</table>
Decision

- Clinical Effectiveness
- Cost Effectiveness
- Stakeholder Comments
- Uncertainty
- Scientific Value Judgments
- Legislation
- Equality
- Diversity
- Human Rights
- Social Value Judgments
- Patient Experts
- Clinical Experts
Current HTA decision framework

- Regulatory decision → HTA decision

  - Yes → NHS pays
  - No → Promising but Research needed
    - What does happen???
    - What should happen???
  - Promising but Research needed → NHS doesn’t (have to) pay
    - Commercial sponsor may or may not decide to do research
The world is changing…

- Health informatics capability and infrastructure
- Personalized medicine
- New types of targeted drugs and technologies
- Rising cost of research and budgetary pressures
- Comparative effectiveness agenda in the US
- EMA Post Authorisation Efficacy Legislation
  - [PAES] May be required for Centrally/nationally authorised products either:
    - At the time of granting the marketing authorisation concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed
    - After granting the marketing authorisation: the understanding of the disease or the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly
- Flexible regulatory options
- Medicines Adaptive Pathways to Patients (MAPPS)
Figure 1: Experimental and nonexperimental study types and methods

Experimental

- Pragmatic Clinical Trials (PCTs)
- Cluster Randomized Controlled Trials
- Crossover Designs
- Delayed-Start Designs
- N of 1 Randomized Controlled Trials

Nonexperimental

- Cohort Studies
- Case-Control Studies

Study Type

Methods

- New-User Designs
- Restriction
- Instrumental Variable Methods
- Subgroup Analysis
- Propensity Scores
- Sensitivity Analyses
- External Information

Adaptive Designs and Bayesian Methods
Potential uses of RWE at NICE

• **Research the effectiveness of interventions or practice** in real-world (UK) settings (e.g. through monitoring outcomes or proxy outcomes). This could be used to inform the modelling of clinical and/or cost effectiveness as part of guidance production. Real-world data can also help to resolve uncertainties that have been identified in existing NICE guidance.

• **Audit the implementation of guidance.** For example, to assess the equity of implementation across different groups (including socioeconomic, geographic, demographic and groups differentiated by different diseases/health conditions); this may also form part of performance monitoring systems.

• **Provide information on resource use** and evaluate the potential impact of guidance.

• **Provide epidemiologic information.** For example prevalence/incidence of diseases, natural history, co-morbidities and information on current practice.
RWE Activities at NICE

1. IMI GetReal- co lead of the policy workpackage
2. MRC highlight notice on methodology
3. Real world data steering group
   – Evaluation of real world data types and sources
   – CPRD proof of concept
   – Co-ordination of data requests
4. Observational data unit (Commissioning through Evaluation)
5. Interventional procedures/MTEP- registry
6. IMI Adapt Smart- co-lead Evidence Generation through the life-cycle
7. Strategy to be produced in late 2015
RWE challenges

- Culture change
- Terminology (RWD ≠ observational ≠ big data)
- Methods
- How to define best practice
  - Critical appraisal tools
- Understanding of potential impact
- Skill development and capacity
- Concerns over confidentiality
- Research or care?
Hierarchies of evidence should be replaced by accepting—indeed embracing—a diversity of approaches.

This is not a plea to abandon RCTs and replace them with observational studies. Nor is it a claim that the bayesian approaches to the design and analysis of experimental and non-experimental data should supplant all other statistical methods.

Rather, it is a plea to investigators to continue to develop and improve their methods; to decision makers to avoid adopting entrenched positions about the nature of evidence; and for both to accept that the interpretation of evidence requires judgment.
Real World Evidence: a real opportunity if ... 

Dr Virginia Acha, Executive Director, Research, Medical & Innovation
A real opportunity if...

- We recognise the potential of RWE to change our paradigm of treatment.
- Our understanding of benefit and risk can advance to realise this change in paradigm.
- Both the infrastructure and skills are in place to ensure real-time, real world evidence.
- We bring people with us.
From rational drug design to rational healthcare design

• Same underlying driver
  – How we translate **new and better data** into greater knowledge to address residual uncertainty and gaps in biological science

• More effective search strategies
  – Instead of random, trial & error, high throughput approaches
  – Accelerating accumulated evidence over time

• Advances in analytical technique and assessment
  – Using data to better anticipate and define targets through improved analytics
  – Rise of **biostatistics** - demand for these skills is outstripping supply [*ABPI Skills Survey Autumn 2015*]
Can we change the paradigm of treatment?

When do we know the value of a medicine?

At first approval / authorisation?

Following a Health Technology Assessment?

After use by patients in a number of settings?

After decades of use?

- Evidence on the **Benefit : Risk** of a medicine accumulated
  - *How well is this evidence fed back (to whom?) Shared? Correlated?*

- When does this evidence shape treatment choices and value assessment?
  - *Scientific literature, peer guidance*
  - *Pharmacovigilance*

- **Hierarchy of evidence?** What drives value of a medicine over time?

Bringing medicines to *life*
A question of evidence – hierarchy or combination?

• Previously held view of a Hierarchy of Evidence
  – ABPI 2011 Guide already noted the change in view that RWE has a place alongside RCT data to meet “the first and second translational gaps”

• Different strengths and weaknesses of both RCT evidence and RWE which can complement
  – Internal validity vs. External validity
  – RWE can address some of the challenges of RCT evidence (cost, sharper questions (search strategies), ethical challenges, slow translation to practice)

What can RWE deliver for medicines?

• Many menus of how RWE can help

Examples of some of the opportunities presented by Real World Evidence

- Early Stage R&D
  - Identify/Demonstrate Unmet Need
    • Develop disease understanding
    • Explore epidemiology
    • Identify patient-reported treatment shortfalls
  - Explore Root Causes and/or Stratify Disease
    • Analyse role of genomics on disease onset and development
    • Understand patient behaviour
  - Manage R&D
    • Support progression decision-making and development asset prioritisation
    • Build R&D collaborations with academia and providers

- Clinical Trials
  - Cohort Selection
    • Recruit actual trial participants
    • Align study protocol to current real world clinical pathways
    • Ensure study represents real world cohorts and treatment practices
  - Trial Management
    • Facilitate new trial designs (e.g. adaptive trials, pragmatic trials)
    • Collect outcome data from new sources
  - Economic Value
    • Undertake positioning & economic value analysis (product/class)
    • Track economic value
    • Monitor adverse events
  - Precision Targeting
    • Improve accuracy of market sizing
    • Define target cohort
    • Reinforce post-reg market access

- Commercial
  - Integrated Solution
    • Design combined offerings (e.g. Rx + device)
    • Design integrated offerings (e.g. Rx + device + pathway change)
  - New Commercial Models (e.g. Value Contracting)
    • Support contract design and contract management

Monitor Deloitte, 2015 Real World Evidence: Enabling the life sciences industry to transform patient care

IMS Consulting, 2011 Real World Evidence: transforming the industry into the ‘prove it works’ era

Taking an active role in RWE provides potential opportunities for manufacturers to optimize portfolio assets, leverage internal efficiencies, and create a platform to build stronger stakeholder relationships.
How do we deliver RWE?

- Part of a wider programme of health data delivery

ABPI and Deloitte, 2014 Big Data Roadmap
Requirements

- Clear understanding of decision makers’ evidence needs
  - Coordination and requirements between authorities – avoiding duplication
- Supportive legal and healthcare architecture
  - Consent and data privacy
  - Access
- Expert knowledge: biostatistics, machine learning, semantics and algorithm development
  - Skills, training at various levels (degree, CPD, etc)
- Right infrastructure – analytical and computing resources
- Collaboration: IMI initiatives for approaches and method
  - ADAPT-SMART, GETReal, Big Data for Better Outcomes
  - Web-RADR
We need to bring people with us

• Trust is the most critical part of the puzzle
  – Across all stakeholders
• Building understanding and awareness needs collaborative action
  – Debunking myths, case studies
• At all ages
  – Consider the kids!
• A broader understanding of RWE
  – Including personal health management

NHS England’s controversial Care.data programme on hold again
ABPI related publications:

Reengineering Medicines Development

ABPI Big Data Road Map

ABPI eHealth and Health Information – Requirements Update

Guidance: Demonstrating Value with Real World Data

The Vision for Real World Data
IMI GetReal: Stakeholder engagement for exploring real-world solutions in effectiveness research and decision making

Pall Jonsson
Senior Scientific Adviser,
Science Policy and Research, NICE
Three-year project

“... to better understand how real-world data and analytical techniques can be used to improve the relevance of knowledge generated during development, e.g., through innovation in clinical trial design”
WP2
Understanding the efficacy-effectiveness gap
simulation of trials to improve design

WP3
Overcoming practical barriers to the design of real-world studies

WP4
Identifying best practice and creating new methods for evidence synthesis and predictive modelling

WP1
Framework Processes Policies
Snapshot of WP1 Activities

Mapping the “landscape”
• Glossary
• Identify relevant policies and perspectives

Simulation work
• Simulation of alternative study designs, and impact on decision making
  - Industry
  - Regulators
  - HTA agencies
  - Payers
  - Patients
  - ...

Fostering engagement and collaboration
• Identification of related initiatives
• Engagement with stakeholders

Supporting policy development
• develop and pilot a framework for assessing options for the inclusion of “real-world” study designs in development strategies
WP1 Case Studies: Redesigning the Development Pathway

**Information Sources**
- Publicly available documents (reg, HTA)
- Stakeholder interviews
- Company commentaries & presentations
- Original company source documents

**Workshop 1 Outputs**
- Discussion summary / minutes
- Key scientific questions (sources of bias and uncertainty in RE)
- Alternative development design options using real-world evidence

**Workshop 2 Outputs**
- Discussion summary / minutes
- Stakeholder insight & reactions to potential options
- Scenario summary
- Contribute to decision framework
- Publications

**Summaries**
- Company Governance
GetReal Case Studies: Building a Supportive Environment

• A unique pan-stakeholder workshop environment with a focus on the use of RWE in medicine development and the subsequent assessment

• Provides a ‘safe harbour’ environment
  – Stakeholder engagement
  – Removing silos

• Identifying and testing acceptability of robust RWE solutions
  – Alternative evidence plans
  – Alternative evidence synthesis
  – Testing acceptability by stakeholders
  – Exploring usability for decision making
WP1 Case Studies

Highlighting aspects of real-world data in pharmaceutical R&D and evidence synthesis

- Non-small cell lung cancer
- Rheumatoid Arthritis
- Multiple Sclerosis
- Metastatic melanoma
- COPD
Early pragmatic clinical trials (PCTs) for measuring effectiveness of COPD therapies

Using the Salford Lung Study as an example, the case study addresses key questions relating to PCTs:

- When and why are early PCTs useful?
- What are the barriers to stakeholder acceptance of early PCTs as pivotal studies in medicine development?
- What are the barriers to acceptability of PCTs?
“real-world” studies in metastatic melanoma

The case study examines the uses of registry data to support efficacy data from RCTs. In particular it will explore if and how:

- registry data can improve understanding of generalisability of trial results outside the trial setting,
- real-world data can be incorporated with clinical trial data into an overall measurement of effectiveness. The acceptability of statistical methodologies will be tested.
- innovative ‘real-world’ trial designs can help address issues patients face when participating in trials.
Towards a shared framework

...based on collaboration between stakeholders

A set of guiding principles which lay out what success looks like

Linking real-world data and methods to decision-making (R&D, regulatory, HTA)

Incorporating stakeholders’ views on tolerance/acceptability

Guidance which supports R&D planning, strategy and scientific exchange

Adaptive to changes in landscape and built with broader engagement
Related IMI initiatives

Data infrastructure in clinical research

Real-world data in drug development

Adaptive pathways MAPPS