Real world evidence

Summary of a joint meeting held on 17 September 2015 by the Academy of Medical Sciences and the Association of the British Pharmaceutical Industry

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The Academy's FORUM was established in 2003 to catalyse connections across industry, academia and the NHS. Since then, a range of FORUM activities and events have brought together researchers, research funders and research users from across academia, industry, government, and the charity, healthcare and regulatory sectors. The FORUM is a major component of the Academy's work to deliver the strategic objective of 'linking academia, industry and the NHS' and its success relies on supporter organisations who make an annual donation. We are grateful for the support provided by the members and are keen to encourage more organisations to take part. If you would like information on becoming a member please contact FORUM@acmedsci.ac.uk.

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The Association of the British Pharmaceutical Industry (ABPI) represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK. Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 90 per cent of all medicines used by the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases. The ABPI is recognised by government as the industry body negotiating on behalf of the branded pharmaceutical industry for statutory consultation requirements including the pricing scheme for medicines in the UK.

Disclaimer

This document reflects the views expressed by participants at the meeting and does not necessarily represent the views of all participants or of the Academy of Medical Sciences or the Association of the British Pharmaceutical Industry. For further information, please contact Liberty Dixon, Policy Officer at the Academy of Medical Sciences (liberty.dixon@acmedsci.ac.uk, 020 3176 2186).

All web references were accessed in October 2015.

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Foreword

The Academy of Medical Sciences and the Association of the British Pharmaceutical Industry are committed to ensuring that the UK has a supportive environment for the research and development of innovative medicines and technologies. Real world evidence offers a complementary resource, or in some cases even an alternative, to the evidence generated by randomised controlled trials. Such evidence can enhance the evaluation of the safety and effectiveness of medicines for the benefit of patients, allowing treatments to be better tailored, tracked and understood for each individual.

However, a number of challenges to maximising the potential of real world evidence remain, most notably a lack of clarity regarding the role of such evidence in regulatory and health technology assessment (HTA) decision-making. Clear direction is needed from regulators and HTA bodies on the evidence they require to appropriately evaluate innovative medicines. Regulators and HTA bodies find it difficult to be prescriptive in requirements in the absence of specific examples, and industry needs to ensure that the type of evidence used is based on the research question. A multi-stakeholder approach involving patients, industry, regulators, and payers, is essential to overcome this cycle of uncertainty and develop clear and transparent evidence requirements. The role of patients is particularly central in this conversation.

Real world evidence has the potential to greatly improve and accelerate the development and delivery of safe and cost-effective innovative medicines to patients and how we approach health and healthcare. The UK has a very real opportunity to develop leadership in this field, and influence the development of a consistent approach across global regulators and other stakeholders. This meeting highlighted the need to take this agenda forward and, in particular, the need to define terminology, establish a coordinated approach to real world data across the healthcare community, invest in patient and public engagement, and communicate more clearly the value of real world evidence for all stakeholders. This coordinated approach will require direction through leadership, and a collaborative effort to deliver the core infrastructure for health. The AMS and ABPI are committed to playing their part in realising this potential for the benefit of patients and the UK innovation landscape.

Sir Alasdair Breckenridge CBE FRSE FMedSci

Chair of the FORUM 'Real world evidence' Workshop

Dr Virginia Acha

Association of the British Pharmaceutical Industry

Summary

On 17 September 2015, the Academy of Medical Sciences, in partnership with the Association of the British Pharmaceutical Industry (ABPI), held a workshop on 'Real world evidence' as part of the Academy's FORUM programme. This workshop aimed to explore the acceptability of real world evidence in regulatory and Health Technology Assessment (HTA) decision-making, with discussion sessions to address the challenges to acceptability and identify ways to overcome these.

For the purpose of this meeting, real world evidence was defined as the evidence generated from clinically-relevant data collected outside of the context of conventional randomised controlled trials (RCTs).[1] It can stem from a wealth of diverse sources such as primary and secondary care data, routine administrative data, registries and social media. Evidence generated from such data has the potential to impact all stages of a product's lifecycle, complementing – and in some cases even replacing – evidence collected from the 'gold standard' of experimental design: the RCT.[2] However, this tool has yet to be integrated into the medicines development process and its role in regulatory and HTA decision-making remains to be fully defined.

Over the course of the workshop, delegates were asked to discuss aspirations for how real world evidence might be used in a regulatory context by 2020, key challenges to be overcome to achieve these, and practical steps to remedy the current challenges. Aspirations for using real world evidence in the future focused on the wider opportunity for use in efficacy and effectiveness evaluation, greater agility in licensing of medicines and the expansion and refinement of indications for existing marketed drugs. It was recognised that real world evidence can be incorporated earlier in the drug development process to provide insight at all stages from study design to post-marketing surveillance, and it was envisioned that in the future it would be considered alongside RCT data as a valuable and complementary resource.

Delegates identified a number of issues that would need to be overcome to achieve these aspirations:

- Regulators and HTA bodies need to provide further clarity on the acceptability of real world evidence (e.g. around different data sources, applications of real world evidence), with better alignment and synergy between the regulatory and HTA requirements. There is a need to define standards and best practice for methodology and analyses both when interrogating real world data with a carefully selected research question to produce robust evidence, and when using real world evidence to assess the safety, efficacy and effectiveness of a medicine; further guidance on where different data types and study designs are best applied is essential.

[1] The full definitions for real world evidence and real world data used at the meeting can be found in Appendix III.

[2] Circumstances where use of real world data might be preferable to RCT data include studies with large effect sizes, small patient populations where patient numbers are not sufficient for an RCT, complex settings such as remote geographical areas, studies where safety is a primary issue and for evaluating devices.

- Coordination and leadership should be established to provide direction and ensure consistency in approaches to using real world evidence, whether at a regional, national or international level. It should be identified where collaboration can further support the use of real world evidence such as pre-competitive consortia for data capture and access.
- A shift in perceptions around real world evidence or 'culture change' must be facilitated whereby all stakeholders are prompted to re-consider the traditional hierarchy of evidence and choose different types of evidence based on the question being asked. This can be driven through clear communication of the value of real world evidence and its different uses to all stakeholders, whether a patient, payer, regulator or to wider industry.
- Academia, industry, regulators, HTA bodies and other key stakeholders should take steps to ensure that the terminology surrounding different evidence types is clearly defined and used consistently. In particular, the distinction between real world evidence and real world data, and efficacy and effectiveness, should be clearly defined and communicated.
- A fit-for-purpose data infrastructure must be built to support linked, multi-source datasets.
- Privacy and consent issues around data access must be overcome through addressing public concerns and in particular, patient perceptions on data sharing.
- Core data standards should be set and the production of high quality data should be incentivised to ensure that the evidence generated from such data is reliable and robust. This will be founded on a better understanding of the value offered by real world evidence from the various stakeholders involved in data extraction and processing.
- Capability and capacity in data extraction, analysis and new technologies must be built in the UK to address and fill the current skills gap using educational programmes and incentives.
- Underlying all of these steps is an immediate need for better stakeholder engagement and in particular, public engagement around data sharing and access, which can be addressed by fully conveying the potential value of data sharing.

Introduction

The life sciences sector has long been aware of the opportunity presented by 'real world data': that is, data collected outside of randomised controlled trials (RCTs).[3] Real world data can originate from a variety of sources, including primary and secondary care patient records, routinely collected administrative data, registries and, increasingly, emerging sources such as social media and data collected via mobile devices and 'apps'.

'Real world evidence' can be generated from real world data and can carry significant value, potentially providing insight at all stages of a product's lifecycle, complementing – and in some cases perhaps even replacing – 'gold standard' RCTs. The benefits of real world evidence are well characterised, and there is the opportunity to translate cost-effective, linked data produced in real-time, into robust multi-source information on the 'value' of a medicine with advantages over expensive and lengthy RCTs.[4,5] Real world evidence thus offers an opportunity to enhance and further support the evidence base for both the safety and effectiveness of medicines and, with a paradigm shift in the drug development process towards personalised medicine and adaptive pathways, it is becoming increasingly accepted that large-scale RCTs may not always offer the best model for evidence collection. As argued by Sir Michael Rawlins FMedSci, then Chairman of the National Institute of Health and Care Excellence (NICE), in his 2008 Harveian Oration:[6]

> *'Hierarchies of evidence should be replaced by accepting – indeed embracing – a diversity of approaches'*

Although there are several reports exploring the opportunity presented by real world evidence, they suggest that its potential is yet to be fully realised.[7] The sector's ability to maximise the potential of this asset has been constrained by a range of factors; notably, a lack of clarity regarding the role of real world evidence in the context of regulatory and health technology appraisal (HTA) decision-making.[5] The path to generating robust and reliable real world evidence which will be universally accepted by the regulatory sector is still to be determined.

On 17 September 2015, the Academy of Medical Sciences, in partnership with the Association of the British Pharmaceutical Industry (ABPI), convened a workshop to discuss this challenge and to identify potential ways to enhance the acceptability and usability of real world evidence in regulatory contexts. The workshop, chaired by Sir

[3] The challenges with terminology are discussed below, but this is how real world data was defined for the purpose of the meeting.
[4] Association of the British Pharmaceutical Industry (2011). *Guidance: Demonstrating value with real world data: A practical guide.* http://www.abpi.org.uk/our-work/library/guidelines/Pages/real-world-data.aspx
[5] Nuffield Council on Bioethics (2014). *The collection, linking and use of data in biomedical research and health care: ethical issues.* http://nuffieldbioethics.org/wp-content/uploads/Biological_and_health_data_web.pdf
[6] Rawlins M (2008). *The Harveian Oration of 2008: De Testimonio. On the evidence for decisions about the use of therapeutic interventions*. Royal College of Physicians
[7] Association of the British Pharmaceutical Industry (2011). *The vision for Real World Data - harnessing the opportunities in the UK*. http://www.abpi.org.uk/our-work/library/industry/Documents/Vision-for-Real-World-Data.pdf

Alasdair Breckenridge CBE FRSE FMedSci, former Chair of the Medicines and Healthcare Products Regulatory Agency (MHRA), brought together over 50 key stakeholders from industry, the regulatory and HTA sectors, academia and policy. The morning session comprised presentations from national and international regulators, NICE, industry and the IMI GetReal initiative, to inform an afternoon break-out session in which participants worked together to identify potential ways forward. This report provides a summary of the speakers' presentations and the subsequent discussions.

We would like to thank Sir Alasdair for chairing the event, the speakers for their thought-provoking presentations and the participants for their active contributions throughout the meeting.

Finally, it should be noted that this document reflects the views expressed by participants at the meeting and does not necessarily represent the views of all participants or of the Academy of Medical Sciences or the Association of the British Pharmaceutical Industry.

Perspectives on the acceptability of real world evidence

Realising the potential of real world evidence

Dr Massoud Toussi, Lead – Pharmacoepidemiology and Drug Safety, IMS Health

The potential uses of real world evidence

Dr Toussi commenced proceedings by arguing that the decision about whether or not real world evidence can be used in regulatory contexts has essentially already been made: it has been used to support mandatory submissions for several years. What remains to be negotiated is whether this use can be expanded beyond safety evaluation to support other aspects of benefit-risk assessment. Given the ongoing paradigm change in healthcare from disease-oriented care to patient-oriented care, Dr Toussi considered that real world evidence could play a significantly wider role in the future.

Dr Toussi explained that there are three steps to generating real world evidence: asking the right questions, finding fit-for-purpose data and using the right methods and analyses to produce robust outputs. He suggested that there is currently an overlap between regulatory and HTA requirements at each of these steps, as shown in the table below, and that these commonalities could be better recognised and aligned to optimise the use of real world evidence.

Stakeholder requirements: is there an overlap?[8,9]

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

* European Medicines Agency (EMA)

** European network of Health Technology Assessment (EUnetHTA)

[8] European Medicines Agency (2014). *Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 1).* 15 April 2014, EMA/838713/2011 Rev 1. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf

[9] European Network for Health Technology Assessment (2012). *Criteria to select and prioritize health technologies for additional evidence generation: Work Package 7*. https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Selection-prioritisation%20criteria.pdf

The supply of real world data

It was argued that the supply of real world data is reaching a crescendo in many countries and that, in particular, an increasing focus on real world evidence is associated with the greater supply of electronic patient-level data. At present, much of this information is unstructured and unexploited, with a large predicted increase in supply of unstructured data continuing from 2010 to 2020. For example, it has been estimated that by 2020 there will be ~40 zetabytes of digital information, of which 1/9th is social media, about 10% of which relates to health, primarily comprising conversations between patients.[10] This wealth of data can potentially shed light on both the safety and effectiveness of medicines being used in the real world, but requires a framework for the supply, governance and application of data. Dr Toussi referred to collaboration in this area between the European Medicines Agency (EMA) and the European network for Health Technology Assessment (EUnetHTA), which is pioneering a coordinated benefit-risk evaluation process, and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), which is working to define a framework for the use of real world evidence in HTA. Dr Toussi proposed a 'T-shaped' framework which combines data covering wide populations but with shallow depth, with data that has greater depth but does not cover a large population, to create a robust, linked database that spans a wide population.

In conclusion, Dr Toussi argued that the increasing use of real world evidence from diverse data sources is '*a real trend*' that has the potential to facilitate a seismic shift in how drugs are evaluated. However, as outlined above, to reach its potential there is a need for greater governance, harmonisation and frameworks, as well as greater appreciation of the potential value of real world evidence.

MHRA perspective on real world evidence

Dr June Raine, Director of Vigilance and Risk Management of Medicines, Medicines and Healthcare products Regulatory Agency

Dr Raine opened by providing an overview of the remit of the MHRA, which assesses the risk-benefit of medicines in clinical use, aiming to reach prompt decisions and constantly seeking to improve and strengthen methodologies while remaining aware of their limitations. She highlighted that the knowledge about the safety of a medicine when it is first licensed is inevitably limited, but that this knowledge is often supplemented by real world evidence. Under this model, real world evidence is involved at every step of safety surveillance, from enabling signal detection in real world use to allowing risk characterisation and minimisation.

Real world data sources and their challenges

The MHRA is increasingly working with industry to plan studies conducted in the real world and utilises a multiplicity of real world data sources, including spontaneous reports of adverse events, longitudinal health record data and registries. Social media is currently also under evaluation as a source.

[10] Wikibon Blog (2012). *A Comprehensive List of Big Data Statistics*. [cited 2015 Feb 09] http://wikibon.org/blog/big-data-statistics/

The UK Yellow Card scheme is a well-established 'real world' tool for detecting safety signals; however, using spontaneous data for signal detection has limitations. For example:

- Individual case reports can rarely be used to estimate the frequency or impact of adverse events on benefit-risk, as they usually lack a denominator; yet it is these data which drive many safety decisions.
- Under-reporting and submission of incomplete data can make assessment difficult.
- Methodological issues with spurious associations and false positives etc when different methods of disproportionality analysis are brought together with various data types to drive signal detection.

One delegate emphasised that spontaneous reporting signals are often overly inferred from to estimate incidence rates, and that real world evidence could add validity to these signals.

Dr Raine highlighted some initiatives to maximise the utility of methodologies for safety monitoring, such as the IMI PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) public-private consortium, which carried out a programme of research to address limitations of some current methods in pharmacoepidemiology and pharmacovigilance. However, a challenge remains where there are high background rates of a given adverse outcome in the treated population – as is the case for anti-diabetic medications and cardiovascular risk, for example – which seriously limits the utility of spontaneous data. This challenge can be mitigated through access to electronic health records (EHRs), and Dr Raine stated that the aspiration of the UK's Clinical Practice research Datalink (CPRD) is to achieve 20% coverage of the population in the UK. For example, EHR data has been key to signal detection for myocardial infarction in diabetes patients, where spontaneous data was not sufficient to assess risk.[11] According to Dr Raine, it is essential that such datasets can be linked to allow wider capture of information, as with the CPRD database, which has the ability to link datasets such as primary care records to disease registries, hospital data and wider social care data. This allows for more sophisticated propensity scores, draws on new technologies to match populations and enables more robust conclusions to be made about causality. However, linking data presents a sizeable challenge in reconciling different data recording techniques and technologies.

Dr Raine also highlighted the importance of other key sources of real world data. Patient and disease registries contain a wealth of longitudinal data; however, their contribution to decision-making can be limited by a lack of accurately captured drug exposure data and in some cases there is concern about their long-term sustainability. Nevertheless, registries have a proven track record for providing useful real world data on specific medicines and classes, and a current initiative led by the EMA is working to improve consistency and interoperability. Social media is also a potentially valuable source of data for pharmacovigilance and it is likely that its use will increase in the future and could supplement evidence from spontaneous data. At present, the IMI WEB-RADR consortium

[11] Brownstein J *et al* (2009). *Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records*. Diabetes Care, **33(3)**, 526-531

is researching the utility of data from social media for signal detection and regulators are working to find the right methodology for harnessing these data.[12]

It was asked whether by 2020 we would likely have seen a shift in the balance from use of CPRD and Yellow Card to newer technologies. Dr Raine responded that although the utility of spontaneous data has well known limitations, we would not yet be ready to discard healthcare observations for rapid signal detection and instead should use the widest possible range of real world data available relevant to particular risk scenarios.

The changing face of regulation

Dr Raine emphasised that *'the world of reactive regulation is the world of the past'*, as regulation becomes increasingly proactive in planning active surveillance, particularly with regards to high standards of protecting public health and in today's society where fast response rates to emerging risk are rightly expected. This involves reviewing data on background rates of events of interest, comparing these with reports by healthcare professionals and patients, and looking to match observed versus expected rates of adverse events in real-time. The introduction of the pertussis vaccine in pregnancy provides an example of real-time monitoring for public health; the vaccine was not licensed for use in the third trimester, but was introduced in this population and then closely monitored for safety and effectiveness. The longitudinal data was examined a year later to validate its use in this population.[13] In subsequent discussion, the example of narcolepsy in young people associated with a particular pandemic flu vaccine was offered as a further example in which initial spontaneous observations – in this case in Scandinavia – had paved the way for real world studies to quantify risk in other countries.[14]

Dr Raine acknowledged that when the MHRA is approached for scientific advice, the majority of interactions currently focus on pre-authorisation work and RCT methodology. However, as several delegates pointed out, projects relating to adaptive pathways consider the whole of the medicine's lifecycle in clinical use and look to find ways to fill the knowledge gaps when a medicine is licensed on the basis of limited efficacy data, leading the way for greater use of real world evidence. It was emphasised that availability of suitable sources of real world evidence should be considered as early as possible in the lifecycle, to enable it to contribute to a better understanding of the benefit-risk of the product.

To conclude, Dr Raine stressed the need to solve issues of scientific validity and move towards addressing and resolving scientific questions on the use of real world evidence. There are vast opportunities for real-time data monitoring with new datasets, methodologies and IT capabilities constantly emerging, and momentum building for approaches that depend on integrating multiple data sources to characterise and quantify risk. The paradigm is shifting with the introduction of early access to medicines and adaptive pathways for licensing which present the challenge and ultimate goal of

[12] Overview of the IMI WEB-RADR consortium: http://web-radr.eu/
[13] Donegan K, King B and Bryan P (2014). *Safety of pertussis vaccination in pregnant women in the UK: observational study*. BMJ, **349,** 4219
[14] Sturkenboom M (2015). *The narcolepsy-pandemic influenza story: can the truth ever be unraveled?* Vaccine, **33(2)**, B6-B13

generating more robust data in real world use more rapidly to better protect public health and develop effective medicines.

EMA perspective on real world evidence

Dr Xavier Kurz, Head of Service, Monitoring and Incident Management, European Medicines Agency

Dr Kurz outlined that real world data is information from clinical use, and this information is used throughout the EMA decision cycle when committees consider the benefit-risk profile of a medicinal product.

The move to proactive safety surveillance

Dr Kurz stated that the EMA has access to a range of data and information to support regulatory decision-making, including EHRs, multiple databases and patient registries. He reiterated the transition – as highlighted by Dr Raine – from the traditionally reactive nature of regulation to a proactive approach using direct access to data to feed information into the decision-making process at an earlier stage. A more integrated approach is now taken to collecting data rather than simply asking companies to conduct studies based on requests.

The EMA has utilised this approach in a drug safety programme funded by the European Commission Seventh Framework Programme, in which safety issues in different countries were identified for further study. From 2007 to 2013, 27 safety topics have been proposed, leading to 11 studies commissioned under the drug safety programme. The results of these studies are used to conduct further benefit-risk evaluation, with a number founded on real world evidence. The EMA also has funds available to commission studies, undertaken by academic centres, on specific drug classes or modular safety issues. In addition, it often transmits data requests to the ENCePP network with regards to the safety of medicinal products. The large EU-PAS (post-authorisation studies) database also acts as a source of information on methodologies used to define issues or perform safety/effectiveness studies.

Regulatory uses of real world evidence: safety vs. efficacy

Dr Kurz drew a distinction between the potential use of real world evidence in supporting decisions on drug safety, and decisions on drug efficacy. With regard to the former, he emphasised that real world evidence can provide timely information on drug utilisation such as dose and switching, and for comparative safety studies between drug classes, indications and populations. For safety evaluation, these data must be longitudinal and relevant with a sufficient sample size to generate robust evidence. For example, real world evidence on switching proved useful in identifying the best replacement for rosiglitazone when it was removed from European market.[15]

Methods for using real world data to provide evidence on efficacy are less developed, but are currently under consideration by the EMA. In 2013, the EMA held a workshop looking

[15] Ehrenstein V *et al* (2013). *Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010*. BMJ Open, **3(9)**, e003424

at the strengths and weaknesses of different efficacy study designs.[16] Three key topics were highlighted during the workshop:

- Pragmatic clinical trials (pRCTs) – There are concerns around the need to assess validity of results against a real world setting and pRCT limitations may include a lack of confirmatory diagnosis. These trials are sometimes considered 'simple' but apart from data collection they are not much less complex than RCTs.
- Observational studies – These studies are not appropriate for demonstrating efficacy but may provide useful information on effect modifiers (e.g. drug doses).
- Registries – Registries provide a variable source of information and can have limitations imposed by data quality, coverage and non-specific disease classification. They can be utilised where there is available data on exposure, outcomes and confounders or when data is linked, and are often a source of subjects for RCTs on marketed medicines.

The use of EHRs for pragmatic trials and methods to control confounding were also topics considered during this workshop.

Dr Kurz, like Dr Raine, noted the steps that his organisation is taking towards using emerging sources of real world data for routine benefit-risk assessment. For example, the EMA is currently monitoring social media with the London School of Hygiene and Tropical Medicine as part of a vaccine assessment programme to research the extent to which information can be captured through this channel and its utility for later assessment. Both speakers anticipated that this type of activity may be used more routinely for benefit-risk assessment in the future, once it is better understood.

In summary, Dr Kurz stated that real world evidence on clinical use of medicines is already fully integrated in regulatory decision-making. However, he acknowledged that to further improve the EMA's ability to assess and monitor the safety, efficacy and quality of authorised medicines, there was a need to strengthen access to real world databases, collaborate with all relevant stakeholders, develop and test better methodologies for safety and efficacy analyses, and explore and expand a range of different data sources.

FDA perspective on real world evidence

Dr Jonathan Jarow, Director – Office of Medical Policy, CDER, FDA

Dr Jarow opened his presentation by questioning the use of the term 'real world evidence', which infers that clinical trials, by contrast, are simulations and not based in the 'real world'. He contrasted this with the FDA's use of the term 'evidence from clinical experience', which he felt more accurately describes the difference between the two sources of evidence.

Dr Jarow explained that, like other regulatory bodies, the US Food and Drug Administration (FDA) considers real world evidence (or evidence from clinical experience) to include a variety of sources such as patient registries, EHRs, and insurance claims data, and these can be used for regulatory decision-making, healthcare economic

[16] A high-level report from the 2013 EMA meeting can be found here: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/11/WC500155692.pdf

research, and comparative effectiveness research. He pointed out that, in the US, substantial evidence is required by law for the demonstration of efficacy for drugs, but not for devices, where a reasonable assurance standard is applied. Moreover, the safety assessment of drugs is not normally covered by the substantial evidence requirement. Thus real world evidence is frequently utilised in the FDA's regulatory decision-making for the safety of drugs and the efficacy and safety of medical devices (of which the latter is governed by the Center for Devices and Radiological Health). Dr Jarow explained that it is very challenging to provide substantial evidence based on real world evidence alone but nevertheless, there have been circumstances when the FDA has utilised real world evidence to make regulatory decisions regarding efficacy of drugs.

Safety and efficacy evaluation using real world evidence

According to Dr Jarow, there is a push in the US to develop better methods and increased utilisation of real world evidence. This has led to the establishment of the Sentinel Initiative, to improve the FDA's capability to identify and investigate safety issues in near real-time.[17] Sentinel utilises claims data from over 178 million patients to perform analyses, which are conducted behind firewalls owned by the data partners, typically insurance companies or healthcare organisations. Sentinel has been used very successfully to address safety issues, but has not been used for efficacy assessment.

Dr Jarow confirmed that there are numerous situations in which the FDA has demonstrated regulatory flexibility in its use of real world evidence to establish efficacy in drug development. Real world evidence has been used in select new drug approvals for very rare diseases, particularly for inborn errors of metabolism disorders where the pathophysiology and natural history is well understood and the efficacy effect size of the drug is very high. In addition, the dose regimen of several vaccines has been based on real world evidence. For example, following a rabies vaccine shortage, real world evidence was used to demonstrate that a four dose regime was as effective as five doses, resulting in a change in CDC (Centers for Disease Control and Prevention) recommendations to four doses as standard of care.[18]

Dr Jarow also highlighted that real world evidence can play a role in hypothesis generation, as shown by CURE-NTD (neglected tropical disease), a tool used for the repurposing of drugs for neglected tropical diseases.[19] This mobile app aids the identification of potential drug candidates for repurposing by capturing real world information about novel uses of existing drugs to treat patients with NTDs.

The use of real world evidence for efficacy is also being investigated through the IMPACT-AF program, which intends to use this information to investigate the lack of prescriptions of anticoagulants for patients with atrial fibrillation. However, Dr Jarow advised that applying real world evidence to efficacy is a 'chicken and egg' situation, as it is difficult to obtain real world evidence for approval unless the drug is already approved elsewhere.

[17] http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm
[18] CDC report on 19 March 2010: *Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices*. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm
[19] Overview of CURE-NTD: http://www.hhs.gov/idealab/projects-item/cure/

The future of real world evidence

Dr Jarow forecast that the FDA's use of real world evidence will remain limited in the approval of new molecular entities over the coming years, but will have a continued and expanding role in safety assessment and medical device approvals. He emphasised that a problem of utilising real world data for approval of a new drug is that in order to have access to this data, a drug must already be on the market. However, there is room for increased use of real world evidence for labelling changes and supplemental indications of already approved drugs. Moreover, he predicted that the use of elements of real world evidence, HER and claims data, will be increasingly incorporated into cluster randomised pragmatic trials to increase their efficiency.

With regards to efficacy, Dr Jarow envisioned that real world evidence in the US will be largely used to support second indications or changes to the indicated population. For example, real world evidence may be increasingly used to assess effectiveness post-approval, paving the way for specific RCTs to confirm these new indications for a marketed drug. This would mark a significant change in current practice as real world evidence is not often available when a marketing decision is made, and, once on the market, drugs are usually only subject to continued assessment by the FDA for safety.

Subsequent discussion highlighted some of the challenges associated with assessing efficacy using real world evidence. For example, a large effect size is often required to demonstrate efficacy based on observational data. However, such data can be extremely valuable in enabling risk-benefit profiles to be re-examined, as demonstrated by the example of sibutramine indicated for weight loss, the efficacy of which, following safety issues, was found to have changed substantially since it was initially assessed on approval.[20]

Health technology assessment and real world evidence

Professor Sarah Garner, Associate Director for Science Policy and Research, National Institute for Health and Care Excellence

Professor Garner began by outlining the decision-making process at NICE, which considers the clinical effectiveness and cost-effectiveness of health technologies, from sources such as health and social care data, alongside many other relevant considerations, including uncertainty, the views of clinical and patient experts, and social and scientific value judgements. This approach was compared with the aims of the drug development process itself which, she argued, in the current environment is designed primarily to achieve regulatory approval and has therefore become focused on efficacy, with less attention given to effectiveness or cost-effectiveness. Professor Garner saw this as a key distinction, contrasting the 'clean' patient groups often used for RCTs with the 'dirty' (that is, variable) patient populations seen in the real world, and highlighting the difficulty in trying to infer expectations from the former in order to draw conclusions about the latter.

[20] Paper demonstrating the re-examination of sibutramine efficacy: Douglas I *et al* (2014). *The effectiveness of pharmaceutical interventions for obesity: weight loss with orlistat and sibutramine in a United Kingdom population-based cohort*. British Journal of Clin Pharm, **79(6)**, 1020-1027

When considering the potential role of real world evidence in HTA, Professor Garner advised that NICE is permissive of different data types and that its current '*Guide to the methods of technology appraisal'* acknowledges some of the strengths and limitations of non-randomised and non-controlled evidence.[21] She stated – and provided examples to demonstrate – that NICE quite frequently draws on real world evidence in its decision-making, and inferences are interpreted as appropriate.[22,23] Whatever the source of evidence, Professor Garner emphasised that uncertainty is key in HTA and regulatory decision-making and it is important to address and manage this. In particular, the path to adoption for a new technology may be clear following HTA if NICE has been able to make a 'yes' or 'no' decision, however, the 'promising, but more research needed' designation often raises questions about how gaps in the evidence base should be filled. Under conditional licensing arrangements, for example, there are often limited data available at the initial review stage, so regulators and NICE need to work together to identify shared evidence requirements which can be fulfilled where possible, without additional RCTs, to prevent further inflating R&D costs. Delegates agreed that the opportunity for synergy of data requirements between regulation and HTA was considerable.

Benefits and limitations of real world evidence and data sources

Like several other speakers, Professor Garner identified a significant shift in the healthcare landscape which she predicted would impact the use of real world evidence by HTA and regulatory bodies. This comprised increasing health informatics capability and infrastructure, new types of targeted drugs and technologies, the rising cost of research, and the emergence of more flexible regulatory options. In particular, Professor Garner suggested that the move towards personalised medicine will drive a shift away from RCTs, as a result of both budgetary pressures and a shortage of patients with the same disease profile.

Traditionally, regulators have drawn a clear distinction between experimental and observational data; however, Professor Garner suggested that rather than making comparisons we should look to understand where and why differences occur and in which circumstances the use of each might be appropriate. For example, pRCTs – in which treatments are administered in routine clinical practice – provide an opportunity for heterogeneous studies to bridge HTA and regulatory barriers, maintaining randomisation but adopting more flexible entry requirements and dosing strategies.

Professor Garner highlighted several ways in which real world evidence could potentially be used by NICE. With regards to HTA, real world evidence can be used to research the *effectiveness* – as opposed to the *efficacy* – of interventions in real world settings, which can in turn inform modelling of clinical or cost-effectiveness and solve uncertainties

[21] NICE (2013). *Guide to the methods of technology appraisal 2013.* https://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf

[22] Observational data used by NICE committee to assess safety of ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion, when compared with unlicensed bevacizumab: https://www.nice.org.uk/guidance/ta283

[23] Registry database used to estimate clinical efficacy for diabetes insulin pumps: http://www.nice.org.uk/guidance/ta151/resources/guidance-continuous-subcutaneous-insulin-infusion-for-the-treatment-of-diabetes-mellitus-pdf

identified in NICE guidance. Post appraisal, real world evidence can also be used to monitor guidance implementation, for example equity of adoption across different groups, in addition to providing epidemiological insights and information on resource use and therefore the potential impact of NICE guidance.

Professor Garner also described some of the work underway at NICE and elsewhere to realise these opportunities, for example the IMI GetReal initiative (see later presentation for further detail) and the Medical Research Council's (MRC) recent highlight notice on methodology for observational data.[24] Similarly, the IMI ADAPT SMART programme will look at the evidence generation requirements throughout the lifecycle of a medicine and link these to adaptive pathways.[25] In addition, a NICE 'real world data steering group' has been established to evaluate various data types and their uses and has recently conducted a proof of concept study with CPRD to create guidance on how the data should be used. Dr Garner indicated that a formal strategy for real world evidence is due to be published by NICE in late 2016.

Real world evidence: the acceptability challenge

Professor Garner concluded by outlining the challenges that would need to be overcome to enable real world evidence to better contribute to NICE's work. These include:

- Changing the culture of both regulators and applicants, to build an understanding of the strengths and weaknesses of different evidence types and of where different data sources and study designs are best applied.
- Improving the consistency of terminology: for example, establishing better distinctions between 'real world' data, 'observational' data, and 'big' data.
- Further developing methodologies for analysis and use.
- Defining best practice.
- Improving our understanding of the potential impact of real world evidence, on healthcare systems, drug development and evidence-based medicine.
- Building skills and capacity.
- Mitigating and alleviating public concerns over confidentiality.

During discussion, participants highlighted the many stakeholders who would need to be involved in resolving the challenges outlined above.

Industry perspective on real world evidence

Dr Virginia Acha, Executive Director – Research, Medical and Innovation, Association of the British Pharmaceutical Industry

Like several other speakers, Dr Acha described the potential of real world evidence to change the paradigm of medical treatment. However, she considered this to be contingent on four essential requirements:

- Recognising the potential of real world evidence.
- Advancing our understanding of benefit and risk.
- Building the necessary infrastructure and skills.

[24] http://www.mrc.ac.uk/funding/how-we-fund-research/highlight-notices/methods-research-observational-data/
[25] ADAPTSMART IMI initiative overview: http://adaptsmart.eu/

- Bringing people with us in our attempts to realise this opportunity.

In fulfilling these requirements, Dr Acha saw a need for industry to reach its goal of achieving rational drug design and to begin to shift its focus towards rational healthcare design. Both are driven by a desire to understand how best to translate data into knowledge, for example, by better using data and methods to enhance and fill gaps in our understanding of disease biology and molecular change. However, rational healthcare design offers an opportunity to draw on the system itself to further enhance data collection and analysis and accelerate the accumulation of evidence over time.

Changing the paradigm: the role of real world evidence

In thinking about the role of real world evidence in changing the treatment paradigm, Dr Acha asked at what point society considers itself to 'know' the value of a medicine and feel comfortable that it has the necessary information to assess this. She suggested that this could vary greatly, from first approval to decades of use depending on the type of evidence available and who it is available to, but that there is an 'opportunity cost' associated with this timeline that real world evidence could help to allay.

Dr Acha pointed out that there has traditionally been a 'hierarchy of evidence' through which the value of a drug can be ascertained, and that this places real world evidence below that collected through RCTs. However, as highlighted in the ABPI's 2011 report, '*Demonstrating value with real world data*', it is now increasingly recognised that real world evidence has a place alongside RCT data and that there is a need to reconsider this hierarchy.[2] That is, real world evidence can complement RCTs and address some of their weaknesses: for example, cost, ethical issues and slow translation to practice.

Key steps to achieving the full potential of real world evidence were outlined by the ABPI in its '*Big Data Roadmap*' (2013). These included: increasing awareness of its potential, building capacity and capability, establishing sustainable data ecosystems and accelerating high value opportunities.[26] In addition, Dr Acha argued that there needs to be clarity on the requirements from decision-makers, plus coordination and avoidance of duplication of evidence needs where possible. She emphasised that, given that drugs are developed for a range of markets, a global view from decision-makers and uniformity of approach is essential. Appropriate healthcare and legal architecture is also fundamental with regards to consent and data privacy, alongside the necessary infrastructure and collaboration between organisations as demonstrated by the IMI initiatives.

Dr Acha also emphasised that it is essential to bring all stakeholders on the 'journey' of this tool, including patients, who must be able to trust this approach through transparency and understanding; patient needs must be taken into consideration early on in the process. The role of payers is also key and it was suggested in discussion that payers are not currently involved in these discussions, yet it is ultimately they who determine the final value of the evidence. One delegate referred to a study on clinician and patient perceptions on data which shows that the more data are structured, the more

[26] Association of the British Pharmaceutical Industry (2013). *Big data roadmap.* http://www.abpi.org.uk/our-work/library/industry/Documents/ABPI%20big%20data%20road%20map.pdf

the data satisfies statisticians, but the less it pleases patients and clinicians who prefer narrative accounts.[27] This is an area where case studies could have a significant impact.

During discussion, it was stressed that the healthcare environment has now moved from being supply-led to demand-led, and stakeholders need to outline their requirements to enable companies to best interpret data and provide relevant information. It was affirmed that industry is gathering real world evidence but does not yet know how to use it, or the best applications for this tool, and companies are at different stages with this resource.

IMI GetReal initiative

Dr Pall Jonsson, Senior Scientific Adviser – IMI GetReal, NICE

Dr Jonsson opened by explaining that the core objective of IMI GetReal is to bring together stakeholders to identify how we can obtain wider information on the effectiveness, and not simply efficacy, of drugs. Expanding on this principal purpose, the three year public-private partnership aims to better understand how real world data and analytical techniques can improve the relevance of knowledge generated early in drug development.

Dr Jonsson outlined the four anticipated outcomes of GetReal: recommendations about methodologies and processes; alignment of policy, tools and frameworks; review of the research agenda and gaps; and subsequent training once skills gaps are identified. Overall, the initiative is working towards a framework with a set of guiding principles, linking data generation with methods and decision-making and incorporating the breadth of stakeholder views on acceptability of real world evidence.

GetReal has identified operational, regulatory, methodological and ethical obstacles to integrating real world evidence into the pre-authorisation drug development process, and these are barriers that the initiative seeks to address. In particular, there is little clarity on how alternative study designs can be incorporated into the development process. Therefore further guidance is required on the various study options that can be applied and their associated costs, feasibility and acceptability, and also the balance needed between pre-authorisation and post-authorisation data provision.

GetReal Work Packages

Dr Jonsson gave a brief overview of the four work packages of GetReal, with work package one (WP1) focusing on policy by mapping the landscape and relevant policies on evidence to create a common understanding of the current environment. For this workstream, stakeholders will be engaged in workshops on case studies where effectiveness issues were faced in different disease areas, in order to define alternative strategies where real world evidence could be used to address these issues. As part of this work package, he confirmed that GetReal is reviewing five case studies, including the Salford Lung Study which addresses key questions relating to pRCTs, and a metastatic melanoma study examining the potential of registry data to support RCT efficacy data.

[27] Banerjee A and Ingate I (2012). *Web-Based Patient-Reported Outcomes in Drug Safety and Risk Management*. Drug Safety, **35(6)**, 437-446

WP2 will then address the efficacy-effectiveness gap and how different trial designs and subsequent evidence can be used to assess effectiveness. Having understood these principles, WP3 will look at overcoming the operational barriers of design and implementation of real world studies and WP4 will investigate evidence synthesis to identify how comparative effectiveness is assessed in an area with multiple competitors, developing options for use of meta-analyses that incorporate real world data to inform best practice.

IMI real world evidence initiatives

Additional IMI initiatives that are investigating aspects of using real world evidence in medicines development include EHR4CR (Electronic Health Records for Clinical Research), which is examining model infrastructures for utilising EHRs, and ADAPT SMART, which focuses on adaptive pathways and use of evidence across the product lifecycle.[28] Dr Jonsson also highlighted EMIF (European Medical Information Framework), which aims to develop a framework of patient-level data that will link up and provide access to diverse data sources.[29]

In the discussion that followed, delegates drew attention to the difficulties with data collection and extraction, as data are often siloed and fragmented with an initial pre-study required to see if the necessary information is contained within the data. It was argued that legacy systems have safety monitoring capabilities and simply require an appropriate system for data extraction; however, it was highlighted that most current systems are still not fit-for-purpose. This is demonstrated in the US where electronic records have been introduced in all hospitals, but many are using different versions of the same software which limits ease of data extraction.

[28] EHR4CR IMI initiative overview: http://www.ehr4cr.eu/views/about/index.cfm
[29] EMIF IMI initiative overview http://www.imi.europa.eu/content/emif

Identifying the challenges to acceptability and practical steps to resolve

During the afternoon, delegates split into groups to discuss aspirations for how real world evidence might be used in a regulatory context by 2020, key challenges to be overcome to achieve these aspirations, and practical steps to remedy the current challenges. The key themes are outlined below.

Aspirations

General aspirations for use of real world evidence in 2020 included being able to use it to provide greater agility in the licensing of drugs, providing the possibility of accelerated approval, and to enable expansion and refinement of indications for existing marketed drugs. It was hoped that real world evidence would also be incorporated earlier in drug development; an ambition that is particularly pertinent to precision medicine, where real world evidence has the potential to add value across the development process, from providing a better knowledge of biological targets and variation in patient response, to informing trial design. Spanning this medicines development process, delegates recognised that there is great potential for real world evidence to be considered and integrated alongside RCT evidence in the future as part of a culture shift, which would streamline the steps between regulatory and HTA review.

More detailed aspirations included that of an internationally linked data infrastructure with interoperability between databases and global data standards. This led to ambitions of pre-competitive data sharing with equitable access. Delegates also discussed the importance of understanding the impact of using real world evidence as one of the inputs into decision-making (particularly if using over other types of evidence), such as for medicines labelling and expansion of licensed indications.

Terminology

Delegates agreed that employing the right terminology is key to advancing our understanding and use of real world evidence and that it is therefore essential to have consistent and precise definitions. It was felt that 'real world data' and 'real world evidence' may not be ideal terms, as they infer – somewhat misleadingly – that this type of evidence is better than other types of evidence such as RCTs, which, it implies are collected outside of the 'real world'. 'Evidence from clinical experience', the term suggested by Dr Jarow, was preferred by several delegates, although it was noted that 'real world' terminology was now well accepted and widely used in Europe, and may therefore prove difficult to change.

Delegates also recognised that there is an important distinction to be made between 'data' and 'evidence', although several use the terms interchangeably in their own organisations (see Annex III), potentially leading to accountability issues. One group also noted two further classes of knowledge: 'real world insights'; for example the

unstructured findings from data such as social media, which can provide some value but fall short of the standards required for 'evidence', and 'real world information', which is the valuable component of any given dataset and is not necessarily equivalent to the entirety of the data. There is also frequent confusion between the terms 'efficacy' and 'effectiveness', with some groups failing to appreciate the need, or how, to demonstrate the latter. Delegates noted that these confusions arise from a need to better define the terms to ensure that they are understood and used appropriately.

Such inconsistencies are seen both between and within organisations, and while delegates felt that this was not necessarily an issue in specialist circles, clarity and consistency of terminology is fundamental to communicating the value of real world evidence to other groups. Careless use of nomenclature can also have more direct consequences; for example, pragmatic RCTs, which are classified as interventional rather than 'real world' studies, require Good Clinical Practice to be met as a result, making them potentially burdensome to run.

Potential steps to resolve: terminology

Delegates suggested:

- Establish a common set of definitions to be used by all stakeholders.
- Delegates to ensure that their own organisations are using terms such as real world evidence, real world data, efficacy and effectiveness accurately and consistently in both internal and external communications.

Data collection and access

Building a real world data infrastructure that is fit-for-purpose presents a significant challenge, as does the need to address issues of data standards and access. There was also discussion around how real world evidence can be generated for drugs that have not yet obtained regulatory approval. This appeared complex unless drugs have been previously approved in other countries or if inferences and predictions can be extrapolated from other drugs in a well established class.

Infrastructure

Given the global nature of the pharmaceutical industry, delegates aspired to building a data infrastructure that spans regions and/or countries and that allows interoperability between databases, particularly with regard to different data sources. This would allow the accumulation of comprehensive external data, with data platforms that would facilitate the conduct of multi-source studies that crossed national boundaries. It was proposed that a country's ability to extract data should be considered a competitive advantage, with hospital data in particular perceived as a relatively untapped resource, which even the UK has only recently demonstrated its ability to extract.

The ability to link data is also essential, particularly where large datasets are lacking, for example due to small patient populations or scarce RCTs. Delegates envisioned a future in which international datasets would be linked, whilst acknowledging that this may initially occur at a regional level, and it was suggested that data 'gaps' in speciality areas could be

filled by data from other countries, for example, supplementing information from England with data from Scotland for UK-wide representation. It was broadly agreed that data should be pulled from across Europe to create a common European database; however, it was recognised that this would require a single point of consent for all data extraction and use, which would pose a challenge. There is also a significant challenge posed in linking heterogeneous data – that is, data from different sources – and databases without unique identifiers, such as those used in Scotland and the Nordic countries. CPRD and the data held by IMS present positive models of how data can be linked, however, such examples are currently limited.

A particular opportunity was identified to better utilise data produced as a result of individual electronic health monitoring. For example, digital and device-based monitoring enables straightforward capture of a greater volume of data than traditional questionnaires, particularly where monitoring is automatic, as in the case of many commercially available health 'apps' and wearable devices. Delegates also discussed the benefits of real-time data capture and how these advances in electronic monitoring would support the need for faster data collection.

Standardisation and data quality

Data captured through different sources, and across different therapy areas, can vary in their quality and features, making standardisation a key challenge.

Heterogeneous data must be made fit-for-purpose before analyses can be carried out, so quality issues must be resolved up front and 'missing data' dealt with if required, particularly if such gaps are 'missing not at random'. 'Dirty' data sources also require filtering and interpretation before use to ensure that the data is relevant and reliable. Delegates agreed that there should be incentives for high quality data capture and standards, as seen in US insurance claim data, which are highly accurate due to financial imperatives.

The voluntary nature of much data collection can make it difficult to maintain the standards necessary for research. For example, healthcare professionals do not tend to record routine information if it falls within normal boundaries – for example, a normal heart rate – as the data requirements for routine care management are different to those for research. Multiple stakeholders with different levels of expertise may also be involved at different points during data capture and storage; for example, NHS data is often initially collected by clinicians, but coded by data entry specialists. As one group described, data is only as good as the individual recording it; automation for data recording and capture would resolve this variability.

Data access

Delegates acknowledged the many legal and ethical challenges that influence access to data; for example, questions of privacy and consent. It was noted that public opinion on data access in continental Europe and the UK differs from Scandinavia or the US, and trust has previously been compromised in the UK. This presents a communications issue for all stakeholders involved, and those such as healthcare professionals, government, payers and industry must better engage patients to ensure that the benefits of sharing health data are clearly understood. Access would also be facilitated through transparency

around data use, particularly with patients and other data 'owners'. It was acknowledged that concerns around consent may pose less of an issue in the future with younger generations perceived as less sensitive regarding the uses to which personal data are put, in part because of extensive interactions with social media.

One delegate predicted a possible scenario where patients would widely consent to data use through 'selling' their personal data, and another suggested a data sharing structure similar to the 'Enigma' project at MIT, which fragments data (including health data) across a cloud, providing an element of privacy protection.[30] Only the data owner has the pieces necessary to pull the data together, allowing them to maintain individual control. However, such arrangements raise questions about data ownership and in the discussion that ensued, it was suggested that, from a legal standpoint, data belongs to the person who last modified it, making the legal defensibility of such arrangements questionable.

It was noted that universities often have access to databases which industry does not, and it was suggested that the development of standardised tripartite agreements between industry, academia and the NHS could help to resolve some of these access issues (a similar approach has been taken by universities and companies intending to undertake collaborative research projects, where a set of standardised 'Lambert agreements' have been developed to facilitate collaboration).[31]

Competition vs. collaboration

During the discussions, it emerged that there is a challenge in attaining clarity on the aspects of data collection and analysis that are competitive and those that are pre-competitive or collaborative. As discussed above, better coordination and collaboration is essential and will require incentives for organisations to work together, as it will be difficult to progress this field whilst data are held as a commodity and not widely available (either freely or commercially). It was proposed that learnings could be borrowed from pre-competitive consortia to facilitate work in this environment.

Potential steps to resolve: data collection and access

Delegates suggested:

Infrastructure

- Establish standard IT monitoring systems in all regions, or standardised programmes which allow healthcare professionals to systematically record data.

Establishing data standards

- Set standards for data collection and capture (a common data model) that can be trained, implemented and audited. This can be flexible rather than imposing Good Practice-like standards, and it was suggested that this could be led by an organisation such as the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
- Kitemark good quality data that have been approved by regulators for specific uses so that researchers are able to identify 'good' data and are reassured of its acceptability

[30] http://enigma.media.mit.edu/

[31] See information on the Lambert toolkit from the Intellectual Property Office: https://www.gov.uk/guidance/lambert-toolkit

for particular questions. This will also contribute towards good data standards and quality.

Improving data quality

- Audit and reflect data quality back to those responsible for its collection.
- Demonstrate the widespread benefits of high quality data.
- Guarantee a return on investment on data and clinical usability of these data, such as financial reimbursement. This would act as an incentive for both collection and quality.
- Consider commercialising data from providers.

Facilitating data access

- Develop standardised tripartite agreements between industry, academia and the NHS.
- Form pre-competitive collaborations to facilitate data access through pre-competitive sharing models.
- Government, regulators and other key stakeholders to inform the public about the importance of sharing data and to ensure transparency around use of data.

Methodology and analysis

Discussions also focused on analysis of data to generate robust real world evidence, as well as methodologies for interpretation of the evidence. Again, as noted in earlier discussions, it was emphasised that standardisation will prove key here to ensuring that the most appropriate methodologies are applied in the right circumstances.

Defining the research question

It was widely recognised that selecting the right research questions for interrogating datasets is critical to producing accurate and relevant evidence, and the questions should play a significant role in informing the data sources and trial design chosen. In particular, it was identified that there should be a distinction between whether an efficacy or effectiveness question is required. To ensure that the most appropriate research question is selected, it was considered important to recognise when and where real world data is needed rather than RCT data, and where it can act as a complementary resource.

It was suggested that to determine the right research questions, it is essential to consider the evidence that will be required for regulatory and HTA approval once a new molecular entity has been developed, and it was asked how industry can be supported to find the right questions that can be answered by the data. One delegate summarised this as: '*we are very data rich and question poor',* which demonstrates the need to develop robust questions to fully exploit the wealth of data available.

Methodology

Producing reliable real world evidence with the potential to complement, or even replace, RCT data requires data analysis using credible statistical methodologies.[32] It was agreed that the methods chosen to study various real world data should depend on the different

[32] The Academy project on 'Evaluating Evidence' is looking at how society uses evidence to judge the risks and benefits of medicines, including a workstream on methods of evaluating evidence for benefit-risk decisions. An overview of the project can be found here: http://www.acmedsci.ac.uk/policy/policy-projects/how-does-society-use-evidence-to-judge-the-risks-and-benefits-of-medicines/

sources of data used, and therefore guidance on the most appropriate methodologies for analysing different data sources would be a valuable resource.

Moving on from data analysis to generate evidence, delegates then discussed methodologies for evidence interpretation. As outlined during the morning presentations, there are many opportunities for real world evidence to be applied continually throughout the lifecycle of a medicine to re-evaluate the benefit-risk profile, looking beyond safety evaluation and quantifying efficacy and effectiveness in clinical practice. Therefore for evidence interpretation, standardisation is additionally required for the methodologies and acceptability standards employed by regulatory and HTA bodies when using real world evidence to evaluate medicines. In particular, it was acknowledged that real world evidence could play an important role in helping to quantify the level of uncertainty for regulatory review. Thus there is a need for increased dialogue with both HTA and regulatory agencies to ensure that the real world evidence supplied is of a standard that is sufficiently acceptable to enable its use in evaluation.

One group envisioned global harmonisation of standardised methodology for evidence interpretation, initially at EU level and then spreading globally, and work is already being carried out in this area such as the IMI-PROTECT initiative described earlier by Dr Raine. At present, it was argued that the lack of national and international standards poses a challenge, and various countries will assess reimbursement differently; however, there is a significant advantage in creating a set of standards or guidelines to ensure the acceptability of real world evidence that is generated. Global harmonisation could also reduce some of the inefficiencies faced by industry by eliminating the need to produce different drug portfolios for each country. As described above, it was reiterated that industry needs clarity on regulatory expectations and scientific advice will be hugely important to achieve this.

Potential steps to resolve: methodology and analysis

Delegates suggested:

- Collaboration between regulators, HTA and bodies such as the HSCIC (Health and Social Care Information Centre) to identify the necessary standards for data analysis methodologies to generate acceptable evidence, then;
- Establish a framework of standards for data analysis using real world data (equivalent to Good Clinical Practice (GCP)).
- HTA bodies to publish guidelines on the methodologies that are important for addressing questions in value/price discussions.
- Utilise EU funding or other sources of funding such as the Bill and Melinda Gates Foundation to establish standardisation of data analysis methodologies at a global level.

Building capacity and capability

Delegates shared concerns about the current skills gap in relation to lack of expertise in extraction and analysis of data, skills which are not traditionally found within industry.[33] This work requires 'informaticians' and those with technical expertise and also a healthcare background to carry out the right methods of analysis based on an understanding of where various methodologies are best applied.[34] An existing 'lack of new thinking' was described during discussions where there is a demand for increasing innovation in the way that data are used and presented, requiring the relevant capabilities to do so. It was suggested that this could be addressed through early career researcher skills training and the creation of a new career pathway, as well as educational programmes similar to the EU2P programme in pharmacovigilance and pharmacoepidemiology that is supported by universities, the EMA and industry.[35] The incentives for consistent, high quality data capture discussed earlier should also help to build capabilities by incentivising the workforce to develop and enhance skills for data extraction and analysis.

Expanding IT capabilities will allow breakthroughs in current processes, however, there needs to be appropriate expertise to exploit these new technologies. An opportunity was identified for drawing expertise from outside industry to utilise knowledge from sectors such as finance where analysts have extensive experience of working with real world data and new technology.

Potential steps to resolve: building capacity and capability

Delegates suggested:

- Engagement with other industries such as IT and finance to draw expertise from those with experience of working with real world data.
- Educational programmes, potentially sponsored by industry, to build the skills base.
- Kitemarking of particular training and educational programmes.
- NHS and Department of Health to facilitate access to new technologies by making these more widely available to researchers.

Culture change

There was general agreement that perceptions about real world evidence and the traditional hierarchy of evidence referred to by Dr Acha need to be re-addressed; there are still perceived prejudices against real world evidence and a view that RCT data is the only acceptable form of evidence. A culture change in terms of an evolution in views about real world evidence is therefore required to tackle the embedded, negative

[33] This skills gap is outlined in the ABPI 2015 skills report: *Bridging the skills gap in the biopharmaceutical industry.* http://www.abpi.org.uk/our-work/library/industry/Documents/Skills_Gap_Industry.pdf

[34] The importance of this expertise has been identified in the Academy *Health of the Public in 2040* project. An interim update can be found here: http://www.acmedsci.ac.uk/download.php?f=file&i=31928

[35] EU2P is a PhD programme in pharmacoepidemiology and pharmacovigilance sponsored by industry http://www.eu2p.org/diplomas-offer/phd

perceptions around its use and to ensure that all stakeholders are less risk averse about utilising this resource. This ranges from patients, who may influence how their data are collected and used, to industry, which drives trends in data collection and analysis, and to regulatory and HTA agencies who determine the acceptability of real world data as a robust source of real world evidence. One group felt that there is a false dichotomy between real world data and RCT data which could be resolved by focusing on the evidence itself and not the source or methodology used. It was hoped that in the future, the opportunity for RCTs and real world evidence to work together effectively and synergistically would be realised, with real world evidence being generated alongside RCTs as common practice. This would facilitate streamlining of the process between regulatory and HTA review, and integrate real world evidence into the medicines development process.

The culture change discussed also involved moving beyond changing ingrained perceptions to the potential change required in the regulatory review process. During the morning discussions, one delegate suggested that it might be necessary to review the regulatory process in the light of new cancer treatments which are fragmented into increasingly small patient populations, and thus where there are insufficient patient populations available to conduct a RCT. The pressure on regulators to facilitate rapid patient access to these therapies was described, and so it was suggested that small, persuasive studies could be conducted to support licensing, with the expectation that the majority of data would be collected post-approval in the real world.

Value proposition

It was recognised that there is great importance in communicating the value proposition of using real world evidence to all stakeholders including government, payers, regulators and patients to establish societal confidence in this tool; it was noted that payers must be engaged from the outset as those who determine the ultimate 'worth' of the evidence. As outlined previously, the value needs to be conveyed across the data collection and evidence generation process from those inputting the data to those evaluating it.

As alluded to during earlier discussions around data access, delegates highlighted that patients should understand the value of sharing data and there should be reassurances about how the wider population which benefits from the data connects with the patient as an individual. It was recommended that this value could be demonstrated by conveying the drug development story to the public to raise awareness of the dramatic reduction in drugs moving through the development pipeline and thus the positive impact of their data in addressing this.[36]

Again, it was suggested that we should look to adopt learnings from other industries for communicating the value proposition; for example, considering the system of Wikipedia where members of society willingly share knowledge without a financial gain, simply through an understanding that they are contributing to the global knowledge base. It was anticipated that we could motivate patients to want to share health data in the same way

[36] The importance of patient engagement is also outlined in the 2015 Academy report on '*Stratified, personalised or P4 medicine: a new direction for placing the patient at the centre of healthcare and health education*'. http://www.acmedsci.ac.uk/download.php?f=file&i=32644

by creating an understanding of the value it adds to society through a robust knowledge ecosystem.

Potential steps to resolve: culture change

Delegates suggested:

- Build understanding and confidence in the utility of this approach with all stakeholders by presenting case studies where real world evidence has been used to demonstrate safety, efficacy or effectiveness. Whether this is with regulators and industry to provide examples of where it has been used successfully, or with patients and payers to prove its value in certain situations.
- Regulators and HTA bodies to provide further clarity on the acceptability of real world evidence.
- Explore the circumstances in which real world evidence could be used as the basis for medicine label changes and indication extensions, and if there are legislative barriers that need to be addressed.
- Increase public and payer engagement on real world evidence and clearly communicate the value to then change perceptions of real world evidence.

Coordination and leadership

There was general consensus that a body is needed to coordinate, set standards and lead best practice for real world evidence use, as for RCTs where standards are set by the ICH through its requirements for GCP. This would allow for greater efficiency in processes where real world evidence is used. There is a strong economic incentive to track safety, efficacy and effectiveness on a global scale, however, the operational challenge of managing this information must be resolved, likely through coordination of standards by an external organisation. When also considering the widely held expectation that real world evidence will be used for continuous monitoring throughout the product lifecycle, it was raised as to whether a public body is required to impose monitoring of real world effectiveness in a certain way, or whether companies should be persuaded to build effectiveness stories themselves by recognising the advantages for benefit-risk assessment. Flexible pricing and reimbursement models would also incentivise this evidence collection by industry.[37] Suggestions for those who could assume responsibility for lifecycle monitoring included NHS England, NIHR, regulators and industry.

Delegates drew attention to the absence of visible leadership in this area which can result in industry and stakeholders adopting different approaches which are not necessarily coherent. It was debated as to whether there is a role for national leadership before international leadership as the latter would be slower to achieve, and with the 2020 timeframe proposed it was indicated that a legitimate goal would be to reach a European-wide initiative. However, several participants advised that in a global environment, it is very difficult to implement change of this scale without global acceptance and leadership

[37] The Accelerating Access Review is looking to facilitate faster access to medicines, devices and diagnostics and has identified reimbursement as one of three potential areas for reform in the UK: https://www.gov.uk/government/organisations/accelerated-access-review/about

amongst principle stakeholders for the guidelines and standards that are being developed, and any form of leadership would be difficult without this global acceptance.

It was suggested that ICH should be involved with the development of this tool as it can bring together global regulators for collaborative working. On the other hand, it is not only regulatory leadership that is required and so ICH involvement may only address part of the process. The Farr Institute and CASMI (Centre for the Advancement of Sustainable Medical Innovation) were also considered as bodies who might play a role in taking forward the idea of standardisation and coordination if funding was available, and it was proposed that George Freeman MP could act as a leadership figure for this area.

Potential steps to resolve: coordination and leadership

Delegates suggested:

- Establishment of a body to oversee the entire process of using real world evidence.
- Industry to lead on sharing best practice and providing active input into discussions around standards.

Conclusions and next steps

At the close of the day, Sir Alasdair Breckenridge CBE FRSE FMedSci reflected on the discussions from the afternoon session, identifying four key challenges to realising the value of real world evidence: terminology, coordination, patient and public engagement, and communicating the value proposition.

Expanding on these four fundamental steps, Sir Alasdair emphasised that it is essential to *'get the terminology right'*, as stakeholders are using terms inconsistently which impedes communications and can present a barrier to utilising real world evidence. Activities within this field also require coordination and leadership and we need to consider whether there is a body at a regional, national or international level that could oversee certain stages or the entire process. Public engagement underlies all of the discussions outlined above, and public, patient and wider stakeholder engagement is vital to allow us to address many of the barriers outlined in this report. Finally, building upon this engagement, consideration must be given to how the value proposition can be communicated and understood at all levels, whether this is the patient, clinician, regulator, HTA body or payer.

In discussion, this was framed as a need to revolutionise the clinical trial enterprise, with a significant role played by real world evidence. There are many groups with a stake in this tool; industry could look to a significant reduction in trial cost; data owners will mediate access to real world data for effectiveness and cost-effectiveness calculations; and payers, whether the NHS or insurance companies, need to develop a sophisticated system which can compare between the effectiveness and efficacy of all currently available treatments. This is then encompassed by the need to begin working towards a common data model at a global level.

Appendix I programme

Thursday 17 September 2015

Royal Institute of British Architects, 66 Portland Place, London W1B 1AD

09:00-09:30	**Registration**
09:30-09:45	**Welcome** Sir Alasdair Breckenridge CBE FRSE FMedSci
09:45-10:00	**Setting the scene: Realising the potential of real world evidence** Dr Massoud Toussi, Lead – Pharmacoepidemiology and Drug Safety, IMS Health
Session 1: Organisational perspectives on the acceptability of real world evidence In each of the following presentations, speakers will be asked to: • Summarise their organisation or sector's approach to using real world evidence • Outline the circumstances in which such evidence is considered acceptable and the opportunities, and • Consider some of the challenges to acceptability, and the ways that these are being tackled.	
10:00-10:15	**Medicines and Healthcare products Regulatory Agency** Dr June Raine CBE, Director of Vigilance and Risk Management of Medicines, MHRA
10:15-10:30	**European Medicines Agency** Dr Xavier Kurz, Head of Service, Monitoring and Incident Management, EMA
10:30-10:45	**US Food and Drug Administration** Dr Jonathan Jarow, Director – Office of Medical Policy, FDA
10:45-11:00	**Refreshment break**
11:00-11:15	**National Institute of health and Care Excellence** Professor Sarah Garner, Associate Director for Science Policy and Research, NICE
11:15-11:30	**Association of the British Pharmaceutical Industry** Dr Virginia Acha, Executive Director – Research, Medical & Innovation, ABPI
11:00-11:45	**Innovative Medicines Initiative** Dr Pall Jonsson, Senior Scientific Adviser – IMI GetReal, NICE
11:45-12:30	**Discussion session: the acceptability challenge** • How might real world evidence contribute to regulatory and HTA decision-making? • What are the challenges associated with the acceptability of this evidence? • To what extent are these challenges being tackled and where are the opportunities?
12:30-13:15	**Lunch**
Session 2: Developing a common plan for change	

13:15-13:25	**Recap of the morning's discussion** Sir Alasdair Breckenridge CBE FRSE FMedSci
13:25-14:30	**Break-out session 1** Each group to discuss their aspirations for how real world evidence might be accepted and used in a regulatory context by 2020, and the key challenges that will need to be overcome to achieve this.
14:30-14:45	**Refreshment break**
14:45-15:40	**Break-out session 2** Each group to discuss practical steps that could be taken to remedy current challenges
15:40-16:55	**Feedback and discussion** To include development of high-level actions for change
16:55-17:00	**Conclusions and next steps** Sir Alasdair Breckenridge CBE FRSE FMedSci
17:00-19:00	**Drinks reception**

Appendix II Delegate list

Mr Anurag Abinashi, Engagement Manager, IMS Health
Dr Virginia Acha, Executive Director Research, Medical and Innovation, ABPI
Ms Holly Baines, Policy Officer, Wellcome Trust
Mr Alan Barcroft, Research and Development – Research Contracting, Information Intelligence and Stakeholder Engagement, Department of Health
Professor Richard Barker OBE, Director, Centre for the Advancement of Sustainable Medical Innovation
Dr Andrew Bate, Senior Director, Analytics Team Lead, Epidemiology, Pfizer
Dr Rozlyn Bekker, Medical Director, Janssen
Dr Betina Blak, Real World Evidence Manager, AstraZeneca
Ms Angela Blake, Head of Outcomes Research, Evidence-Based Medicine and HTA Policy, Pfizer
Dr Jill Boorman, Clinical Operations Manager, Abbvie
Sir Alasdair Breckenridge CBE FRSE FMedSci (Chair), Former Chair, MHRA
Dr Robert Chipperfield, Director Medical Affairs – Cardiometabolic, Merck Sharp & Dohme
Mr Chris Chinn, Head of Real World Investigations, Sanofi
Mr Adam Collier, Head of Real World Evidence Solutions, IMS Health
Dr Ben Cottam, Policy and Communications Officer, Faculty of Pharmaceutical Medicine
Dr David Crosby, Programme Manager for Methodology and Experimental Medicine, MRC
Professor Adrian Davis OBE, Director, AD Cave Solutions
Dr Stuart Dollow, Chief Executive, Vermilion Life Sciences
Mr Stephen Fawbert, Senior Policy Advisor - Life Sciences & Innovation, MHRA
Dr Peter Feldschreiber, Barrister, 4 New Square
Professor Sarah Garner, Associate Director for Research & Development, NICE
Professor Martin Gibson, Honorary Professor/Consultant in Diabetes/Endocrinology, University of Manchester
Dr Jeremy Haigh, Chair, Cogent Skills
Dr Shahid Hanif, Head of Health Data & Outcomes, ABPI
Professor Bernie Hannigan, Director of Research & Development, Public Health England
Professor Harry Hemingway, Professor of Epidemiology and Public Health, University College London and Centre Director of the Farr Institute @ London
Mr Rob Hemmings, Statistics Unit Manager, MHRA
Ms Lesley Howell, Founding director, pH Associates
Dr Jonathan Jarow, Director, Office of Medical Policy, FDA
Dr Pall Jonsson, Senior Scientific Adviser - IMI GetReal, NICE
Dr Kate Knobil, Senior Vice President - Value Evidence and Outcomes, GSK
Dr Xavier Kurz, Head of Service, Monitoring and Incident Management, EMA
Ms Claire Methven, Real World Evidence Manager, Janssen
Ms Bharti Navsariwala, Senior Director Regulatory Affairs – Oncology, Takeda
Ms Enkeleida Nikai, Director of Real World Evidence, Eli Lilly
Dr Susana Pinheiro, Senior Teaching Fellow and Programme Director, University College London

Dr June Raine CBE, Director of Vigilance and Risk Management of Medicines, MHRA
Dr Andrew Roddam, Vice President & Global Head Epidemiology, GSK
Ms Sunayana Shah, Head of Regulatory Affairs and Pharmacovigilance, ABPI
Dr Aliki Taylor, Director, Global Outcomes and Epidemiology, Takeda
Dr Alex Thompson, Strategic Epidemiology Lead, UCB
Professor Darren Toh, Associate Professor, Harvard Medical School & Harvard Pilgrim Health Care Institute
Dr Massoud Toussi, Lead, Pharmacoepidemiology and Drug Safety, IMS Health
Professor Adrian Towse, Director, Office of Health Economics
Dr Irwin Tran, Group Health Outcomes Manager, Roche
Professor David Webb FRSE FMedSci, Christison Chair of Therapeutics and Clinical Pharmacology, University of Edinburgh
Dr Tim Williams, Head of Research, Clinical Practice Research Datalink
Sir Kent Woods FMedSci, Chair of the Management Board, EMA
Dr Mark Wright, Acting Head Interventional Research, Clinical Practice Research Datalink
Dr Hakim Yadi, Chief Executive, Northern Health Science Alliance

Secretariat
Ms Victoria Charlton, Head of Policy, Academy of Medical Sciences (FORUM lead)
Ms Liberty Dixon, Policy Officer, Academy of Medical Sciences (project lead)
Mr David Bennett, Policy Officer, Academy of Medical Sciences
Dr Claire Cope, Senior Policy Officer, Academy of Medical Sciences
Ms Clio Korn, Policy Intern, Academy of Medical Sciences

Appendix III Delegate survey responses

Ahead of the meeting, delegates were asked to respond to the following two questions:

1) How would you/your organisation define: a) 'real world data', and b) 'real world evidence'?

2) What data sources do you consider to be included within these categories?

A summary of the responses can be found below.

Question 1: How would you/your organisation define a) real world data and b) real world evidence?

There was significant variation in responses, with some delegates using the terms 'real world data' and 'real world evidence' interchangeably, while others drew several key distinctions between the two.

Most were agreed that **real world data are clinically-relevant data routinely collected at the point of care and outside of the context of conventional randomised controlled trials**. Some felt that such data could be collected either prospectively, for example through forward-looking clinical or observational studies, or retrospectively, through the analysis of existing data; however, others drew a distinction between data collected for the purpose of experimentation and 'post hoc data gathering'. As one delegate described it:

> *'In practice I think that real world data and real world evidence are terms used interchangeably by most people, and reflect data used for decision making that are not collected in conventional controlled randomized clinical trials. However, I think there is a nuance here: many data are collected from intentional experiments that don't involve randomisation and control, in other words these are data sets which are form part of a specific plan to study a medical intervention. I would contrast these data with those that might be generally available (case reports, epidemiological analyses) that are recruited after the fact to understand more about a particular situation. Essentially, the distinction is therefore a priori experimentation rather than post hoc data gathering and I would use real world evidence for the former situation and real world data for the latter.'*

Others who distinguished between the two terms, **saw real world evidence as the 'outcome' or 'value' derived from the synthesis and analysis of refined real world data, usually applied to the understanding of a specific research question**. In the words of one delegate, real world evidence is the 'so what?'. According to this view, the collection of real world data does not automatically lead to the generation of real world evidence. Rather:

> *'Generating real world evidence requires the right data, the appropriate tools and methods to structure and interrogate it, and grounded science to turn it into actionable insights and engage stakeholders appropriately.'*

Question 2: What data sources do you consider to be included in real world data/evidence?

Delegates highlighted a variety of sources of real world data and evidence. The most commonly mentioned were relatively 'traditional', for example patient and disease registries and electronic health records. However, the responses also revealed the wide and rapidly increasing array of potential sources of real world data, which include emerging technologies such as social media, mobile devices and health apps, as well as other clinical (e.g. prescription records, CPRD, adverse event data) and non-clinical sources (audits, ONS mortality data, birth registration records).

The aggregated responses of all delegates are illustrated in the word cloud below:

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