FORUM
Academy of Medical Sciences

Next steps for using real world evidence

Summary report of a FORUM follow-up roundtable held on 24 January 2018

The Academy of Medical Sciences

The Academy of Medical Sciences

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Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, or its Fellows.

All web references were accessed in February 2018.

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Contents

Executive summary

The Academy of Medical Sciences convened a roundtable on 24 January 2018 as a follow-up to the FORUM workshop held jointly by the Academy and the Association of the British Pharmaceutical Industry in 2015.[1] In general, it was clear that progress in application of real world evidence (RWE) since 2015 has been relatively limited. Regulators, health technology assessment bodies and research organisations are committed to exploring its potential but to date, progress in use of RWE beyond pharmacovigilance has been incremental rather than transformational. Although there remains a strong interest in this field, further research is critical for better understanding the strengths and limitations of RWE, associated methodologies for its use in decision-making, and the different contexts in which it might be acceptable.

Key areas of discussion included:

- **Terminology** – there is still a **lack of consensus on the terminology** for real world data (RWD) and RWE which results in confusion about how these tools might be used. It was agreed that a clear set of definitions is needed with buy-in across key stakeholders, including further granularity on different terms within RWE such as RWD, real world treatment and real world treatment assignment. Study design (or methodologies for evidence generation) including treatment assignment such as randomisation is *separate* to RWE and lies outside of its definition.
- **Acceptability of RWE** – further **guidance is still needed on the acceptability** of different types of RWE and for different purposes. It was argued that this would stimulate innovation in the field by reducing uncertainty around the acceptability of new study designs. In addition, there remains a **dearth of case studies using RWE**, particularly in assessment of effectiveness, which needs to be addressed to build confidence in using this evidence.
- **Hierarchies of evidence** – It was widely agreed that traditional concepts of hierarchies of evidence should be replaced by **instead selecting evidence based on the research question** and what is most relevant and useful for answering this. This will require a robust understanding of the strengths and limitations of different types of evidence and

[1] Academy of Medical Sciences and the Association of the British Pharmaceutical Industry (2015). *Real world evidence.* https://acmedsci.ac.uk/file-download/38667-573d8796ceb99.pdf

more research is needed to explore the impact of different evidence generation methods and methodologies for using RWE in decision-making.

- **Data interoperability and standards** – there are still significant issues surrounding **lack of standardisation of RWD** which compromises the quality and utility of both the data and RWE that it generates, and also **limits interoperability** between different datasets. Minimum requirements for data input and collection may be needed to ensure high-quality data and interoperability, possibly using existing standards or coding guidance that are applied uniformly at a national level in clinical practice.
- **Building a learning health system** – **capacity and capability is needed to ensure routine collection of high-quality RWD** and this may require supporting the clinical workforce around data entry and standards as well as ensuring sufficient capabilities in data science and collection methods to enable use of such data. A learning health system was envisioned that embeds research in routine clinical practice, and this requires engagement with patients, clinicians and commissioners to foster an understanding of the value of research and data.
- **Study infrastructure** – The infrastructure for real world studies can be costly and complex as it can require substantial change to routine clinical practice and associated clinical pathways, and the establishment of associated infrastructure such as IT systems. Such costs and complexity can deter industry investment. In addition**, sustainable funding is needed** beyond simply financing the study duration, to maintain such infrastructure which can be capitalised upon for future studies at much lower cost and with greater ease.

Introduction

As the research and healthcare landscape shifts towards increasing personalisation of treatment, rising emergence of rare diseases and earlier access, it is simultaneously grappling with the challenges posed by the high costs and lengthy timelines of delivering medicines to patients. Real world evidence has the potential to help facilitate access and address some of this burden, whilst also providing a better understanding of medicines use in the 'real world'. However, significant challenges remain around generating and using real world data and developing it into robust real world evidence that can be used for decision-making. With an estimated one million patient interactions with the NHS every day in the UK alone, a wealth of potentially valuable information is being generated that is still severely under-utilised, so how can we better capitalise on this?[2]

Real world evidence (RWE) can provide a range of information about a treatment or clinical pathway such as efficacy, safety and effectiveness through to understanding clinical practice and disease stratification, generated using real world data (RWD). This data is collected outside of the highly controlled environment of a traditional randomised controlled trial (RCT) and can include data generated during the course of routine clinical practice (including pragmatic trials) as well as from outside the clinic such as through mobile devices. RWE could be used to support and complement the evidence generated through clinical trials such as RCTs, for example to make the findings more generalisable to real world usage, and in some cases to fill evidence gaps that are not addressed by RCTs such as populations where they are impractical such as in paediatrics.

RWE has been used for post-marketing authorisation safety monitoring and assessment for many years. However, there are few examples and a limited understanding of its role in effectiveness evaluation. The 2015 workshop held by the Academy and the Association of the British Pharmaceutical Industry elucidated some of the challenges to using RWE for this purpose which centred on the RWD used to generate the evidence, difficulties posed by using RWE in decision-making, and the general culture – including capacity and capability – around using this tool.

[2] Department of Health (2005). *Chief Executive's report to the NHS: December 2005.* http://webarchive.nationalarchives.gov.uk/20071204134909/http://www.dh.gov.uk/prod_consum_dh/idcplg?IdcService=GET_FILE&dID=11878&Rendition=Web

Therefore, the Academy held a follow-up workshop in 2018 to scope and explore progress against some of these challenges and understand the key aspects that need to be addressed before RWE can be used more widely for medicines. This built upon the following key challenges which were identified at the 2015 workshop as impeding use of RWE:

- The need for regulators and health technology assessment (HTA) bodies to provide further clarity on the acceptability of RWE and provide guidance on where different types of RWE might be applied to assess safety, efficacy and effectiveness.
- Lack of coordinated leadership to provide direction and ensure consistency in approaches to using RWE.
- The requirement for a shift in the perceptions of key stakeholders around the utility of RWE and how different types of RWE might fit into the evidence hierarchy for different uses.
- Absence of consensus on the terminology surrounding different evidence types, which is needed to ensure that they are clearly defined and used consistently.
- The need for a fit-for-purpose data infrastructure to support linked, multi-source datasets.
- The importance of addressing privacy and consent issues around data access through public and patient engagement.
- Variable data quality which demands clearer and more uniform data standards to be applied to ensure that the evidence generated from such data is reliable and robust.
- Improved capability and capacity in data extraction, analysis and new technologies is needed in the UK to address and fill the current skills gap.

In addition to considering the progress towards overcoming these challenges, the roundtable also aimed to explore whether there was value in, and appetite for, examining some of the challenges in greater detail at a future workshop.

Perspectives on real world evidence

Findings of the National Academies of Sciences, Engineering and Medicine

Dr Greg Simon, Senior Investigator, Kaiser Permanente Washington Health Research Institute, and Co-Chair of the National Academies of Sciences, Engineering and Medicine (NASEM) real world evidence (RWE) workshop series, opened by exploring the learnings from a recent workshop looking at incentives for using RWE.[3] This highlighted five dialectics that should be considered when discussing RWE.

Key considerations for RWE

The first of these themes is better defining real world data (RWD) and RWE, as lack of clarity is causing continued confusion amongst stakeholders. Dr Simon described real world data as data – or observations – that are *derived* from the real world, whereas real world evidence is the *relevance* of these data to the real world. RWD could include data from routine clinical care or observational data obtained outside the clinic such as through mobile devices. In general, RWE is generated using RWD, however, RWD does not always equal RWE.

The second dialectic is the level of curation that is appropriate for RWD. Curation can allow obstacles such as lack of standardisation to be overcome, but also risks homogenising data to the extent that crucial elements may be lost. Dr Simon posed the question of what curation model would be most appropriate, describing two extremes of where data entries could be highly restricted and based on expert management, or non-curated open datasets with unrestricted access.

The third consideration is how we identify true exemplars - *'icons'* – for using RWE and learn from them rather than being distracted by *'idols'*; the latter are case studies that may incorrectly appear exemplars but without true critique. This leads into the fourth key aspect around understanding the necessities of using RWE against the virtues of using this tool. To demonstrate this, Dr Simon challenged participants to consider emerging situations where evidence needs to be gathered more efficiently and at lower cost (and larger scale) possibly outside of an RCT, and what they might be prepared to trade in order to allow this, such as data quality. RWE may also have particular virtues in some circumstances over other forms of evidence (not just used for necessity) such as relaxation of conditions outside of a tightly controlled trial.

The final message was around the value of information in terms of the credibility and validity of evidence sources. Credibility implies an established evidence base but is not synonymous with validity which means an accurate prediction. For example, RCTs are a credible source of

[3] National Academies of Sciences, Engineering and Medicine (2018). *Examining the impact of real-world evidence on medical product development: I. Incentives: Proceedings of a workshop – in Brief* www.nap.edu/read/25024/chapter/1

evidence but have, in some cases, been shown not be valid in subsequent systematic reviews or meta-analyses. Instead, Dr Simon emphasised that the quest should be for sources of evidence that are valid and robust, with the caveat that these could be more complex, obscure or diffuse than traditional sources of evidence and so more challenging to use.

Key requirements for RWE

Dr Simon then outlined four key qualities that RWE needs to be a suitable evidence source:

1. *Generalisable* – This is whether the evidence generated now will apply later on. RWE should be able to predict outcomes and not just replicate trials or reflect a known set of outcomes. These predictions are accountable and can be tested in the near-future. The accountability of predictions of RWE are still in the early stages but its ability to predict is essential for its future utility.
2. *Relevant* – The use of RWE should be specifically selected on the basis of a research question about the real world where this type of evidence can be practically applied to provide a useful answer. RWE should be fit for the stakeholder, research question and research purpose to support decision-making.
3. *Adaptable* – RWE must accommodate the heterogeneity of patients, providers and systems. RWE should strive for utility in a range of contexts, however, adaptability to all scenarios is unlikely and therefore the answers will not apply in all contexts.
4. *Efficient* – RWE should be innovative and iterative in its design, as well being efficient to allow its use and adaption at pace and low cost, particularly because answers may be disposable and context-specific. Without these qualities, it will be difficult to justify the use of RWE alongside RCTs.

He highlighted that randomisation is considered an essential component of robust evidence, but that it is not *'all or nothing'*; there are different levels of randomisation that may be chosen depending on the context and lack of individual-level randomisation should not cause a study to be disregarded. For example, RWE may be more acceptable for safety assessment as adverse events may be rare or triggered by other factors such as contraindication which may be impractical to study in an RCT. Therefore general principles on when researchers might consider moving down different levels of randomisation would be useful. He noted that such situations include: large effects; proximal outcomes that are well understood with a simple causal pathway between treatment and outcomes; influences on assignment that are known and measurable; and when the question is urgent.

The UK regulator's perspective

Dr Katherine Donegan, Pharmacoepidemiology Research and Intelligence Unit Manager, Medicines and Healthcare products Regulatory Agency (MHRA), described how the MHRA sees RWE as data from routine clinical practice including electronic health records (EHRs), pragmatic trials, registries, observational data, monitoring devices and other sources. Such data has been critical in pharmacovigilance but is now also being used to extend indications or removing contraindications post-licensing, especially in sub-populations where pre-licensing studies are highly challenging, such as in pregnancy. There is a drive to improve RWD quality and robustness to optimise it for these type of activities beyond safety assessment.

New sources of data for pharmacovigilance

In the UK, the Yellow Card scheme remains a key source of RWE for pharmacovigilance.[4] However, the limitations of spontaneous reporting schemes are well understood and the MHRA are working on a number of ways to better capture and collect such data. Dr Donegan referenced the WEB-RADR initiative which is a collaboration exploring new methodologies for capturing adverse events via mobile devices and using these data for signal detection.[5] Through WEB-RADR, the MHRA is also working with other national regulatory bodies to explore the use of artificial intelligence and machine learning to mine social media for reports of adverse effects. For example, it was demonstrated that social media could have detected a risk of hallucinations associated with the use of the drug guanfacine several months prior to a label change for the drug reflecting this risk in 2013 by the US Food and Drug Administration (FDA).[6]

Dr Donegan also outlined the potential for greater integration of EHRs with spontaneous adverse event reporting systems and the MHRA is working to integrate data from the Clinical Practice Research Datalink (CPRD) much earlier into its assessment of signals arising from spontaneous reports through the use of a purpose-designed routine analysis platform. This aims to support routine pharmacovigilance by providing rapid insight into the clinical context of the signal including medical history and medication use of the exposed population, which may influence the risks of adverse events. It also facilitates additional exploration of the temporal association between the exposure and the event in a larger population not influenced by under-reporting in the same way as spontaneous reporting systems.[7] RWD from EHRs can also be used for other pharmacovigilance activities beyond signal detection such as monitoring effectiveness of risk minimisation and impact of regulation. For example, CPRD and data on prescribing practices has been used to monitor use of sodium valproate during pregnancy, which is known to cause congenital malformations and neurodevelopmental disorders in babies of women exposed during pregnancy.[8] Dr Donegan noted that these data have demonstrated the importance of improving integration of regulators with clinical practice to ensure safety messaging is effective.

Improving RWD

Dr Donegan noted some of the limitations of RWD such as gaps in data, misclassification, inconsistency and lack of structure. There is a need to continue identifying ways to improve upon the breadth and quality of RWD and some of these limitations can be addressed through combining data sources. For example, CPRD has developed a pregnancy register that links nearly one million pregnancies to the child's EHR, and this database is now being combined with other data sources for studies.[9] Continued efforts to link data sources in this way will be essential.

Uses of RWE beyond pharmacovigilance

Dr Donegan stated that EHRs may have the greatest potential in areas where RCTs cannot effectively generate information, for example in populations that would not qualify for an RCT. EHRs can be a valuable source of data for study design such as for identification of eligible

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[4] https://yellowcard.mhra.gov.uk/
[5] https://web-radr.eu/
[6] Caster O, *et al. (*2016). *Performance of Disproportionality Analysis for Statistical Signal Detection In Social Media Data*. Pharmacoepidemiol Drug Saf 2016, 25(S3), 3–679.
[7] www.cprd.com/home/
[8] Medicines and Healthcare products Regulatory Agency (2016). *Valproate and risk of abnormal pregnancy outcomes: new communication materials.*
[9] www.cprd.com/isac/Protocol_17_011R.asp

trial participants and recruitment brokering. They can also enable streamlined data collection and trial reporting and facilitation of large-scale pragmatic RCTs (pRCTs). Following trials, EHRs can also be used to explore the generalisability of trial results.

She advocated the need to consider the advantages of RWE, such as increased generalisability and 'real world' relevance of data against the limitations, including the information that can be captured and challenges in interpretation and finding causal associations. In addition, there are logistical complications when considering access to large patient populations and so it is important to capitalise on existing infrastructure such as that from the Salford Lung Study, or to invest in sustainable infrastructure for the future.

Vision for the future

Finally, Dr Donegan envisioned that RWE will continue to play a growing role in the regulation of medicines and so improving the availability and quality of the technologies and methodologies to collect and analyse RWD are a key priority. The continued drive towards personalised medicine and development of treatments for rare indications pose challenges to using RCTs for evaluation. However, there is a need to develop robust data and validated methodologies for RWE, and fully understand its limitations. She concluded by noting that all data and analyses must be considered on their own merit, and so challenged participants to consider where RWD can be used to complement other resources across the full lifecycle of a medicine.

The Early Access to Medicines Scheme (EAMS)

Dr Daniel O'Connor, Expert Medical Assessor, MHRA, described how the Early Access to Medicines Scheme could act as a vehicle for collecting RWE, not only for pharmacovigilance but also for effectiveness. EAMS aims to provide early patient access to medicines in an area of high unmet need where there is no licensed treatment available.[10] It has two stages where initially, a therapy is awarded a Promising Innovative Medicine (PIM) designation which acknowledges the potential of a therapy, and it may then may receive a further Scientific Opinion on the risks and benefits of the intervention.

EAMS could support products with a Scientific Opinion through a framework for RWE generation including what data could be collected and how, and whether by existing or novel methodologies. A therapy typically spends six months in EAMS before marketing authorisation during which there is the opportunity for gathering RWE to support future decision-making.[11] However, collection of RWD in pre-authorisation settings is particularly challenging and EAMS Scientific Opinion periods have been relatively short to date so there has been limited opportunity to collect RWD outside of pharmacovigilance requirements. Therefore, there is an opportunity to encourage industry to engage earlier to allow a longer period for RWD collection in the pre-marketing authorisation setting. In addition, Dr O'Connor identified several initiatives that will improve RWE generation as part of EAMS. For example, the Accelerated Access Review recognised that small and medium-sized enterprises (SMEs) may struggle to provide RWE for EAMS in order to support commissioning in the NHS.[12] A funding scheme will be launched to help address this by supporting effective evidence generation in EAMS. In addition, the EAMS Office for Life Sciences taskforce that focuses on the

[10] Further information on EAMS can be found at www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams
[11] PwC (2016). *The Early Access to Medicines Scheme (EAMS): An independent review* www.gov.uk/government/uploads/system/uploads/attachment_data/file/509612/eams-review.pdf
[12] Accelerated Access Review (2016) *Accelerated Access Review: Final Report* www.gov.uk/government/uploads/system/uploads/attachment_data/file/565072/AAR_final.pdf

development of the Scheme has been looking into the potential of RWE as part of its ongoing work.

In conclusion, Dr O'Connor outlined the need for a framework to guide data collection. Once companies confirm the types of data needed and the objectives for collection, such a framework could aid them in considering the practicalities of data collection, appropriate collection methods, surrounding regulatory frameworks and who they may wish to engage with to understand the evidence requirements.

Case study – Salford Lung Study

The pioneering Salford Lung Study is a pragmatic randomised controlled trial (pRCT) to test the safety and effectiveness of a novel treatment for asthma and chronic obstructive pulmonary disease (COPD) in routine care – a 'real world' setting – compared with current treatments. The study is a collaboration between GSK, NorthWest e-Health (NWeH), the University of Manchester and Salford Royal NHS Foundation Trust, amongst others, and involved over 2800 patients with 80 GP practices and 130 pharmacies.

The Salford Integrated Record (SIR) links primary and secondary care data in real-time to provide integrated health records at the individual patient level. The NwEh group then used the data from SIR to develop a linked database which extracts and integrates other data such as HES to create a comprehensive patient-level health record in almost real-time. The pRCT enables the inclusion of patients in routine clinical practice and captures a potentially much wider population than that reflected in a similar RCT.

The European Medicines Agency perspective

Dr Alison Cave, Principal Scientific Administrator, European Medicines Agency (EMA), began by discussing which to areas RWD may bring additional value; where was the need? She highlighted that rapid scientific advances enabling a personalised medicine approach can sometimes result in smaller, more focused RCTs, or lead to situations where an RCT is no longer feasible. In addition, although not new, the unknown generalisability of clinical trial results to normal clinical practice, in particular for high risk groups such as paediatrics and geriatrics, who are often excluded from RCTs, demands new approaches to gather complementary evidence. There are multiple other applications in which RWD may provide additional insight to complement the clinical trial; for example RWD may provide a clearer picture of current treatment and outcome patterns and may also be able to validate shorter-term surrogate endpoints with data on the long-term clinical relevance. All of these opportunities are underpinned by an increasing availability of healthcare data which, when accompanied by technological advances, provides new capabilities for storing, mining and analysing data from across multiple sources.

The acceptability of RWD

Dr Cave reiterated that RWD is already in routine use for safety assessments in Europe, predominantly for marketed products in drug utilisation and safety monitoring studies. Opportunities to capture robust data around safety are often limited and thus pharmacovigilance must utilise multiple data sources of sometimes variable quality to build a picture of a medicine's safety profile; RWD forms part of this jigsaw. In 2016, the EudraVigilance network received one million pharmacovigilance reports, of which only ~2000 possible signals were detected. Of these, 48 were validated for further consideration but a third were not considered to require further regulation, and a further third required more data to better understand the signal.[13] This illustrates the challenge in pharmacovigilance, and as a result it is currently more acceptable to use RWE to support pharmacovigilance decisions than effectiveness decisions where there are usually other mechanisms to capture data. Thus, which evidence is acceptable will vary according to the research question, the product life cycle stage, the decision being made, the unmet need, data quality, available methodologies and opportunities to capture other data.

It is also important to note that pharmacovigilance decisions often involve restricting access to a medicine, thus reducing exposure, while evidence on effectiveness may widen availability, thus increasing exposure. For the former decision, a regulator may likely be more willing to take on slightly less robust data. This is particularly challenging for a pre-marketing authorisation where there is limited information on the safety of a medicine. One of the few examples where RWD has been used to inform on effectiveness pre-authorisation is Zalmoxis, for which historical controls derived from RWD were accepted as part of its application for conditional marketing approval (see case study).

Case study – Zalmoxis

Zalmoxis, an immunogene therapy for high-risk haematological malignancies, was awarded conditional marketing authorisation in 2016 following a single arm trial using historical controls. An initial Phase II study showed promising efficacy but had no control arm and as a result, the Committee for Medicinal Products for Human Use requested a comparison to historical control groups using the European Society for Blood and Marrow Transplantation registry to match this group to the parameters and criteria of the control arm of the ongoing Phase III trial. The comparison to the control groups showed efficacy and so Zalmoxis was awarded conditional marketing authorisation while the Phase III trial was still underway. The high unmet need and the potential significant delay in capturing further data from the Phase III trial helped to facilitate this conditional decision. However, there were still uncertainties about the baseline characteristics of the historical controls and the long-term relevance of the surrogate marker for outcomes. Therefore, a post-authorisation, non-interventional study to determine long term safety and efficacy was requested as part of the approval.

[13] European Medicines Agency (2016). *EMA Annual Report* www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2017/05/WC500227334.pdf

The challenges of RWE

Converting RWD into sufficiently robust evidence for regulatory decision-making is difficult and progress is needed in developing robust methodologies to transform these data into valuable RWE. RWD may be unstructured, unvalidated and of unknown provenance which mostly results in more uncertainty than the traditional data used for regulatory decision-making. However, Dr Cave acknowledged that there are also uncertainties for RCTs such as their applicability to the entire population.

She went on to outline some of the uncertainties but began by reminding participants that RWD is not 'generated' for research, but is produced during the course of delivering clinical care and thus the data can be subject to systematic and unknown errors with issues around consistency, accuracy, completeness and representativeness. For example, there are over 5000 descriptions of codeine dosages in The Health Improvement Network (THIN) database and better standardisation of dosages could improve analyses and reliability. In addition, heterogeneity *between* datasets is a key challenge. For example, Madigan and colleagues systematically studied heterogeneity across 53 drug outcome pairs, 10 databases and 2 widely used study designs and reported that despite holding study design constant, 20-40% of observational database studies can deliver opposing results, swinging from statistically significant in one direction to the opposite direction depending on the choice of database.[14] Therefore database choice is critical. Heterogeneity in methodologies used for analysing datasets is also a potential source of inconsistency in results. For example, two studies examining the effect of bisphosphonates on oesophageal cancer risk found opposing results, despite using the same data source, time period and drug.[15] Progress is thus still needed in developing methodologies that can effectively turn these different data sources into evidence.

Next steps

Dr Cave proposed a series of solutions to build confidence in RWE including:

- Developing a deep understanding of the strengths and limitations of different data to allow the evidence generated from their analyses to be appropriately challenged.
- Improving interoperability and harmonisation of data sources across Europe and building common data models and registries. This needs consensus on the minimum requirements for data collection and transparency and standards around study design to allow direct comparisons, enable verification and build confidence.
- Access to data and considering use of 'data for the common good'.
- Robust privacy and governance arrangements to build patient trust in data use.

Dr Cave emphasised that while RCTs remain the gold standard for delivering an unbiased estimate of efficacy, disease areas where RWE has already been used could provide common learnings around requirements. For example, the EMA has an active patient registry initiative which brings together registries across Europe to facilitate collection of the same basic data elements within disease areas to improve standardisation and consistency and address data gaps. It is also looking at the opportunities for implementation of a common data model across European EHRs to facilitate timely data access so that safety questions, for example, can be answered more quickly. Ultimately the question should not be about RCT versus RWD but on how the two may complement each other to provide additional insight.

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[14] Madigan D, *et al*. (2013). *Evaluating the impact of database heterogeneity on observational study results.* Am J Epidemiol. **178(4),** 645–651.
[15] Green J, *et al.* (2010). *Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort.* BMJ **341**, c4444.

A global perspective: FDA

What are the goals of RWE?

Dr Jacqueline Corrigan-Curay, Director of the Office of Medical Policy, Center for Drug Evaluation, FDA described the key opportunities presented by RWE for better reflecting clinical practice in regulatory decision-making.[16] It can mirror the diversity of patient populations, improve efficiencies such as patient identification for trials and reducing duplicative data capture, and fill evidence gaps. However, it is essential that high regulatory standards for evidence are maintained at the same time. Given this potential, the FDA is evaluating the potential uses of RWE to support new indications or satisfy the requirements of post-approval studies. It is also aiming to impart further clarity around RWD and RWE by establishing the following definitions:

- *RWD* – data relating to patient health status and/or the delivery of health care routinely collected from a variety of data sources (including outside of the clinic such as wearables).
- *RWE* – clinical evidence regarding the usage and potential benefits or risks or a medical product derived from RWD analysis.

Evaluating the quality of data and methodologies

The FDA is examining ways to evaluate the quality of RWD and the methodologies used for analysis to determine the acceptability of RWE for different purposes, and has already produced guidelines for using EHR data in safety evaluation. The guidance advises that there should be procedures in place to ensure completeness, consistency and accuracy of data collection and errors or changes in data should be considered as criteria for the use of data sources.[17] In addition, study design should include comparator groups and consider the time frame, milestones, data sources, outcomes of interest and methods to control for bias.

Using RWE in regulatory decision-making

Again, the FDA has already used RWE in safety assessment activities with considerable experience of working with claims pharmacy data, for example through Sentinel (see case example).[18] To date, the FDA's use of RWE in determining effectiveness has been mainly limited to rare diseases and cancers in the form of single arm studies with large effect sizes and historical control groups derived from other RCTs. Evaluating effectiveness more widely is limited by concerns about the quality of data and the evidence base for such approaches, however, RWE could be highly valuable for filling evidence gaps such as heterogeneous populations. Dr Corrigan-Curay noted that claims data tends to be better curated and referenced estimates that 80% of EHR data are unstructured. Heterogeneity is also present in more structured data such as blood tests and medical image analyses. EHR data could add the clinical granularity lacking in claims data but better linkage and interoperability are needed to enable this. In addition, mobile technologies are potentially valuable tools for incorporating patient reported outcomes into data captured from the healthcare system. An additional challenge in the US healthcare system is that patients frequently move from one health insurer to another and the extent which healthcare data are siloed in the insurance-based system can make longer-term follow-up challenging.

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[16] Sherman RE, *et al.* (2016). *Real-World Evidence — What Is It and What Can It Tell Us?* N Engl J Med **375;** 2293-2297.
[17] Food and Drug Administration (2013). *Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.* www.fda.gov/downloads/drugs/guidances/ucm243537.pdf
[18] www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm

Demonstration projects

The FDA is running several demonstration projects on RWE which aim to test the feasibility of different trial methodologies and strategies for selecting trial sites and recruiting participants. These projects include an ancillary study to a large cardiovascular outcomes study in collaboration with the Duke Clinical Research Institute and GlaxoSmithKline, to examine the potential for EHRs to facilitate patient recruitment, populate baseline characteristics and identify endpoints for trials.[19] A second collaboration with the American Society of Clinical Oncology and CancerLinQ aims to examine RWD on oncology patients to learn about real-world use of cancer immunotherapies.[20] Dr Corrigan-Curay recognised that in thinking about possible models for conducting RCTs in a healthcare setting, certain characteristics of the intervention may make such studies more feasible. For example, approved medications with a well understood safety profile so that the intervention could be administered in practice and where outcomes might be reliably assessed even in the absence of blinding or placebos. Regarding non-randomised study designs, there is still concern as to whether observational data can provide reliable information on causality or whether it may only be a complementary evidence tool. FDA is funding researchers at Harvard Medical School who will be using RWD analyses from claims databases to attempt to replicate the findings of Phase III/IV RCTs.

Finally, Dr Corrigan-Curay outlined the FDA's priorities for expanding the use of RWE. The first is to engage with stakeholders to recognise the challenges and collaboratively identify gaps in collective knowledge. Following this, the FDA, in collaboration with others, hopes to develop a framework for an RWE programme to assist both its own processes and its partners.

Case study – Sentinel Initiative

The Sentinel Initiative is the FDA's electronic records system primarily intended for safety monitoring of medicines. It is a distributed data system in which partners provide access to their insurance claims data to answer safety questions. Sentinel data alone has already been used in various safety assessment activities such as the safety of rivaroxaban versus warfarin, and when linked with adjudicated medical records it has been used to examine the association between intussusception and rotavirus vaccinations.[21,22] In efforts to expand Sentinel beyond safety monitoring, the IMPACT-Afib trial is using Sentinel claims, pharmacy and laboratory data to find eligible patients for recruitment into the trial on whether an educational intervention can improve the management of patients with atrial fibrillation.[23] As Sentinel matures, the FDA is seeking to make it a national resource and has an initiative to allow access for private sponsors.

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[19] www.ctsi.duke.edu/news/events/nih-collaboratory-grand-rounds-leveraging-electronic-health-data-multinational-clinical
[20] www.asco.org/about-asco/press-center/news-releases/cancerlinq-partners-fda-study-real-world-use-newly-approved
[21] Chrischilles EA, *et al.* (2018). *Prospective surveillance pilot of rivaroxban safety within the US Food and Drug Administration Sentinel System.* Pharmacoepidemiol Drug Saf **24(2)**, 1-9.
[22] Yih WK, *et al.* (2014). *Intussusception Risk after Rotavirus Vaccination in U.S. Infants.* NEJM. 370, 503-512.
[23] https://clinicaltrials.gov/ct2/show/NCT03259373

Using RWE in Health Technology Assessment

Dr Linda Landells, Associate Director - Technology Appraisals (Cancer Drugs Fund), National Institute of Health and Care Excellence (NICE), described how NICE is working to evaluate methods for collection of RWD and its synthesis into useful evidence.[24] At present, NICE primarily uses RWE to support evidence in ultra-rare diseases, corroborate trial data, inform areas of modelling outside of effectiveness such as utility/cost or regularly for the evaluation of devices. However, there are other potential ways for RWD to support HTA. There is an opportunity to use EAMS data for appraisals before marketing authorisation although this has not yet been done because, as outlined by the MHRA, the time between EAMS approval to full marketing authorisation is currently too short to obtain robust evidence for decision-making. Dr Landells noted that evolving evidence needs in areas such as rare disease and adaptive licensing are driving changes in NICE's decision-making processes in response to earlier licensing and use of a more 'uncertain' evidence base. She stressed that NICE are receptive to RWE being presented as part of the evidence to support HTA.

The Cancer Drugs Fund and using RWD for managed access

The Cancer Drugs Fund (CDF) is a managed access fund where RWE may play an increasing role. In addition to, or sometimes instead of, ongoing clinical trials, post-HTA RWD is used. This data is typically obtained from the Systemic Anti-Cancer Therapy (SACT) dataset, which collates outcomes for drugs in the CDF and baseline commissioning, aiming to create a high-quality resource that can supplement ongoing clinical trials. There are ambitions for SACT to incorporate hospital data but the lack of linkage and variable quality of these data means that smaller, higher-quality datasets are currently used for CDF decisions.

Challenges and opportunities for RWE

Dr Landells described how NICE appraisal committees still rely on long-term evidence and other sources of evidence will need to be proven to be widely incorporated into appraisals. One of the challenges of using alternative sources of evidence are heterogeneities such as variable dosing regimens and coding, as well as robustness of historical controls. Similarly, obtaining baseline quality of life data can be challenging in the real-world setting. This is important because clinical trials are often stringent with measured outcomes and may not capture the full extent of quality of life benefits of a therapy in diseases that are poorly understood, such as ultra-rare diseases. For example, Dr Landells described a trial of a treatment for mucopolysaccharidosis which included quality of life measures but that did not fully capture benefits experienced by patients such as a marked decrease in the duration of fatigue, which were in fact key for patients.[25] As a result, the drug was recommended for managed access with the intention of obtaining observational evidence on the benefits. She noted that maintaining consistent methodologies for observational studies, especially using prospective data collection, will be challenging due to changes in practice over time. EUnetHTA is looking at strategies for homogenising registries across Europe to account for differences in clinical practice across countries.[26] Finally, she noted that there is still a lot of uncertainty around determining relative effectiveness for single arm trials.

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[24] www.imi-getreal.eu/
[25] Hendriksz CJ *et al.* (2015). *Multi-domain impact of elosulfase alfa in Morquio A syndrome in the pivotal phase III trial* Mol Genet Metab **114(2);** 178-185.
[26] www.eunethta.eu/

Challenges to further progress in using real world evidence

Participants discussed progress in the following key areas from the 2015 workshop held by the Academy and the Association of the British Pharmaceutical Industry: terminology; hierarchies of evidence; methodologies for using RWE; capacity and capability; and data access, standards and interoperability. The various drivers for better using RWE were considered which, in part, lie in the rising demand for early access to therapies and robust post-authorisation effectiveness studies. However, although progress has been made in using RWE for safety assessment, there has been little development in use of such evidence for post-authorisation effectiveness studies.

Professor Andrew Morris CBE FRSE FMedSci, Director of Health Data Research UK, envisioned that success in using RWE will be finding the right balance of a composite of evidence for therapies, with RWE as one tool in a portfolio of options. He noted that RCTs cannot answer all questions and there are times when observational data are important. However, there is a need to demonstrate confidence in such data through improving methodologies and the surrounding data framework, and he advised of the need to harness data science in how we execute RWE.

Professor Morris noted the drive to better capitalise on RWE caused by the rising unsustainability of the clinical trials enterprise. Separation of trials from clinical practice and routine service delivery is a fundamental issue and convergence is needed to reduce costs and improve generalisability of trial results to the 'real world'. He underlined the value of a *'learning health system'* where research influences practice and vice versa, employing randomisation wherever possible. In the future, RWE might be used for active rather than passive surveillance as a collaborative process embedded in the healthcare system and underpinned by analytics throughout a product lifecourse rather than discrete, one-off studies pre- and post-marketing authorisation.

Terminology for real world evidence

There is still confusion and ambiguity around the terms RWE and RWD and definitions differ across stakeholders. It was agreed that much **greater precision is needed around this terminology** and clearer, more accurate definitions must be established alongside guidance on using these tools. There was general agreement that RWD refers to observations from the real world whereas RWE is how these observations may be used to make relevant predictions. RWE might incorporate a range of data, including RWD, to make such predictions about an outcome in the real world (such as use of a medicine, incidence of a disease or behavioural patterns). Clear distinctions between RWD and RWE are also important as they do not necessarily require the same criteria. For example, we want high-quality evidence but this does not necessarily demand high-quality data.

Precision of terms

The discussions emphasised that is critical to clarify that RWE is *not* the opposite of RCTs, nor does it reflect whether data is randomised or not. There are two aspects to RWE; the first is where the contributing data is obtained from, such as from the real world or traditional clinical research, and the other is the method of study which may or may not include randomisation. **RWE must not be considered a substitute for randomisation** and randomisation is separate to the type of data used, instead relating to the methodologies used and treatment assignment. One participant proposed that RWE may be better termed as *'practice generated data'* to clarify that assignment is specific to the methodology rather than the data used. Participants then suggested that a further subset of terms might help to separate RWD and RWE from how they are generated or used, and so it was agreed that consensus is needed on the following terms: RWD; real world treatment; and real world treatment assignment. Real world treatment was proposed as a term for the generation of evidence of effectiveness in a real world setting such as from pragmatic randomised controlled trials (pRCTs) and real world treatment assignment covers study design and randomisation related to this.

When to use RWE and how?

Overcoming hierarchies of evidence

Overall, participants recognised the need to move away from evidence hierarchies and instead consider the strengths of different types of evidence. Evidence selection should be based on what is most useful and suitable for answering a research question, particularly when there are many different types of RWE. It was generally agreed that **a composite of evidence is often needed for decision-making**. Rather than using an inflexible hierarchy, it would be helpful for the research and regulatory communities to agree guidelines for the criteria that need to be met by RWE to ensure its acceptability for regulatory and HTA decision-making.

A key area of discussion was the need for clarity on the role of RWE in supplementing – or in some places complementing – RCT data. It was generally felt that RCTs remain the gold standard for evidence of effectiveness and should not necessarily be *replaced* with RWE-based methodologies or even supplemented with such evidence unless it adds real value alongside RCT data. However, it was argued that in some cases RWE can be particularly useful such as for small patient populations or those where there is an urgent unmet need. In addition, when there is a very heterogeneous target population, RWE may identify adverse events not present in a homogeneous highly controlled population, better reflecting later 'real world' use. RWE can also play a role in accelerated access pathways such as EAMS where conditional

approval may allow therapy use before full licensing. Although existing schemes typically require medicines to have completed Phase III trials which demonstrate efficacy, there may be opportunities to use RWE during Phase III to enable access whilst gathering effectiveness data from real world usage at the time. The French 'Temporary Authorisation for Use' (ATU) scheme, similar to EAMS, already proactively collects RWD so that products undergo continual review on benefits and risks over the course of the licensing period.

In addition, changes in evidence needs and health trajectories may make RWE an increasingly valuable tool. For example, it was suggested that real world studies could be particularly useful in studies of multi-morbidities. Rather than using a traditional RCT to look at a specific outcome associated with a product, an RWE approach may enable researchers to explore effects on multiple intermediate and related outcomes without using a disease-centric approach.

One participant expressed concern that focusing on use of observational real world studies may be incorrectly trying to address the challenge of increasing cost and complexity of randomised trials caused by ICH-GCP guidelines, such as their failure to address key scientific principles, misapplication beyond drug registration trials for which they are designed and over-interpretation due to lack of clarity. The participant suggested that this can instead be overcome through establishing guidelines that facilitate randomised trials and management of biases, based around the underlying scientific principles of randomised controlled trials, to support appropriate and informed use of randomisation in trial design.

How can RWE be used to explore effectiveness?

Use of RWE is still primarily limited to pharmacovigilance with reasonable confidence in its use for safety assessment and monitoring by regulators compared with evaluation of effectiveness. A key limiting factor for use in effectiveness studies is the scarcity of exemplars to demonstrate the robustness and utility of using RWD to generate this evidence. There are a few examples emerging of using RWE to assess effectiveness, but many more are needed to build confidence and understand its potential utility for different purposes. **Thus, there was a call for greater clarity from regulators on the types of RWE that are acceptable and for what purpose.** Such guidance would incentivise change by encouraging exploration of new methodologies that fulfil these acceptability criteria, whilst building learning around the potential uses and limitations of RWE.

Despite limited progress in RWE effectiveness studies, some participants noted an increase in appetite to explore different methodologies for evidence generation. However, there is uncertainty around the potential risks of using RWE as supporting evidence for drug authorisation or new indications. Regulators noted that this could be addressed, in part, by establishing more robust development plans earlier in the product lifestyle that consider the different instruments that are available. Confidence is particularly lacking in the assignment of treatments and randomisation, and the general acceptability of clinically generated data as a robust evidence source. A better understanding of bias and confounding with RWE is also needed. It was noted that the Salford Lung Study indicates willingness to accept data and provision of treatment in clinical practice but it still involved random assignment. This highlights that **data source, treatment delivery and assignment can be separate aspects to consider in study design for RWE** and indeed, all types of evidence. It was noted that adapting all three of these things (alternative data source and delivery such as routine clinical practice, as well as non-randomised assignment) is a huge challenge.

HTA typically uses RCTs as the primary substantive evidence source. More recently, systematic reviews and meta-analyses are emerging as robust evidence for efficacy; however,

such reviews often do not occur until years after a product is licensed and so do not support licensing decisions but rather continued use of a product as a treatment of choice. A better understanding of the potential of RWE and possible methodologies for *prospective* comparative effectiveness research is needed to support approval. In addition, assessing comparative effectiveness for single arm trials is very challenging and there are ongoing efforts to explore how this evidence can be generated. For example, there is research being undertaken into the best methodologies for eliminating bias from indirect comparisons and IMPACT-HTA, an Innovative Medicines Initiative (IMI) project, will look at methods for adjusting bias in single arm trials.

Randomisation

A key challenge pertaining to methodologies and how RWE is used is randomisation. As a keystone for generating quality evidence, randomisation removes potential sources of bias and generates objectively comparable evidence between groups. As outlined above, the term RWE does not reflect whether data is randomised or not, this is an assignment choice specific to a study methodology. However, randomisation can be challenging. For example, randomisation in research practice aims to reduce confounding by eliminating bias, however, clinicians want to offer the best possible care to patients and so may be hesitant to randomly assign patients to a clinical pathway which may not offer this. It was concluded that the strengths and weaknesses of randomised and non-randomised data need to be understood to avoid confusion around different methodologies and how these might be applied to RWE.

Building capacity and capability

Creating research infrastructure for real world studies

Whilst highly successful, it was acknowledged that pRCTs such as the Salford Lung Study require significant investment in the infrastructure (including data management processes) and human resource needed for the study. It was suggested that the cost and uncertainty around the acceptability of study results may disincentivise others from pursuing similar approaches, and funding needs to be sustainable but is often short-term to cover the study duration. Therefore, maintaining the infrastructure can be problematic without additional centralised, sustained support. One advantage of this support is the continued availability of infrastructure for future studies to be conducted at much lower cost. It was felt that a collaborative approach to investing in this infrastructure for studies will be most effective as it is unrealistic to expect all costs to be covered by a single stakeholder. There was also a strong message to consider a more coordinated national approach rather than piecemeal investment, building on the pioneering approach of the studies that have taken place so far.

Building capabilities in data collection

The management of diabetes in Scotland through the Scottish Care Information Diabetes Collaboration (SCI-DC) is a useful exemplar for establishing appropriate infrastructure to effectively accumulate and link data across various healthcare services.[27] SCI-DC uses a common data model spanning primary, secondary and tertiary care across many NHS Trusts and GP surgeries in Scotland, demonstrating a viable model of registry-based care in diabetes. The registry can be appended with additional data such as genomics and imaging and also allows patients to be screened for study eligibility and contacted for recruitment.

[27] www.sci-diabetes.scot.nhs.uk/

Participants felt that it was valuable to apply learnings from the SCI-DC to the UK more broadly, but that scaling up of this smaller initiative across the entirety of the UK population in many disease areas may be challenging. In addition, this exemplar demonstrates **the need for building the relevant capabilities for data management and handling within the NHS** and making this part of everyday practice. For wider roll-out, software such as registries needs to be intuitive and easy to use to ensure high data quality. Culture around data sharing across healthcare professionals and different healthcare silos also needs to be addressed to overcome the challenges in integration of data and continuity of care across clinical boundaries that arises from the fragmentation of care pathways and data repositories.

Real world studies require appropriately qualified staff for both high-quality data collection and its generation into high-quality evidence. There was concern that the UK might not have the capacity of data scientists to sustain a widespread RWE approach, and it was agreed that capacity building is necessary in the short-term to address this. In addition, suggested approaches for improving data recording in the NHS ranged from training and IT system support to incentives such as the Quality Outcomes Framework which could encourage more systematic data entry, and has already improved the quantity of data collected. The approach which is selected must ensure the collection of research-grade data in the clinic.

Creating a learning health system

Today, the practical challenges of collecting RWD remain significant. Participants expressed concern that other industries have more quickly realised the opportunities afforded by digitisation and system integration. In part, it was felt that this is due to a lack of recognition of the important role of research in the healthcare system where ideally every clinician would act as a researcher and every patient as a research participant. This vision of a learning health system where evidence generation, research and clinical care are integrated is key to capitalising on the potential of data and tools such as RWE. Health Data Research UK will have a role in championing the transformation into such a system. It was noted that Scandinavian countries are particularly advanced in establishing such learning health systems.

Public engagement and data access

In addition to the need for culture shift in the clinical community, participants stressed the importance of buy-in from the public and patients both for use of RWE in regulation and HTA and creating an understanding of how health data can be used to improve care. The importance of building public trust was highlighted and the need to engage with organisations such as Understanding Patient Data, Connected Health Cities and citizen's juries to raise awareness of the benefits and risks of RWE and data sharing and better understand patient needs.[28,29]

A common data model: data standards and interoperability

To date there has been little progress to address challenges around data standardisation and interoperability, and to enable unstructured data to be used in a robust way. There are two types of unstructured data, the first of which are fully unstructured from sources such as social media. The utility of such vastly unstructured data remains unclear, and although

[28] https://understandingpatientdata.org.uk/
[29] www.connectedhealthcities.org/

progress will likely be in the very long-term, there is potential for these data to act as complementary sources of evidence. The second form are semi-structured data where some coding may exist but not to the appropriate standard for direct use. Therefore, participants reiterated an essential, short-term goal of **establishing a common data model with clear data standards** (whilst avoiding duplication of existing standards), and Health Data Research UK can play an important role here.

Data standardisation

Participants agreed that a minimum level for processing or curation of data may be required to allow its practical use as RWE. Standardisation of coding across the healthcare system therefore provides a real opportunity. Complete standardisation is challenging but it was agreed that minimum data standards should at least be highlighted, with better guidance on coding and terms to ensure consistency. In particular, clinician support through software and training could ensure that data are coded correctly. Appropriate incentives can also ensure accurate coding and participants referred to the US where financial incentives have driven some improvement in coding processes. However, it was noted that the NHS requires a wider culture change to fully recognise the relevance of clinical practice and associated data for research. Although new technologies such as natural language processing may have potential to enable interpretation of unstructured data, more consistent and accurate coding of data sources would greatly increase the reliability of analyses and RWE.

Interoperability of datasets

Datasets often need to be combined for RWE and this can be challenging if only some of the datasets are structured and coded whilst others are unstructured. Inefficiently combining structured and unstructured data, or even high and low-quality data, risks reducing the quality and utility of the data to the *'lowest common denominator'* – that is, reducing the robustness of the entire dataset to that of the lowest-quality/most unstructured data that is incorporated.

Hospital data is particularly challenging as it is fragmented and variable in quality, particularly across Europe. There is a drive to improve standards and linkage but with smaller datasets rather than broader linkage nationally or internationally. Interoperability is important across silos both within and outside of health systems as triangulation of data from primary care records, hospital records, HES and other data is essential to ascertain full outcomes. For example, one delegate noted that for research into cardiovascular disease (CVD) outcomes, there is about 80% ascertainment with CPRD and HES data, but myocardial infarction data from MINEAP is needed for CVD outcome trials to ensure 98% ascertainment.

Priorities for the future

The roundtable highlighted that progress in most areas since the 2015 workshop has been incremental rather than transformational. Notably, this area is still lacking tangible case examples. However, it also underlined the general appetite, and increased activity amongst industry, researchers and regulators, to better explore the potential of RWE beyond pharmacovigilance. Moving beyond these discussions around using RWE to address existing paradigms, participants advocated the importance of looking at its potential to address future evidence needs in 20-30 years' time such as the shifts in the healthcare environment, including the rising pressure of multimorbidities.

Future priorities arising from the discussions to enable the ambitions for using RWE to be fully realised included:

- Establishing clearer terminology around RWD and RWE including a better understanding of the definitions with RWE and how to clearly distinguish RWE from separate, more general discussions around methodologies.
- Building a learning healthcare system where RWE generation is embedded as part of clinical practice, fostering a research culture within the healthcare system that closely engages clinicians and patients.
- Leadership and guiding principles are needed on acceptability of different types of RWE in different contexts – what RWE is used and how – to be developed by regulators with buy-in from stakeholders wherever possible.
- Identifying technologies and bringing together guidance for data standards and interoperability to ensure baseline collection of high-quality RWD.
- Developing a richer repository of case studies demonstrating the robustness of RWE for different purposes or its limitations, and for better understanding the practicalities of collected and interpreting RWD and evidence, and where further research is needed.

Annex 1: Agenda

08.45-09.15	**Tea, coffee and registration**
09.15-09.25	**Welcome and introduction from the Chair** Professor Sir Alasdair Breckenridge CBE FRSE FMedSci (Chair), Former Chair, MHRA
09.25-09.50	**US workshops on RWE: findings so far** Dr Greg Simon, Senior Investigator, Kaiser Permanente Washington Health Research Institute
Real world data to real world evidence: how are we using RWE?	
09.50-10.20	**Medicines and Healthcare products Regulatory Agency** Dr Katherine Donegan, Pharmacoepidemiology Research and Intelligence Unit Manager, MHRA & Dr Daniel O'Connor, Expert Medical Assessor, MHRA
10.20-10.45	**European Medicines Agency** Dr Alison Cave, Principal Scientific Administrator, EMA
10.45-11.00	**Tea and coffee**
11.00-11.25	**US Food and Drug Administration** Dr Jacqueline Corrigan-Curay, Director, Office of Medical Policy, FDA
11.25-11.50	**National Institute for Health and Care Excellence** Dr Linda Landells, Associate Director - Technology Appraisals (Cancer Drugs Fund), NICE
11.50-12.00	**Summary** Professor Sir Alasdair Breckenridge CBE FRSE FMedSci (Chair), Former Chair, MHRA
12.00-12.30	**Lunch**
What is the vision for RWE in the future, and how can we achieve this?	
12.30-12.50	**Hierarchies of evidence: the acceptability of RWE** Professor Andrew Morris CBE FRSE FMedSci, Director, Health Data Research UK
12.50-14.00	**Discussion: What needs to be done to fully maximise on the potential of RWE?** *Chaired by Professor Andrew Morris CBE FRSE FMedSci, Director, Health Data Research UK* • What progress has been made to date on using RWE, particularly for efficacy and effectiveness assessment? In particular, this might look to explore the themes from the 2015 workshop including: acceptability of RWE; methodologies; hierarchies of evidence; data infrastructure; capacity and capability. • Overall, what are the short-term, and long-term, aspirations for using RWE? • What are the remaining challenges to using RWE; and how do these compare across the UK, Europe and globally? • What are the next steps to addressing some of these challenges? • In light of these discussions, what are the **five key priorities** for the next five years to overcome current challenges and enable the aspirations for using RWE to be met?
14.00-14.10	**Summary from the chair and close** Professor Sir Alasdair Breckenridge CBE FRSE FMedSci (Chair), Former Chair, MHRA

Annex 2: Attendees List

Co-chairs
Sir Alasdair Breckenridge CBE FRSE FMedSci, Former Chair, Medicines and Healthcare products Regulatory Agency
Professor Andrew Morris CBE FRSE FMedSci, Director, Health Data Research UK

Speakers
Dr Alison Cave, Principal Scientific Administrator, European Medicines Agency
Dr Jacqueline Corrigan-Curay, Director of the Office of Medical Policy, Center for Drug Evaluation, Food and Drug Administration
Dr Katherine Donegan, Pharmacoepidemiology Research and Intelligence Unit Manager, Medicines and Healthcare products Regulatory Agency
Dr Linda Landells, Associate Director - Technology Appraisals (Cancer Drugs Fund), National Institute for Health and Care Excellence
Dr Daniel O'Connor, Expert Medical Assessor, Medicines and Healthcare products Regulatory Agency
Dr Greg Simon, Senior Investigator, Kaiser Permanente Washington Health Research Institute

Participants
Dr Virginia Acha, Executive Director, Global Regulatory Policy, MSD
Mr Bart Barefoot, Director, VEO & Real World Evidence Policy & Advocacy, GlaxoSmithKline
Ms Angela Blake, Head of Outcomes Research, Evidence Based Medicine & HTA Policy, Pfizer
Mr Adam Collier, Director, Real-World Evidence NEMEA Region, IQVIA
Professor Sir Rory Collins FRS FMedSci, Professor of Medicine and Epidemiology and Head of Nuffield Department of Population Health, University of Oxford
Professor Carol Dezateux FMedSci, Professor of Clinical Epidemiology and Health Data Science, Queen Mary University London
Dr Peter Feldschreiber, Barrister, 4 New Square
Professor Martin Gibson, Honorary Professor and Consultant in Diabetes & Endocrinology, University of Manchester
Dr David Gillen, Vice President international Medical Affairs, Vertex
Dr Shahid Hanif, Head of Health Data & Outcomes, Association of the British Pharmaceutical Industry
Mr Peter Holland, Life Sciences Industry Innovation Adviser, Oracle
Dr Pall Jonsson, Associate Director R&D, National Institute for Health and Care Excellence
Professor Kamlesh Khunti FMedSci, Professor of Primary Care Diabetes and Vascular Medicine, University of Leicester
Dr Brendan Krause, Vice President for Europe, OptumLabs
Mr Andrew Matthews, UK Life Sciences Lead, Global Business Services, IBM
Ms Claire Methven, Real World Evidence Manager, Janssen
Ms Tamsin Morris, Real World Evidence Lead, AstraZeneca
Mr Jonathan Plumb, Head, Global Real-World Data & Evidence Sciences, UCB
Dr Andrew Roddam, Vice President & Global Head Epidemiology, GlaxoSmithKline
Mr Morgan Romine, Managing Associate, Robert J Margolis Center for Health Policy, Duke University
Dr Carolyn Shore, Director, Forum on Drug Discovery, Development, and Translation, National Academies of Sciences, Engineering, and Medicine
Dr Simon Tilley, Life Sciences Director, Northern Europe, SAS

Dr David Tyas, Associate Director of Health Economic and Outcomes Research, Bristol-Myers Squibb
Ms Amanda Wagner Gee, Program Officer, National Academies of Sciences, Engineering, and Medicine
Professor David Webb FRSE FMedSci, Christison Chair of Therapeutics and Clinical Pharmacology, University of Edinburgh
Dr Tim Williams, Head of Data Tools and Technology, Clinical Practice Research Datalink
Dr Louise Wood, Director of Science, Research and Evidence, Department of Health

Secretariat
Ms Liberty Dixon, FORUM Policy Manager, Academy of Medical Sciences
Mr James Squires, Policy Officer, Academy of Medical Sciences
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