CIRS CONTEMPORARY INSIGHTS WORKSHOP

Real-world data to real-world evidence for assessing efficacy and effectiveness:

Opportunities and challenges for new medicines development, regulatory review and health technology assessment

23-24 JUNE 2016

TYSONS CORNER, VIRGINIA, US

A BRIEF SUMMARY

CIRS Centre for Innovation in Regulatory Science

Synopsis authors

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CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of the Intellectual Property and Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

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BACKGROUND

The use of new analytical tools applied to large, diverse, complex data sets, so called “big data”, the development of devices to track and gather real-time healthcare data and information and the use of digital media are on the increase in the healthcare environment and have the potential to be of great value if harnessed and utilised appropriately. These benefits include improving the ability to positively impact patient outcomes through understanding of disease characteristics and treatment patterns, enhancing medicines compliance and aiding in interpreting treatment outcomes for individual patients.

The opportunity to use these technologies and derive their potential benefits to assess the efficacy and effectiveness of therapeutic options is in its infancy. Although they could be the key to establishing a credible new generation of fit-for-purpose real-world evidence (RWE), pharmaceutical companies have been cautiously investigating the use of the various technologies that contribute to big data collection (e.g., social media, electronic health records) and the application of analytics to these data sets. This may be related in part to the lack of clarity of regulatory requirements, privacy and legal concerns and a lack of consensus around the use of robust and acceptable collection and analytical methodologies.

Questions have been raised as to how best to deploy innovative collection and analytic technologies to maximise their effectiveness. Approaches such as the Advancing Medical Innovation initiative encourage the FDA to identify opportunities to use big data to streamline and support pre- and post-approval activities. In Europe, collaborative projects in the area of post-authorisation efficacy studies have identified the need for companies and agencies to be able to measure efficacy and effectiveness in the real-world use of new medicines. This is mirrored by the need for HTA agencies to make difficult decisions regarding how new medicines will be used in the real world and to confirm the expected benefit and value, often derived largelyfrom controlled clinical studies.

Over the last 3 years the potential of real-world data and analytics has been discussed in CIRS Workshop syndicates as opportunities to enhance patient engagement, reduce uncertainty in the development and approval space, as well to serve as a natural process for the collection of benefit and risk data post-authorisation. Collecting data from a mix of evidentiary experiences would support novel flexible regulatory pathways that accelerate reviews and access to medicines, and therefore, will likely play a key role in transforming medicine development and access over the next decade. The CIRS Scientific Advisory Council therefore, proposed that CIRS organise a workshop in 2016 to discuss RWD sources and RWE with a focus on the utilisation of this novel information to illuminate efficacy and effectiveness.

WORKSHOP OBJECTIVES

- Discuss how sources of real-world data and the special analytics being applied to them could provide a robust platform for the collection and use of real-world evidence in company, regulatory and HTA decision making
- Identify the types of data sources, collection technologies and methodologies that could provide robust, fit-for-purpose information and the potential hurdles for these being used in regulatory and HTA decision making
- Recommend the opportunities for use of new collection and analytical methodologies and technologies using RWD to enable the assessment of efficacy and effectiveness in the post-authorisation period

WORKSHOP CHAIRS

Dr Richard Moscicki, *Deputy Center Director for Science Operations, CDER, FDA, USA*

Prof Hans-Georg Eichler, *Senior Medical Officer, European Medicines Agency*

Professor Sir Alasdair Breckenridge, *Former Chair, Medicines and Healthcare Products Regulatory Agency, UK*

WORKSHOP PROGRAMME

SESSION 1: UTILISING REAL-WORLD DATA FOR INSIGHT INTO EFFICACY DURING DEVELOPMENT– WHAT IS THE POTENTIAL?	
Chair's welcome and introduction	**Dr Richard Moscicki**, *Deputy Center Director for Science Operations, CDER, FDA, USA*
Utilisation of RWD and RWE in medicines development and utilisation, today and tomorrow – a disruptive shift or slow evolution for more informed decision making?	**Dr Massoud Toussi**, *Lead, Epidemiology and Drug Safety, North Europe, Middle East, South Asia and Africa, Real-World Evidence Solutions, IMS Health, France*
Stakeholders perspective on the potential barriers and opportunities of utilising relevant, robust and credible RWD or RWE to support quality decision making around efficacy and effectiveness	
FDA viewpoint	**Jonathan Jarow,** *Director Medicines Policy, FDA, USA*
HTA viewpoint Industry viewpoint	**Prof Sarah Garner,** *Associate Director, Science Policy and Research, National Institute for Health and Care Excellence (NICE), UK* **Brande Ellis Yaist,** *Senior Director- Global Patient Outcomes and Real-world Evidence, Eli Lilly and Company, USA*
Use of real-world data and real-world evidence for safety: What are the learnings, and how can they be applied to the use of real-world data for efficacy/effectiveness?	**Dr John Skerritt,** *Deputy Secretary, Department of Health, Australia*
How can companies blend traditional development strategies with real-world data to enable improved internal and external decision making? How can robust data generated through non-RCT sources be made acceptable to regulatory agencies? What sort of RWD generated during development would be possible and fit for HTA agencies purposes?	**Dr Margaret McDonald,** *Senior Director, Real-world Data & Analytics, Global Health and Value Pfizer, USA* **Prof Hans-Georg Eichler,** *Senior Medical Officer, European Medicines Agency* **Brent Fraser,** *Vice-President of Pharmaceutical Reviews, Canadian Agency for Drugs and Technologies in Health (CADTH)*
SESSION 2: REAL-WORLD EVIDENCE: HOW TO MAXIMISE ITS USE TO OPTIMISE THE EFFECTIVENESS PROFILE OF NEW MEDICINES POST-APPROVAL	
Chairman's introduction	**Prof Hans-Georg Eichler,** *Senior Medical Officer, European Medicines Agency*
Infrastructure and stakeholder collaboration: Is this the key to harnessing RWD and enable improved translation of clinical research into clinical practice?	
USA collaborative case study **–** Green Park Collaborative	**Dr Sean Tunis,** President and Chief Executive Officer, Center for Medical *Technology* Policy, USA
New approaches/technologies to describe the benefit/harms profile and value proposition in the post-approval phase – What are the practical regulatory and HTA challenges?	
Regulatory agency view point on post-approval efficacy studies and how big data could be used to provide real-world data – European Medicines Agency	**Dr Peter Mol,** *Principal Clinical Assessor, Medicines Evaluation Board, The Netherlands*

WORKSHOP PROGRAMME

Agency viewpoint on how companies can best "prove" value and how could RWD (EHR, disease state registries, claims) be harnessed to provide real-world evidence?	Prof Luca Pani, *Director General, AIFA, Italy*
Utilization of connected electronic health databases	**Prof Marion Bennie,** *Professor of Pharmacy, University of Strathclyde, UK*
From efficacy to effectiveness and the role of HER-enabled pragmatic clinical trials: The Salford Lung Studies	**Andrew Roddam,** *VP & Head Real-world Evidence and Epidemiology, GSK, UK*
SESSION 3: SYNDICATE SESSIONS	
Topic A: How could real-world data and alternate data sources shape a more predictive process of "efficacy to effectiveness assessment" using evidence generated both in and outside the clinical drug development process**?** Topic B: What framework needs to be in place to ensure fit-for-purpose real-world data and what would be the most important attributes of pilot initiatives to increase availability, reliability and utility of real-world evidence? Topic C: Current barriers and possible solutions to the implementation of real-world data collection, analysis and reporting and how non-regulatory stakeholders will use real-world evidence to inform their decisions	**Chair: Dr Sean Tunis,** *Founder and CEO, Center for Medical Technology Policy, USA* **Rapporteur: Dr Karen Weiss,** *Vice President, Global Policy and Intelligence, Janssen Research and Development, USA* **Chair: Prof Richard Barker,** *Founding Director, CASMI, UK* **Rapporteur: Gracie Lieberman**, *Director of Regulatory Policy, Genentech, USA* **Chair: Prof Mark Trusheim**, *Visiting Scientist, MIT Sloan School of Management, USA* **Rapporteur**: **Dr Patrick Brady,** *Vice President, Head of Regulatory Policy and Intelligence, Bayer, USA*
SESSION 4: SYNDICATE SESSIONS FEEDBACK	
Chairman's introduction	**Prof Sir Alasdair Breckenridge**
Early access schemes: How can real-world data be used as part of the conditions for early access? Why facilitated access pathways are important and how real-world data will be crucial to these processes	**Prof Richard Barker,** *Founding Director, CASMI, UK* **Prof Mark Trusheim**, *Visiting Scientist, MIT Sloan School of Management, USA*
SESSION 5: BEYOND EFFECTIVENESS: THE POTENTIAL FOR RWD TO ENABLE NOVEL APPROACHES TO PRE-AND POST-APPROVAL MEDICINES DEVELOPMENT	
Optimizing the patient journey - Use of RWD in the wider healthcare environment to enable better decisions and dissemination of evidence to inform good treatment decisions	
Improving healthcare – a payer perspective Patient viewpoint	**Dr Murray Ross**, *Director and Vice President, Kaiser Permanente Institute for Health Policy, USA* **Ann Lucas,** *Co-Director, DuchenneConnect Registry, Parent Project Muscular Dystrophy, USA*
Big data – a critical component of a learning healthcare system	**Jean Slutsky,** *Chief Engagement and Dissemination Officer and Program Director for Communication and Dissemination Research, Patient-Centered Outcomes Research Institute (PCORI), USA*

SYNDICATE SESSION RECOMMENDATIONS

Topic A: How could real-world data and alternate data sources shape a more predictive process of "efficacy to effectiveness assessment" using evidence generated both in and outside the clinical drug development process?

Chair: **Dr Sean Tunis,** *Founder and CEO, Center for Medical Technology Policy, USA;*
Rapporteur: **Dr Karen Weiss,** *Vice President, Global Policy and Intelligence, Janssen Research and Development, USA*

Recommendations

- Industry should engage in earlier discussion with stakeholders to improve the quality of real-world evidence at registration
- Industry should catalogue available real-world data within administrative systems to determine if they are fit for purpose to evaluate disease and outcomes
- Industry should make clinical trials more pragmatic; including the development of nested trials, the broadening of inclusion criteria**,** the inclusion of concurrent controls for payers; the expanded use of alternative endpoints using patient-reported and technology-derived outcomes and the provision for expanded access for serious disease
- All stakeholders should enable a culture shift in which patients own their medical records and unique patient identifiers enable the collection of extended real-world treatment information; healthcare professionals would be incentivized to change prescribing behaviours and in this new environment, risk is shared among patients, payers and industry

Topic B: What framework needs to be in place to ensure fit-for-purpose real-world data and what would be the most important attributes of pilot initiatives to increase availability, reliability, and utility of real-world evidence?

Chair: **Prof Richard Barker,** *Founding Director, CASMI, UK;*
Rapporteur: **Gracie Lieberman**, *Director of Regulatory Policy Genentech, USA*

Recommendations

- Conduct case studies (pilots), focusing on therapeutics and economic challenges that cannot be addressed with randomised clinical trials; engage new technology players to facilitate access to real world data
- Perform a systematic review of past and current efforts and studies of the use of real-world evidence
- Conduct stakeholders surveys of current engagements/projects, future interests, challenges/threats and feedback on potential framework
- CIRS should consider sponsoring workshops on the topic of adapting real-world evidence to current regulatory systems or understanding how these data could serve as a platform for creating creatively new systems

Topic C: Current barriers and possible solutions to the implementation of real-world data collection, analysis and reporting and how non-regulatory stakeholders will use real-world evidence to inform their decisions

Chair: **Prof Mark Trusheim**, *Visiting Scientist, MIT Sloan School of Management, USA;*
Rapporteur*:* **Dr Patrick Brady,** *Vice President, Head of Regulatory Policy and Intelligence, Bayer, USA*

Recommendations

- Regulators and HTA bodies should collaborate in developing scientific standards for real-world data and evidence, taking global applicability and the need for local flexibility into consideration
- Understand how key stakeholders value and use real-world evidence in decision making through ongoing CIRS research
- Engage patients more in the process, development and use of decision making
- Stakeholders should collaborate in the co-creation of transparent incentives demonstrating a commitment to real-world data and evidence collection and use, potentially developing a thought paper
- Stakeholders should embrace a paradigm shift to encourage a focus on efficiency in the use of real-world data and evidence.

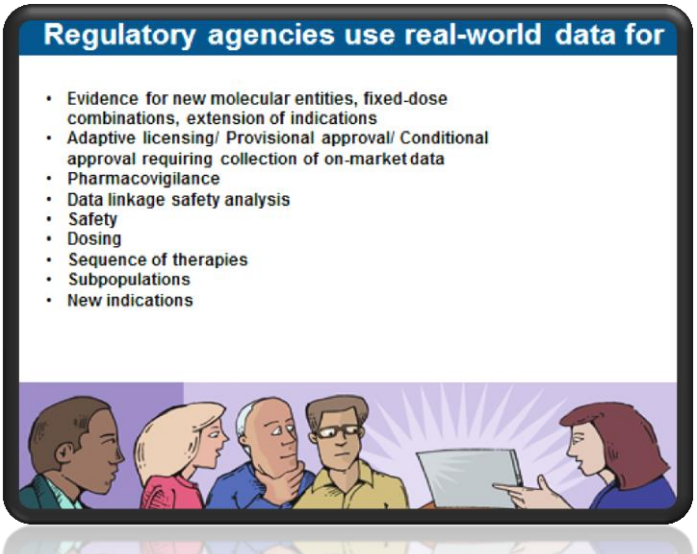
PRESENTATION HIGHLIGHTS

SESSION : UTILISING REAL-WORLD DATA FOR INSIGHT INTO EFFICACY DURING DEVELOPMENT – WHAT IS THE POTENTIAL?

In this session, stakeholders provided their perspective as to how real-world data are currently being used to support quality decision making as well as potential barriers and opportunities for its continued evolution

The recent growth in real-world evidence for medicines supports the evolution from disease-oriented to patient-oriented care and brings additional insights regarding the benefit-risk value of a drug as it is used in real life. However, as **Dr Massoud Toussi,** *Lead, Epidemiology and Drug Safety, North Europe, Middle East, South Asia and Africa, Real-World Evidence Solutions, IMS Health, France* reminded Workshop participants, there is need for frameworks to create meaningful insight from real-world data and to detail how decision making includes real-world evidence. Harmonisation in the supply capacity and governance of real-world data is also required but European multi-stakeholder forums such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) can help by bridging issues in capacity and knowledge about how to address the requirements.

Dr Jonathan Jarow, *Director Medicines Policy, FDA, USA* agreed with Dr Toussi that governance issues are key in the use of real-world evidence including patient privacy, data security, transparency and confidentiality , access, conflict of interest and intellectual property and the fact that separate governance structures are likely to have different funding models. There is no statutory barrier to the use of real-world evidence in the regulation of medicines in the United States, however, and Dr Jarrow provided six examples of its use in submissions for new indications. He concluded that for progress to occur in this area, it is crucial that stakeholders engage healthcare providers and patients, promote adherence to practice guidelines and patient prescription compliance , establish a framework for confidentiality and security, adopt a common approach to configuring digital healthcare data and eliminate barriers that promote complexity, while ensuring appropriate data safeguards.



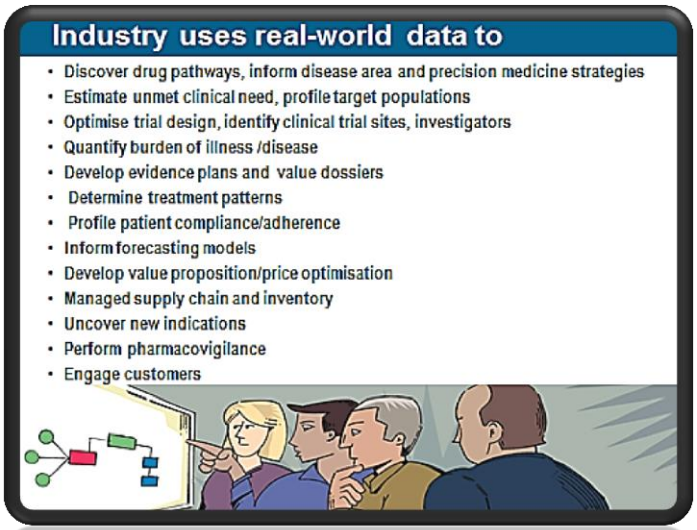
Adapted from presentations of Dr Jonathan Jarow, FDA and Dr John Skerritt, TGA

Prof Sarah Garner, *Associate Director, Science Policy and Research, National Institute for Health and Care Excellence (NICE), UK* also presented multiple examples of the use of real-world evidence. At NICE, such evidence is used to research the effectiveness of interventions or practice in real-world in UK settings, provide epidemiologic information and information on current practice and resource use and to audit the implementation and potential impact of guidance. Prof Garner pointed out that the biases against the use of real-world data are topic specific and must be understood and mitigated. Further methodologic investment is essential and presents an opportunity for collaboration. Substantial 'up-skilling' and resources are required and general and project-specific roles and responsibilities including costs must be agreed upon, with data privacy and ethics and informed consent assured. Evidence standards must still be met for regulators, health technology assessors and payers and the use of real-world data will not obviate the need for confirmatory trials when appropriate.

Providing an industry perspective, **Brande Ellis Yaist,** *Senior Director- Global Patient Outcomes and Real-world Evidence, Eli Lilly and Company, USA* said that the most important aspect of real-world data is its ability to provide relevant information about patients and that the increasing trend of integration with technology and daily life makes it more possible to get a 360^{o} view of this most important stakeholder.

In addition, industry uses real-world data to understand disease mechanism, progression, prevalence, and unmet need, to inform, design and execute randomised controlled trials, observational studies and health economic models, to conduct safety surveillance and to support regulatory approval and inquiries. Ultimately, real-world evidence is a necessary part of the drug development and authoorisation processes and is critical to achieving and sustaining reimbursement. The scientific standards and appropriate use of this evidence is a dynamic set of issues and opportunities that must be addressed by all stakeholders.

Dr John Skerritt, *Deputy Secretary, Department of Health, Australia* said that most regulators currently use real world evidence for post-market safety and pharmacovigilance studies and this use is expanding to explore big data. There is also increasing use of real-world evidence in market authorisation in support of extensions of indications, the adaptive or conditional licensing of new molecular entities and open label or observational trial data for rare, life-threatening conditions. Challenges include the fact that incentives to collect real-world data may be limited, the validity of real-world data may be hard to confirm and sources poorly connected. In addition, the use of different standards makes it hard to combine data sets, linkage for data collected for different purposes is difficult to achieve, there may be regulatory and privacy constraints to transferring data and health records may not be detailed enough to determine specified outcomes. Despite these challenges, greater use of real-world evidence could help reduce the gap between regulatory approval and access.

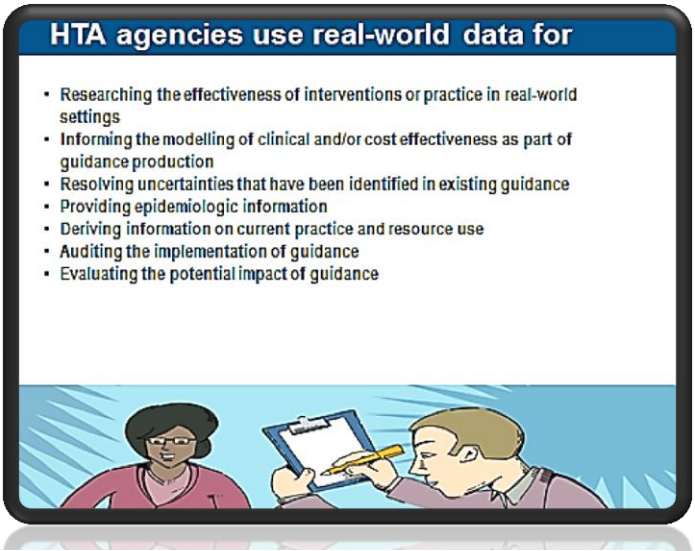


Adapted from presentation of Dr Margaret McDonald, Pfizer

Despite being variable in quality, real-world data are being increasingly used in healthcare decision making and can provide useful, actionable insights for payers and industry. **Dr Margaret McDonald,** *Senior Director, RWDnA Global Health & Value, Pfizer Inc* provided examples of current and potential uses of real-world data across the life cycle of medicine development including the ability to estimate unmet medical need, optimise clinical trial design and execution, develop evidence plans and value dossiers and perform pharmacovigilance. For example, to prioritise subpopulations of obese patients for drug target development based on frequency of comorbidity and severity of disease burden, Pfizer integrated and analysed clinical and claims data, ultimately discovering different healthcare resource use according to comorbidities but little differentiation across body mass index ranges. It is anticipated that the digital data era will revolutionise the development and targeting of new medicines. New technologies and analytics may reduce the time to insights and self-service tools lead to increased analytic efficiencies and broader use.

Prof Hans-Georg Eichler, *Senior Medical Officer, European Medicines Agency* suggested that rich information regarding past and current patients from real-world data and randomised clinical trials may overcome the “stigma” that can be associated with evidence not derived from randomised clinical trials. This resource was not available to the randomised clinical trial pioneers in the mid-20th century and we are now starting to develop the methodology and skill set to make use of it. For example, existing patient-level randomised control trial data could be used to augment the information for the control arm of a clinical trial, allowing for the more efficient allocation of trial resources to the test treatment with fewer patients randomised to the control group. In another example, control groups can be constructed from real-world data and/or data from past randomised clinical trials. After an efficacy threshold, study protocol and analysis plan are determined by agreement from relevant decision makers, patients would be enrolled in a single-arm study and a sensitivity analysis would be performed. Efficacy would then be established if the threshold is crossed. An inconclusive result would lead to a randomised clinical trial or a second single- arm study and poor results would result in product termination.

There is often a gap between the evidence supporting health technology assessment recommendations and the needs of the payer, with questions arising as to a product's place in therapy; its impact on healthcare resources and costs and quality of life; the effect of comorbidities on utilisation and the cascading effect of new technology. Real-world data might answer some of these questions, but according to **Brent Fraser, VP,** *Pharmaceutical Reviews, Canadian Agency for Drugs and Technologies in Health (CADTH,* the use of these data in Canada has been largely ad-hoc. There has been limited experience and some challenges with both the use of registries and evidence-building programmes, particularly with obtaining the necessary input from healthcare practitioners. Real-world data presents the potential to manage challenging questions such as those around rare or orphan diseases. It also allows the ability to identify subsets of patients that have a greater response to manage early recommendations. It should be recognized that real-world data does not supplant confirmatory data but is rather used to supplement decision making and that processes need to be in place to evaluate these data. In addition, an awareness of real-world analyses that are underway can help inform health technology assessment, expert committees need to be comfortable with reviewing real-world evidence to inform recommendations and payers must support its use.



Adapted from presentation of Prof Sarah Garner, NICE

SESSION: REAL-WORLD EVIDENCE: HOW TO USE TO OPTIMISE THE EFFECTIVENESS PROFILE OF NEW MEDICINES POST-APPROVAL

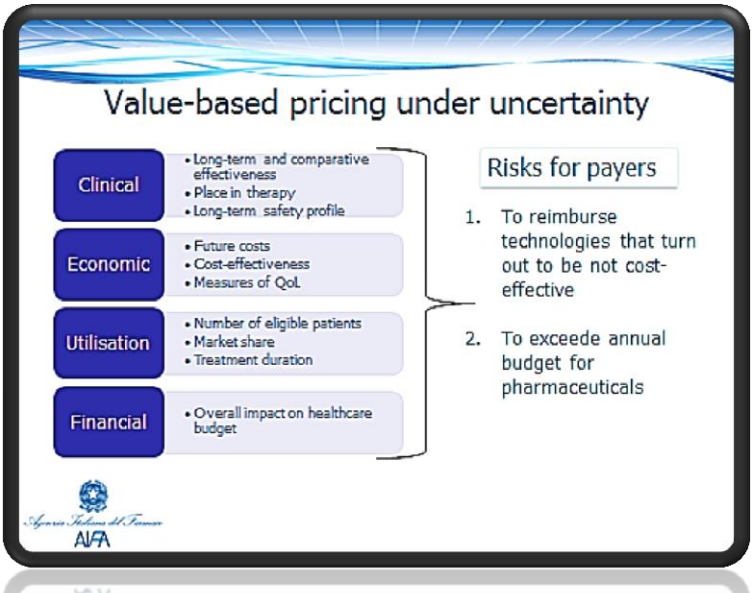
In this session, speakers proposed techniques to add to information about new medicines including developing frameworks, harnessing registries, using outcomes-based reimbursement, linking databases and tracking results of adaptive pathways.

The Green Park Collaborative is a multi-stakeholder forum in the US that is working to clarify the evidence expectations of post-regulatory decision makers. The Collaborative observed that although several groups have produced methods guidance that can be used to develop or evaluate observational or real-world evidence studies, no single guidance has involved significant breadth and depth of stakeholder perspectives representing a broad range of real-world evidence users and there is no clear consensus or transparent way that decision makers can identify "good" real-world evidence for decision making. **Dr Sean Tunis,** President and Chief Executive Officer, Center for Medical *Technology* Policy, USA detailed the efforts of the Green Park Collaborative Real-World Evidence Project, a group whose objective is to develop a framework and tools to guide decision makers to use real-world evidence appropriate for their decision-making purposes more confidently and consistently. It is envisioned that the group will develop an initial draft framework for assessing real-world evidence, will incorporate stakeholder feedback into a revised framework and accompanying draft recommendations or best practices, develop and implement a communication plan for uptake of the final framework and recommendations.

In current regulatory practice, registries are primarily used for the monitoring of safety of orphan products or products approved under exceptional circumstances, although they are also used for more innovative products that meet unmet clinical needs despite remaining uncertainty. However, existing disease registries are under-utilised and could be improved in terms of an increase in recruitment rates, enhancement in data quality and an improvement in the representative nature of

registry populations. **Dr Peter Mol,** *Principal Clinical Assessor, Medicines Evaluation Board, The Netherlands* explained that the European Medicines Agency Initiative on Patient Registries aims to support benefit-risk decision making by collecting high-quality data from existing available and adequate registries and working toward improvements in existing registries. The feasibility and usefulness of a proposed approach by the Initiative will be tested in a pilot. The Initiative is also exploring the careful development of the use of real-world data for effectiveness. There is limited experience but increasing potential for its use in this regard and will require collaboration between and among stakeholders.

Dr Luca Pani, *Director General, Italian Medicines Agency (AIFA)* outlined the Italian experience using outcomes data for managed entry agreements (MEAs) that enable the reimbursement of a medicine subject to specific conditions. AIFA MEAs use certified registries at the national and patient levels to collect real-world data on safety and effectiveness aftermarket authorisation to mitigate the impact of uncertainty in cost and effectiveness and expenditures and to enable patients to access promising new drugs in a context of uncertainty. The advantages to industry for outcomes-based agreements are earlier market access and maintenance of a list price. The advantages to payers are that the risk of paying for unsuccessful treatments is shifted to manufacturers and the actual price to the payer is lower than the list price. This provides incentives for manufacturers to find the target population that is most likely to benefit from the new treatment.



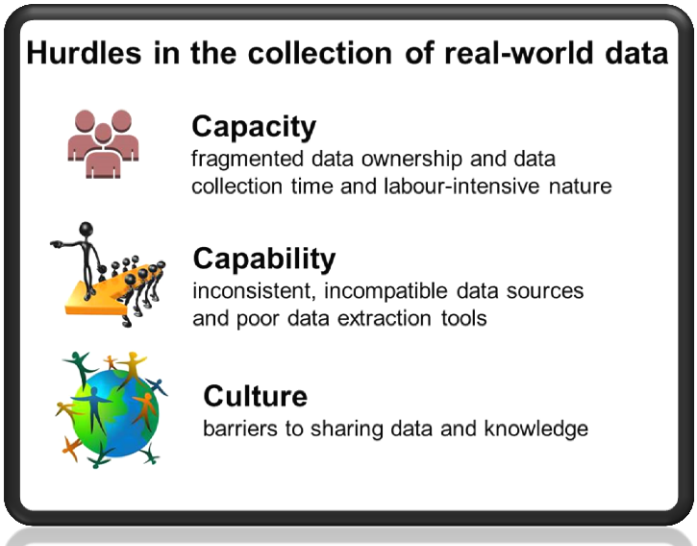
From presentation of Dr Luca Pani, AIFA

Prof Marion Bennie, *Professor of Pharmacy, University of Strathclyde* discussed case studies of research by the Farr Institute, facilitated by connected electronic health datasets within the Scottish National Prescribing Information System , which covers 5.3 million (96%) people in Scotland and employs unique patient identification numbers. By analysing data from multiple sources and collaborating with the government, public sector, academia and industry, the Farr Institute aims to unleash the value of vast sources of clinical, biological, population and environmental data for public benefit. In one case example, estimating the association between community prescription of antimicrobials and *Clostridium difficile* infection (CDI) using data linkage, an association between community-acquired CDI and community prescribing of antimicrobials was clearly demonstrated and quantified differentially by the type of antimicrobial. This analysis generated information to potentially populate clinical decision support tools to guide clinicians on the risk of antimicrobial prescription in individual patients.

The first study of its type in the world, the Salford Lung Study was a pragmatic, randomised phase III real-world effectiveness trial of a treatment of chronic obstructive pulmonary disease (COPD). **Dr Andrew Roddam,** *VP and Head Real World Evidence and Epidemiology, GlaxoSmithKline, UK* explained that the study employed constant real-time data collection of all healthcare interventions and safety monitoring. In the study, 2800 patients aged forty years and older diagnosed with COPD who had experienced disease exacerbation in the previous three years were randomised 1:1 to a new open-label inhaled therapy versus continuing their existing therapy. The Salford Study, which was randomised, with an active control and a robust primary endpoint maintained scientific rigour. In addition to linking databases, it combined the experience, expertise and technology of its individual and organisational participants. Whilst the study required an enormous logistical effort, it can offer important information for clinicians, healthcare decision makers and most especially patients and will provide valuable information about how to conduct these types of studies in future.

Real-world data is an important part of the Medicines Adaptive Pathways for Patients (MAPPs), a collaboration between the Massachusetts Institute of Technology Center for Biomedical Innovation's New Drug Development Paradigms Initiative, the

EMA, patient, payer and health technology assessment groups, the European Federation of Pharmaceutical Industries and Associations, and the Innovative Medicines Initiative. According to ***Professor Richard Barker,*** *Founding Director, Centre for the Advancement of Sustainable Medical Innovation (CASMI),* MAPPs incorporates collaborative upfront cross-stakeholder discussion of evidence requirements, adaptive, conditional licensing to allow earlier access (before phase 3 trials), precision medicine for stratification and risk management, real-world data as part of the evidence base for broader, longer term marketing authorisation and adaptive or alternative pricing mechanisms. MAPPS adaptive licensing pilots and the ADAPT-SMART project under IMI are underway and CASMI work on ethics, patient engagement and data collection is finished but the concept remains of adaptive licensing remains controversial. In addition, there are challenges for real-world data collection related to capacity, that is, fragmented data ownership, data collection that is time and labour intensive; related to capability, that is, inconsistent, incompatible data sources and poor data extraction tools and related to culture, that is, barriers to sharing data and knowledge



Adapted from the presentation of Prof Richard, Barker, CASMI

Prof Mark Trusheim, *Visiting Scientist, MIT Sloan School of Management, USA* presented a discussion of the work of the Massachusetts Institute of Technology New Development Paradigms (MIT NEWDIGS) programme that concerns adaptive biomedical innovation (ABI) and real-world evidence. ABI focuses on improving early, appropriate and sustainable /patient access to new treatments. Core to ABI is explicitly recognising, managing and reducing the uncertainties inherent in medicines. Beyond the scientific, these include the real-world clinical, operational and stakeholder financial uncertainties. ABI emphasises enabling and improving the decisions that impact the flow and availability of new medicines to patients and has a large role for real-world data and the resulting evidence. The EMA Adaptive Pathways pilot is one implementation of ABI principles. The MAPPs and adaptive pathways pilot have caused some to assert that the early approval of medicines reduces patient safety. However, MAPPs development, with its emphasis on early use by a target population tracked via real-world data repositories may detect adverse events with fewer total patients unknowingly exposed to risk compared with the historic approach of RCTs followed by use by all comers in all indications, using traditional adverse event reporting systems

SESSION: **BEYOND EFFECTIVENESS: THE POTENTIAL FOR REAL-WORLD DATA TO ENABLE NOVEL APPROACHES TO PRE-AND POST-APPROVAL MEDICINES DEVELOPMENT**

In this session, combining the experience and expertise of thousands of healthcare practitioners and real-world data from millions of patients and their carers informs high-quality, cost-effective treatment decisions.

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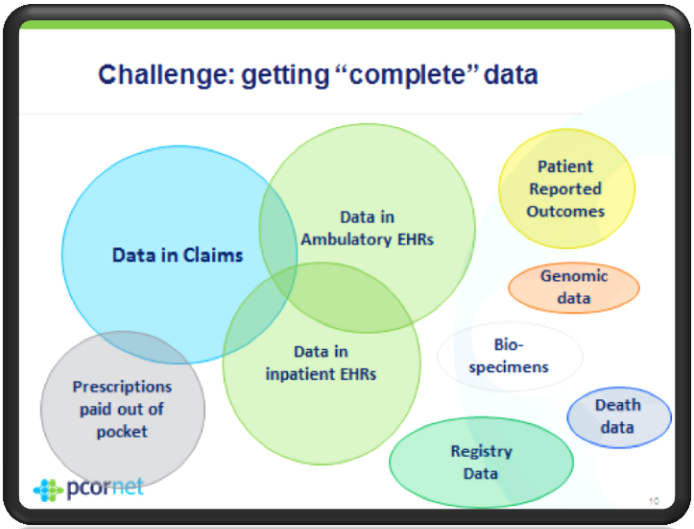
Serving approximately 10.5 million people in 8 states and the District of Columbia with 38 hospitals and 19,000 physicians, Kaiser Permanente is the largest private integrated healthcare delivery system in the United States. **Dr Murray Ross**, *Director and Vice President, Kaiser Permanente Institute for Health Policy, USA* said that this disaggregated system, with its homogenous electronic records, terminology and data standards enables the analysis of real-world observational data to understand the clinical outcomes of treatment over time and across large populations. Although these data have been

primarily used to change approaches to clinical care, Dr Ross detailed one example in which proposed premium pricing for gender-specific joint replacement was denied, after a two-year trial among Kaiser Permanente patients did not show advantage in terms of repeat surgeries, rehabilitation time or general patient experience. In another example, the use of real-world data showed that improved clinical outcomes were achieved for colorectal screening with faecal occult blood testing kits compared with colonoscopies, as measured by fewer end-stage colorectal cancer diagnoses together with improved morbidity and mortality rates. In this case, the volume of patients who were willing to use the kits outweighed their comparative lack of precision.

Duchenne Muscular Dystrophy (DMD) is a rare paediatric disease with no treatment or therapy and the Parent Project Muscular Dystrophy (PPMDI) is the largest advocacy organisation focused on this condition. In 2007, PPMD created DuchenneConnect (DC) to bridge the gap between clinical trials and patients. **Ann Lucas**, *Co-Director, Duchenne Connect Registry, Co-PI, DuchenneConnect PPRN* related that there are over 3500 registrants in the DC patient registry, two thirds of whom are from the United States. The registry collects patient data to identify individuals with specific mutations, using validated measures from the Patient Reported Outcomes Measurement Information System and the Pediatric Outcomes Data Collection Instrument. In addition, the group is part of Treat NMD, an international group of neuromuscular registries enabling researchers to use data from around the world to report on over 7000 DMD mutations. As one of twenty patient-powered research networks in the National Patient Centered-Clinical Research Network (PCORnet), DC can participate in projects involving computable phenotypes, healthcare utilisation and comparative effectiveness. Finally, the Duchenne Regulatory Science Consortium Data derived from registries, trials, natural history studies and other academic researchers has been used to develop a Duchenne disease progression model to make clinical trials more efficient and successful.



From the presentation of Jean Slutsky, PCORI

Jean Slutsky, *Chief Engagement and Dissemination Officer and Program Director, Communication and Dissemination Research, Patient-Centered Outcomes Research Institute* said big data are a critically component of a learning healthcare system. In furtherance of the Patient-Centered Outcomes Research Institute (PCORI) mission to increase value and decrease waste in research, the National Patient-Centered Clinical Research Network (PCORnet) was developed to improve the nation's capacity to conduct clinical research more efficiently by creating a large, highly representative, national patient-centered clinical research network . This network conducts both randomised and observational comparative studies, allowing large-scale research to be conducted with enhanced accuracy and efficiency within real-world care delivery systems, supporting a learning US healthcare system,. PCORnet is a network of clinical data research networks such as hospital systems and patient-powered research networks such as DuchenneConnect, 130 health systems and over 60 data centres across the United States and curates data for more than 100 million patients. Getting complete data for research purposes requires extensive coordination. Patients get care at multiple institutions and sites, data are stored within multiple, disparate systems that are not interoperable and there are various factors critical to health that payers/providers do not capture, such as social determinants of health, patient-reported outcomes and genomic data and there are perceptual barriers that need to be addressed. Despite these barriers, sharing and trust among stakeholders will ensure a continuously learning healthcare system.

WORKSHOP ATTENDEES

Regulatory agencies		
Prof Sir Alasdair Breckenridge	Former Chairman	Medicines and Healthcare products Regulatory Agency UK
Dr Katherine Donegan	Pharmacoepidemiology Research and Intelligence Unit Manager	Medicines and Healthcare products Regulatory Agency UK
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
Dr Esa Heinonen	Head of Sector Marketing Authorisation	Swissmedic, Switzerland
Dr Jonathan Jarow	Senior Medical Advisor	Food and Drug Administration, USA
Dr Alyson Karesh	Acting Division Director, Division of Clinical Trial Quality, Office of Medical Policy	Food and Drug Administration, USA
Marion Law	Director General	Therapeutic Products Directorate, Health Canada
Prof John Lim	Deputy Director of Medical Services and Executive Director, Centre of Regulatory Excellence	Ministry of Health, Singapore and Duke-NUS Graduate Medical School, Singapore
Dr Peter Mol	Principal Clinical Assessor	Medicines Evaluation Board, Netherlands
Dr Richard Moscicki	Deputy Center Director for Science Operations, CDER	Food and Drug Administration, USA
Prof Luca Pani	Director General	AIFA, Italy
Dianne Paraoan	Team Lead, Division of Clinical Trial Quality, Office of Medical Policy	Food and Drug Administration, USA
Dr Eyal Schwartzberg	Head of Pharmaceutical Division	Ministry of Health, Israel
Dr John Skerritt	Deputy Secretary	Department of Health, Australia

Academic and inon-profit institutions		
Prof Richard Barker	Founding Director	CASMI, UK
Prof Marion Bennie	Professor of Pharmacy	University of Strathclyde, UK
Dr James Leong	Head of Education	Centre of Regulatory Excellence, Duke-NUS, Singapore
Ann Lucas	Co-Director, DuchenneConnect Registry	Parent Project Muscular Dystrophy, USA
Dr Murray Ross	VP and Director	Kaiser Permanente Institute for Health Policy, USA
Dr Sean Tunis	President and CEO	Center for Medical Technology Policy, Inc, USA

Health technology assessment and reimbursement agencies		
Sylvie Bouchard	Director	Institut National d'Excellence en Santé et en Services Sociaux, Canada
Brent Fraser	VP, Pharmaceutical Reviews	Canadian Agency for Drugs and Technologies in Health (CADTH)
Prof Sarah Garner	Associate Director, Science Policy and Research	National Institute of Health and Care Excellence (NICE) UK
Prof Mamoru Narukawa	Professor	Kitasato University Graduate School of Pharmaceutical Sciences, Japan
Jean Slutsky	Chief Engagement and Dissemination Officer and Program Director for Communication and Dissemination Research,	Patient-Centered Outcomes Research Institute (PCORI), USA
Mark Trusheim	Visiting Scientist	MIT, USA

Pharmaceutical companies and pharmaceutical service providers

Dr Jay Backstrom	SVP, Regulatory Affairs and Pharmacovigilance	Celgene Corporation, USA
Annetta Beauregard	VP, Regulatory Advocacy and Policy	Vertex Pharmaceuticals Inc, USA
Dr Murtuza Bharmal	Director, Global Evidence and Value Development	Merck KGaA, Germany
Fabio Bisordi	Head of International Regulatory Policy	F. Hoffmann-La Roche Ltd, Switzerland
Dr Anders Rething Borglykke	Senior Epidemiologist	Novo Nordisk A/S Denmark
Dr Carmen Bozic	SVP, Global Development	Biogen, USA
Dr Patrick Brady	VP, Head of Regulatory Policy and Intelligence	Bayer, USA
Dr Hui Cao	Executive Director, RWE, Global Medical Affairs	Novartis, USA
William Capra	Real World Data Science Global Head of Oncology	Genentech Inc, USA
Michele Cole	Senior Medical Liaison	Actelion Pharmaceuticals, USA
Dr Felipe Dolz	Head, Global Regulatory Affairs Policy and Intelligence	Sanofi, USA
Andrew Emmett	Senior Director / FDA Liaison	Pfizer Inc, USA
Dr Thomas Evers	Global Market Access – Director HEOR	Bayer Pharma AG, Germany
Dr Aaron Galaznik	Senior Director, Global Outcomes Research	Takeda, USA
Dr Tim Garnett	Chief Medical Officer Chief Medical Officer and SVP, Medicines Development Unit	Eli Lilly and Company, USA
David Goldberger	VP, Global Regulatory Affairs	Otsuka America Pharmaceuticals, Inc, USA
Dr David Guez	R&D Special Projects Director	Servier, France
Mette Hammer	Director of HEOR RWE	Novo Nordisk, Denmark
Mark Hope	VP, Global Head of Regulatory Affairs	UCB BioPharma SPRL, Belgium
Dr Solomon Iyasu	VP and Head of Pharmacoepidemiology	Merck & Co, USA
Elena Izmailova	Senior Director	Takeda Pharmaceuticals, USA
Dr David Jefferys	SVP, Global Regulatory, Government Relations,, Public Affairs and European Product Safety	Eisai Europe Ltd, UK
Emmanuelle Lecomte-Brisset	Head EU and Int Regulatory Affairs	Shire International GmbH, Switzerland
Julie Lepin	VP, Regulatory Oncology, Immunology and In Vitro Diagnostics	Merck & Co, USA
Gracie Lieberman	Director of Regulatory Policy	Genentech, USA
Dr Fabio Lievano	VP, Safety Science, Medical Safety Evaluation	AbbVie, USA
Olivia Maurel	VP, Therapeutic Area head, Global Regulatory Affairs	Shire, Switzerland
Dr Margaret McDonald	Senior Director, Real World Data and Analytics, Global Health and Value	Pfizer Inc, USA
Paul McInulty	Executive Director, Regulatory Affairs	Celgene Corporation, USA

Rebecca Meisberger	Director, Project Management and Operations, Global Patient Outcomes and Real World Evidence	Eli Lilly and Company, USA
Alwin Otten	Director, Regulatory Affairs Lead	Janssen, The Netherlands
Dr Shamik Parikh	VP, Head of Enabling Safety Science and Risk Management	AstraZeneca, USA
Paul Robinson	HEOR Director	Otsuka Pharmaceutical Europe, UK
Dr Andrew Roddam	VP and Head Real World Evidence and Epidemiology	GlaxoSmithKline, UK
Troy Sarich	VP, Real World Evidence	Janssen Pharmaceuticals, USA
Dr Chun-Pyn Shen	Director, Global Regulatory and Scientific Policy	EMD Serono, USA
Natalie Tolli	VP, RA Global Labeling, US Ad/Promo, Regulatory Policy and Intelligence	Abbvie Inc, USA
Dr Massoud Toussi	Head of Epidemiology, Safety and Risk Management	IMS Health, France
Yuen Tsang	Senior Medical Liaison	Actelion Pharmaceuticals, USA
Dr Kristin Van Goor	Director, Global Regulatory Policy	Biogen, USA
Montserrat Vera-Llonch	Senior Director (HEOR)	Shire, USA
Dr Karen Weiss	VP, Global Policy and Intelligence	Janssen Research and Development, USA
Patrick Wire	Senior Director, Global Regulatory Affairs	GlaxoSmithKline, USA
Brande Ellis Yaist	Senior Director- Global Patient Outcomes and Real World Evidence	Eli Lilly and Company, USA

Centre for Innovation in Regulatory Science	
Lawrence Liberti	Executive Director
Dr Neil McAuslane	Director
Madga Bujar	Research Analyst
Patricia Connelly	Manager, Communications
Sandi McIntyre	Project Manager
Prisha Patel	Manager, Global Development Programme
Professor Stuart Walker	Founder
Tina Wang	Portfolio Manager, HTA Programme