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Insights from a conference co-hosted with the London School of Economics

REAL-WORLD EVIDENCE IN ONCOLOGY

Towards Innovative and Affordable Patient Care

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FORWORD

IQVIA and the London School of Economics and Political Science are delighted to have hosted this unique and timely meeting on real-world evidence (RWE), and would like to thank the speakers for their expert and informative insights into this innovative and increasingly important area of medicine.

Combining authoritative presentations, new information about key topics and lively discussions, the meeting highlighted a number of key themes:

- The UK is leading the way in the use of RWE through a combination of creative and well planned industry and government activities to generate real-world data (RWD) and make these data available for research without compromising patient confidentiality
- RWD are increasingly being used by payers and regulators to enhance and offer added value to randomised clinical trial data
- Innovative technologies, such as the E360™ technology suite, are becoming commercially available to allow data scientists to extract, manipulate and analyse highly dimensional RWD in near real time
- Large-scale genomic testing has the potential to fundamentally change health care delivery and research, for example, by identifying specific molecular signatures that can be used to guide treatment. The combination of genomic sequencing data with patients' clinical records offers a unique opportunity to generate a lifelong view of the impact of genomic factors on patient outcomes
- Patient centricity is key to both the generation of RWE and to its appropriate use and governance

Both IQVIA and the LSE are actively working to advance the collation and use of RWD, both in the UK and worldwide. In a noteworthy example of this work, IQVIA is collaborating with Health Data Insight CiC on the Simulacrum, a simulated version of the Cancer Analysis System (CAS) held in Public Health England (PHE) that allows researchers to test hypotheses without compromising patient confidentiality.

The IQVIA team of health economists and data scientists have been working over the past year to demonstrate how the data in the Simulacrum and the CAS can be used to inform and guide new advances in cancer care. The Simulacrum will be made freely available to researchers when this comprehensive validation is complete.

Another exciting initiative is the Collaboration for Oncology Data in Europe (CODE), a collaborative initiative established by IQVIA with support from leading biopharmaceutical companies to provide timely information back to the healthcare system on how anti-cancer medicines are used in clinical practice, by establishing an Oncology Data Network. The goals are firstly to support clinicians and other stakeholders in improving patient care, and secondly to help address the challenge to financial sustainability by facilitating the implementation of novel models of access to innovative medicines.

To find out more about the Simulacrum, CODE and our broader portfolio of RWE services, please contact **iqvia.com/contactus**

IMPORTANT MESSAGES

Real-world evidence (RWE) is increasingly being used to inform reimbursement decisions and patient access schemes, and to aid clinical decision-making in conditions – such as cancer – that are hallmarked by heterogeneous patient populations and diverse treatment pathways. The use of RWE in oncology was reviewed at a meeting jointly organised by IQVIA and the London School of Economics and Political Science (LSE), *Real-World Evidence in Oncology: Towards Innovative and Affordable Patient Care*, which took place in London in July 2017. This meeting was particularly timely, as it took place just a few days after the publication of the Chief Medical Officer's annual report for 2016, *Generation Genome*.[1] This report describes in detail how genomics is currently used in the UK healthcare system and how its potential may be developed – an area where RWE is set to play a central role.

Opening the meeting, **Professor Alistair McGuire from the LSE** pointed out that RWE has a long history, having first been used in landmark cardiology trials, such as the West of Scotland Coronary Prevention study (WOSCOPS),[2] in the late 1980s. Subsequent years have seen great improvements in the use of RWE, a trend at least partly driven by the increasing need for evidence-based reimbursement decisions. It may be anticipated that advances in digital technology will facilitate the collection and analysis of real-world data (RWD), with potential benefits for patients and healthcare systems alike. However, important issues will have to be addressed, including the protection of patient confidentiality in large data sets.

A NUMBER OF IMPORTANT MESSAGES EMERGED FROM THE MEETING

- **The UK is a world leader in the collection and use of RWD**, although more work is necessary to ensure that such data are made available in a timely manner to researchers in academia and the life science industry in a way that maintains patient privacy
- RWE can complement, but not replace, information derived from randomised clinical trials (RCTs)
    - RWE can supplement RCT data, for example by providing information on disease progression and overall survival over time periods that extend beyond the duration of follow-up in clinical trials
    - RWE can be used to assess treatment effectiveness in patient subgroups or niche indications where it is unlikely to be feasible to conduct adequately powered RCTs
    - RWE can also answer questions that are not usually addressed in RCTs, such as which drugs are actually being used in clinical practice
    - However, the distinction between how RCT data and RWD are used is likely to become more blurred as pressure grows to introduce new therapies for cancer or rare diseases as quickly as possible
- **RWE can help to determine the value of treatment**, which may reflect a variety of outcomes, including overall survival, quality of life, or adverse effects of treatment:
    - In this context, the collection of RWE should focus on those issues most likely to affect decision-making about the clinical- or cost-effectiveness of treatments

- In addition, **RWE can provide valuable clinical insights** into standard of care, disease progression, patient selection and budgetary impact of treatment
- **RWE plays a useful role in informing health technology assessments** (HTAs), particularly for highly specialised technologies (HSTs)
- **The use of RWE in reimbursement decisions is increasing**, particularly for drugs approved under the new Cancer Drugs Fund (CDF)
- **RWE offers the potential for a new cancer treatment paradigm**, in which patients actively collaborate in their own personalised care
- **It is essential that patient confidentiality is not compromised**; a patient-centred approach, in which patients are fully informed about the use of their data, is essential for continued generation of RWE
- **Additional efforts are needed to develop data infrastructure**, as well as analytical tools that are capable of rigorously generating insights from RWD
    - An example of such a tool is the Simulacrum, a simulated copy of Public Health England's Cancer Analysis System (CAS). This tool allows researchers to test hypotheses using non-sensitive data
- **Potential challenges to the use of RWE** include issues around data quality, access to data, and governance

Real-World Evidence in Oncology conference in London, July 2017

"DATA RICH, INFORMATION POOR"?

USING RWE TO IMPROVE PATIENT CARE

Dr Helen Bulbeck, from the brain cancer charity Brainstrust and the patient movement Use MY Data, argued that we are currently "data rich, information poor," as there are already large amounts of data that could be used more effectively. She suggested that the failure to use RWE effectively is "the biggest lost opportunity in Britain today" because "people die when information is not shared." At present, there exists a "near-perfect storm" of circumstances that would favour the effective use of RWD to drive improvements in patient care (Table 1). Nevertheless, it is necessary to create a better case in order to drive this forward.

Table 1. The "near-perfect storm" favouring more effective use of RWD

☑ Patients want a better experience
☑ Carers want a better experience
☑ Clinicians understand the benefits of using RWE
☑ Third sector funders want to support a better experience for the patient community
☑ Governments understand the importance of RWE

Effective use of RWE will be key to achieving the promise of personalised medicine offered by advances in genomics. Patients can provide valuable insights into their own personal circumstances, and also into their family history. If this can be combined with the patient's clinical, genetic, molecular and treatment outcome data, a new approach to research and treatment becomes possible, in which the patient effectively becomes a "co-pilot" in their care. Secure data sharing will be key to achieving this: "the more data we can share in a secure and standardised manner, the fewer people will die or have harmful interventions" said Dr Bulbeck. Importantly, pilot studies in brain cancer patients have shown that patients are willing to freely share their data, subject to concerns about data security and confidentiality being addressed.

Dr Bulbeck emphasised the importance of identifying the RW issues that are most relevant or meaningful to patients, and providing appropriate information on these in real time. For example, issues around quality of life appear to be far more important to brain cancer patients than treatment-related concerns. In other words, conversations between physician and patient should shift from "what's the matter with you?" to "what matters to you?"

> *"the more data we can share in a secure and standardised manner, the fewer people will die or have harmful interventions"*

USING ONCOLOGY RWE IN ENGLAND: "THE TIME HAS COME"

Dr Jem Rashbass, Director for National Disease Registration at Public Health England, said that "the time has come" for RWE, as a result of two factors:

- The growing potential for personalised medicine (since population-level data are needed to understand the significance of findings in individuals)
- The well recognised limitations of randomised controlled trials (RCTs), such as their cost, difficulty with patient recruitment and questionable generalisability

A major issue in the trend towards personalised medicine has been the difficulty of obtaining good-quality RWD on cancer phenotype that can be linked to genomic data. This has been addressed by Public Health England's National Cancer Registration and Analysis Service (NCRAS), which was launched in 2013 as part of a 5-year project to merge the eight existing cancer registries in England. This single registration service – one of the most granular cancer registries in the world – provides timely data, with detailed clinical information, on all 350,000 cancers diagnosed annually in England, in addition to having more than 141 million historical cancer records extending back over 30 years.[3] The data are captured in a range of formats from multiple healthcare sources, including hospitals and histopathology laboratories. The number of data records processed each year has grown from 500,000 in 2011 to 32 million in 2016, and this figure is set to rise still further when primary care prescription records are incorporated into the registry. Data from the CAS have recently been used in a study of 30-day mortality rates associated with the use of systemic anti-cancer therapies in patients with breast or lung cancer.[4]

> *"We have the best, largest, and most real-time data set in the world for cancer, but it is essential to use this sensitively"*

Dr Rashbass emphasised the importance of ensuring that patient confidentiality is protected, and that RWD collected by NCRAS are only used for health care purposes. The registry data are protected by law and by PHE's strict information governance processes. To increase the use of these data in research whilst protecting patient privacy, an alternative approach to data release has been developed. A simulated data set – the Simulacrum – has been developed by Health Data Insight working with PHE that has the same properties and in the same data structure as the original data set held in the Cancer Analysis Server (CAS), but contains no actual patient data. Since it contains no real patient data, this simulated dataset can be interrogated without the need for ethical approval. Dr Rashbass showed that, among the 488,000 simulated cancers in the Simulacrum for 2014, there were 37,896 lung cancers – exactly the same number as in the original CAS data set – and that these simulated cancers matched the real data set in terms of age distribution, tumour stage, chemotherapy received, and other measures. Health Data Insight is currently working with IQVIA and AstraZeneca to develop the Simulacrum, and the data tables will be made freely available when fully validated; more information can be found here (https://healthdatainsight.co.uk/project/the-simulacrum/). Dr Rashbass concluded that "we have the best, largest, and most real-time data set in the world for cancer," but it is essential to use this sensitively.

USING RWE TO INFORM NICE TECHNOLOGY APPRAISALS

Dr Linda Landells, Associate Director at the National Institute for Health and Care Excellence (NICE), reviewed the use of RWE in NICE Technology Appraisals. She noted that the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) defines RWE as "data used for clinical, coverage, and payment decision-making that are not collected in conventional RCTs," but suggested that an alternative definition is necessary in the context of the Cancer Drugs Fund (CDF): in this context, RWE is likely to be a non-interventional trial (as defined by the NHS Health Research Authority).

Evidence generated for the CDF is likely to be neither derived from research nor collected during a clinical trial. In general, RWE is mainly used within NICE by the Diagnostics and Devices team; it does not have a central role in medicines health technology appraisals, where it is mainly used in the absence of other sources of data, or to corroborate clinical trial data. However, it is more widely used in appraisals of drugs for ultra-rare diseases conducted through the NICE Highly Specialised Technology (HST) process. Dr Landells pointed out that the regulatory environment is changing, with a trend towards earlier licensing with less certain evidence bases.

WHERE DOES RWE FIT IN HTAs?

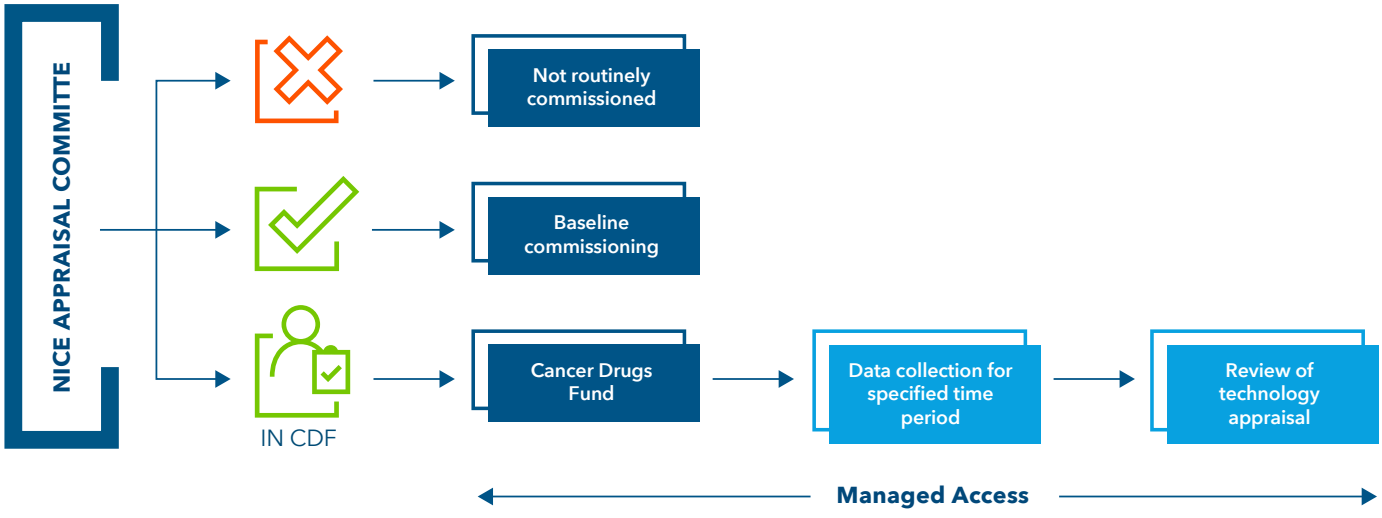
RWE is often submitted to NICE in appraisals, but is not currently used to its full potential.

Areas where RWE can provide useful information include:

- Defining the standard of care
- Burden of illness
- Disease progression
- Resource utilisation
- Patient-reported outcomes (PROs)

However, at present it is mainly used in the absence of other evidence sources, as 'supportive evidence' to corroborate trial data or to inform other areas of the modelling (e.g. utility and costs). To date, there is no experience of using data from the Early Access to Medicines Scheme (EAMS) in HTAs, largely because most products appraised so far have only been available for short periods that are not conducive to data collection.

Figure 1. RWE can be used to inform reviews of cancer drugs available on managed access schemes via the CDF.



However, with the recent changes to the CDF, RWE now has an important role in addressing clinical uncertainties for drugs approved in managed access schemes via the CDF (Figure 1). The Public Health England Systemic Anti-Cancer Therapy (SACT) dataset is strongly preferred for the collection of RWD in this context because the infrastructure (including data protection and information governance processes) is already in place, data are already being collected, and progress can easily be monitored. Other potential sources of data include analyses from ongoing studies, or new studies if time and resources permit. Data from SACT, and potentially other PHE datasets, will be used to inform reviews of technology appraisals for a number of cancer drugs. Previous examples of RWE use are presented in Table 2.

Table 2. RWE has been used successfully to inform NICE HTAs

APPRAISAL NO.	PRODUCT	INDICATION	CLINICAL UNCERTAINTY	DATA SOURCES	OUTCOME
TA416	Osimertinib	Locally advanced or metastatic EGFR T790M mutationpositive NSCLC	Uncertainty in overall survival and generalisability to clinical practice	SACT, clinical trials	Recommended for use in CDF
TA446	Brentuximab vedotin	Treatment of CD30+ Hodgkin's lymphoma	Uncertainty in transplant rate after treatment	Retrospective analysis from Public Health England	Recommended for use in CDF
HST2	Elosulfase alfa	Type IVa mucopolysac-charidosis	Mismatch between trial results and patient experience	12-year disease registry	Recommended for managed access
HST3	Ataluren	Duchenne muscular dystrophy resulting from nonsense mutation	Mismatch between trial population, marketing authorisation and greatest anticipated benefit in clinical practice	NorthStar database	Recommended for managed access

WHAT ARE THE CHALLENGES TO COLLECTING RWD?

A number of potential challenges to the collection of data in HST appraisals have been identified. These include:

- Difficulties in collecting baseline quality of life (QoL) data
- Securing adequate funding to maintain a database and support staff
- Information technology issues, including access to databases and the use of firewalls with some Clinical Commissioning groups (CCGs)
- The lack of a clear control group, or difficulties in obtaining patient consent to be included in a control group

Dr Landells concluded that, for RWD to be incorporated into HTAs most effectively, it is essential to focus on the key clinical uncertainties, as identified by the appraisal committee, and on the factors that have the greatest influence on incremental cost-effectiveness ratios (ICERs).

HOW IS RWE USED ELSEWHERE IN EUROPE?

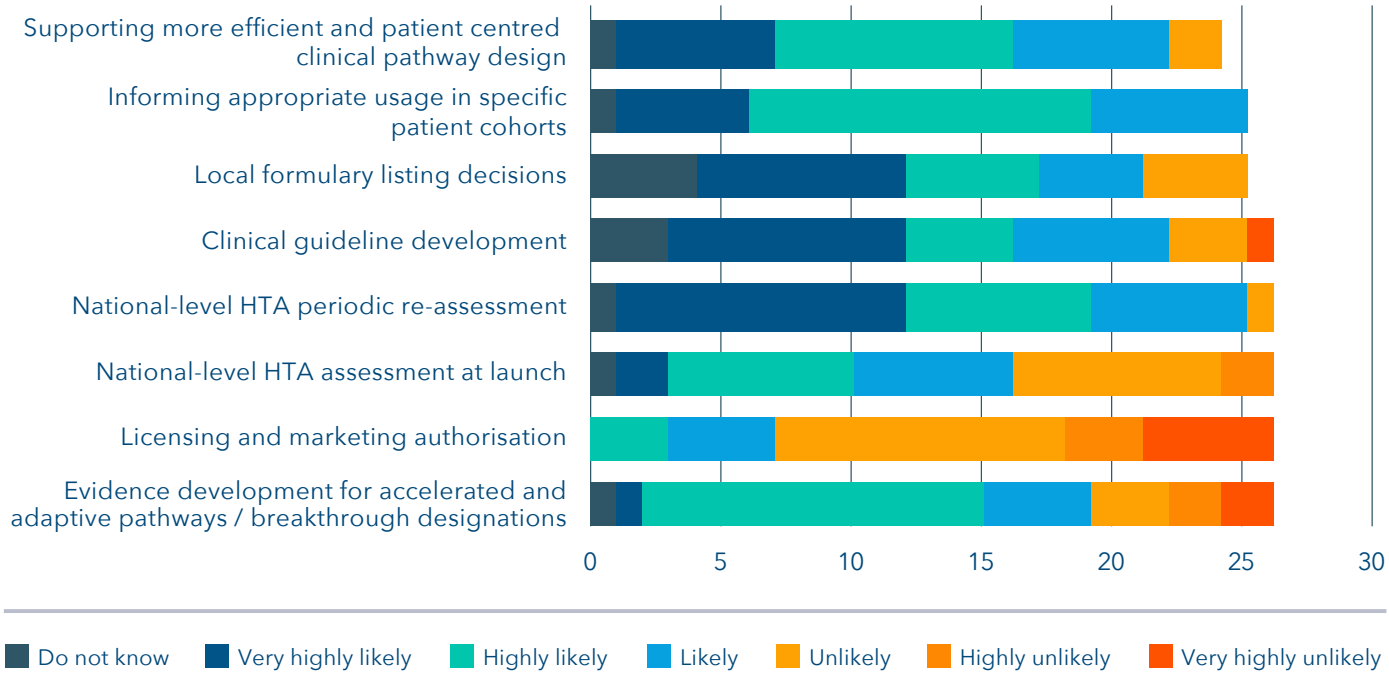
During the meeting, several speakers emphasised the UK's leadership in RWE collection and analysis but, as described by **Mackenzie Mills from the LSE**, attitudes to RWE vary markedly across Europe. In order to understand the use of RWE in Europe, LSE researchers sent questionnaires to 260 stakeholders, including academics, healthcare professionals, patient representatives and HTA bodies, from 17 European countries. The responses received as of May-June 2017 revealed that there is some degree of consensus around the current and future use of RWE, although there were a number of differences between countries.

In general, respondents agreed that RWE has a role in decision-making, and that this role is likely to expand in the future. In addition, most responders believed that RWE is most likely to influence clinical decision-making, whereas it is unlikely to have as significant a role in licensing and marketing authorisation (Figure 2). Respondents from 12 countries reported specific examples where RWE has already been used to inform decision-making, including:

- Cancer and other disease registries in Bulgaria, Italy and the Czech Republic
- Compassionate use programmes in the Czech Republic (in situations where RCT data were not available)
- A quality-adjusted life-year (QALY) study in Russia
- Cohort studies and managed access schemes in the UK

Figure 2. Across Europe, RWE is most likely to be used to inform clinical decision-making, rather than licensing and market authorisation.

In what specific situations do you see RWE being able to support improved decision-making?

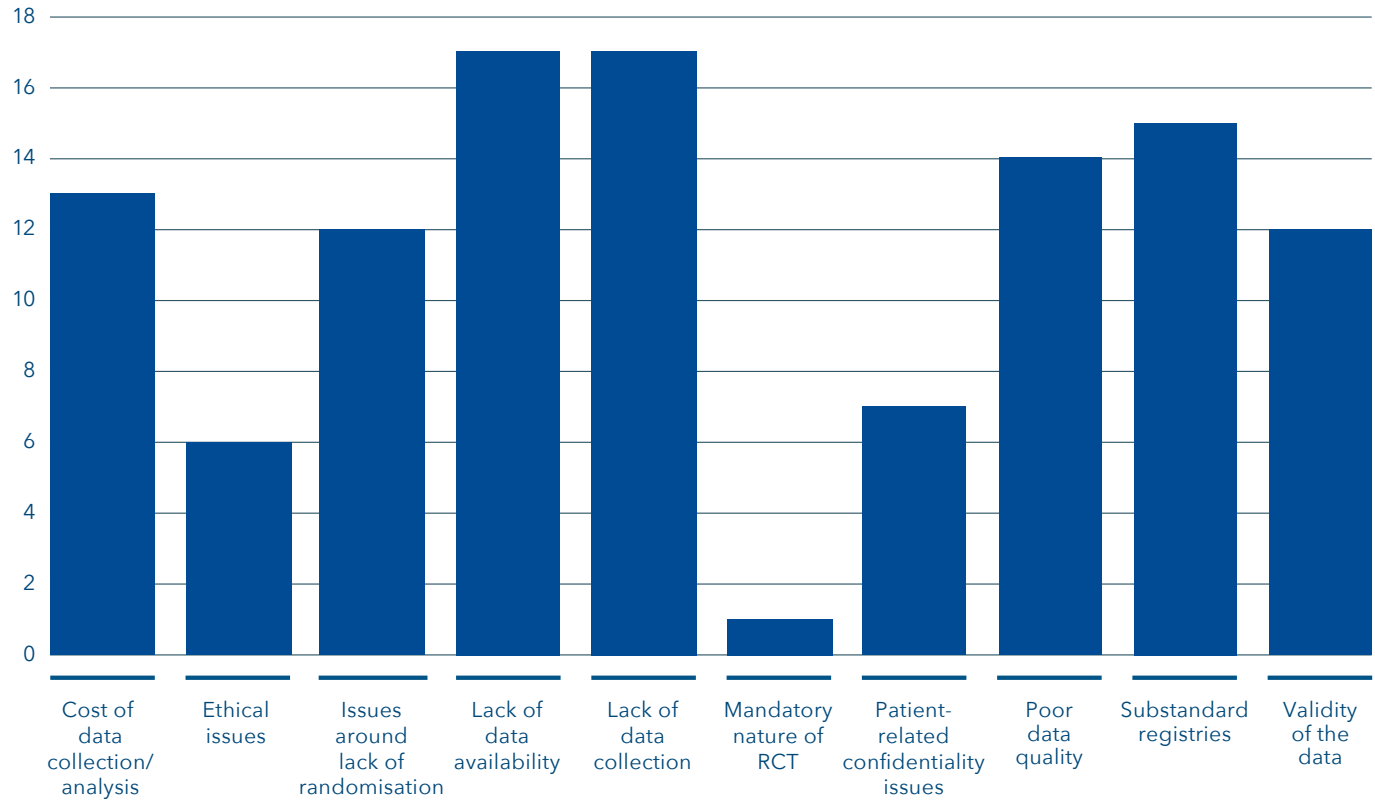


The survey also highlighted a number of potential barriers to the use of RWE in licensing or coverage decisions, the most important of which were a lack of data and concerns about data quality (Figure 3). Education and increased awareness of the importance of RWE were considered to be key to overcoming these barriers.

> *"Education and increased awareness of the importance of RWE were considered to be key to overcoming barriers"*

Figure 3. Lack of data and concerns about data quality, are seen as important barriers to expanding RWE use.

What do you see as the barriers to enhanced use of RWE in either licensing or coverage decisions?



TOWARDS REAL-WORLD EVIDENCE-BASED DECISION-MAKING

Dr Sebastian Salas-Vega

Dr Ashley Woolmore

The use of RWE to support value-based pricing (VBP) and reimbursement decisions was discussed in a joint presentation by **Dr Sebastian Salas-Vega from the LSE and Dr Ashley Woolmore from IQVIA**.

ADDRESSING "FINANCIAL TOXICITY" THROUGH AN IMPROVED EVIDENCE PLATFORM

As Dr Salas-Vega pointed out, advances in cancer therapeutics have led to significant improvements in survival rates, but at the cost of sharply increasing costs – "financial toxicity."[5] As a result, it has been proposed that VBP may offer a means of rationalising cancer drug costs while maximising the health benefits to patients. With this approach, value is defined in terms of health outcomes achieved per unit of cost, and hence a high price can be justified if a drug offers a substantial clinical benefit. VBP requires both objective measures of clinical impact and evidence of the economic impact of treatment. However, this has proved difficult for a number of reasons, including:

- Historically, no single dataset of patient-level information on use and cost of cancer drugs has previously been available
- Cancer is associated with unpredictable responses, making it difficult to anticipate treatment costs in an individual patient

RWE may offer a means of addressing these knowledge gaps, especially if it is used to complement traditional data sources, such as clinical trial data. However, at present RWE is often difficult to access and leverage, particularly at an international level. Furthermore, RWE is often only available after a product is launched, making it difficult to use for initial pricing decisions.

Analytical tools can help to overcome these problems, both by pooling various data sources, and by using established empirical methods to address limitations in the available evidence. They can therefore play a key role in informing VBP decisions. One such tool is MEDec©, a proprietary technology solution that generates deep insights into the use and cost of medicines. MEDec© uses peer-reviewed empirical methods to manage uncertainty around clinical and economic variables. Preliminary studies using this tool have shown that the UK has a stronger link between cancer drug prices and value to patients than France, Australia or the USA.

> *"RWE may offer a means of addressing knowledge gaps, especially if it is used to complement traditional data sources, such as clinical trial data"*

HOW CAN RWE SUPPORT VALUE-BASED PRICING?

Introducing his presentation, Dr Woolmore commented that the efforts over the last 20 or more years to establish and develop national cancer data (see page 7) have "pulled England out of the European pack" in terms of the richness of registry data. Regarding VBP or payment approaches, he highlighted the particular challenges of embedding the use of RWD, which relate to issues of latency and periodicity of the data (i.e., how soon after a product is used in a clinical setting can we 'see' that use in the data, and how frequently are the data refreshed to ensure that we are looking at an up-to-date view?). He emphasised that a move towards new payment approaches is being driven by the tremendous pace of the arrival of new innovative treatments and the complexity of the determination of value in cancer treatment. The value of a drug will depend on the circumstances: the same drug can have different clinical value in different tumours, different combinations, or different lines of therapy.

The determination of value is also complicated by the fact that outcomes may be assessed in various ways, including overall or disease-specific survival, acute complications, health-related QoL, and duration of end-of-life care. It should also be noted that pricing and reimbursement decisions are commercial, rather than clinical. Furthermore, when considering implementation of VBP, it is necessary to consider whether 'outcomes' need to be collected for each individual patient being treated, or whether the alternative model of studying outcomes for a specific patient population can then be combined into the decision-making process for the execution of agreements and payment schemes. With this in mind, Dr Woolmore went on to describe the characteristics of a real-world data system for pricing or payment decisions that could be developed around three types of data source.

1. "Independent Variable Sources", such as molecular, genomic, tumour or therapy characteristics, where high precision is required, but the data items change relatively infrequently
2. "Healthcare Encounter Sources", which are required to understand how patients are coming into contact with the healthcare system, including details of where and when they are being treated. These data need to be kept up-to-date, as they change very frequently
3. "Outcome Measure Sources", which can cover a range of complexity and sophistication of measurement. Here, a different approach is required to ensure that outcomes, once attained and measured, can be made available promptly

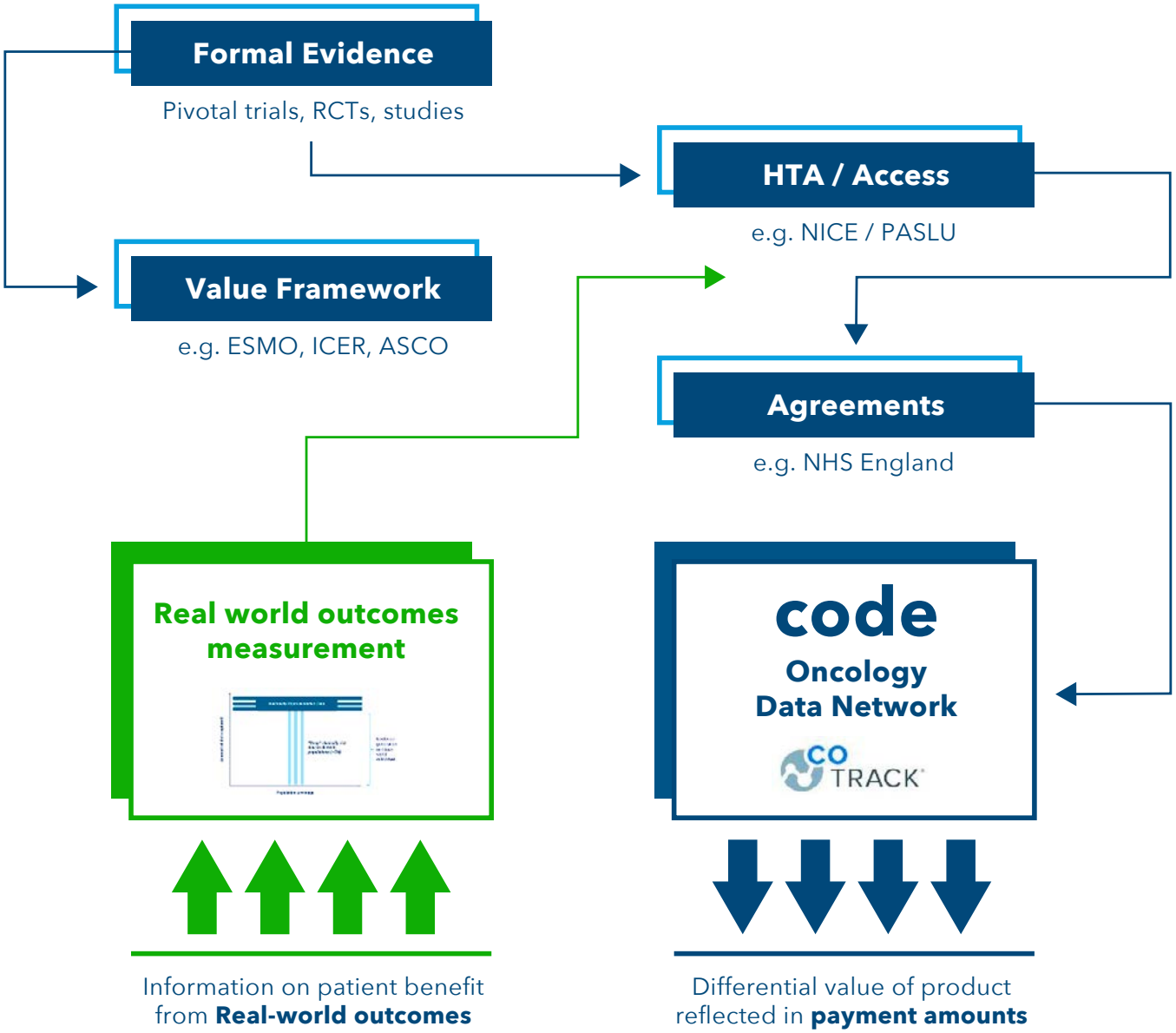
An example of the work being done to build a system for these data types is the Collaboration for Oncology Data in Europe (CODE),[6] a collaborative initiative led by IQVIA with support from leading biopharmaceutical companies. This ambitious initiative aims to build a large scale Oncology Data Network able to collate anti-cancer medicine usage data for all types of cancer, all patients, and all treatment centres in Europe that wish to join. In doing this, CODE is working to address an unmet need for timely information to be provided back to the healthcare system, on how anti-cancer medicines are used in routine clinical practice to help achieve two goals:

- To support clinicians and other stakeholders in improving patient care
- To facilitate novel access models to support oncology patients' access to innovative medicines while helping to address the challenge of financial sustainability

The network infrastructure created through the CODE initiative can be used to support new models of access and payment, and provides the means to implement a broad range of schemes, including those based on products' clinical value and RW outcomes, as shown in Figure 4.

" A move towards new payment approaches is being driven by the tremendous pace of the arrival of new innovative treatments "

Figure 4. The CODE project combines RW and clinical trial data to derive a direct monetary estimate of treatment value.



RWE AND OUTCOMES-BASED COMMISSIONING IN ONCOLOGY

The question of whether RWE can be used to support outcomes-based commissioning in oncology was discussed by **Mr Peter Huskinson, National Commercial Director, Specialised Commissioning, at NHS England**. Specialised services currently account for about £1 in every £7 spent by the NHS, of which about 25% is attributable to high-cost drugs; RWE could help commissioners better understand the likely impact of this expenditure on outcomes.

A recent (October 2016) lecture presented at the American College of Surgeons concluded that, as cancer treatment options expand, "there are simply not enough patients, time or money to examine every open question in cancer care with clinical trials."[7] RWE offers the opportunity to fill these expanding knowledge gaps, provided that the data are reliable and reproducible. This, however, focuses attention on the definition of RWE. There is a potential concern that too broad a definition ("anything that isn't an RCT") could actually result in less healthcare gain for all because more treatments are approved on less stringent criteria. Mr Huskinson suggested that a more robust definition should be "the aggregation and analysis of high-volume data generated from routine clinical practice using quantitative research methods." Thus defined, RWE complements, rather than substitutes, RCTs.

HOW IS RWE BEING USED IN THE SPECIALISED SERVICE SETTING?

RWE is currently being used in a number of settings within the NHS, including:

- The 100,000 Genomes project (see page 14)
- The NHS England Commissioning through Evaluation (CtE) programme, which allows limited numbers of patients to receive treatments that are not funded through the NHS
- Managed access agreements

It is noteworthy that the use of RWE in reimbursement decisions is increasing. A notable example of this is the recent recommendation of asfotase alfa for the treatment of paediatric-onset hypophosphatasia, an ultra-rare condition that affects between 1 and 7 babies each year in England.[8] In the absence of RCT evidence, this recommendation was based on small Phase 2 studies, retrospective non-interventional studies, and submissions from patient representatives. This evidence enabled the manufacturer, Alexion, to work with NICE and NHS England to develop a 5-year managed access arrangement, reducing the cost of asfotase alfa to the NHS and enabling patients with the greatest need to be identified.[7]

RWD are also being used to inform new CDF decisions. This will be particularly helpful in conditions such as renal cell carcinoma, where numerous treatment combinations are in use; in such situations, RWE can be used to guide treatment decisions for combinations that are not supported by RCT data. RWE may also be used to guide conditional reimbursement, depending on factors such as feasibility, transaction overheads, clinical uncertainty and differences in RW value between products. "We should certainly use conditional reimbursement in areas where we genuinely think it will solve a problem," commented Mr Huskinson.

RWE: A "LIVING RESOURCE" IN THE 100,000 GENOMES PROJECT

Professor Mark Caulfield, from Genomics England, explained how RWE derived from NHS practice is being used to improve the fidelity and usage of genomic data in the UK.

The 100,000 Genomes Project is aiming to sequence the genomes of 70,000 patients with rare diseases, cancers or infections, and their family members. The objective of this ambitious project is to drive equity and accessibility of genomic data in healthcare, and to place the UK in the vanguard of the application of such data to healthcare.

Participants are being recruited from 85 NHS Trusts in 13 genomic medicine centres, and the project involves about 1500 NHS staff and 2500 researchers and trainees from around the world, together with a number of academic and industry partnerships. Crucially, the sequencing data are linked to patients' medical records, generating a lifelong view of the impact of genomic data on patient outcomes (Figure 5).

Professor Caulfield emphasised that "genomes themselves are not of much value without the associated clinical data." Currently, clinical data are available from 2 million hospital episodes in 31,781 participants – an average of about 63 episodes per person – of whom 98% have linked sequencing data (Figure 6). About 5000 of these participants have cancer.

Figure 5. RWD have a central place in the 100,000 Genomes Project.

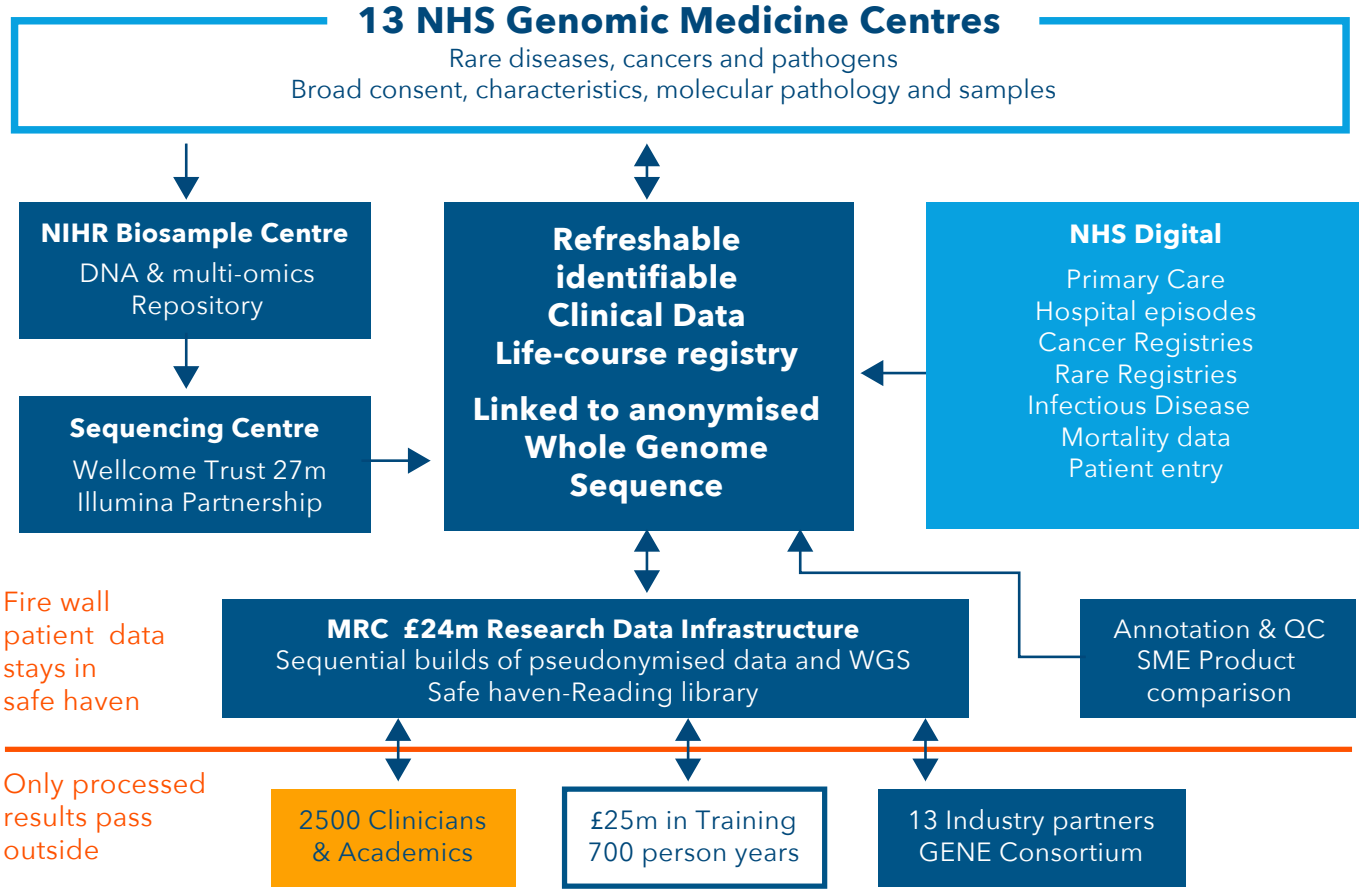
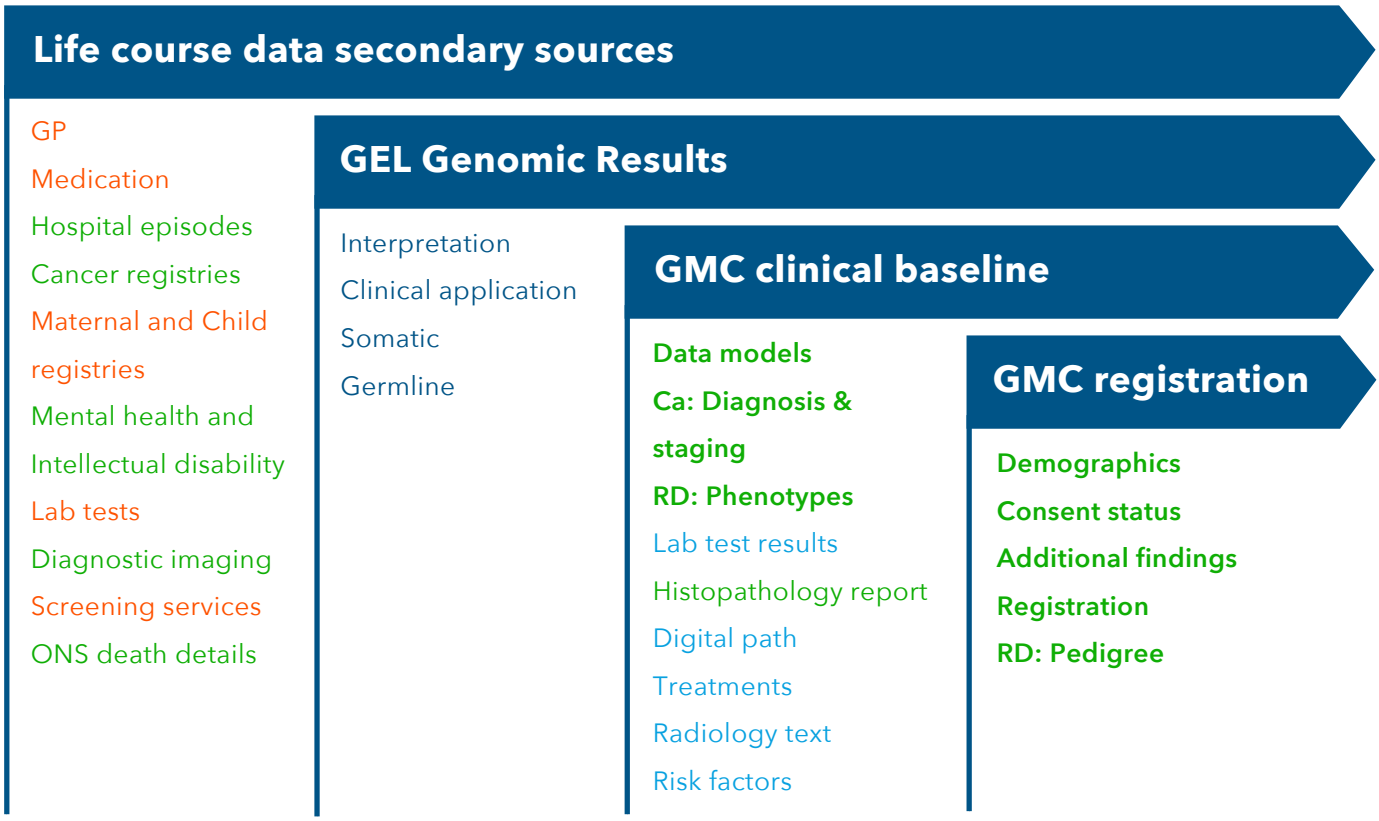


Figure 6. The 100,000 Genomes Project links genetic sequencing data with RWD from multiple sources.



GEL: Genomics England; GMC: Genomic Medicine Centre

Cancer can present a challenge to genomic studies because conventional biopsy procedures involving the use of preservatives are not conducive to sequencing, but pilot studies have shown that the use of fresh tissue biopsies allows high-quality sequencing, with a turnaround time of 18 days. Preliminary studies using fresh tissue samples have already shown that it is possible to identify specific molecular signatures that are associated with poor outcomes. This raises the possibility that the presence of such signatures could be used to guide treatment decisions, for example, by identifying patients who might benefit from expensive targeted therapies.

Professor Caulfield reported that NHS England is preparing to commission whole-genome sequencing from March 2018. "We are on the cusp of becoming the first healthcare system in the world to embrace whole-genome sequencing in healthcare," he said. Importantly, the genomic and RW database will be continually updated, making this a "living resource" for clinical practice and research. The ambition, concluded Professor Caulfield, is to make the UK knowledge base in genomics "the best in the world."

> *"The ambition is to make the UK knowledge base in genomics "the best in the world"*

RWE: ACCELERATING DRUG DEVELOPMENT AND DELIVERY

As described by **Dr Virginia Acha, from the Association of the British Pharmaceutical Industry (ABPI)**, RWE contributes to all stages of drug development, and the UK has the potential to become a world leader in the use of RWD.

RWE IN DRUG DEVELOPMENT

The pharmaceutical industry continues to invest heavily in cancer therapies: in 2015 cancer accounted for 28% of pharmaceutical research and development expenditure globally.[9] This investment comes at a time of new advances in cancer therapy, including an increasing focus on personalised treatment, growing availability of immunotherapies, and emerging technologies such as CRISPR and gene editing. These trends have important implications for new drug development, requiring new insights and evidence sources to demonstrate the value of innovative therapies in clinical practice.

RWE can provide useful information during all stages of drug development, from discovery to lifecycle management of a licensed product (Figure 7). For example, during the initial stages RWE can help to identify unmet treatment needs, while post-marketing evaluations can demonstrate the impact of a new treatment at the population level.

This trend is likely to continue as RWD handling and analytical techniques improve (Figure 8), offering the possibility of a new treatment paradigm in which the patient plays an active role. This new approach may be described as "4P medicine:"

- Personalised
- Predictive
- Preventative
- Participatory[10]

Figure 7. RWE can contribute to all phases of drug development and lifecycle.

Discovery	Early Development	Full Development	Registration/ Market Access	Lifecycle Management
How many people suffer from the condition and also have co-morbidities x and y? What drugs are currently used in the treatment of the condition and to what extent are clinical guidelines being followed?	Given efficacy and tolerability results from the early trials, how might current treatment pathways be affected with our new drug? How costly are the specific areas of unment need that a drug with this target product profile might address?	In designing the Phase III trial, what are the underlying rates of adverse events we expect to see in the trial population? Where can we modify the eligibility criteria in the Phase III protocol to reduce possible recruitment problems?	What is the likely budget impact of introducing the new drug across different patient segments? What potential saftey issues do we see with the early use of the drug in practice?	How can we run a large clinical trial using electronic medical records to show the relative effectiveness of our drug? In which patient groups are there compliance issues with the drug?

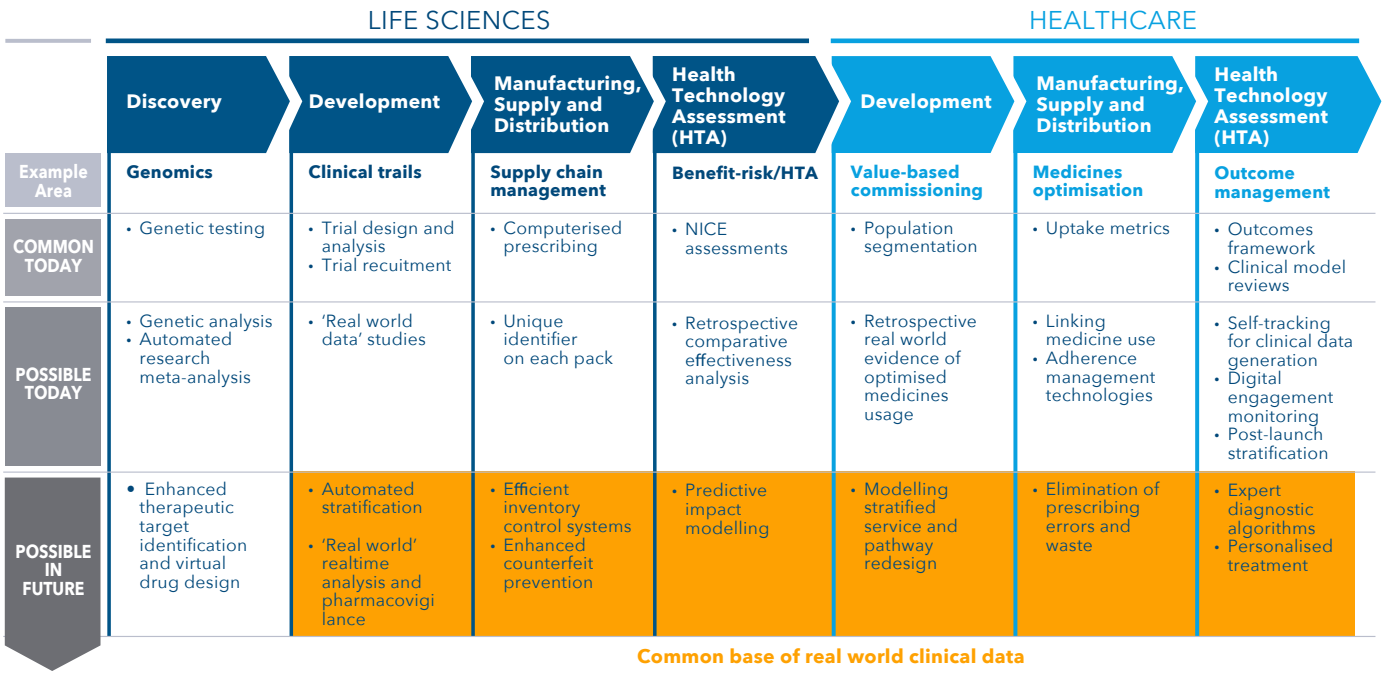
BENEFITS AND CHALLENGES: MAKING THE UK A WORLD LEADER

Dr Acha emphasised that good quality RWD will be accepted by regulators, and described several cases where such data have been used successfully to expand patient access to cancer treatments. For example, data from Phase 2/3 studies and retrospective observational studies have been used to secure Marketing Authorisation for the use of a product as first-line therapy for adult patients with advanced (unresectable or metastatic) melanoma. Similarly, good quality historical data from the USA have been used to support accelerated FDA approval of a product for relapsed or refractory acute lymphoblastic leukaemia – a condition for which palliative care is often the only option.

The use of RWE does, however, present a number of challenges, both in terms of exploiting existing RWE sources and establishing new ones. These challenges largely relate to data quality, access to data and governance. Dr Acha argued that "we need to make the UK a world leader in health data," and that these challenges will need to be addressed if this is to be achieved. Partnership between all stakeholders is therefore essential if the potential of RWE is to be fully realised. It will be necessary to:

- Engage with the public to foster trust in the use of health data, while protecting patient privacy
- Develop an appropriate infrastructure for RWD, including the 100,000 Genomes Project, that allows easy access, via a single site, with clear and appropriate governance
- Establish mechanisms to facilitate clinical trials that generate robust RWD

Figure 8. Increasing use of RWE throughout the treatment lifecycle offers the potential for "4P medicine": Personalised, Predictive, Preventative, Participatory.[10]



KEY ISSUES IN RWE

DISCUSSIONS HIGHLIGHTED KEY ISSUES IN RWE

The meeting concluded with a panel discussion and a series of 'speaker surgeries', during which the panellists discussed key issues informally with members of the audience. The panellists were:

- **Professor Mike Drummond** (University of York)
- **Mr Rob Kotchie** (IQVIA)
- **Dr Matthew Williams** (Imperial College, London)
- **Mrs Pesh Doubleday** (Public Health England)
- **Mr Peter Huskinson***[1]

THESE DISCUSSIONS HIGHLIGHTED A NUMBER OF KEY ISSUES RELATING TO THE CURRENT AND POTENTIAL USE OF RWE

Where are we in terms of the evolution of RWE in precision medicine?

There was broad agreement that, in the words of one panellist, "We are on the cusp of something great" in terms of precision medicine, although at present the benefits may be greater in haematological malignancies than in solid tumours. It is noteworthy that, of 80 medicines with genetic stratification included in their license by December 2016, 30 had received this stratification after approval: this would imply that RWE was highly influential in the stratification process. However, the infrastructure needed to integrate molecular and other data is often inadequate: the UK is currently lagging behind the vision set out in the Chief Medical Officer's report.[1]

How should RWE be used to advance precision medicine?

The concept of value is critical to precision medicine, and in the absence of clinical trial data this is likely to be assessed by means of decision analytical models. RWE may have a role in informing such models, because it can provide useful insights into how clinicians interpret test results and what action they take in response to these results. A key issue here will be the linkage of genomic and clinical data, and work will be needed to facilitate this. Importantly, systems for collecting and analysing RWD must be able to function within a decentralised infrastructure.

Demonstration of the value of treatment may be particularly important for drugs for solid tumours because in this case the aim is to prolong good-quality survival, rather than to achieve a cure; as a result, patients who respond to treatment may be receiving expensive drugs for long periods, resulting in high costs to the NHS. RWE can help to determine the extent to which expensive treatments return value (which may be defined in various ways) to the NHS.

> *"We are on the cusp of something great in terms of precision medicine, although at present the benefits may be greater in haematological malignancies than in solid tumours"*

* Speaker surgeries only

HOW ARE WE ADAPTING TO THE INCREASING TREND TOWARDS APPROVING DRUGS ON THE BASIS OF SPECIFIC MUTATIONS?

RWE is likely to become highly important in HTAs as increasing numbers of new cancer drugs reach the market on the basis of immature clinical trial data; indeed, the distinction between how RCT and RWE are used is likely to become blurred as pressure grows to introduce new therapies as quickly as possible. Data obtained in actual clinical practice are also likely to be essential to address statistical issues arising from crossover of patients in clinical trials from the control to the active treatment arm. Appropriate analysis of RWD will be essential in such situations, and work is needed to determine the best way to analyse observational data.

As prescribing becomes more complicated due to the increasing availability of drugs targeted against specific mutations, prescribing algorithms based on machine learning are likely to become increasingly important. This raises potential issues with regard to governance. For example, who is responsible if an algorithm generates an incorrect diagnosis: the prescriber, the developer of the algorithm, or some other party? A lack of transparency in the decision-making process could also be a concern with algorithm-driven prescribing. Furthermore, depending on the data set used to develop an algorithm, there is a risk that the algorithm could 'learn' societal biases that might result in some patients being denied potentially beneficial treatment; examples of this have already been seen with algorithms used to guide sentencing in the US criminal justice system.[11]

HOW SHOULD QUALITY OF LIFE AND SIMILAR DATA BE OBTAINED?

At present, the NHS does not have established procedures to routinely collect data on quality of life and other patient reported outcomes. It was suggested that simple instruments, such as the EQ-5D, should be used initially in order to gain experience.

HOW MIGHT THE USE OF RWE AFFECT PATIENTS' RIGHTS?

It is essential that the use of RWE should not compromise patients' confidentiality. While healthcare professionals are used to handling sensitive information, care will be needed when handling large RW data sets. When using RWE, the rights of the individual must be balanced against the overall benefit to society. This is particularly true in the case of genomic data, which provide information on both the patient and close family members such as parents or identical twins. A patient-centred approach, in which patients are fully informed about the use of their data, is essential for the use of RWE.

" It is essential that the use of RWE should not compromise patients' confidentiality. When using RWE, the rights of the individual must be balanced against the overall benefit to society "

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