

The Eighth Joint BIA/MHRA Conference

Collaborative Working in the UK, Driving Innovation Forward

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Introduction

It is an important part of the Medicines and Healthcare products Regulatory Agency (MHRA) remit to support innovation, improving access to new medicines and promoting public health gains.



The record number of delegates at the eighth annual joint conference between MHRA and the BioIndustry Association (BIA) reflects the value of continued dialogue in helping to achieve this objective and to drive innovation forward, and is particularly important in the context of the negotiations on the terms of the UK's future relationship with the EU, said **Dr Ian Hudson, Chief Executive of the Medicines and Healthcare products Regulatory Agency**, opening the conference.



Echoing this, co-chair **Alan Morrison, Chairman of the BIA Regulatory Affairs Advisory Committee and Vice President, Regulatory Affairs International, MSD**, said the high-level line-up of speakers from across regulators, industry, medical research charities, academics and government was testimony to the commitment to collaborative working in delivering innovation to patients.



The UK regulatory environment now and into the future including Brexit

MHRA's active role as part of the UK and global innovation ecosystem



In parallel with its role in ensuring the safety and effectiveness of medicines, MHRA has specific processes in place through which it applies its expertise in regulatory science to support companies in bringing innovation to market, as **Dr Ian Hudson, Chief Executive of the Medicines and Healthcare products Regulatory Agency** described.

First, a cross-agency team of experts meets regularly to conduct horizon scanning, identify new science and techniques coming out of academic labs and early discovery, and consider how they should be regulated.

That work is informed by the MHRA Innovation Office, which talks directly to companies and academics seeking advice on the development of new technologies and therapies.

Building on its understanding of the types of novel products coming through the pipeline, MHRA has a number of channels for offering advice. In addition to the Innovation Office, these include help lines, a service dedicated to providing advice on regenerative medicines, and access to scientific advice, including providing joint advice with NICE (the National Institute for Health and Care Excellence). The joint advice is intended to enable companies to shape clinical development programmes that will simultaneously provide data for regulatory approval and health technology assessment.

In regenerative medicine, companies can cast the net further and get coordinated advice from MHRA, the Health Research Authority (HRA), the Human Fertilisation and Embryology Authority (HFEA), the Human Tissue Authority (HTA) and the Health and Safety Executive, Dr Hudson noted.

In the five years since the Innovation Office was established, it has dealt with 570 enquiries and held 120 meetings, including 60 one-stop shop consultations on regenerative medicines. There is “quite a spread” of users, with 33 percent from SMEs, 30 percent from academics, 14 percent from the NHS or not for profit bodies.

The value for the industry in having a source of advice on advanced therapies is underlined by the fact that 28 percent of approaches to the Innovation Office relate to this area. There is also significant demand for advice on medical devices, manufacturing methods and clinical trial design.

Early Access to Medicines

Since its launch by MHRA in 2014, the Early Access to Medicines Scheme (EAMS) has become a key mechanism for bringing innovation safely to market, said Dr Hudson. Through EAMS, MHRA

gives regulatory opinions on the unlicensed or off-label use of medicines for life-threatening or seriously debilitating diseases without adequate treatment options.

The first step – securing Promising Innovative Medicine (PIM) status – provides a signal that a product could be a candidate for EAMS. “It has been a useful designation,” Dr Hudson said.

Following PIM designation, MHRA issues a benefit – risk opinion in the context of the intended use of a product. Of 55 PIM designations granted to date, 20 have translated through to EAMS scientific opinions. “It has been more successful than we thought it would,” said Dr Hudson. “Earlier access is important, but it has to be in the right circumstances.” There is more uncertainty, so it is necessary to collect in-market safety data and respond if there are any safety issues.

At the same time, “regulation is just one part of the puzzle,” of ensuring uptake, Dr Hudson said. “We work with NICE and the NHS to make sure things are followed through to facilitate patient access.”

The MHRA is similarly engaged at an EU level in the EU network, and at the intersection of drugs and devices, helping to decide how combination products should be regulated.

Also at an international level, MHRA is active in the International Coalition of Medicines Regulatory Authorities (ICMRA), a group established to look at strategic issues faced by national regulators. In addition to aspects including safety, crisis management, supply chain integrity and pharmacovigilance, the Coalition recently established a working group on innovation.

The innovation group will do horizon scanning to assess major trends for which regulators need to prepare, set out novel approaches to licensing medicines and identify barriers to market.

“We are in a rapidly-changing environment,” said Dr Hudson. “We recognise the need to support innovation for public health gain at a national, EU and global level.”

National Institute for Biological Standards and Control (NIBSC) collaborative role in supporting research and innovation

From its formation in 1975, in the early days of the medical biotech era, NIBSC has been a driving force for innovation, developing assays and providing independent assurance of the quality of biological medicines.



The Institute has unrivalled expertise and resources and is recognised as a world leader in the international standardisation of biologics, having developed some 90 percent of the World Health Organisation’s international standards, **Dr Christian Schneider, Director of NIBSC**, told delegates.

NIBSC is also home to the Centre for Biological Reference Materials, the Influenza Resource Centre, the UK Stem Cell Bank and the Creutzfeldt Jakob Disease Resource Centre.

As an example of the role its international standards and analytical methods play in supporting innovation, Dr Schneider referenced NIBSC's work to develop a lentiviral vector standard for integration copy number, enabling the standardisation of assays and comparison of respective trial results of lentiviral vector delivered gene therapies and of products from different manufacturing sites. "This increases regulatory certainty, but doesn't lock the field into one standard," Dr Schneider said.

Other capabilities supporting innovation include world-leading research and development in methods of freeze-drying biologicals, and support for the development of manufacturing processes.

In addition, NIBSC carries out independent regulatory testing in Europe for vaccines, blood-derived products and biotherapeutics, testing around 4,000 batches of medicines and plasma each year.

In research, NIBSC has work streams on assuring monoclonal antibodies as biological medicines; addressing the threat of global infectious diseases; assays for regenerative and cell-based therapies; applying biologics to overcome antimicrobial resistance; and support for clinical applications of stratified medicines and genomics.

Central to bringing its expertise and the fruits of its research to bear for public health gain are the broad range of partnerships NIBSC has across government departments, with key agencies such as Public Health England and national blood services, leading academics and external experts, and international organisations like WHO, and regulators around the world.

Inevitably, there are concerns about the impact of leaving the EU, but Dr Schneider stressed the UK has a strong and connected life sciences infrastructure, with a large number of world class companies and academic centres.

One example of this is the UK's rapidly developing advanced therapies infrastructure. Underpinned by the Medicines Manufacturing Industry Partnership, the Advanced Therapies Manufacturing Action Plan and the Cell and Gene Therapy Catapult, this is about to be translated into clinical practice with the formation of six NHS advanced therapy treatment centres across the UK.

Roll-out of advanced therapies, with all the complexities of quality assurance and control "requires an embedded and strong regulator," Dr Schneider said.

The ability to manage and regulate all the complexities of advanced therapies also illustrates how the UK has brought together all aspects of oversight into a "one-stop regulatory engine" for innovation, from early scientific advice, to providing starting materials and assays and good manufacturing practice inspections.

Schneider acknowledged concerns that the UK may not be perceived as such a good place to carry out clinical trials after Brexit. But he said, "Development of a medicine is a scientific task, so the regulatory agency has to be a scientific agency. So if you develop a sound product, it is hard to believe that it won't be accepted elsewhere."

Clinical trials environment in the UK in 2019 and beyond



Following a sharp drop from 1,500 to 1,000 between 2004 – 2005, the number of clinical trials staged in the UK has remained stable at around 1,000 per year. That is about the same as Germany, noted **Dr Martyn Ward, Group Manager, Licensing Division, MHRA.**

The trend has been for fewer phase I and phase IV studies and an increase in phase II/III. Meanwhile, the number of trials conducted in Europe as a whole has fallen from 4,336 in 2006 to 3,521 in 2017. “We are just under 30 percent overall; there isn’t yet any post-referendum effect that we can detect,” said Dr Ward. Indeed, in 2017, the number of first in human trials starting in the UK was at its highest level in any of the past eight years, at 104.

However, there is some evidence from the Voluntary Harmonisation Procedure (VHP), under which companies can get a coordinated assessment of a multinational trial, that Brexit could have an effect in the future.

In the first five months of 2018, the UK was involved in 37 VHPs, compared to 57 in the same period of 2017. “There has been a clear decline,” said Dr Ward.

Although the UK government has stated it wants continued close cooperation with the EU across all aspects of medicines regulation, MHRA is preparing to respond to all outcomes, including there being no withdrawal agreement in place by March 2019 and also looking for clarity on a number of issues relating to the position of the Agency if the proposed implementation period to the end of 2020 is agreed.

One significant event due to take place during the proposed implementation period is the coming into force of the Clinical Trials Regulation (CTR), which MHRA had a lead role in shaping.

Under CTR, it will be possible to make a single electronic application to conduct a trial in a number of EU countries, and to get a single, coordinated, response from each country.

MHRA began preparatory work for CTR in 2014. As one example it is establishing a process for conferring with ethics committees to arrive at a single decision. A pilot began in April, with the first application submitted on 29 May. “We are well-placed to implement many of the [CTR] provisions,” said Dr Ward.

Assuming it comes into effect before the end of the implementation period, CTR will apply in the UK, giving access to the single portal for submitting files and the supporting databases and networks. However, it is not clear at present if MHRA will be able to act as lead assessor, coordinating the response of fellow regulators.

In the event CTR does not come into effect during the implementation period, or that there is no withdrawal agreement, the UK government has committed to remain aligned with CTR, to the extent that is possible. Dr Ward said MHRA “is working on parallel processes, so for example, the EU application could be submitted to the UK without change.”

MHRA will maintain its current competitive timelines and ensure its process is as streamlined and efficient as possible. If the UK were to be outside the system, MHRA would no longer need to align its processes with multiple EU-27 member countries authorities and would be able to offer more competitive timelines.

Dr Ward noted it will still be open for UK sponsors to run multisite trials across the EU and elsewhere, and that data generated in UK trials will be admissible to support marketing authorisations in the EU and globally.

Whatever the outcome of the Brexit negotiations, MHRA is prepared so clinical trials continue. The MHRA has done a lot of work “in the background” looking at if there is no agreement. “We are ready to implement if necessary,” Dr Ward said.

Industry Perspective: Preparations for Brexit, key priorities and opportunities



Despite being quick off the mark in establishing a working group to identify industry priorities, and a desire by the UK and the EU to collaborate in medicines regulation, two years on from the referendum the sector faces numerous imponderables about what it needs to do to prepare, said **Alan Morrison, Chairman of the BIA Regulatory Affairs Advisory Committee and Vice President, Regulatory Affairs International, MSD.**

Perhaps the starkest manifestation of this, is that the proposed implementation period still needs to be agreed “We are a long cycle industry, so this uncertainty is cause for concern,” Mr Morrison said.

In the absence of an agreement, the European Commission and EMA are telling businesses to have completed all preparations by March 2019, a deadline that many will find impossible to meet.

With the life sciences industry in the UK and the EU facing possible disruption, the sector has adopted a common position on its requirements of the withdrawal agreement and the future relationship. “There is a very, very highly aligned view,” Mr Morrison said.

This encompasses the need to ensure mobility of talent and the protection of reciprocal citizens’ rights; an implementation period to allow all the work required to guarantee patient access to medicines to be completed; maintaining close cooperation in medicines regulation; and business continuity planning to ensure supply chains can cope with any customs delays.

The biggest challenges will arise in the event of a ‘no-deal’ scenario. That will involve significant upheaval and the setting up of duplicate facilities across manufacturing and supply, clinical trials, regulation and pharmacovigilance. As one example of the workload, 60 percent of members of the European Federation of Pharmaceutical Industries and Associations have batch release from the UK.

“The pharma industry needs clarity on the legal and regulatory position for medicines,” said Mr Morrison. “Without clarity, companies must plan for all outcomes.”

Despite the industry’s efforts to ensure business continuity, duplication of product testing and release makes it likely there will be capacity constraints. “We need an arrangement to address re-testing of batches,” Mr Morrison said. “The UK should unilaterally accept EU testing.”

The industry welcomes the UK government and MHRA’s commitment to continuing cooperation with the EU on medicines regulation, but would like reassurance that regulatory alignment and

moves to protect supplies of medicines from day one after the UK leaves the EU, will be a priority in the Brexit negotiations.

In addition, Mr Morrison called for “help to support public health and avoid disruption to existing supply chains.”

Brexit: Patient and medical research charities perspective

The 140 members of the Association of Medical Research Charities (AMRC) collectively invest £1.6 billion each year in UK R&D. This funds 17,000 scientists and equates to almost half of all public sector medical research by value, across all stages from basic research, to translation and funding clinical trials.



“This could all be affected by Brexit,” said **Dr Catherine Ball, AMRC Policy Manager**. In particular, AMRC is concerned about the rights of EU-27 researchers in the UK and in the ability to attract talent in the future. The Association also wants to see regulatory cooperation and a guarantee of frictionless trade in medicines; maximum collaboration on clinical trials; and continued collaboration on research, with the UK remaining part of the ongoing

Horizon 2020 research programme and having associate membership of its 2021 – 2027 successor, Horizon Europe.

AMRC is working with the wider Brexit Health Alliance to safeguard the interests of patients, and the healthcare and research they rely on, as the UK leaves the EU. “We want to maintain and build on links with the EU,” Dr Ball said.

UK and EU patient groups are united in efforts to ensure there is no negative impact on patients and are stressing that both EU-27 and UK patients could be affected. AMRC and a number of EU- and UK-based patient organisations have been in touch with EU and UK negotiators to outline patients priorities, said Dr Ball.

Panel Discussion and Q&A



Patrick Carey, Deputy Director for EU, Brexit and International Policy at MHRA, underscored the Agency’s commitment to ensuring patients are not disadvantaged, and to supporting companies to get innovation to market as soon as possible.

“Assuming the implementation period to December 2020 is ratified, there will be no change in market access and businesses will have the time they need to put in place any new arrangements, so no sudden change or ‘cliff edge’ for yourselves or patients,” Mr Carey said.

The exact nature of MHRA’s future involvement in the European Medicines Agency is yet to be agreed. The White Paper, setting out the UK’s government’s position on how it wants to shape

the future relationship with the EU [published just after the conference on 12 July] envisages a special partnership, with close and continued cooperation in medicines regulation.

While that is the preferred outcome, Mr Carey reassured delegates MHRA is preparing to support the industry under all possible scenarios, including no deal (i.e. no withdrawal agreement and no implementation period). Highlighting the principles set out in the MHRA's web statement, published in January 2018, he said "We will be pragmatic in how we set up any new UK requirements and will ensure minimum possible disruption". He also highlighted that the UK Parliament had passed the EU Withdrawal Act, transposing EU law to the UK statute book – a key step in ensuring there will be no sudden changes to the regulatory framework. He acknowledged this did not cover new regulations due to apply during the implementation period, but highlighted the Government's recent commitment to align with the new EU Clinical Trial Regulation as evidence Government is listening and is committed to resolving such issues.

What are the challenges for innovative SMEs?



Andrew Fox, Vice President of Regulatory Affairs at PsiOxus Therapeutics Ltd, reflected the Brexit tensions faced by a small innovative company that has ambitions to be a world leader in cancer gene therapy, and which has programmes in clinical development, but no products on the market as yet.

While it is "fantastic to see the emphasis on fostering innovation in the UK", the two years of uncertainty since the referendum about the UK's future position, makes it hard to plan. For example, the company is at the stage where it should be considering where to site a manufacturing facility. "In the face of the uncertainty, it will be going outside the UK," Mr Fox said.

Similarly, with a small regulatory department, it is not possible to take advantage of MHRA's support for innovative companies, with Mr Fox saying it would be "hard to find the bandwidth" to get scientific advice from MHRA, as well as EMA and FDA, if the UK is not part of the EMA medicines regulatory network.

The same will apply when PsiOxus reaches the point of making a marketing authorisation application. "I'll focus on the US and EU-27 – I can't send in multiple parallel applications," said Mr Fox.

What are the options for companies with marketed products?

While as a development-stage company, PsiOxus can put off decisions until the outcome of Brexit negotiations are clear, companies with products on the market are being forced to prepare for a "cliff-edge scenario", and are moving testing to the EU-27, said Alan Morrison. "As the clock ticks down without a mutual recognition agreement, they will move to ensure they are compliant," Mr Morrison said.

How can the value of scientific advice be maintained?

Dr Hudson stressed MHRA will continue to be a source of scientifically sound and relevant advice, no matter what. “We want to be pragmatic and would encourage all companies to take advantage of ongoing dialogue,” he said.

Dr Schneider agreed, saying scientific advice is an enabling function. “I don’t see that changing, because MHRA has this embedded in the system. For example, we can help you find the right animal model to generate the right data for an international trial,” he said.

Dr Ward too, stressed the value of taking scientific advice at the earliest stages of designing a clinical development programme. “There is some reluctance to do that, particularly on the part of academics, because to them regulators are an unknown quantity, he said. “Come to us; we can help you with setting the right direction.”

That message was reinforced by a member of the audience, who said MHRA’s advice on an early stage product was “pragmatic and useful.” When the programme was subsequently presented to European regulators, the response was favourable.

Another delegate observed Brexit could mean UK patients are not well represented in European trials, suggesting a specific effort may be required to ensure the UK remains an attractive place to conduct clinical studies.

Dr Ward acknowledged the UK’s attractiveness is not down to the medicines regulator alone. The NHS, high quality university hospitals and leading principal investigators, are all essential elements of the mix. There is “definite recognition” of the need to work together on ensuring the UK remains attractive in the future, said Dr Ward.

Are there any benefits from Brexit?

For Mr Fox, the uncertainty is making it hard to detect any upside, but he said, “We have to find the benefits.” Mr Carey suggested that ultimately we would have to wait and “see what the new world looks like” once negotiations finish. However, he observed, “People are reviewing the established order across all areas and asking can we do things faster or be more competitive – and that the thinking is likely to be useful, whatever the outcome” he said.

Dr Schneider agreed there are bottlenecks in the wider system that could be unblocked in the UK. An example is the slow pace of regulating Advanced Therapy Medicinal Products. He also suggested the UK could be in a position to apply its world-leading expertise in “pure” scientific advice more broadly.

From the “heads down” perspective of focussing on the preservation of public health, it is hard to think opportunistically, said Mr Morrison. But, he noted, the UK has a fantastic science base, particularly for early stage research saying, “The universities will still be there after Brexit.”

For Dr Ball, one opportunity would be in resetting the way we collaborate, to better capitalise on the power of joint working. The threat of losing the ability to collaborate across the EU has really brought home its value, she said.

Working together in the accelerated access pathway for breakthrough therapies and technologies

Keynote address



The pathway by which new medicines are developed is well-known, but said **Sir Michael Rawlins, Chairman of the Medicines and Healthcare products Regulatory Agency**, regulatory approval is not the end of the story because new products have to be assessed by health technology assessment bodies to demonstrate cost-benefits and then be adopted by the healthcare system, before patients get access.

The Accelerated Access Review, led by Sir Hugh Taylor, made a series of recommendations on how the pathway could be optimised, capitalising on the UK's strong biosciences research and its life sciences industrial base, to improve patients' outcomes, and "make the UK the best place to design, develop and deploy," innovative medicines.

The Accelerated Access Collaborative was established at the start of 2018, with a brief to implement the recommendations. Its roles include horizon scanning for breakthrough products; streamlining the development pathway for these products; promoting the use of real world data to demonstrate effectiveness once products are on the market; encouraging the adoption of flexible pricing arrangements; and supporting adopting and diffusion of breakthrough products via the Academic Health Science Networks.

Sir Michael said, "The crucial part is that 6 – 10 transformative innovations per year have to be identified." These must improve patient outcomes and have the potential to increase efficiency of the healthcare system, he said.

The Accelerated Access Review dovetails into Sir John Bell's Life Sciences Industrial Strategy and a number of cross-cutting themes in both are "of special relevance" for MHRA. These include the use of novel clinical trial designs; setting up a new managed access pathway; a call for regulators to work more closely together; the development of supporting regulatory science; and a commitment to work more closely with those in other parts of the system to create a seamless pathway.

"Clinical trials got particular attention," Sir Michael noted. "MHRA has got to engage to facilitate this part of the Life Sciences Strategy."

That will include assistance and advice to sponsors on designing smaller, and more targeted clinical studies, for example, in cancer, using basket trials that group patients by mutation rather than the site of a tumour; umbrella trials that take patients with the same type of cancer and assign them to different arms of a study, based on what mutations are present in their tumours; and adaptive designs in which data from one cohort is used to inform the treatment strategy for subsequent groups.

Rather than everything hanging on trials being statistically powered to deliver a go/no go p value, the use of Bayesian statistics, accompanied by biomarkers and other surrogate endpoints, should

be applied to demonstrate safety and effectiveness of breakthrough products in smaller trials. Real world evidence should then be collected once a product reaches the market, to ensure the expected benefits are delivered.

Sir Michael noted MHRA had already taken steps towards the Accelerated Access Pathway in the Early Access to Medicines Scheme (EAMS), established four years ago.

EAMS allows patient access to medicines before they are formally licensed, by carrying out an initial assessment and awarding a Promising Innovative Medicine designation, entitling a product to be considered for EAMS. This is followed up by an EAMS scientific opinion, enabling the sponsor to make a product available to the NHS in advance of marketing authorisation.

“There have been 20 EAMS approvals so far and a recent independent review of the scheme was positive,” Sir Michael said. The review made recommendations for the early involvement of health technology assessment and for the collection of real world evidence, to further improve access.

Sir Michael acknowledged more needs to be done to promote uptake once a product gets EAMS scientific opinion, suggesting the Academic Health Science Networks could be a source of the cultural change required to introduce any necessary modifications of the care pathway and promote more rapid adoption. MHRA will work closely with the government to implement the recommendations of the Accelerated Access Review, through the Life Sciences Industrial Strategy Board, whilst in parallel cooperating with academics, industry and patients’ groups to ease access to innovative therapies.



Panel Discussion and Q&A

Following on from the Accelerated Access Review, the Accelerated Access Collaborative was established in January 2018, with representatives from the NHS, government, NICE, MHRA, industry, Academic Health Science Networks and clinicians, to oversee implementation of the Review.



The chief task of the Collaborative is to identify transformational products to enter the Accelerated Access Pathway. The first group of products is due to be considered within the next few weeks, **Will Field, Head of Accelerated Access Implementation at the Office for Life Sciences**, told delegates. The pathway, “is not a new and different thing” but rather, “how the processes we have now can be better,” in particular by moving from working sequentially to working in parallel, Mr Field said.

As part of its commitment to accelerating access, the government is investing £86 million. Amongst other measures, that will fund the Academic Health Science Networks to take on an expanded role and to support small companies in doing real world evidence collection.

There is work going on internally with NHS England, looking at how to streamline processes and reduce duplication. It is still “relatively early days” in implementing the Accelerated Access Review, Mr Field said. “The next step in the autumn, will be to launch the Pathway and start work.”



Dr Louise Wood, Director, Science, Research and Evidence at the Department of Health and Social Care, highlighted the pivotal role the National Institute for Health Research (NIHR) plays in supporting collaborative research in the NHS, with 20 centres focussed on bridging the early stage translational gap.

Examples of clinical studies that have been supported include Oxford BioMedica plc’s phase I trial of its gene therapy for Parkinson’s disease; a trial of an immunotherapy for treating Type I diabetes being developed by UCB Pharma; and a study by BioMarin Pharmaceuticals of a gene therapy for treating Haemophilia A.

“First in human studies are increasingly carried out in patients, not healthy volunteers and NIHR supports those sorts of studies,” Dr Wood said.

There has been a concerted effort in recent years to shape NIHR into the most integrated clinical research system in the world, supporting research from bench to bedside. While there is more to do, 79 percent of NHS trusts are involved in studies with commercial sponsors and 73 percent of commercial trials conducted in the NHS complete to time.

An ambition for the future is to present an integrated service with the UK’s leading clinical research assets, including UK Biobank, the Clinical Practice Research Datalink and the 100,000 Genomes Project, Dr Wood told delegates. “We need to join up assets and present as a more compelling offer to industry. We are working on this with the Office for Life Sciences,” she said.



Innovation in the UK sits in a challenging place between the ambition everyone has and the capacity the system has to deliver on that ambition, said **Sir Andrew Dillon, Chief Executive of the National Institute for Health and Care Excellence (NICE)**.

Given this gap, it is necessary to concentrate on delivering innovation in the context of fiscal pressure and budget responsiveness. It is “an enormous challenge to reconcile all the signals and do it in a way you can deliver on the ambition to use innovation,” said Sir Andrew.

As the UK leaves the EU, it is necessary to persuade global life sciences companies the UK remains a great place to do business. Sir Andrew said, “I think we can do that.” One aspect of achieving this is for the NHS to become better at adopting innovative products.

In support of this, NICE is engaging with companies well in advance of products being licensed, to discuss their potential and where they would fit into current practice, and also encouraging early conversations with NHS England, as principal commissioner. “So it’s known where a product sits in the system, and [the system] is engaged to make sure that’s what happens,” said Sir Andrew.



Companies look at the UK environment in the round, and while they celebrate the upstream scientific excellence and clinical research infrastructure, there is a challenge downstream in the “problems of access”, said **Sam Graham, UK Director for Public Policy and Government Affairs at Biogen**. One manifestation of this is the difficulty in getting access to rare disease therapies, an area where the UK currently lags.

“I hope the [Accelerated Access Collaborative] will be open in how it picks innovation,” Graham said. “There needs to be recognition that [addressing] unmet needs will increase costs.” It is also necessary to translate what is learned through Accelerated Access for highly innovative products, to inform conversations about broader reform. “We need to see the Accelerated Access Pathway is not the only solution to getting innovation into the system,” said Mr Graham. “Innovation can be delivered in the NHS, with the right messages and incentives.”



For medical research charities, there is “a lot of frustration” about how much time it takes to move products from research and into clinical development,” said **Dr Arthur Roach, Director of Research at Parkinson’s UK**. Research over the past decade, funded from public donations, has “delivered fantastic insights” but is still years from the clinic. Meanwhile, products in phase II and phase III clinical trials for Parkinson’s disease coming up the pipeline, “need to be speeded through,” Dr Roach said.

In the past, Parkinson’s UK has funded trials of products that showed benefits but were not taken forward. That raises the question of, “how to make sure there is a plausible path to commercialisation,” said Dr Roach.

In addition to funding research, medical charities could take on a more explicit role in driving adoption, Dr Roach suggested. Parkinson’s UK has a “network of excellence” which monitors care to identify best practice and where care is being delivered to a lower standard, driving up quality overall. “This could be done in other areas; charities could take a lead on making sure there is awareness of new therapies and getting access,” Dr Roach said.

What would it take to promote a wholesale change in methodologies to speed development and promote access?

The example of how vaccines and therapies for treating Ebola virus infection were speeded through regulatory scrutiny and into ethically approved trials during the 2014 – 2015 outbreak in West Africa is testimony to what can be achieved when there is a concerted effort to expedite development and access, said Sir Michael.

Another case in point comes from basket trials that led onto FDA approvals of two molecularly-targeted cancer drugs. Both were approved on the basis of positive data from small single-arm trials. In the case of Loxo Oncology Inc's tropomyosin receptor kinase inhibitor, larotrectinib, approval was based on data from just 55 patients. Taken together they had tumours that arose in 17 different locations. Sticking to the traditional approach would have required separate trials for each location. Sir Michael said he would like to see faster adoption of such trial designs in the UK.

How will the regulatory system handle new genomics technologies such as the use of machine learning techniques to assess response to treatment by monitoring changes in tumour DNA?

"We are interested in how [such techniques] work and how good they are," said Sir Michael. The difficulty is that of their nature machine learning algorithms continuously evolve. Given this it will be necessary "to regulate the process not the product," he said.

Dr Hudson noted these technologies fall under the medical devices regulation and also regulatory guidance on software. Regulating machine learning is a "very difficult evolving area," he said. MHRA recognises it needs to respond and adapt to the digital transformation of the broader ecosystem.

Whose equipoise is it? There are plenty of examples of patients having greater tolerance to risk than regulators. Given this, should the UK consider quick triage studies based on the risks patients are prepared to take?

Dr Roach agreed individual patients do have a higher tolerance of risk than regulators or society currently allow for.

However, Sir Michael said there are lots of different kinds of risk, including the risk to the system of investing in treatments at the point where not enough is known about them. "It's ambition versus capacity again. We want to deliver benefits as soon as possible, but you still have to balance patient risk against the risks the system takes," he said.

How can the UK retain talent and keep the innovation stream going when it leaves the EU?

As Mr Morrison noted, the subject was addressed by the Life Science Industry Coalition report published in December 2017, which underlined how the UK leaving the EU presents a significant challenge to the way that medicines are developed, trialled, regulated and supplied to patients. Amongst other issues, the report said the life sciences workforce, including families and spouses, should be protected by a solid citizens' rights agreement.

On skills, Dr Wood suggested a wholesale review of training is required. For example, on digital skills there is a massive gap. "We need a new strategy to ensure we have got the skills sets of the future," she said.



Drug device combinations – supporting innovation and addressing regulatory challenges

Overview from MHRA

The medicines/device borderline is blurring, and a significant number of marketing authorisation applications now include a device component, whilst increasingly devices include a medicinal component.



“In the past you knew what a medicine was, and what was a device. Now there are drug and device kits and the regulatory pathway is challenging”, said **Elizabeth Baker, Group Manager, Licensing Division, MHRA.**

Yet it is necessary to decide if a product is a medicine or a device because there is no combination product classification, or a separate legal basis for regulating them. As a result, “regulatory gaps are emerging”, Ms Baker said.

The decision on whether a product is a medicine or a medical device depends on how it achieves its mode of action, in the claims made for it.

If the primary intended purpose is achieved by pharmacological, metabolic or immunological means, it is a drug/device combination. If the effect is through physical, simple chemical, mechanical or digital means, it is a device/drug combination.

In practice, there is a spectrum of combinations from standalone medicine to stand alone medical device and the two sets of legislation “mesh together”, said Ms Baker.

However, there is currently an imbalance in that the medicines regulation does not cover provisions relating to drug/device combinations; medical device legislation recognises and controls these. The revision to the EU Medical Devices Regulation that came into force on 26 May 2017 includes further provisions for device/drug combinations.

The Medical Devices Regulation will introduce stricter control and regulatory oversight of devices and non-medical products analogous to devices (for example breast implants) requiring increased attention to design and manufacture, and to compatibility if multiple devices are intended to be used together.

There will also be improved transparency and ability to monitor for any in-market faults through an EU database of medical devices, a tracing system based on unique device identification and a patient “implant card” with information on implanted medical devices.

Reinforcing these measures, manufacturers will face greater requirements to conduct in-market surveillance and there will be improved EU-level oversight.

Under the new Regulation, when a device incorporates a medicinal product, the opinion of a medicines competent authority must be sought as now. Mirroring this, for medicinal products with an integral device component, manufacturers will have to get an opinion from a Notified Body on the device component before submitting the file to a medicines regulator. What this will look like and how the process will work in practice is being discussed.

The Medical Devices Regulation may affect the drug/device borderline, Ms Baker noted. “It may be that some substance-based products will be moving from medicine to device control,” she said. The European Commission is setting up a Medical Device Coordination group to consult on borderline cases.

Implementation of the Regulation presents challenges in the oversight of combination products, with stricter controls raising questions about the capacity of Notified Bodies, whilst medicines regulators, including the EMA, must also take on new responsibilities.

At the same time there will be an increasing number of generic and biosimilar combinations and off-label use medicines in combination with devices to oversee.

In addition, there is the complexity of regulating a new generation of point of care products, for example, 3D printing of medical implants. “How do you regulate something that doesn’t exist until it’s about to be used – that is a challenge for the confines of our current legislation,” Ms Baker said.

Notified Body perspective

Following on from the entering into force of the Medical Devices Regulation there is a three-year transition period (five years for in vitro diagnostic medical devices), before the rules apply.

Amongst other aspects, the transition allows for the designation of Notified Bodies as qualified to oversee the Regulation.

Of particular relevance to the pharma and biotech industry, that will include Notified Bodies building the competence to give an opinion on the device element of a medicinal product, as required by Article 117 of the Medical Devices Regulation.



As **Dr Sophie Tabutin, Notified Body Regulatory Lead, BSI Medical Devices**, noted, the Article 117 process needs further definition, and guidance is in preparation. “For example, we don’t yet know what level of detail is required in the Notified Body assessment, or if the Notified Body confirmation is required as part of the initial marketing authorisation application (MAA), or can be concurrent with the MAA review,” Dr Tabutin said.

Notified Bodies will only be able to accept applications for an opinion once designated under the Medical Devices Regulation. Dr Tabutin advised companies to speak to a Notified Body early to understand if and when they can accept an application and to factor these activities and associated timelines into project planning.

Industry Perspective



Tim Chesworth, Senior Director, Medical Devices and Combination Products, Global Regulatory Affairs, AstraZeneca, scoped the issues and complexities swirling around the new emerging category of digital therapeutics, which he defined as the use of a connected device, sensor or software to optimise the effect of a medicine.

Optimisation could be through encouraging patients to take medicines as prescribed; helping with self-management of adverse events and enabling easier interaction with healthcare producers; and allowing for point of care data collection.

In AstraZeneca's view, digital therapeutics will both improve the patient experience and the clinical outcome, optimising medical practice.

As one example, patients with chronic obstructive pulmonary disease (COPD) can be encouraged by digital therapeutics to change behaviours following hospitalisation for an exacerbation of the chronic lung disease. This can improve self-management, enable them to detect any deterioration and take steps to avoid further exacerbations. "It is also good from a payer and provider perspective," Chesworth said. "They can spend time and resources elsewhere."

The real-life efficacy of AstraZeneca's Symbicort for treating COPD is reinforced when used in combination with the Turbu+ digital therapeutic, which logs when patients use their Symbicort inhaler. The information is sent via Bluetooth to a smartphone app that issues reminders, tracks adherence and sends motivational messages. Healthcare professionals can access the information on a secure portal, supporting a more informed dialogue with their patients.

For digital therapeutics in which the medicinal and digital elements are developed in parallel, it will become increasingly difficult to separate the medical effect from the digital effect. This will raise challenges of how to regulate the digital element as part of the overall product, Mr Chesworth said.

Currently there is a lack of regulatory guidance on issues including how to incorporate digital tools into clinical studies; what are the routes to regulatory approval; what information is required to support approval; and how post-market changes are managed.

Applying digital therapeutics to clinical trials will change the way they are conducted. There will be "fewer patients but enhanced insights," said Mr Chesworth. Rather than multiple clinical sites, the use of connected drug delivery devices, medical sensors and environmental data collected by internet-connected devices will enable treatments to be assessed at home, in the environment where they will be used.

Machine learning can be applied to this rich data source "to learn how patients use a product and give them feedback on how they could use it better," Mr Chesworth said.

Algorithms that AstraZeneca is starting to work on will take data from a patient and other information sources to continuously assess if a patient is making progress, rather than making an episodic assessment at a three-monthly appointment.

Clarity is required on the exact nature and extent of the data that will be required in a marketing authorisation application to allow a digital therapeutic to be included within the label of a medicinal product.

Once on the market, change management will be a key challenge. With a traditional medicinal product post-approval changes are minimised. However, digital therapeutics are readily and frequently updated. That will be increasingly problematic as digital therapeutics become an intrinsic part of a medicine.

Mr Chesworth proposed that changes and variations to digital therapeutics can be adequately controlled if they are managed within a recognised quality system such as that described in the international standard ISO 13485. "The cadence of change [in digital therapeutics] is so rapid, we can't work in the current variations system," he said.

Q&A

How can sponsors verify that the device element of a medicinal product will work as planned from the early stages of development?

Dr Tabutin suggested consulting a Notified Body. “They have got the software and engineering expertise,” she said. In addition, they are preparing to regulate Article 117 and can advise companies on how to meet the requirements. However, she noted also that the Medical Devices Regulation was a long time in the drafting and Article 117 was written before some of the more complex combinations of drugs and device came along.

To what extent is the Medical Devices Regulation enabling?

For Ms Baker, there are still two very distinct sets of regulations governing medicines and devices. “They are very different in how they operate and that’s a challenge,” she said.

Mr Chesworth agreed the silos are a problem, noting the FDA has recognised the need to break down barriers within their own organisation.

In addition to the ongoing separation between medicines and medical devices, the EU Medical Devices Regulation adopted in 2017 does not particularly advance the software agenda. “Regulation of software as a medical device is still uncertain and it is then made worse when you overlay medicinal products [requirements],” said Mr Chesworth.

What is the answer to the drug/device regulatory divide? Could MHRA be more like the FDA after Brexit?

One company alone cannot bridge the divide, and given this the European Federation of Pharmaceutical Industries and Associations has set up a Digital Working Group to try and figure out collectively how to go forward, Mr Chesworth said. “There will need to be third party facilitation of these discussions to bring together all the different threads.”

While there has been discussion of the need for drug/device collaboration, Ms Baker said for now, it is necessary to find solutions within the current regulatory framework. MHRA is one of the very few competent authorities to combine medicines and medical devices oversight and Brexit could be an opportunity to imagine how to do things differently, she said.

Real world evidence – sources for data collection and role in regulatory decision-making

Overview and regulators learnings



The question “Do regulators accept real world evidence?” is frequently asked, but is too imprecise to answer; rather the question should be, “Will regulators accept real world evidence from this specific data source, used in this specific manner, for this specific regulatory purpose?” said **Robert Hemmings, Manager, Licensing Division, MHRA and chair of the CHMP’s Scientific Advice Working Party, European Medicines Agency.**

Regulators are already accepting real world evidence to inform the way in which drugs are developed, for example, to understand the epidemiology of a disease, to inform trial design and, in certain situations, as an external control arm.

The potential benefits of real world evidence sources are clear. However, whilst considerable experience is available in using such data for pharmacovigilance, Mr Hemmings said more experience is needed in using real world evidence to quantify beneficial effects of medicines, either in reducing uncertainty post-approval, such as in Conditional Marketing Authorisation, and for use in extending indications.

The same principles should be applied to demonstrating efficacy in clinical practice, as to pre-approval clinical development programmes. “To make progress in accepting specific proposals, conversations have to be structured and linear,” Mr Hemmings said. “You’ve got to start with the objective: what, precisely, is the research question to which you want the answer?”

That research question or objective will dictate the design of a real world evidence study, including the need for a control arm, randomisation and the data to be collected. Those can then determine which data sources should be used. Finally, a detailed statistical analysis plan is required that addresses potential sources of bias in the estimation of treatment effects.

Objectives of a real world evidence trial must be agreed in advance between the regulator and the sponsor, and they must be precise. “It’s not just a case of saying “*post-authorisation we will set up a registry*”. “Objectives should be identified that fit the development plan or that address uncertainties in the database that supports licensing” said Mr Hemmings.

The frequent lack of randomisation and blinding in real world evidence studies risks the introduction of bias. However, it is not the case that all real world evidence need suffer from these problems. It is for example possible to conduct randomised “pragmatic trials” or randomised trials using a registry as a data source, measuring the benefit a treatment produces in routine clinical practice, providing all the necessary data is captured. Other observational study designs, such as case control trials, might also find more frequent use, though the risks of important bias, difficult to address through design and statistical analysis, is an important limitation that must be transparently discussed on a case-by-case basis.

In real world evidence trials, it can be harder for sponsors to control data acquisition, quality and completeness. This points to the importance of early dialogue with the regulator, said

Mr Hemmings. “For example, if planning to use a disease registry you must be sure that it is collecting all the data you need,” he said. “If not, initial experience tells us that making changes to data collection in established registries can take some time.”

It is possible to have a conversation on the acceptability of a particular data source for a particular regulatory purpose through the EMA qualification procedure, Mr Hemmings noted. In one such case, EMA agreed the European Cystic Fibrosis Society Patient Registry could be used as a data source in the context of certain studies.

Similarly, EMA, industry and registry owners (EBMT) met to discuss objectives, data collection and data sources for dealing with post-authorisation uncertainties around CAR-T cancer cell therapies.

“In other words, there are positive messages and examples of where real world evidence has been built into regulatory opinions in a structured way,” said Mr Hemmings.

That still leaves the difficulty of applying inferential analysis to reliably estimate treatment effects in routine clinical practice datasets.

Mr Hemmings illustrated this with the example of a sponsor proposing to conduct a study using data from patients in clinical practice to provide evidence of efficacy of a product outside the labelled indication in lieu of a prospective randomised controlled trial. Specifically, the hypothesis being tested was that changes in a biomarker which is routinely used for monitoring the disease could be used to establish superiority of the product over standard of care. The data was to be sourced from three electronic health record systems.

The analysis needed to accommodate multiple possible sources of bias, for example, are the patients in the proposed electronic healthcare records representative of the target population? In what ways are the treated and untreated patients systematically different, and can that those differences be adjusted for? In addition, with this type of real world evidence there is no point of randomisation, so measuring changes of the biomarker had to be linked to some other clinical event, such as failure of previous treatment, or a clinic visit at which the need for initiation of, or change in treatment, was identified. Furthermore, a patient might get a drug, improve and switch to standard of care and then be treated again, thus being included in both study groups. Use of three data sources adds further complexity.

Having an open conversation with the company meant all the complexity and potential bias “was on the table,” Mr Hemmings said. “This level of detail, the transparency over potential sources of bias, and the discussion of epidemiological approaches to address those was critical. Combined with the particular clinical context, MHRA said yes – do it.”

That points to the importance of having a preliminary dialogue around the objectives, potential designs and data sources for post authorisation studies, sufficiently early to investigate whether any data source already collects, or can be revised to collect, information that will be necessary to execute a particular trial design and statistical analysis. There should then be a later discussion to confirm the objectives, the design, the accuracy of data sources and details of the statistical analysis. “You need to refine the research questions based on the emerging data and the specific research question and confirm that the trial and the statistical analysis will work in practice,” Mr Hemmings said. “You need to be confident the design, data sources and analysis addresses the questions you want to address. Let’s not pretend it is easy.”

Clinical Practice Research Datalink database and case studies on use of CPRD data in clinical research

The Clinical Practice Research Datalink (CPRD) is one of the richest repositories of health data in the world, containing 30 years of anonymised NHS primary care data from 10 percent of all GP practices across the UK. It currently contains 30 million longitudinal cradle to grave records and covers close to 15 percent of currently registered patients, providing a representative sample of the UK population by age, sex and ethnicity. There are records of over three billion consultations with details of prescriptions, symptoms, referrals, laboratory tests and vaccinations.



“It is a very, very valuable data source,” said Dr Puja Myles, Head of Observational Research at CPRD.

CPRD acts as a research service supporting observational and interventional research based on GP records covering all the data recorded in primary care and also through linkages to hospital records, cancer registries, death records and other data sources.

GP records are electronic and Dr Myles said, “the most exciting area” is electronic health record-enabled pragmatic trials.

Researchers in 20 countries have used the data, resulting in more than 2,000 peer-reviewed journal papers.

CPRD is a premier resource for classic epidemiological studies, for example looking at trends in incidence, prevalence and mortality of arterial fibrillation; exploring the association between thrombocytosis (raised platelet count) and the risk of developing cancer; comparing the frequency of asthma exacerbations and healthcare utilisation by patients in the US and UK; and determining the cost effectiveness of different models of care, for example how effective fracture liaison services are in preventing secondary fractures in elderly patients.

The database is constantly updated, meaning it is a powerful resource for pharmacovigilance and also can be used for comparative effectiveness studies, Dr Myles said.

Examples include post-authorisation safety studies; implementing near real-time vaccine safety surveillance; doing long-term follow up studies to assess how a drug performs in a real world setting; and doing matched cohort studies to compare the effectiveness of different drugs in the same indication.

“CPRD gets a daily data flow from GPs. We do a monthly snapshot for researchers and therefore sequential analyses are possible for near real-time surveillance,” said Dr Myles.

A system is in place enabling researchers to supplement the data. For example, it is possible to go via CPRD to collect samples from a patient or gather patient-reported outcomes. In addition, patients can be recruited to clinical trials and sponsors can use CPRD data to assess the feasibility of study designs and to set up pragmatic randomised trials.

The power of the CPRD database is illustrated by the way it was used to assess if it would be safe to vaccinate pregnant women against pertussis (whooping cough). The study was carried out in response to an increased incidence of whooping cough in new borns.

CPRD data for 20,074 pregnant women who received the pertussis vaccine, matched to an unvaccinated historical control group, showed there was no increased risk of stillbirth. As a result, since April 2016, the vaccine is routinely offered from 20 weeks of pregnancy.

Another study investigated concerns that there was a link between the use of incretin-based drugs for diabetes and heart failure. Results from CPRD were pooled with Canadian and US health data, to cover 1.5 million patients. The analysis showed the rate of hospitalisation for heart failure did not increase with incretin-based drugs, compared to other diabetes drugs, even in patients with a history of heart failure.

However, “there are caveats when using electronic health record data,” Dr Myles noted. For example, being issued a prescription does not prove the drug was taken; there are no records of over the counter medication or drugs a patient may have been prescribed in hospital. In addition, groups including prisoners, the homeless and private patients are not included in the database.

Industry perspective



Emma Du Four, Head of International Regulatory Policy and Intelligence at AbbVie described the company’s vision for using real world data insights to support decision-making and increase the sustainability of healthcare, from the first stages of research and development, to providing the evidence for outcomes-based reimbursement.

“Real world data has a place across the whole value chain,” Ms Du Four said. There are opportunities to deliver value for all stakeholders, using the same datasets.

The fundamental requirement for successful use of real world data is to clearly define the research question. That informs the selection of data sources of the right quality and rigour, the design of a trial and the statistical analysis plan. Moving from real world data to real world evidence “is a high bar”, but said Ms Du Four, “you can also get insights that take you onto the next stage and shape your thinking.”

AbbVie has started to use real world evidence and real world data in its drug development programmes, applying it to frame the unmet medical need, support initial approval and to identify questions to be answered through post-authorisation evidence generation.

“The initial focus was on safety, but we are now seeing a shift to explore real world evidence in efficacy,” Ms Du Four said.

In the course of this work, it has become clear that data sources have different utility, depending on the question that is being addressed. “To date, there has been a lot of speculation about real world evidence,” said Ms Du Four. “Now we need to provide examples of how it can supplement development programmes.”

Those examples should be across the drug development life cycle, from using epidemiological data and information about gaps in treatment options in the discovery phase; to setting the scope for early scientific advice for regulatory and health technology assessment; optimising trial designs both pre- and post-authorisation; and monitoring the performance of a product once it is on the market.

While the potential is clear, there are challenges in tapping existing real world data sources and establishing new ones. “The will and the desire are there, but there are problems of sustainability, data quality, getting access, governance, linkage and interoperability,” said Ms Du Four. “Sustainability is key, but not all data sources have good long-term funding.”

It is also important to establish agreed principles governing the use of real world evidence. For AbbVie, these would include a stipulation that use of real world evidence must remain optional, proportionate to the question being addressed and driven by the science. Ms Du Four called for quality and analytical standards/recommendations to be put in place, ensuring generation of valid real world evidence, saying these must be based on an open dialogue, and informed by experience.

Examples of where AbbVie has used claims databases and electronic medical records include establishing the background occurrence of a disease to support orphan drug designations and paediatric development plans; to study pregnancy outcomes; to identify disease hotspots when selecting clinical trial sites; and to track adherence.

Ms Du Four suggested social media could be a potential source of information to understand the patient experience and support development of patient-reported outcomes. However, she said, “there is a lot of noise.”

In the US, FDA is in the thick of public workshops, pilots and reports that are intended to form the basis of guidance for the use of real world evidence/real world data in drug development, with draft guidelines promised in September 2021.

Meanwhile, in Europe, the Innovative Medicines Initiative is building on the GetReal project’s work in developing methods of real world evidence collection and synthesis, in the European Health Data Electronic Network. The project, in which AbbVie is participating, is part of the wider IMI2 Big Data for Better Outcomes Programme. It will build a secure, distributed network to enable access to relevant health data sources for use across the pharma health value chain.

Work on real world evidence has matured to the point that standards, definitions and methodologies are starting to be shaped. Aspects related to privacy, consent and data quality have got to be robust and the regulatory evidentiary standards must be clear, said Ms Du Four. “That can only come from examples,” she said. The focus should be on ensuring those who get treatments are likely to respond and to limit exposure of those who will not.

Q&A

How long before real world evidence replaces randomised controlled trials? Can real world evidence be used to address the industry's productivity woes?

"We are possibly already towards saturation point in using real world evidence to optimise clinical trials," Ms Du Four suggested. To make further progress there is a need for better real world evidence systems and broader investment to join everything up and consistently collect data. "But there is a long way to go," Ms Du Four said.

How reliable is social media as a source of real world evidence?

Ms Du Four said AbbVie has been doing research to see where social media fits into the real world evidence picture. "It seems like it could be a fantastic resource and we have done some natural language processing that has given some insights," she said. However, it can be difficult to validate information gathered in this way, and it can distract from signals coming from other data sources.

Mr Hemmings said that he has not seen any examples of evidence from social media being put forward as part of a regulatory proposal. However, in terms of novel approaches to endpoint collection, there would appear to be significant potential in capturing data from wearable devices. One example would be assessing gait and tremor in Parkinson's disease. While the integrity of the data may be dependent on the motivation of the wearer, there does appear to be potential for such approaches for data collection, also for use in reducing uncertainty post-authorisation.

What is CPRD doing to address shortcomings in data linkages with other parts of the NHS, for example, hospital prescribing?

The main obstacle to be overcome in creating linkage is data governance, said Dr Myles. "You have to make sure the right consents have been given; we are working to navigate the data governance landscape," she said.

