Real world evidence is changing regulatory policy

Hardly a day goes by without the pharmaceutical industry, patients and the various national and supranational pharmaceutical regulatory agencies in Europe discussing how they can leverage the power of real world evidence (RWE) in order to improve access to valuable treatments and medical technologies. This was illustrated by a recent success story on the use of RWE in a US retrospective study of more than 3.8 million electronic medical records of people who received a seasonal influenza vaccine. This revealed that the MF49-adjuvanted seasonal influenza vaccine was more efficacious than other similar vaccines in real-world settings[1].

RWE has long been explored as a tool to enable a targeted and faster approval of health technologies but also in the context of the health technology assessment (HTA) and reimbursement of innovative treatments. RWE is understood to refer to the analysis and inference about the effects of different treatments from all the types of clinical data and outcomes that result from real-life use of treatments outside of a clinical trial. This so-called real world data, although significant in assessing the value of a treatment, may not be adequately captured in traditional clinical trial endpoints.

Real world data from alternative sources of evidence such as registries, electronic health records, healthcare professional and patient-reported outcomes may be equally, if not more valuable in describing the overall effect of a treatment. Consequently, decision-making taking into account RWE can factor in parameters that are more relevant to the intended patient population as opposed to participants in clinical trials, who for certain conditions may be 'artificially homogenous' yet not representative cohorts and therefore produce non-generalisable data. This is so, especially given that the patient populations that may use a health technology will inevitably differ from the populations studied.

Therefore, RWE can be beneficial not only in the context of applications for a marketing authorisation where comprehensive clinical data is lacking due to, for example, a small patient population with a rare disease, or a gene therapy where long-term efficacy data is needed. It can also be beneficial in drug repurposing, when a number of clinically relevant parameters are already available from clinical practice. In each of these cases, reliable RWE can provide a key source of data to navigate complexity and enable the licensing, safe use and reimbursement of treatments faster and at lower cost.

Although all stakeholders, ranging from regulators to researchers, patients and HTA bodies, have identified the need to increase the uptake of RWE, there are still hurdles to overcome. Thus far, RWE has mostly been used in the context of pharmacovigilance rather than in decision-making processes. There is also a lack of a homogeneous approach and an understanding of what sources of RWE will have sufficient quality and gravity to be acceptable.

Initiatives at European and UK level

The question that emerges then is how regulators and HTA authorities can ensure that the true value of RWE is harnessed. The Covid-19 pandemic has accelerated this discussion in Europe and globally[2]. Notably, the European Medicines Agency (EMA) has set up projects that are aimed at collecting data on vaccines in Europe, performing real-time monitoring of vaccine safety, including projects with other countries[3]. The various cross-jurisdictional collaboration initiatives focus on observational studies and evidence generation from health records. Recently, the EMA co-chaired a workshop convened by the International Coalition of Medicines Regulatory Authorities to discuss the use of RWE and observational studies in assessing Covid-19 therapeutics and vaccines.

Guidelines on how to utilise RWE are starting to emerge. The EMA has published a draft guideline on the use of registry-based studies as a source of RWE, which is open for public consultation until the end of the year[4]. The guideline aims to optimise the use of registry-based studies either in the pre- or post-marketing authorisation phase. It includes considerations regarding the quality and type of data, the feasibility of and quality control measures around, additional data collection, and it provides direction about how the study protocol and the collection, quality management, analysis, and reporting of the data should be addressed. Registry-based studies are to be used as complementary, rather than in lieu of, existing clinical data and post-authorisation safety and efficacy studies. Marketing authorisation holders should account for the registries in the study protocol. The final guideline is expected in 2021.

In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) has been active in enlisting RWE in its assessments and encouraging industry to engage with the regulators, relying on specific data sources of high quality and on the basis of concrete proposals and study designs. Indeed there is a precedent for the MHRA agreeing to rely on a RWE study instead of a randomised control trial to assess the efficacy of a drug outside its authorised indication. This precedent involved a study where data was gathered in clinical practice and based on evidence from three different sets of electronic health records. The company had proposed using inferential analysis and the MHRA accommodated the proposal whilst ensuring that any potential biases were adequately addressed in the analysis.

It is essential for applicants wanting to rely on RWE to engage with the relevant national competent authority before using a registry-based study in order to discuss feasibility, acceptability and relevance. In fact, the MHRA has demonstrated its willingness to enable and improve on existing means of incorporating RWE in decision-making in its announcement of a new licensing pathway for innovative medicinal products, available from 1 January 2021. This new policy will consist of an 'adaptive authorisation pathway' incorporating RWE, continuous benefit/risk assessment, novel clinical trial design, and other regulatory measures. The pathway is aimed at the early stages of development of a medicinal product, even before clinical data become available.

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The MHRA has published a draft guidance on the use of RWE in randomised clinical trials, launched for consultation on 30 October 2020. The agency recognises that although RWE is routinely collected, mostly in the monitoring, pharmacovigilance and post-approval clinical trial setting, it can also support and accelerate regulatory decisions and reduce the cost of development. The current draft guidance addresses clinical trial design including the choice of endpoints and requirements for safety data, database quality, and inspections. Randomised clinical trials using RWE can be particularly useful for drug repurposing. The agency plans to issue a number of guidance documents on this subject.

HTA authorities have historically been reluctant to accept real world data and RWE in the cost effectiveness assessment of new technologies, which has often resulted in a divergence from the regulatory viewpoint. But RWE has an important role to play in addressing gaps in evidence and reducing uncertainties. It can also support market access tools such as outcome-based agreements.

In Germany, which is considering revisiting its procedure known as AMNOG for evaluating and pricing new medicines, the Federal Joint Committee (G-BA) has the right to request and evaluate RWE for the purpose of assessing clinical data. There is also a discussion underway about doing the same thing for pricing and reimbursement. In other jurisdictions, such as the UK, this has already been taking place albeit on a case-by-case basis, and often stems from initiatives from companies. This has been the case for orphan conditions and advanced therapy medicinal products, where the scarcity of data has necessitated looking into sources outside of randomised controlled trials in order to deduce the benefit of a treatment.

Digital tools hold much promise in delivering and maximising the value of RWE, provided they meet certain quality standards. Often, the power of RWE lies in analysing large volumes of data, and digital tools can automate and accelerate their collection and analysis, and generate meaningful conclusions.

For example, traditional methods of collecting patient input through questionnaires or records can be burdensome, both for the patients and healthcare professionals who are asked to systematically provide input, as well as for the registry operators who must log and follow up the reported outcomes. However tools such as wearables can automate this process and also routinely capture a wide range of measurements that patients otherwise would not be able to do with the same frequency. Patient input has been an important, yet neglected, source of data on efficacy. As patients have been advocating for a more patient-centric approach in regulatory decisions, these tools come at the right time to enable hearing the patients' views on a drug's effect and to gather the data that would ultimately develop into RWE.

Artificial intelligence (AI)-powered systems can further enhance this process and help capture more subtle endpoints, in particular within large data sets. Algorithms can extract, analyse and interpret large volumes of data for a number of different questions. The computing power of these systems and their ability to sift through and analyse volumes of unconnected data, can profile a patient's response to a treatment and map disease progression.

As we are still in the relatively early days of these technologies, legislators and regulators are seeking to establish an effective framework to ensure that these tools can be used in a safe and trustworthy manner. The European Commission is keen to utilise the value of big data and has set out a European strategy for data, providing for a digital transformation over the next five years. To this end, it has published a Data Strategy and a White Paper on Artificial Intelligence which have been subject to an open public consultation. Undoubtedly, developing guidelines on the role of AI and its use in data collection will complement the thinking at UK and European level about a supportive framework within which RWE can be fully and systematically utilised.

Looking forward

From the perspective of regulators and assessors, RWE should provide good quality and reliable data responding to a predefined question, set out in the study protocol. It is clear that there is significant momentum from all stakeholders to embrace the gathering of reliable real world data to both accelerate the approval of promising new technologies, as well as to facilitate HTA. With more sophisticated health technologies reaching the market, the real effect on patients can often only be captured from the collection of long-term data of the drug in clinical practice, which is being accepted as the new norm. Accordingly, HTA agencies should also accept data from these sources in 'real clinical practice' in the context of HTA. This will ensure that new technologies are not only authorised by regulatory agencies but that they are reimbursed so that they can reach the patients who need them. With more draft guidance being published, now is the time for industry to provide comments in the ongoing consultations and bring their experience to the developing framework of RWE.

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