The networking approach

Europe embraces real-world data

In Europe, patient registries have long been a source of information about how new medicines entering a market for the first time are being used. These registries can be product registries set up by pharmaceutical companies to monitor their own drugs. Or they can be disease registries set up by public health authorities to track the prevalence of specific illnesses or infections.

In 2015, the European Medicines Agency set up a task force to review the different types of registries across the EU to find out whether the information contained in these files could support a more systematic and standardised approach to evaluating new medicines. The answer was a resounding yes. The registries had been used in the past, particularly to monitor safety, but not systematically for other types of research. Usage for safety monitoring was illustrated by data from 2007 to 2010. This showed that at least one registry was included in the risk management plans of 43 approved products, or 37% of the product total, during this period. In nine cases, the EMA required companies to include this data in their plans.[1]

The EMA concluded that patient registries could have a wider use. But this was being held back by the heterogeneity of data in these repositories. This was not an isolated problem. Other healthcare data also required management to ensure its quality and consistency. In response, the European Commission started a project to upgrade the EU's entire data infrastructure called the European Health Data Space. In parallel, the EMA started work on a network that will give it access to healthcare databases across the EU. This network is called the Data Analysis and Real World Interrogation Network (DARWIN EU).

> ***"DARWIN EU is based on the principle of secondary use of healthcare data."***
>
> *Peter Arlett*

The new project

DARWIN EU will have access to databases containing information on real-world data, or data that is collected about a patient's health or the delivery of care from a variety of sources other than clinical trials. The analysis of this real-world data will generate real-world evidence which can then be used in regulatory decision making.

"The fairest way to represent DARWIN EU is to say that it is a network initiative," said Peter Arlett in an interview. Dr Arlett is head of the EMA's data analytics and methods taskforce and a member of the DARWIN EU advisory board. The network consists of data providers and those who standardise, analyse and use the data. In the broadest sense, this includes regulators, industry, public health officials, payers, health technology assessors, healthcare providers and patients. Representatives of these groups all sit on the advisory board.

The board's role is to advise the EMA, which has legal and budgetary responsibility for the project. It will also play a role selecting data partners with access to specific subsets of data. "DARWIN EU is based on the principle of secondary use of healthcare data. So we will be on-boarding data where the data are already held…It could be, for example from a hospital or it could be one of the big national databases of GP electronic health record data," Dr Arlett said. Whatever the source, the principal model is to use data that has been collected for another purpose. The project will then standardise the data using a common data model.

A key player in the network is a coordination centre which will manage real-world data sources across the EU and conduct studies for the EMA. The real-world data will be standardised to the observational medical outcomes partnership (OMOP) common data model (CDM) – a platform already in use in the US. This is a technology that can harmonise different coding systems – in healthcare records for example – to a common vocabulary. In effect, the nomenclature can support collaborative healthcare research across the world.

The coordination centre

On 10 February, the EMA selected the Erasmus University Medical Center in Rotterdam, the Netherlands to run the coordination centre. Managing the centre will be Peter Rijnbeek, associate professor of health data science at the medical centre. Professor Rijnbeek, in addition to his academic responsibilities, is also co-leading another European project using the OMOP-CDM data model.

In its first year, DARWIN-EU is expected to run a number of pilot studies for the EMA and its scientific committees, including its main scientific committee, the CHMP. While it is still too early to say what these studies will entail, there are already examples of how real-world evidence has been used to inform decisions during the Covid-19 pandemic. The most recent case is the EMA's advice in early April that it was too early to consider using a fourth dose of the messenger RNA (mRNA) vaccines in the general population to protect against the Omicron variant of the SARS-CoV-2 virus. The agency, together with the European Center for Disease Prevention and Control, however did say that a fourth dose could be helpful for adults 80 years and older. The data supporting this advice came from a real-world study in Israel.

Dr Arlett said that the use of real-world data and evidence is now the accepted practice for many medical applications. "Real-world evidence is totally established in terms of safety modelling," he commented. It is also established for

monitoring drug utilisation, or how a medicine is used, at what dose, and in which patients. It is established in disease epidemiology to monitor the spread of a disease and the fatality rate. And it is established as a way of demonstrating the standard of care in a particular healthcare system, he added.

Moreover, in the context of a clinical trial, real-world evidence can provide information on the effectiveness of a medicine in additional patient populations – populations not included in the trial. "If you demonstrate the primary efficacy [of a drug] in a clinical trial, so you know the drug works against placebo, you know the drug works against an active comparator, you can then demonstrate, using real-world evidence, that the same benefit is seen in the very elderly or younger patients, or in women of child-bearing potential who were excluded [from the trial]," he said.

Additionally, real-world evidence can help evaluate the effectiveness of drugs for rare diseases. An example is a decision in early April by the US Food and Drug Administration to give an accelerated approval to a drug from Novartis for the treatment of PIK3CA-related overgrowth spectrum, a group of rare genetic diseases that cause overgrowth in parts of the body. The FDA based its approval on real-world evidence – a retrospective chart review of patients who had received the drug in a compassionate use setting. The drug's efficacy will still need to be confirmed in follow-up clinical studies in order to qualify for a full approval.

The randomised controlled trial

The randomised controlled trial is often described as the 'gold standard' of clinical research. This is because of its potential to limit bias. In these trials, participants are randomly assigned to two or more groups, one of which receives the experimental drug and the other, an alternative intervention, or no intervention at all.[2] At the end of the trial, outcomes of the experimental treatment and the comparator are measured, and any differences in response are statistically assessed.

The ascendancy of real-world evidence has led to a debate, particularly in academic circles, as to whether this evidence might overtake the randomised controlled trial as the new standard in clinical research. When asked his view, Dr Arlett said that real-world evidence complements the randomised controlled trial. "The whole point of randomisation is to deal with bias. You need to account for that and consider it very carefully if real-world evidence is being used as one of the principal sources of evidence for efficacy," he noted.

On the other hand, real-world evidence can be used to contextualise clinical trials. "Let's say a company has done a particular clinical trial in a particular disease in a particular population. Does that population represent the patients that actually have the disease in the European Union? Have they included the elderly, or the very elderly? Is this disease actually something that affects the very elderly and the frail? We can do that with real-world evidence to complement decision making in the CHMP," he said.

One of the principles of the DARWIN EU project is that data used in the project remains local, with the providers. This is a federated model which ensures privacy because raw data is kept on the providers' devices. However, aggregated data will be sent to the coordination centre for use in regulatory studies. In addition to conducting studies, the project will keep a catalogue of the study protocols and results.

Overall, the project is expected to have a profound impact on the way the EMA operates. The first impact is likely to be on the way the agency offers scientific advice to developers. Small companies, in particular, are likely to benefit from access to real-world data in designing their clinical trials. "We could potentially look at the feasibility of doing a real-world evidence study. We could potentially advise them on the number of patients that could be recruited to do a clinical trial," Dr Arlett said. Real-world evidence could inform strategies for investigating new medicines in children, and it will certainly give the regulators a better grip on the prevalence of diseases for which new drugs are being proposed, he added.

The view from industry

The role of industry in the DARWIN EU project is central because it is their products that will be evaluated under the new procedures. The European pharmaceutical industry federation Efpia has an observer role on the project's advisory board. The Efpia representative is Álmath Spooner, director of regulatory policy and intelligence at AbbVie Inc. In an interview, Dr Spooner identified four principles that industry would like to see incorporated into the programme. The first is transparency about the data. "There needs to be clarity on how we go from data to evidence. One of the things we at Efpia would be emphasising is the importance of transparency around the analytical eco-system so we can understand how data are being analysed, what kind of algorithms and methods are being used," she said.

Second, industry would like the project to begin with well-established use cases in order to develop confidence in the platform and third, to learn from and share experiences with the US, which is also expanding the use of real-world evidence in regulatory decision making. Finally, industry would like regulators to take the opportunity presented by the new data to reconfigure scientific advice into a more iterative scientific dialogue.

Conclusion

A huge shift is underway in how regulators gain access to, and evaluate, information that is used to determine the safety and efficacy of new drugs. This is likely to have an impact on how drug discovery and development programmes are designed and executed, and how diseases are monitored and treated. It may even shed light on what is commonly referred to as society's 'unmet medical need.'

References:

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