Carrots and Sticks: The Changing Incentives for Use of Real-World Evidence

Interview with Rob Thwaites

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Rob Thwaites

Rob Thwaites, MA, MCom, is Senior Director at Takeda and one of the leaders of the IMI GetReal Project (www.imi-getreal.eu). GetReal aims to show how robust new methods of real-world evidence (RWE) collection and synthesis could be adopted earlier in pharmaceutical R&D and healthcare decision making processes. As co-project leader for Work Package 1, Rob has collaborated with a wide range of stakeholders in medicines development to assess the acceptability and usefulness of approaches to the use of RWE in assessing the effectiveness of new medicines. Rob has over 20 years' experience in healthcare, working for both industry and consultancies, and has worked in the UK, the U.S., and Australia. Rob holds degrees in Economics from the University of Cambridge and the University of New South Wales.

This interview was conducted by Radek Wasiak, PhD, Vice President and General Manager, Real-World Evidence and Meta Research, Evidera.

Three key features of real-world evidence are emerging: increased collaboration, need for stakeholder-relevant outputs, and increased speed of getting results. Regarding the first of these, there appears to be substantial fragmentation in RWE. IMI's GetReal is a great example of a collaboration effort bringing people together to address these issues.

Yes, that is the hope. People often are using the same data but for different decisions, so there is not only fragmentation of research, but also fragmentation of aims and of attitudes as well. In the work I have done on the IMI GetReal project, there has been a lot of feedback that this has been a great opportunity for us to work together with others in the healthcare sector and there is a true collaboration amongst people trying to tackle the same set of problems. I have seen good working relationships built, and real trust.

It is encouraging to hear. However, it does seem that new developments often take a long time to reach payers and health technology assessment (HTA) agencies, and consequently, real-world evidence and real-world data are still under-utilized, as many novel approaches are not well publicized.

Well, the information is available, but as you know in this field, people are often working with their own tried and tested methods in mind. For example, on the industry side, everything is focused around project teams and there is pressure to attain project goals, whether that is a drug in development or a drug already on the market, and if more novel approaches appear riskier than these well-established, though logical approaches, there can be resistance.

With the "hot topic" continuing to be big data or real-world data, CEOs and other pharmaceutical industry leaders are paying attention to RWE — a stark difference from a few years ago. This often resulted in the creation of RWE-focused teams. What has changed and what was the impetus?

The concept is not new but real-world evidence is still the "buzz word." Pharmaceutical companies have always used real-world evidence and real-world data, for example, to track safety once a drug hits the market. What is new is the extent of the data and the recognition that it can be used in so many different ways.

There are a number of factors driving it on the supply side, including the increasing availability of electronic, patient-level data for research, advances in methods, and the ability to link data sets. On the demand side, there is a much greater recognition among decision makers and their advisors that we have to complement clinical evidence with real-world evidence. We have seen this in the proliferation of HTA agencies and the increasing sophistication of advisors, formulary bodies, and HTA bodies. On the demand side, then, there has been huge growth in the need for this real-world evidence data and the recognition that this data has a role to play in decision making. So, because there is attention on both the supply and demand sides, there is now a stronger push for discussion and for collaboration among those who create and use the evidence.

Is it safe to say that RWE was "nice to have", at times mandated, but something that researchers "dabbled in" to help demonstrate product value, and now commercial and marketing teams actually need these data for market access and pricing and reimbursement purposes?

I think in the early years, companies did dabble a bit; if you go back to the formation of the first pharmacoeconomics departments in companies in the late `80s and early `90s, there wasn't really a great demand for this type of data from agencies that needed it for formal assessments. It is only once it started with the agencies, such as in Australia in 1992, where the requirement for evidence was introduced as part of a much bigger package to encourage investment in R&D in that country, that companies really started to invest in RWE.

I think you touched on a few things already, but thinking specifically of real-world data, what do you see as the key barriers to greater adoption of this type of evidence? And what would you see as facilitators to overcome those barriers?

I think there are barriers at different stages. There are challenges in terms of creating and accessing the data, and then again in synthesizing that data. After that, there is also a challenge in making sure the resulting evidence is used in decision making. I think some of the biggest barriers at the moment are more around the availability and the quality of the data. Secondly, there are barriers around the agencies' willingness to accept the data. There are some agencies that are quite open-minded about real-world data and are willing to live with imperfect data – data where there is uncertainty, and they are willing to try and understand it. NICE, for example, is constantly pushing to find ways of looking at different methods and different techniques whereby real-world data can be used. On the other hand, we have seen some agencies, in Germany, for example, where clinical trial data are still at the center of evaluations.

Going back to the issue of the content of the data, would you say that the easily available data are fit for purpose?

The measure of whether these data are helpful is whether the evidence from them is influential in decision making. If it helps people in healthcare, whether they be physicians, agencies, or even patients, make decisions, and hopefully better decisions, then that is really the measure of whether the data are getting to be good enough. We know there are pockets of data that are very good and are used often and routinely. For example, primary care data in the UK, claims data in the U.S., and registry data in the Nordics – there are a lot of good data sources. Where there's a gap in the data is when we have to resort to reverting back to clinical data alone. But even then, you still have to extrapolate and think about to what extent the data – whether it is clinical or real-world data in other settings – is transferrable to your specific setting. There are still questions about what methods of simulation or synthesis are going to be acceptable, for example. A lot of progress has been made, with acceptable approaches in that area by many decision

makers for over 20 years now. It is important to note, however, that these discussions are not just about the generation of new evidence, but also about simulation from existing evidence, how evidence is synthesized to ensure it is transferrable, or that the implications are transferrable from one setting to another.

You mentioned advances in methods. It seems that industry's willingness to accept more novel solutions and approaches is still limited. Do you see a way forward that is leading to some of the novel but highly relevant RWE approaches becoming standard and accepted by payers?

It is an interesting question about the acceptability of data and new approaches and the unwillingness within industry to push on that front. That is why collaborative efforts, such as IMI GetReal or other projects, are good because they do force different groups (academics, decision makers, suppliers, etc.) to work together to evaluate the acceptability of approaches to providing evidence. I think these collaborative efforts can be influential in pushing companies to think about other ways of generating evidence and forcing a dialogue between companies and decision makers.

Do you foresee any policy trends that would actually help with these earlier discussions?

We have to think about how we satisfy decision makers' demands for data and get patients access to medicines earlier, and that means providing evidence earlier in the decision making process. For example, if you wanted to get effectiveness evidence prior to approval, you could either set up a real-world study prior to approval, which is very unusual, or you could find ways of trying to model effectiveness from the efficacy data that you get. These are complementary, but really it comes down to the decision makers, the HTA bodies in particular, who will insist on use of real-world data as well as modeling. Modeling alone is no longer the answer because decision makers also want evidence of what is going on in real-world clinical practice.

One of the challenges with well-designed, real-world studies is that they can be quite expensive, yet there is a belief that the data are easily available and can produce results quickly. How can we overcome this perception?

The cost of research is definitely underestimated, and this is where education is so important. It is incumbent upon leaders and collaborative groups undertaking policy around these studies to clarify the processes and costs, but also the benefits associated with this investment. The assumption is that the data are there and easily accessed and synthesized, when in reality, the data are fragmented and often not clean, and every study is a bespoke study. As long as that is the case, the research is going to come with a higher cost. However, this research is still going to be cheaper than experimental or prospective research, for example. I also expect the cost of research will eventually decrease over time as we get better data, better knowledge, and more efficient research centers.

Another challenge I see is access to data, particularly in Europe where privacy laws are more stringent. Will this issue continue to play a role in the use of real-world data?

The question of access to data is a big issue in some countries, and yes, specifically in Europe. There has been an ongoing discussion at a European level about data protection and regulation over the last couple of years, and the proposed regulations were looking very unfavorable for research. From the UK, the ABPI, Wellcome Trust, and medical charities all responded quite strongly to those proposed regulations, and since the end of last year, there is a revised agreement between the European Commission and the Parliament council which looks more favorable for research. When implemented, that European model will then cascade down to individual countries, which will then have two years to implement the new regulations. Countries like the UK are quite positive about continued access to data for research purposes so that patients can get access to needed treatments, but the ethos in some other countries is quite different and I do see that as a big challenge for research in the future.

Where do you see sources like social media and data generated as part of activities of daily life (for example, personal device data) coming into play? Do you think these data are an unnecessary distraction right now, or should they be incorporated now as a part of the standard package of evidence? Safety, for example, is one area where use of social media is becoming more common and complementary of other adverse reporting mechanisms.

It's quite interesting, actually. We are used to working with clean data, and now with real-world data that may not be so clean but is still typically recorded by physicians or healthcare professionals. Now we have this spontaneously recorded information by the general public through social media, and it's a different type of data generated with a

different motivation. This is definitely an important trend, and I think we need to look at this data not as proof, but as indicators of what patients are experiencing or find relevant, for example, issues of safety or how treatments are being used. People in the industry will be looking at this data more and more, and it could prove to be quite helpful in understanding conditions and how these conditions affect patients. For example, what is important to patients with the disease, what issues they have with the condition, how they perceive their current treatment. I think there is a lot we can understand about unmet needs in the patient world, and I think we could do that now.

As we wrap up, let me ask where do you see this field in five years? If initiatives like the IMI GetReal are successful, what will be achieved?

I see two parts to that question. One is what is going to happen in the next four or five years. Secondly, where does the success lie? I think some of the trends that we are currently seeing will continue. Better data, better quality data, more linked data sets within countries, and some of the newer issues we just discussed will expand as well, such as social media and public data. We should be in a better situation in terms of data in general.

In terms of what we would like to see, we need to think about why we want access to this data, which is ultimately to advance and improve the quality of healthcare. I think the biggest single thing we will see in the foreseeable future is earlier access to new medicines. With so much activity in this area, such as the early access to medicine schemes (EAMS), the real-world initiatives such as Green Park in the U.S. and IMI GetReal in Europe, or the activities going on in individual countries, patients should hopefully be seeing earlier access to medications than they previously would have.

Is the true challenge then to bring it all together? Somehow to make sure the separate initiatives work together as an overall solution instead of seeing solutions vary between the U.S. and Europe, for example, or even worse, individual countries within Europe? Is that the biggest barrier to overcome?

I think your point about collaboration in the first place is a big barrier, yes. Changing cultures and the way people think about collaboration, acceptance of new evidence, and then implementation of that evidence into decision making – those are all needed to make a real change, but they are also extremely challenging. The efforts we are seeing now, for example, are a great first step in this process, but I would expect that external mandates requiring specific types of evidence at certain timepoints in the lifecyle process are probably what will be needed to truly see effective change. If, for example, all the major HTA agencies in Europe agree that certain evidence is needed, then there is obviously a better chance of consistency and acceptance.

We already see that some agencies, such as the EMA, mandate that drugs need to show evidence of safety in the real world. Some countries want data to prove that drugs are actually effective in the real world, and without that data, access or prices could be reduced. So, it may be that we don't see actual mandates for real-world evidence, but repercussions if that evidence is not provided. I think that is the only way development teams in industry will sit up and take these changes seriously. Otherwise, there will always be pushback from people within the industry, with concerns about the cost – and timelines – of studies that are not mandated, or that studies might show that their product's effectiveness is not as good as the efficacy shown in trials, or their product may not prove to be as good as the competition.

In the end, it is up to the agencies to set the requirements for this evidence.

It always comes back to incentives, doesn't it?

Yes. Carrots and sticks.

Carrots and sticks. That's a good way of finishing. Carrots and sticks.