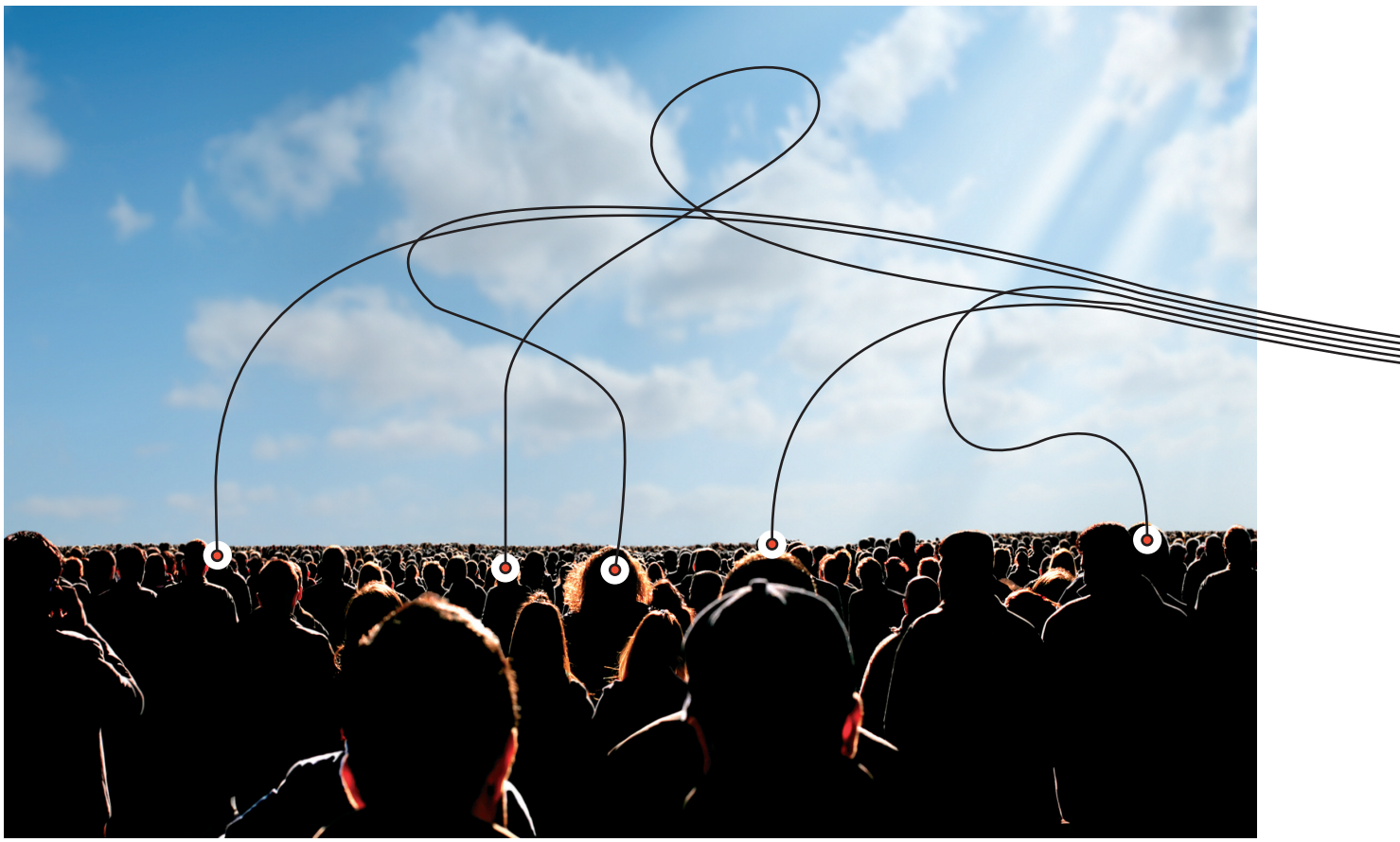
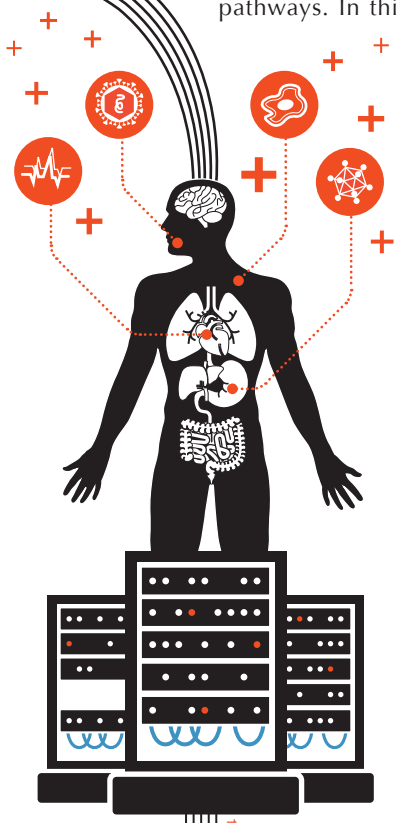


Out of the trial and into the real world

REDEFINING EVIDENCE Only a small fraction of carefully selected patients are allowed to enroll in randomised controlled trials involving new compounds – the gold standard of drug assessment. But trying to acquire the most significant efficacy and safety results for a new drug is one goal, treating patients every day in hospitals or practices with it is something else entirely. Discrepancies are inevitable. Now "real-world data" that's been gathered in large observational studies is attempting to close the gap between experimental, artificial study settings and clinical realities.

Jim Omel has an intimate knowledge of drugs from many different perspectives. For years he prescribed them as a physician. As a pharmacist, he learned about how they're produced and developed, as well as their biochemical properties. As a consultant for the US drug approval authority (FDA) and National Cancer Institute, he viewed them as a regulator. And for almost two decades, he's added the unfortunate long-term patient's perspective to his experiences. In 1997, Omel was diagnosed with multiple myeloma, a rare type of cancer of the blood-building plasma cells in the bone marrow. Since then he's had three relapses, and been through treatments ranging from radiation to stem cell transplants to drugs-in-testing. In the course of that journey, the now retired physician suffered from a seemingly irreconcilable frameshift. He moved between the world of highly controlled, hypothesis-driven drug testing in RCTs and the often chaotic, chance-and-circumstance related treatment reality that patients experience in the 'real world' of hospitals. "Patient perspective," wrote Omel in a 2011 article on trials and treatment, "is rarely considered in trial design."

"Real Word Trials" (RWT), "Real World Data" (RWD) and "Real World Evidence" (RWE) activities are now seeking to close this gap by designing studies better able to predict how drugs perform in everyday settings, and how they alter patients' lives. Although the "Real World" label has often been (mis-)used, pharma companies and governmental authorities are now aware that efficacy information on drugs tested in clinical trials doesn't tell the whole story when it comes to meeting individual patient needs. "Real-world evidence can be defined as evidence from data collected outside of conventional randomised controlled trials," says Peter Arlett, Head of Pharmacovigilance and Epidemiology at the European Medicines Agency (EMA). That includes sources like electronic health records, registries, hospital records and health insurance data. Increasingly, says Arlett, other data – like biobank, genomic and digital phenotyping information – are also being integrated into real-world evidence datasets. "Regulators need real-world evidence throughout the decisionmaking process, e.g. to support pharmacovigilance activities, assess safety signals and measure the impact of regulatory measures, understand the benefit-risk balance and effectiveness of medicines, inform on resource utilisation and support HTA decisions." Activities like these are key not just to authorised medicines, but also to innovative medicines, orphan medicines and medicines included in adaptive pathways. In this respect, 'real-world' data are not a novelty. In fact, the use of registries to collect data on orphan medicines is quite common in the pre-authorisation phase. "Companies regularly use electronic health records to better understand the diseases they intend to treat, while the use of epidemiological study designs – based on insurance and health records – has been common in safety monitoring for many years", says the EMA's pharmacovigilance chief.



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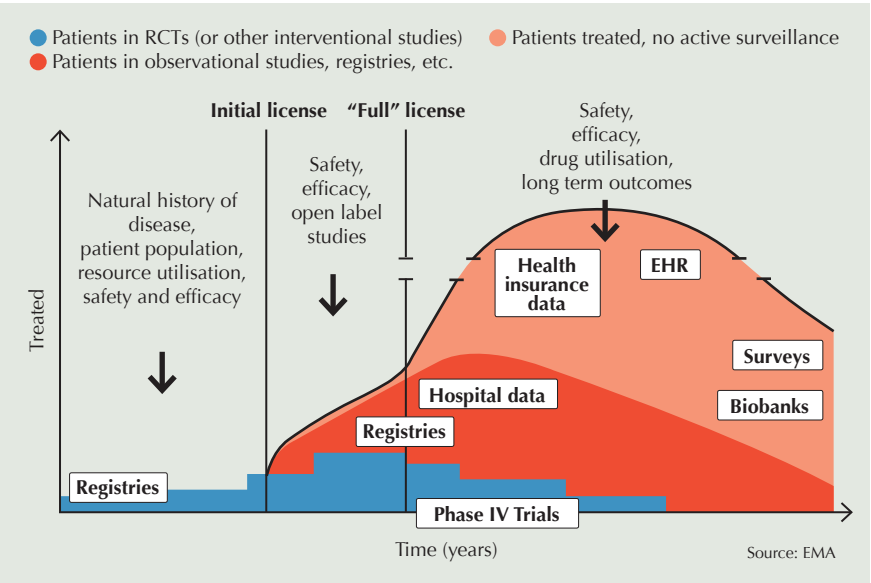
The current spike in interest is being driven by two primary factors, according to Arlett. The first is self-evident. Technological advances are simply making it far easier to collect and analyse real-world data. In other words, real-world data is one facet of Big Data. "Secondly, there's a realisation that real-world data can complement evidence from controlled trials and address questions that trials can't – particularly the performance of a medicine when used in clinical practice," Arlett says. To develop this concept, the EU has granted €16.3m to the Innovative Medicines Initiative's GetReal project. It's aimed at developing ways to capture and incorporate real-life data into drug discovery and development.

Insights into complex interactions with drug combinations

One example of a trial seeking to add RWE to RCT-based knowledge about the treatment of multiple myeloma is the INSIGHT-MM study (NCT02761187). It's sponsored by Japanese pharmaceutical company Takeda, which asked Jim Omel in 2015 to join the study's steering committee as a myeloma patient advocate. "The main interest of the study is how patients fare when they take one or more of the available multiple myeloma drugs," says Omel. A couple of different drugs are currently approved as treatments, and that has changed the probabilities of therapeutic success dramatically. In the last two decades, five-year survival rates have improved from around 30% to almost 50%. "Although this is good news," says Omel, "we now have a dilemma: finding out how to combine these drugs effectively." Which drug should be given first? What's the best combination? And how do the drugs interfere with a patient's daily life? "It's not feasible to answer those questions with standard RCTs, as we would need too many of them," says Liviu Niculescu, who heads Medical Affairs at Takeda from a small office at the company's US headquarters in Cambridge. "The only way to come up with answers – or at least hypotheses – is to observe patterns of treatments



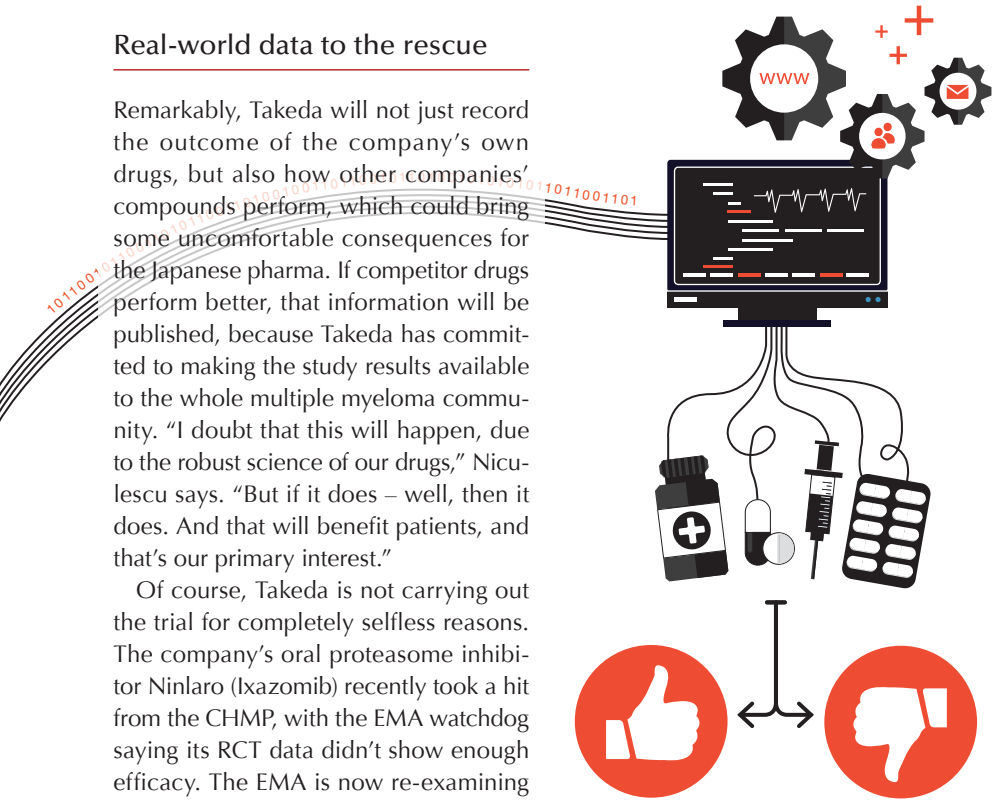
Real World Data could improve the drug development process at many stages, either before or after (conditional) approval.

that emerge in real-life situations and see what the outcome is." Working together with about 150 centres worldwide (about 35 in Europe), Takeda is collecting treatment data from 5,000 multiple myeloma patients over five years – the largest observational trial ever in this indication.

Real-world data to the rescue

Remarkably, Takeda will not just record the outcome of the company's own drugs, but also how other companies' compounds perform, which could bring some uncomfortable consequences for the Japanese pharma. If competitor drugs perform better, that information will be published, because Takeda has committed to making the study results available to the whole multiple myeloma community. "I doubt that this will happen, due to the robust science of our drugs," Niculescu says. "But if it does – well, then it does. And that will benefit patients, and that's our primary interest."

Of course, Takeda is not carrying out the trial for completely selfless reasons. The company's oral proteasome inhibitor Ninlaro (Ixazomib) recently took a hit from the CHMP, with the EMA watchdog saying its RCT data didn't show enough efficacy. The EMA is now re-examining the approval request. In the US, where the drug is already on the market, sales of Ninlaro – which costs US$8,000 for four weeks of treatment – are still a long way from blockbuster hopes. Real-world data showing the oral drug improves quality of life, compliance or efficacy in combination treatments would therefore come in handy, and could help Takeda convince the EMA. If the trial reveals that the convenience of oral drugs supports patient compliance, Takeda would be pleased. "The duration of therapy is key to keep the tumour under control," Niculescu says. "If you discontinue early, the tumour has the potential to come back again."



Ensuring compliance is an endemic problem in comparing real-life settings with RCTs, as patients and physicians taking part in the latter are highly motivated to comply with trial protocol. In real-life settings, patients are much more likely to drop treatments. Statistics show that multiple myeloma patients comply for about six months in taking injection-based therapies, but Niculescu affirms that RCT efficacy data relies on staying on the drugs for about a year. "For us," he says, "real-life data is attractive because it gives you advantages – knowing what happens to patients outside of RCTs."

The study is therefore seeking to gather information from the thousands of patients who are generally not involved in clinical trials. "Only 3% of patients are included in RCTs, which means 97% of the information is lost," says myeloma survivor Jim Omel. "And this doesn't just include efficacy data for certain drug combinations, but also how the drugs improve a patient's quality of life (QOL). QOL data, either good or bad, are being taken more and more seriously by both the FDA and EMA, and that can have a definite effect on a drug's approval status." The physician knows what he's talking about at a personal level. He also has to take care of his wife, who suffers from multiple sclerosis, so if he had to drive to a treatment centre to get his infusions two days a week, it would be a huge burden. For Omel, oral treatments have distinct advantages: "If I take an oral proteasome inhibitor, I have one capsule and I'm done for the whole week," he says, emphasising that this is a 'real-life' advantage for patients like him. "That's so important, because it gives me time to care for my wife, in-

Pictures: Icon (thumb) made by Gregor Cresnar from www.flaticon.com, beatpavel/fotolia.com (monitor), 32 pixels/fotolia.com (medicine)

stead of sitting for two days in an infusion centre."

How 'real' patients differ from hand-picked RCT patients

RCTs focus on empiric outcomes such as overall survival, progression-free survival or similar endpoints. But they usually ignore other destinies – such as how many months a patient spends in hospital. And there are other effects that RCTs can mask – especially when patients with comorbidities like diabetes, renal failure or cardiovascular issues are excluded so as to minimise confounder factors and influences 'unrelated' to a disease. In real-life situations, however, patients have complex disease backgrounds. And physicians generally have no clue how the drugs they prescribe could interfere with such preconditions. "In real-world studies like Takeda's, a patient's age, renal status and other factors vary," says Omel. "And if we see groups of fifty or a hundred patients within the same age and the same comorbidities who improve due to a certain drug or compound combination – this will have a huge value for the treatment of multiple myeloma."

But observing and collecting data from 5,000 patients at 150 sites is "a hugely complex endeavour" says Niculescu. If you include physicians, healthcare providers and families, then over 10,000 people are involved in providing data. "It's relatively easy to enroll patients," he says, "but much more difficult to keep them on trial, collect the data, and follow them for the relevant time frame of five to eight years." The recruitment has just started, with less than a hundred patients enrolled.

Although Niculescu appreciates the value of RWE, he is also aware that even large observational studies like Takeda's lack randomisation – the key to evaluating drug efficacy and safety. "The best you can get from observational studies are hypotheses," the Takeda Medical Affairs chief admits. "Even so, they're very useful, because they direct investment in subsequent interventional trials."

Observational studies are limited in significance, say critics like Jürgen Windeler, the Director of the Institute for Quality and Efficiency in Health Care (IQWiG) in Cologne. And that's why not all stakeholders welcome the RWE concept. Windeler even rejects using the term at all, because he believes it supports the "foolish implication that randomised clinical trials have nothing to do with the 'real world', although 'non-randomised' trials might." At a 'Real World Data' meeting in Cologne last year, the clinical epidemiologist claimed that the "notion that non-randomised studies, so-called 'Real Life Data', have a higher external validity is – per se – wrong," at least compared to strictly controlled RCTs. According to him, "the external validity – the fit between study results and situations of concrete decision – is worthless as long as it's based on shabby, unreliable data."

PETER ARLETT
Head of Pharmacovigilance and Epidemiology at EMA

? What limits the gathering of useful real-world data?

! *Currently there is limited access to and analysis of real-world data by regulators. There are several barriers to this, including fragmentation and lack of interoperability of resources, governance issues, privacy concerns, inadequate methods to integrate and analyse heterogeneous data, underuse of technological advances, lack of cross-border collaborations and lack of sustained funding mechanisms to secure access to and analysis of real-world data. To further enable the contribution of real-world evidence to decisionmaking, we need a framework that provides the EU regulatory network with access to and analysis of an extensive range of multinational real-world data. Components of this framework considered important by EMA include developing sustainable multi-stakeholder governance and funding mechanisms, a comprehensive characterisation of EU-wide sources of high-quality real-world evidence, identification or development of methods to integrate and analyse data and collaboration across stakeholders and borders.*

Doubting the value of non-RCTs for the benefit assessment

In spite of statements like that, the director of Germany's powerful HTA, an organisation responsible for reimbursement-related risk and benefit assessment, apparently agrees that there are standard situations where observational studies make sense. For example, where randomised trials are not necessary to answer questions such as: 'What penetration do drugs achieve? How many patients are affected? What are the costs of a drug, a therapy or best supportive care?' Windeler also agrees that observational studies could help identify risks or long-term effects that RCTs can't detect. Even so, he remains skeptical. "Despite all the examples and proposals for complementation, I still don't see a contribution of non-RCTs benefiting assessment."

Critics of real-world evidence often fall into the trap of assuming that such evidence is somehow supposed to replace clinical trials, the EMA's Arlett replies. "This is a false assumption, as randomised clinical trials are best targeted to address certain questions – such as establishing the efficacy of a medicine in precisely defined populations – while real-world data may better inform different questions, including safety and effectiveness in everyday medical practice." A well-informed treatment decision will draw on the best evidence to answer

Picture: EMA

a specific question. Sometimes that will be provided by an RCT, sometimes by real world evidence, and sometimes by a combination of the two, Arlett adds.

A randomised study in a 'real-world' setting

A good example of such a combination is the Salford Lung Study, which is an "attempt to carry out a randomised study, but in a real-world setting," according to Jørgen Vestbo from the Division of Infection, Immunity and Respiratory Medicine at Manchester Academic Health Sciences Centre and the University of Manchester. Sponsored by British pharma company GSK, the study tested the drugs Relvar and Ellipta on patients with Chronic Obstructive Pulmonary Disease (COPD) and asthma in an everyday clinical practice setting. "The real attractiveness of real-world studies is that the patients who go into RCTs aren't the ones who end up getting the treatments," says Vestbo. "The problem is that we do all these fancy efficacy studies, but they aren't representative."

He recognizes the importance of real-world trials, but also emphasizes that they need to be performed "right" to prevent the "real-world" label from becoming an excuse for poor study quality. "We need to have the same standards when we look at broad populations as when we look at experimental populations," Vestbo says. And that's where the Salford Lung Study differs from many other Real World attempts. It includes randomisation.

"The reason we chose Salford was that they have an electronic health record that's shared between primary and secondary care, and is updated in real-time," Vestbo says. If a patient is admitted to hospital and receives a treatment, the results – including safety monitoring – don't just stay at the hospital. They're automatically shared with the patient's GP. The reverse is also true.

"This gave us good opportunities to do a study where we had minimal contact with patients and minimal intervention, but could still get all the safety information that the medicine regulation agency required." More than 2,800 COPD patients were included at about 80 primary care sites, and followed for about a year. "We got a lot of data, millions of pieces of data, and sorting through that was a much, much bigger job than we ever thought it would be," Vestbo admits. There was also a substantial price tag attached. "You end up spending money on one thing or the other, but clinical trials are expensive, no matter how you do them." Still, Vestbo says it's worth it. "It proves that your drug or therapy not only can work, but actually will work in the real world." For him, the Salford Lung Study has been an ongoing success, because it's made it possible to gather data on patients who under other circumstances are excluded from clinical trials due to comorbidities like cardiovascular disease or asthma. Even the gender ratio – around half women, half men – was different than in other COPD studies, where men usually outnumber women 3:1. Apart from the positive efficacy results for GSK's drugs, for Vestbo the real pioneering outcome is "that we could study a population that has never been studied before." Whether the study really reflects the 'real world' is open to discussion. But more than any attempt in the past, it certainly does seek to close the gap between trial and reality.

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Examples of Real World Data initiatives

Name of data initiative	Lead/host organisation
Data Quality	**Academic**
› Clinical Data Interchange Standards Consortium	CDISC
› Quality Metrics Initiative	International Society for Pharmaceutical Engineering
› Public Health Data Standards Consortium	PHDSC
Data Access	
› CancerLinQ	American Society of Clinical Oncology
› Coalition Against Major Diseases	Critical PATH Institute
› ENCePP	European Medicines Agency
› European Medical Information Framework	Innovative Medicines Initiative
› Health Care Cost Institute (HCCI)	HCCI
› Optum Labs	Optum Labs
› PCORNet	PCORI
› Sentinel	US Food and Drug Administration
Methods	
› GetReal	Innovative Medicines Initiative
› Observational Medical Outcomes Partnership	Foundation of the National Institutes of Health
› PROTECT	Innovative Medicines Initiative
› Safer and Faster Evidence-based Translation	Innovative Medicines Initiative

Table: BIOCOM (Source: Oye et al., Clinical Pharmacology & Therapeutics, Vol 98, No 5, Nov- 2015, p. 514 ff); Illustration: Modification. Original from 32 pixels/fotolia.com