WHAT IS REAL WORLD DATA?

AN INTRODUCTION TO THE DEFINITIONS USED, SOURCES OF DATA AND POTENTIAL USES

FPM REAL WORLD DATA WORKING GROUP

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Introduction

The last two decades has seen an evolution in healthcare systems due to rising costs and capacity challenges, and, in tandem, the pharmaceutical industry has had to evolve with it. This evolving outlook has resulted in many new processes and pathways, including the increasing use of Health Technology Assessments (HTAs), and has impacted areas of drug pricing, access, and reimbursement, placing increasing pressure on life sciences companies. It is no longer the case that a product (drug, device etc.) will be used simply based on pivotal, registration studies. Wider data sources and consideration of the impact on the healthcare service are now key factors when assessing new technologies. This includes the overall financial impact of the product (not just acquisition costs), impact on the capacity of the healthcare service to provide the new technology (e.g. infrastructure for intrathecal medicines) and the funding mechanisms in place.

This need for broader types of information from a variety of sources beyond the randomised controlled trial (RCT), has led to a greater focus on Real-World Data (RWD) collection and the evidence that it generates (Real-World Evidence (RWE)).

The Faculty of Pharmaceutical Medicine (FPM) has several working groups focused on various innovative aspects of pharmaceutical medicine, including a RWD/RWE Working Group. Below we discuss the outputs of the working group, which looked into the various definitions of RWD/RWE and the wider implications.

Selected Definitions

Currently, there is no single definition of what is meant by RWD or RWE. However, with increasing interest in real-world outcomes, several learned societies, regulatory bodies and other relevant organisations have commissioned their own reports with definitions, that the FPM RWD working group has summarised in Table 1 (overleaf), with comments. Some organisations have made an important distinction between RWD and RWE.

The definitions of RWD tend to sit outside of randomised-controlled trials, but this definition alone doesn't necessarily capture all potential data sources. The U.S. FDA definition, currently in medical device guidance, seems to be the most comprehensive in terms of naming multiple examples of data sources. However, strictly speaking, only the ISPOR definition includes all RWD collection beyond the clinical setting (whether normal or routine).

In reality, the vast majority of a patient's time is spent living with disease away from clinical touch points and, whilst clinicians can collect information during consultations, this time spent away from the clinical environment represents an opportunity to learn more about the disease in the real world. Newer technologies are allowing this to occur in some cases with the use of wearable technology and connected devices, for example, but several of the definitions presented in Table 1 are still too narrow in this regard and focus on "normal clinical practice" or "routine care". This seems like a missed opportunity to include the patients themselves in the definitions. Thus, most common definitions of RWD are still at odds with the "patient centric" approach that both regulators and life sciences companies purport to be taking.

To further compound this apparent paradox, regulators are in fact looking at wider sources of data and types of information. For example, the FDA is already incorporating the "patient's voice" through disease specific Patient-Focused Drug Development (PFDD) meetings in order to expand understanding of living with the respective conditions. Similarly, the European Commission has recently stated its commitment to raise the level of interest in and use of Real World Data[5]. RWE collected directly from patients (through wearables, internet or testimonies) can help to guide research by answering questions related to burden of disease, burden of treatment and patient perceptions. This will not only help companies understand the patient experience of care better but also understand their experience of their disease thereby helping to make portfolio, research and development decisions. Clearly, therefore, this wider consideration 'beyond routine care' should also be incorporated in future definitions of RWD.

Furthermore, RWD does not only relate to medicines and can be related to any data collection outside of controlled environments like RCTs. This might include natural history studies, healthcare utilisation studies, patient reported outcomes, cost effectiveness studies, studies characterising costs associated with different treatment pathways as well as comparative effectiveness outcomes.

The term "real-world data" can, therefore, potentially be applied to any data gathered outside of a controlled experimental setting.

Table 1. Selected Definitions of RWD & RWE with FPM Working Group Comments

Organisation	RWD	RWE	Working Group Comments
The Association of the British Pharmaceutical Industry – ABPI[1]	Data collected outside the controlled constraints of conventional RCTs to evaluate what is happening in normal clinical practice		A narrow definition as it contains "outside controlled environment" and limits scope to data collected within clinical practice. No reference to data collected directly from patient sources. Also raises the issue of what is "normal" clinical practice. Controlled pragmatic trials would be excluded in this definition.
European Medicines Agency – EMA[2] (STAMP commission expert group)	Observational data not collected under experimental conditions (randomised clinical trials), but data generated in routine care from information related to a patient's treatment. It can come from patient registries, electronic health records, insurance data and web/social media.	Real world evidence is generated from such data sources according to a research plan. The research pan can be studies that are established to collect the data specifically for research purposes (primary data) or evidence coming from data collected for other purposes (secondary data)	Distinguishes between data and evidence by inclusion of the term research plan to generate evidence from the data. Specifically mentions web/social media as potential data source. Raises the question of what is "routine" care. Apparent contradiction between including web/social media while limiting to "routine care". Maintains "experimental and randomised" clinical trial in definition, therefore positioning of a pragmatic trial is unclear.
International Society for Pharmacoeconomics and Outcomes Research – ISPOR[3]	Data used for decision making that are not collected in conventional RCTs		This is the broadest definition in that it does not limit RWD to the setting (e.g. routine medical care) or the source (e.g. patient). The scope has a clear start (RCT) and open end, thus avoiding the issue of defining "normality" or "routine", and includes also novel methods like pragmatic trials
U.S. Food & Drug Administration – FDA (medical devices draft guidance)[4]	Data collected from sources outside traditional clinical trials, may include large simple, pragmatic trials, observational /registry studies, database studies, case reports, healthcare claims, EHRs, public health investigation /surveillance, registries. Typically derived from electronic systems used in healthcare delivery, medical devices, tracking the patient experience during care including home-use settings.	Evidence derived from aggregation and analysis of RWD elements	Clear distinction (like EMA) between RWD and RWE, specifying terminology "aggregation and analysis". Patient sources (in terms of medical devices) included in definition, but Patient and care giver surveys are not mentioned as sources neither is social media specifically mentioned and neither are claims databases Pragmatic trials specifically listed as included in scope.

RWD vs RWE

The terms Real-World Data and Real-World Evidence are often used interchangeably but, in reality, they are different concepts. RWD is the actual raw data, retrieved from a myriad of sources (registries, electronic health records, patient reported outcomes, wearables, testimonies, surveys etc.), that may be unstructured or structured. RWE is derived from the aggregation and analysis of this data. It is the product of analysed RWD and results in meaningful insights into the disease area. This can range from individual studies published in peer-reviewed journals to the use of analytics engines to give real-time insights using data sets.

Both EMA and FDA make a clear distinction between "data" and "evidence", the latter specifically calling out the aggregation and analysis of data elements to develop evidence, and the EMA focusing on the need for a research plan to be in place for such scientific approach.

This distinction between RWD and RWD is indeed very relevant. Whereas historically (in RCT) the scientific rigour was applied to source (physician), nature (medical) and analysis (stats) of data, what is happening with RWD is that the first two (source and nature) are being broadened. The third, however, remains what turns data into evidence. The regulatory authorities have been quite clear on this point, including in a recent public FDA workshop: what makes RWD into RWE (and thus the only thing they will consider) is the data and its analyses meeting scientific rigour (especially the criteria of representativeness and significance), for which you need a plan before you start analysing (even collecting). Pharmaceutical physicians have an important role to play in raising the understanding of this difference.

The common theme of RWD and RWE is one of data collection outside of artificial environments. A randomised controlled clinical trial usually has strict inclusion/exclusion criteria; patients are also randomised and the study population is, therefore, not necessarily representative of the target patient population. In addition, the monitoring is highly controlled and not necessarily representative of clinical practice. The aim of RCTs is to minimise bias and confounding in order to answer a specific question; in the case of the pharmaceutical industry this is usually to provide proof of efficacy of a medicine against placebo or standard of care, establishing causality between wanted and unwanted effects of a medicine. In contrast, real-world data collection is focused on the use of the medicine in clinical practice where the population is much more heterogenous compared to RCTs, may have many co-morbidities and may receive concomitant medication.

As such, RWE evidence can be (and is increasingly being) used beyond the context of drug approval, pricing and reimbursement. RWE can, indeed, also help to make better decisions earlier in the life cycle, including as far as the selection of research areas. RWE may thus inform direct clinical decision making on the choice of medicines (e.g. comparative effectiveness or natural history studies) or decisions related to the economic impact of technologies (health economic outcomes research) or improving patients' experience of care (e.g. through social listening in a hospital setting), benefit-risk assessments or setting R&D priorities.

This distinction between RWD and RWE highlights the importance of the (planned) purpose of the data collection, of the scientific rigor used to develop meaningful insights to inform decision making. Data without purpose has no utility; data without method is not evidence. The same RWD might be used to produce various types of RWE and this will depend on the specific question asked and the analytical methods used.

RWE Complements RCT Evidence

One of the key objectives of RWE (for the pharmaceutical industry) is to understand outcomes in routine clinical practice and in this regard, RWE complements the efficacy and safety data generated by RCTs. RWE doesn't fit into the traditional hierarchy of evidence (Fig 1), where RCTs are still the gold standard in determining efficacy, but can provide valuable information for populations not assessed in the trial environment, for example. RCTs test specific questions in a controlled, experimental environment with carefully developed protocols and, therefore, do not represent actual use of the medicine or device in clinical practice. The data they provide is essential in terms of proving causality, whilst RWE can provide information on overall effectiveness in wider patient groups. Outside of the highly prescriptive environments of clinical trials, confounders such as adherence and co-morbidities are not controlled for, giving us a better picture of how the drug performs in the target population.

The U.S. FDA and the EMA have both formally acknowledged the need for the increased use of RWE in supporting medicines whilst, in Asia, Japan has already begun their "Rational Medicine" initiative to make the Japanese health care system more patient-centric and evidence-based[8]. Regulators around the world are incorporating RWE into their decision-making as evidenced by the FDA's aim to produce formal guidance on the use of RWE by 2021 and the EMA's adaptive pathways approach[9,10]. Life sciences companies naturally need to ensure they are evolving and adapting to this increasing demand for RWE.

Figure 1. Hierarchy of Evidence[6,7]

The use of RWE has, to date, largely been restricted to the period just before launch and through the post-marketing phase, to better understand patient populations, drug safety and for comparative effectiveness studies against existing products. These studies may also be incorporated into health economic modelling to inform pricing, reimbursement decisions based on cost effectiveness and the wider impact on the healthcare system by evaluating resource allocation. As the use of RWE becomes more well established, with regulators making licensing decisions, more companies are starting to incorporate it into earlier stages of clinical development programmes. Some companies are also leveraging RWE to guide their research efforts, based on a better understanding of more dimensions of the burden of disease, which can help to identify new patient relevant targets. However, whilst the potential to improve development relevance and thus impact is clearly an attractive proposition, many companies are still waiting for more clear guidance and standards from healthcare decision makers.

Conclusions

There is increasing recognition within the life sciences sector and the healthcare industry of the need for a variety of evidence beyond RCTs when it comes to developing and evaluating therapy areas (including medicines). This is reflected in the increasing volume of real-world studies being published, the increased recognition by regulators of the value of RWE and the increased use of RWE to convey messages around (cost) effectiveness and safety. However, there are many hurdles to overcome before real-world studies are universally accepted. Some of these hurdles will be overcome with the publication of guidance and standardised methodology, whilst other hurdles will be overcome with greater transparency from industry and improved education of stakeholders.

As discussed above, three themes emerge from this review:

1) 'Data collected outside of RCTs' seems to be the common theme in current definitions of RWD/ RWE, but the differences beyond that introduce uncertainty or limit the scope.

2) The distinction between RWD and RWE is important and relevant to decision making and starts with a plan. RWE can drive decisions throughout healthcare and the medicine livecycle.

3) Real-world studies complement and do not replace RCTs.

Interactive question...

The FPM Real World Data working group is planning to organise a workshop on advanced topics in real world data in December - which specific aspects of RWD would you like to see covered?

Disclaimer: By completing the above form you consent to your comments being read by the real world data working group. Comments will not be printed or shared without your express permission. Your name and email will not be shared.

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