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COMMENTARY

Report on the current status of the use of real-world data (RWD) and real-world evidence (RWE) in drug development and regulation

Radically expanding use of real-world data (RWD) and real-world evidence (RWE) holds the potential to substantially impact drug development, pharmaceutical regulation, and payment within health care systems. Central to this is the reconfiguration of data gathering and transformation of data to information, which can be used as evidence for decision making. We discuss applications of this paradigm in the light of recent developments in both the United States and Europe on RWD and RWE.

1 | INTRODUCTION

Life sciences have become fertile ground for employment of RWD to improve many procedures in the delivery of health care, including research and development of pharmaceuticals, regulatory decision making, health technology assessment (HTA), pricing and reimbursement decisions, and treatment. The potential for RWD to contribute to a "Learning Healthcare System" has been cogently articulated by Eichler and his colleagues.[1]

RWD can be defined as "data related to healthcare status, routinely collected from a variety of sources, outside of randomised clinical trials (RCTs)."[2] These sources include primary and secondary patient care records such as those in electronic health records (EHRs), insurance claims data, routinely collected administrative data, product and disease registries, and emerging observational sources such as social media and data collected from mobile devices and apps.

Our current paradigm for demonstrating the efficacy of a drug is largely limited to results from controlled clinical trials, where a medicine is administered to a carefully monitored, circumscribed group of patients. Once marketing authorization is achieved, the drug is prescribed to patients exhibiting a wider range of patient ages and characteristics, with more comorbidities and concomitant drugs than clinical trial subjects included in the registration trials. Therefore, a realistic understanding of the clinical and cost effectiveness in the real world clinical population is often lacking.

How can RWD be used to generate RWE for the development and regulation of medical products? In this context the term "regulatory" embraces both conventional regulatory parameters of safety, quality, and efficacy and also HTA. Schneeweiss[3] has outlined such cases where RWD might be usefully employed for RWE analysis.

RWE can be defined as "clinical evidence about usage and potential benefits or risks of a medicinal product derived from analysis of RWD."[2] RWE has the potential to provide value in all stages of a product's life cycle, complementing and in some cases even replacing "gold standard" RCTs, by provision of convincing evidence for the safe, effective, and efficient development of medicinal products. Furthermore, mining RWD may reveal opportunities for discovering novel therapeutic approaches to common conditions by linking drug responses to genetic polymorphisms and for "repurposing" already approved drugs to treat other conditions.

With the paradigm shifts in the drug development process towards personalized medicine, expedited regulatory pathways for product approval,[4] and early access to important new medicines, it is becoming increasingly apparent that large-scale RCTs may not always offer the optimal model for evidence collection. As argued by Rawlins in his 2008 Harveian Lecture,[5] "Hierarchies of evidence should be replaced by accepting – indeed embracing – a diversity of approaches." From a regulatory perspective, this may result in a shift from market access via pre-approval RCTs to post-approval safety and efficacy studies using RWD/RWE. In the future, large, expensive, and non-representative phase 3 clinical trials could be replaced by a graded release of a new medicine into the general population, combined with real-time analysis of patient responses (both therapeutic and adverse). This approach will lead to fresh problems, such as data and hence analysis quality, which will have to be addressed.

At the center of the discourse on the roles of RWD and RWE is attention to how data can be transformed into information which in turn can become qualified evidence for use in decision making. Herein, RWE can be further refined as "regulatory grade" RWE which requires

- Defining the scientific question which should be meaningful and answerable with RWD
- Identifying the appropriate study design
- Selecting the RWD to be used
- Defining data standards/analytical methods and strategy
- Complying with regulatory standards.

In order to be usable, RWE must be generalizable across health care systems, clinically relevant, adaptable, efficient, and an accurate reflection of treatment effects, allowing RWD analysis to result in meaningful insight. Ideally, these data should be gathered as part of routine clinical care in a format that allows data analysis.

Regulatory perspectives on RWD and RWE have recently been presented by the US Food and Drugs Administration (FDA) in its Framework for Real World Evidence Program (December 2018).[2] Further clarifying terminology, aspirations, and approaches have been three National Academy of Medicines workshops on Real World Evidence Generation and Evaluation of Therapeutics (2017),[6] two UK Academy of Medical Sciences Workshops on Real World Data and Real World Evidence (2015 and 2018),[7] reports from several European Union Innovative Medicines Initiatives (IMI) programs,[8] and the report from the European Heads of Medicine Agencies/European Medicines Agency Joint Big Data Taskforce, February 2019.[9]

In this paper, we reference the role of RWD and RWE in regulatory and HTA decision making, the main challenges to be overcome, and promising examples of progress to remedy them. To date, RWD and RWE in the current drug development paradigm have largely been applied in early discovery, the post market phase of safety surveillance, and for comparative effectiveness evaluation, although this is changing.

2 | CURRENT USE OF RWD FOR EVIDENCE GENERATION

2.1 | Drug safety

Regulatory authorities have hitherto largely used RWD to monitor the safety of marketed medicinal products and to a lesser extent, medical devices.

Spontaneous reports of adverse events or harms following drug treatment are reported to health authorities by health care professionals, patients, and industry and comprise signals which give rise to hypotheses of drug safety. Known as passive surveillance of safety, all National Competent Health Authorities have such schemes, e.g., the US Adverse Event Reporting System (AERS), the European Eudravigilance Network, and the UK Yellow Card Scheme.

Safety signals can be transformed into RWD by the process of active surveillance, which is a systematic approach to population-based drug safety capture and analysis and which is employed to ascertain the number of adverse events by means of a continuous organized process. This information can be used to evaluate the hypotheses generated from signals emanating from passive surveillance. For example, since 2016, the European Eudravigilance Network has received over 1 million adverse event reports from which 2000 signals were detected and 48 of which were validated.[7]

Active safety surveillance entails mining safety data from real world clinical data, including from the following resources and examples:

2.1.1 | Patient registries

For single drugs

Tysabri, a monoclonal antibody treatment for multiple sclerosis, was approved for marketing in 2004, then withdrawn in 2006 following several fatal cases of progressive multifocal leucoencephalopathy (PML). Tysabri was reintroduced into the market following the creation of a patient registry in 2008.[10]

For groups of drugs

The British Society of Rheumatology Biologics Register, launched in 2001, successfully achieved the primary aim of capturing the long-term safety outcome of patients with rheumatoid arthritis treated with biologic agents, including anti-TNF drugs.[11]

Disease registries

These may offer considerable advantages in following up individual patients before, during, and after multiple drug regimens. Orphan diseases are a useful example.

2.1.2 | Patient medical records

Single databases

Electronic Health Records.

Record linked databases

Clinical Practice Research Data Link (CPRD) provides researchers with access to information of potentially 64 million patients in the United Kingdom.

The Sentinel (US) program

This has become a critical component in the FDA's implementation of its mandate under the 21st Century Cures Act by providing data to support incorporation of RWD into regulatory decision making in addition to safety assessments.

Health care professional/prescription linked databases

PHARMO is the Netherlands system whereby patients are registered not only with a doctor but also a pharmacist, permitting information from prescription and dispensing data to be linked to hospital records and clinical outcomes.

Social media

In the future, RWD from various forms of social media may become sources of RWD, but at present, this is not well enough developed despite the fact that 10% of all social media traffic relates to health care issues and half of this concerns the safety and efficacy of medicines.[7]

RWD obtained in these various ways can become the source of RWE by integration in the following:

- Observational studies (retrospective or prospective)
- Clinical Trials (Pragmatic trials or large simple trials)

Examples from the use of CPRD for RWE:

- Use of antidiabetic agents and the risk of pancreatic cancer[12]
- Dopamine agonist use and the risk of heart failure.[13]

Examples from the FDA of RWE investigations include

- Risk of strokes after antipsychotic therapy[14]
- Incidence of seizures following ranazoline therapy for angina pectoris.[15]

2.2 | Drug effectiveness

Increasing use is being made of RWE to inform regulatory decisions on drug effectiveness and benefit–risk balance, using the steps outlined above. Calibration of RWE against RCTs is desirable, provided the questions asked are the same.[16]

Regulatory authorities have accepted RWE in marketing authorization decisions in

- Oncology and rare diseases where only single arm studies are possible and only an historical control arm using RWD to assemble research cohorts is possible. For example, in the EU, Zalmoxis, the immune-gene therapy for high risk hematological malignancies, was granted Conditional Marketing Authorization following a single arm study using historical controls from the European Transplantation register. Post authorization effectiveness and safety studies were required.[7]
- Effectiveness and dose finding of vaccines, e.g., rabies[6]
- In specific real-world, community-based pragmatic trials such as the Salford Lung Study[17] in which patients with chronic obstructive pulmonary disease (COPD) or asthma were randomized in an open label pragmatic trial comparing continuation of their usual treatment with a once daily combination of the inhaled corticosteroid fluticasone fumarate and the long-acting beta 2 agonist vilanterol over 12 months. Routine clinical real-world data were collected from over 7000 patients. Significant reduction in the number of COPD exacerbations and in respiratory function were shown in patients treated with the novel drug combination, and there was no difference in adverse events. It should be pointed out that the set-up of this study required significant upfront investment on the part of the sponsor.

These examples show how analysis of RWD can lead to RWE and how a treatment is delivered in routine medical care.

The use of RWD/RWE is also being explored to identify new biomarkers of disease and drug responsiveness, to inform priors for Bayesian analyses of clinical trials, and to generate models of hypotheses of randomized clinical trials.[6]

We posit that reconfiguration of health care systems to radically expand capture of RWD will have benefits in pharmacovigilance, drug development, and efficient deployment of capital within health care.

3 | CHALLENGES

There are many challenges to the future use of RWD and RWE for regulatory purposes.

Health authorities must provide greater clarity on the acceptability of RWE in decision making and provide guidance on standards and best practices of both methodology and analysis when interrogating RWE. Adequate regulatory guidance is not available for the design of RW studies which are acceptable.

Privacy and consent issues are likely to be very important as data gathering can only occur with the permission of individuals and populations. This strongly implies that public information is vital for this area of medicine to develop. This is a complex problem and beyond the scope of this paper.

The logistical challenges of reconfiguring health care systems to gather usable RWD as part of routine health care have not been addressed—an important aspect of which is the incompatibility of many EHR systems. Even within unitary health care systems such as the UK National Health Service, individual hospitals and health care authorities frequently have diverse electronic systems.

4 | CONCLUSIONS

We are at an opportunistic crossroads in our potential uses of RWD and RWE. We have briefly described the current use of RWD for evidence generation and work in progress addressing the challenges to realization of the full potential of RWE, which can be used to improve:

- Safety of marketed medicines
- Effectiveness of medicines, in particular dose selection, sequence of therapies, subpopulations for drug use, and co-prescribing
- New drug indications (repurposing)
- HTA decisions.

The potential benefits from RWE in all aspects of health care are very large. What is needed is regulatory oversight, appropriate patient information, and reconfiguration of data gathering within health care systems.

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COMPETING INTERESTS

There are no competing interests to declare.

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