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"DADOS DA VIDA REAL" NA DETERMINAÇÃO DO VALOR DO MEDICAMENTO

REAL-WORLD DATA AS A TOOL FOR ESTABLISHING THE VALUE OF A MEDICINE

Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica da Doutora Mª Teresa Herdeiro, Professora Auxilar Convidada da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

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resumo

Nos últimos anos tem sido discutido em que medida são fornecidos dados suficientes para estimar o valor clínico do medicamento durante o processo de aprovação e autorização de introdução no mercado (AIM). Apesar dos ensaios clínicos randomizados (ECR) possuírem extrema validade interna na avaliação da segurança e eficácia de novos produtos, não permitem a extrapolação dos dados de eficácia para a vida real (efetividade).

Alguns peritos têm discutido o potencial uso dos dados recolhidos na vida real (DVR) na contribuição de uma avaliação mais robusta de produtos e resultados em saúde.

Os avanços nas tecnologias da informação permitem recolher, partilhar, analisar e utilizar grandes quantidades de informação a um custo relativamente baixo. Neste contexto, os DVR podem ser usados em conjunto com ECR e outros dados médicos para proporcionar perspectivas sobre resultados clínicos reais. Se esses dados e metodologias puderem ser canalizados para a pré-AIM, os titulares serão capazes de direccionar o desenvolvimento de medicamentos para áreas onde o valor é susceptível de ser elevado para os doentes e sistemas de saúde. Assim, as agências regulamentares e de avaliação de tecnologias da saúde terão informação suficiente para tomar decisões devidamente fundamentadas sobre a eficácia relativa de novas intervenções em saúde.

O principal objetivo desta tese é promover uma análise da utilidade dos DVR, como criadores de valor, em todas as fases de desenvolvimento de medicamentos e discutir o papel-chave de todas as partes interessadas no uso de DVR.

keywords Real-world data; real-world evidence; randomised clinical trials; safety; efficacy; effectiveness; value.

abstract

It has long been discussed to which extend the licensing procedure should assure the availability of sufficient data to assess the clinical value of a new dug at the time of marketing introduction. Despite the high internal validity of randomised clinical trials (RCTs) generated evidence and its ability to robustly indicate the safety and efficacy of new products, it falls short of allowing for extrapolation from efficacy to clinical effectiveness.
A number of analysts and academics have signalled the potential of real-world data (RWD) to contribute to improved health products and outcomes. Advances in computing allow collecting, share, analyse and use large quantities of data routinely at a relatively low cost. In this context, RWD can be used in conjunction with RCTs and other medical data to provide insights into real-world clinical outcomes. If such data and methodologies could be harnessed in pre-authorisation drug development, drug manufactures would be able to direct drug development to areas where value is likely to be highest for patients and health systems. In addition, regulatory and Heath Technology Assessment (HTA) agencies would be able to make better-informed decisions on relative effectiveness of new health interventions.

The main goal of this thesis is to analyse the usefulness of RWD collection, as creator of value, in all drug development phases and discuss the key role of all stakeholders in use of RWD.

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List of Abbreviations

ADR	Adverse drug reactions
AS	Ankylosing spondylitis
ATV	Added therapeutic value
B/R	Benefits/Risks
BKP	Balloon kyphoplasty
CED	Coverage with Evidence Development
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Ciclo-oxigenase-2
CPRD	Clinical Practice Research Datalink
CR	Cardiac rehabilitation
EBM	Evidence-based medicine
EHR	Electronic health records
EMA	European Medicines Agency
EMR	Electronic medical record
ENVI	Environment, Public Health and Food Safety
EPAR	European Public Assessment Report
EU	European Union
EU-CORESM	European Cubicin Outcomes Registry and Experience project
EUnetHTA	European network for Health Technology Assessment
FDA AERS	Food and Drug Administration Adverse Event Reporting System
GP	General practitioner
HRQoL	Health-related quality of life
HTA	Heath Technology Assessment
IMI	Innovative Medicine Initiative
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
JIA	Juvenile idiopathic arthritis
MAA	Market Access Agreements
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICHSR	National Information Center on Health Services Research and Health Care Technology
NPC	National Pharmaceutical Council
OPLA	Operative placebo with local anaesthetic
OPM	Optimal pain management

P4P	Payment for Performance
PASS	Post-Authorisation Safety Studies
PCORI	Patient-Centred Outcomes Research Institute
PRO	Patient reported outcome
PsA	Psoriatic arthritis
PSUR	Periodic Safety Update Reports
PV	Pharmacovigilance
PVP	Percutaneous vertebroplasty
QALY	Quality-adjusted life-year
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised clinical trials
REA	Relative efficacy/effectiveness assessments
RMP	Risk management plans
RWD	Real-world data
RWE	Real-world evidence
RWS	Real-world study
SEED	Shaping European Early Dialogues
TAVI	Transcatether aortic valve interventions
VAESCO	Vaccine Adverse Event Surveillance and Communication
VCFs	Vertebral compression fracture
WHO	World Health Organization

1. INTRODUCTION

During pre-authorisation drug development phases, pharmaceutical manufacturers invest considerable time and funds in conducting phase III clinical studies to provide robust data on the safety and efficacy of their products. Such studies are designed as randomised clinical trials (RCT's) which typically have strict inclusion and exclusion criteria for trial subjects and within which experimental products are often conventionally compared to a placebo arm, rather than an active treatment. Consequently, experimental products being presented for marketing authorisation are accompanied by data that provides safety and efficacy data with very high internal validity but whose results are perhaps not easily generalised to the broader, more heterogeneous clinical population[1]. Medicine use in clinical practice frequently differs widely from the (pre-approval) clinical trial settings. Patients are diverse, with varying disease histories and co-medications and they do not always comply with instructions and persist with treatment over time[2].

Selective ciclo-oxigenase-2 (COX-2) inhibitors provide an example of the challenges in generalising evidence from authorisation RCTs to routine clinical practice. The main RCTs of rofecoxib and celecoxib that were used to obtain the marketing authorisation restricted study eligibility to patients with severe osteoarthritis or rheumatoid arthritis who were expected to use the study drug daily for the duration of the studies (six to nine months)[2–4]. However, an analysis found that the large majority of patients using selective COX-2 inhibitors in routine clinical practice would not have been eligible for these main RCTs as they did not have severe osteoarthritis or rheumatoid arthritis and this not use these medicines every day for a number of months. The results of authorisation RCTs are, therefore, not always generalizable to patients in routine clinical practice[2,5,6].

Authorisation RCTs typically assess the efficacy of a medicine, that is, the effects under ideal circumstances. On the other hand, effectiveness concerns the effects of a medicine under routine clinical circumstances. There are various reasons for differences between efficacy and effectiveness. One reason leading to these differences is the adherence of patients to the medication and the recommended dosage instructions. Another reason for the discrepancy between efficacy and effectiveness are differences in dosages. A challenge in the generalizability of evidence from RCTs to real life concerns patients who were not eligible for the RCTs[2].

It has long been discussed to which extend the licensing procedure should assure the availability of sufficient data to assess the therapeutic value of a new drug at the time of market introduction[7]. Regulatory agencies are those faced with the issue of making decisions based upon data with inherent uncertainties on the aspects of real-world effectiveness. Similarly, health technology assessment (HTA) agencies and healthcare

payers often refer to RCT-generated evidence available at the time of initial authorisation to pass judgement on the relative effectiveness of the new products. Thus, in the light of making decisions with high uncertainties on post-marketing performance of new drugs, regulatory and HTA agencies alike increasingly require applicants to fulfil post-marketing data collection commitments (e.g. post-marketing safety/efficacy studies, risk-sharing agreements). Such data is better suited to answering questions on clinical safety and effectiveness, owing to the fact that they are collected from patients representing routine practice[1].

A number of analysts and academics have signalled the potential of real-world data (RWD) to contribute to improved health products and outcomes. Advances in computing allow collecting, share, analyse and use large quantities of data routinely at a relatively low cost – as never before. The increased use of new technologies in the healthcare sector has changed the ways in which patient level information are collected, stored and used[8]. If such data and methodologies could be harnessed in pre-authorisation drug development, drug manufacturers would be able to direct drug development to areas where value is likely to be highest for patients and health systems[1].

A range of stakeholders in health research, innovation and care delivery hope that the combination of RCT data and RWD can be used to help develop more targeted drugs and to encourage better use of those drugs by clinicians and patients. Data relating to patient experience in using drugs and to the contexts and settings in which drugs are used could potentially play a role in the way that trials are designed and conducted, the processes of drug registration and post-marketing benefit risk assessment, as well as create novel incentives for open health research. In the context of the severe cost and productivity challenges that health researchers and innovators have experienced in recent years, the prospect of data and mechanisms that could improve efficiency at multiple levels of the health research ecosystem without the cost of clinical trials is welcomed by many[8].

The main goal of this thesis is to analyse the usefulness of RWD collection, as creator of value, in all drug development phases and discuss the key role of all stakeholders in use of RWD.

2. DEFINITION OF REAL-WORLD DATA

In 2007, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) created an International Task Force to develop a framework to assist health-care decision-makers in dealing with RWD. From the outset, the Task Force grappled with the definition and appropriate characterization of RWD. It seemed self-evident that RW outcomes data should come from RW situations. Part of the Task Force's charge was to consider uses and limitations of evidence not obtained from RCTs. On the other hand, it was also clear that decision-making is a highly integrative process of synthesizing information from different sources—both "laboratory" and real-world. They settled on a definition that reflects data used for decision-making that are not collected in conventional RCTs (for methodological, ethical or other reasons)[9,10]. This is not to say that data from RCTs are irrelevant or not used by decision-makers; indeed, they remain the critical foundation for almost all initial coverage and payment decisions[9].

In the last years some alterations have been made in the definition of RWD, created in the Task Force. In 2014 RAND Europe adopted the following explanation:

RWD is any data not collected in conventional randomised controlled trials. It includes data from existing secondary sources (e.g. databases of national health services) and the collection of new data (e.g. pragmatic trials; observational studies), both retrospectively and prospectively[8,11].

The Task Force also deliberated distinctions between the terms RWD and real-world evidence (RWE). Evidence is generated according to a research plan and interpreted accordingly, whereas data is one component of the research plan (Figure 1). Evidence is shaped, while data simply are raw materials and alone are non-informative[9]. In general, RWE is what happens to data. Building the evidentiary portfolio requires the systematic unbiased collection of data. The validity of the evidence is dependent on the accuracy of the data and the appropriate organization to allow interpretation, analysis, and conclusions[12]. Simply stated, RWE is the application of RWD to derive insights that can be generalized to usual care settings[13].

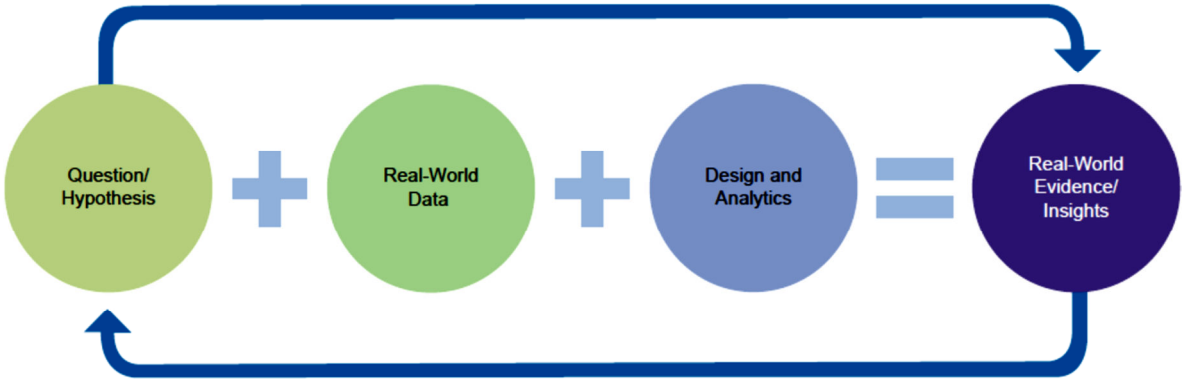

Figure 1. RWE is generated by applying a question or testing a hypothesis using RWD and applying analytical techniques set out in the study design[14].

Real world studies (RWS) was defined as all clinical studies investigating health interventions whose design does not follow the design of a randomised controlled clinical trial and aims to reflect health intervention effectiveness in routine clinical practice. RWS do not typically include randomisation of trial subjects, but there are exceptions (e.g. pragmatic clinical trials). RWS include, but are not limited to, the following: pragmatic clinical trials, non-interventional/ observational studies, drug utilisation studies, post-authorisation efficacy/safety studies. RWS, by definition, generate RWD, which can subsequently be analysed and/or synthesised to produce RWE[1,15].

The design used in an RWS needs to have rigour appropriate to the disciplines it is drawn from. Table 1 sets out the possible elements of an RWS.

Table 1. The design of RWS[14].

Element of RWS	Design of an observational study
Subjects	• Includes those eligible for care from the health system • Clinical topics where case finding and outcomes are measured using routine data • Large number of cases • Case definition will be that of usual practice • Wide range of other therapies and co-morbidities • Few inclusion/exclusion criteria
Setting	• Routine care • Range of treatment pathways • Comprehensive use of computerised medical records, across the care pathway • Need to infer meaning from 'messy' routine data
Intervention/exposure	• Prospective (including pragmatic RCTs) and retrospective studies are possible • Open label/neither clinician nor patient will be blinded • May be over a long period of time • That delivered as part of usual care/generally no additional visits • Standard patterns of adherence, no attempts to change beyond those that are part of routine care
Outcome measure	• Defined from routine data • Loss to follow-up of those who move out of area/out of system • Avoids recall bias • Can include health economic impact
Comparator group	• Differences in exposure • From different localities • Before and after • Stepped introduction of programme

3. CHARACTERIZATION OF REAL-WORLD DATA

There are several ways in which one might characterize RWD. One is by type of outcome: clinical, economic, and patient-reported outcomes (PRO). An advantage of this approach is that it corresponds to the way in which many decision makers conceive of data. A downside is that it provides broad categories, each of which combines many types and sources of evidence[9].

A second characterization involves traditional hierarchies of evidence, which rank evidence according to the strength of the research design. Traditionally, RCT data has been regarded as being at the top of the hierarchy of evidence quality, followed by data from non-randomised intervention studies, followed by epidemiological studies and so forth. Evidence hierarchies provide a useful ranking based on the rigor of the research design; however, they do not provide a complete picture of RWD. The results from many RCTs are not generalizable to a broader population. Conversely, a well-conducted observational study may prove highly useful in certain situations provided that potential biases have been adequately addressed. Indeed, there has been recognition among key opinion leaders that RWD have a place alongside RCT data providing valuable evidence of use in clinical practice that cannot be gained from RCTs[9,16].

Finally, one might consider RWD by types of data sources. The value of this classification is that it identifies tangible sources of information. A potential drawback is that it represents a simplification that does not capture important design issues within each source of evidence[9].

Each of the three characterizations provides a different perspective on RWD. Collectively, they provide a useful portrait of the strengths, weaknesses, and complexities inherent in the topic[9].

3.1 TYPES OF OUTCOMES

Clinical outcomes: Clinical outcomes include biological measures of morbidity (e.g., blood pressure, cholesterol level, symptoms, and side effects) and mortality. Clinical outcomes include both surrogate (intermediate) and long-term measures[9].

Much of the data collected in phase III registration trials involves clinical outcomes. Clinical outcome data are also found in many other sources, such as patient registries or observational databases[9].

Economic outcomes: **"**Economic outcomes" are narrowly defined here to include estimates of medical and non-medical resource utilization and their associated costs. Such data are used to project the expected cost of an intervention in the real world-e.g., in the numerator of a cost-effectiveness ratio. Many sources of RWD are useful in providing use and cost information[9].

PROs/quality of life (QoL). PRO is the term adopted internationally to encompass any report coming directly from patients about a health condition and its treatment, including symptoms, functional status, health-related quality of life (HRQoL), treatment satisfaction, preference and adherence[9].

Over recent years, the importance of the patient perspective has risen to the top of the agenda. Patients' views are key to two aspects of RWD. First, systematically recording and evaluating patients' experiences of their health care, including their satisfaction with the delivery of services, is increasingly recognised as relevant to assessments of the quality of health care. Capturing patient feedback has been recognised as a significant driver for improved services, essential for service design and delivery, monitoring improvements and key to ensuring high quality care for all[9,16].

Second, there is increasing recognition that patients' views of their own health, measured using validated and reliable survey instruments (Patient Reported Outcome measures – PROs, or PROMs) provide an important and highly relevant way of assessing the effects of treatment, which are complementary to conventional clinical endpoints. The researchers have long recognized that self-reports of outcomes related to disease, injury, treatment or policy are important, because they provide the only direct voice that an individual has in the health decision making process[9,16].

As people live longer with chronic conditions, PROs have become increasingly important to pharmaceutical manufacturers in assessing the impact of emerging chronic treatments and in communicating the benefits of these drug treatments in label and promotional claims[9].

3.2 EVIDENCE HIERARCHIES

Historically, evidence hierarchies have been linked to "evidence-based medicine" (EBM). The thrust of the EBM movement is to ground clinical practice in rigorous research. EBM proponents emphasize that traditional medical practice incorporated local practices and expert opinion that were not tested in controlled studies. They stress the need for clinical researchers to document all study protocols, utilize appropriate analytical techniques, and strive for internal consistency. Studies are to be considered externally valid when

findings are generalizable beyond local clinical practices. A scientific body of evidence became reliable and generalizable when similar results were reported by different researchers across a range of study designs and patient populations. For these reasons, RCTs were placed at the top of the evidence hierarchy[9].

In accordance with Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament, evidence for the medical-therapeutic evaluation is assessed according to six types of evidence. The first group (prospective, double-blind, randomised-control studies representing a large population, or meta-studies of such studies) are assigned the highest level of validity. They are followed (in descending order) by 2.systematic reviews; 3.randomised-control studies with less data; 4.non-randomised and uncontrolled studies; 5.consensus judgements of an expert committee; 6. statements of experts[17].

Decision makers, however, quickly recognized the impracticality of basing all of medicine on RCTs. For one thing, RCTs are expensive. For another, even the best RCT reflects a limited controlled experiment that may not generalize to populations, settings, or conditions not reflected in the trial. The need for non-RCT information became apparent, raising the question of how to grade information that by definition was of "poorer quality?" [9].

3.3 DATA SOURCES

RWD can also be categorized by type of data source. The ISPOR Task Force defined six such sources: 1) supplements to traditional registration RCTs; 2) pragmatic clinical trials (also known as large simple trials or practical clinical trials); 3) registry studies; 4) claims databases/administrative data; 5) health surveys; and 6) electronic health records and medical chart reviews[9].

Supplements to RCTs. To provide additional data alongside standard clinically focused RCTs, researchers often gather information on variables such as PROs, medical resource use, and costs. Such efforts can add valuable evidence on treatment patterns for common events, e.g., such as the doses of drugs used to treat rejection in kidney transplantation[9].

Limitations to such data are also well known: their primary aim is to measure a key clinical efficacy endpoint in a carefully limited population and clinical setting. Furthermore, trials are not usually powered statistically to measure precisely the probability of rare adverse or other events and hence are of limited use in measuring the associated resource utilization and costs. RCTs are generally conducted over a shorter time frame than what is

relevant for determining the overall clinical and economic impact of an intervention, and resource use is often protocol-driven[9].

Pragmatic clinical trials. Large simple trials (also called practical or pragmatic clinical trials) involve prospective, randomised assignment but aimed at larger more diverse real-world population. Practical clinical trials have the important strength of randomisation, which minimizes bias in the estimation of treatment effects. These trials are by design larger than conventional RCTs. For this reason, they are more likely to have sufficient power to capture significant differences in key outcomes of interest, such as hospitalizations[9].

Because the focus is on obtaining policy-relevant outcomes, costs and cost-effectiveness are more likely to be central endpoints, and the results can be more readily generalized to the relevant treatment population than those obtained from conventional RCTs: costs are less likely to reflect protocol-driven health care use; well-documented variations in resource use across various ethnic, racial, age groups and genders can be better captured by opening the trial to a more diverse population; people more at risk for adverse events are less likely to be excluded from the trial, and the related economic effects are more likely to be captured; and resource use and costs are more likely to reflect those observed in community-based settings where most people obtain their care, especially since study drugs in phase III trials are generally provided for free[9].

However, the large size of a practical clinical trial increases the cost of data collection and raises some concerns about the quality of data collected. Costs are increased not only because a larger number of patients are enrolled, but also because a larger number of settings are involved. Some of the issues raised by economic data collection within practical clinical trials are: identification of where subjects receive care may be more difficult (less in a closed system); data collection systems of community-based settings may be less sophisticated than those of academic settings (for example, more likely to use paper rather than electronic records, thus increasing the likelihood of data entry errors); there is more likely to be a lack of standardization in financial and billing systems across different settings of care; and more study coordinators will be involved in the data collection effort[9].

Registry studies. Registries are prospective, observational cohort studies of patients who have a particular disease and/or are receiving a particular treatment or intervention. They can be used for understanding natural history, assessing or monitoring real-world safety and effectiveness, assessing quality of care and provider performance, and assessing cost-effectiveness[9].

Registries involve prospective data collection of clinical, economic, and PRO information, and are increasingly relying on real-time data capture. They typically include a larger and more diverse group of patients than what is generally studied in phase III RCTs; therefore, they better reflect real-world patients, management practices, and outcomes. Patients are often followed over a longer timeframe, allowing for an assessment of longer-term outcomes. Most registries have very few, if any, required visits, evaluations, or procedures; therefore, the treatment patterns reflect the everyday clinical decision-making that is most relevant to providers and payers. Disease registries enable providers and payers to gain insight into the most cost-effective treatment approaches[9].

Because registries do not involve random assignment to treatment, care must be taken in analysing and interpreting the results due to the inherent limitations of observational studies. There is no guarantee that patient groupings are comparable: therefore, registries may not be suitable to test hypotheses, but are useful to generate them. Furthermore, there are limitations in terms of the amount of data that can be collected, and because visit schedules are not required, data cannot necessarily be obtained at fixed intervals. Registries sometimes include study sites that are not experienced in conducting research, and without appropriate oversight, data integrity could be in question. However, the use of real-time data capture is likely to improve data monitoring and integrity. Registries are, in some cases, established to collect post-marketing safety data, either in response to specific safety concerns or to fulfil regulatory obligations established as a condition of marketing approval[9].

Claims databases. Administrative data (typically retrospective or real time, if possible) are collected primarily for reimbursement, but contain some clinical diagnosis and procedure use with detailed information on charges. Claims databases lend themselves to retrospective longitudinal and cross-sectional analyses of clinical and economic outcomes at patient, group, or population levels. Such analyses can be performed at low overall cost and in a short period of time. Given the sheer size of claims databases, researchers can identify outcomes of patients with rare events more easily, assess economic impact of various interventions, and gain insight into possible association between interventions and outcomes[9].

Administrative claims databases can prove very useful in measuring resource use and costs, provided some basic principles are met. A clear research question needs to be defined and addressed by an appropriate design from a well-defined perspective. Available statistical tools can be used to help control for some of the potential biases**.** Methods and results should be reported in a clear and transparent fashion, so that other researchers are able to understand and reproduce the analyses[9].

Beyond challenges posed by privacy issues, the validity of retrospective claims database analyses has been challenged on several fronts: data quality (missing data, coding errors-whether random or "intended"-and the lack of comprehensive data across health care settings); the lack of or very limited clinical information on inpatient stays, health outcomes, health status, and symptoms; limited validation; absence of a population denominator; and the lack of distinction between costs and charges. Of course, the large size of these databases may be able to overcome the issue of missing data if they are missing at random. If data quality can be ascertained and privacy issues addressed, then treatment selection bias in the sample is the most common and challenging methodological issue. Estimates of the effects and costs can be biased due to a correlation between unobserved factors associated with treatment selection and outcomes, such as baseline health status[9].

Health surveys. Health surveys are designed to collect descriptions of health status and well-being, health care utilization, treatment patterns, and health care expenditures from patients, providers, or individuals in the general population. Health surveys typically collect information on representative individuals in the target population, whether patients, physicians or general population, and are methodologically rigorous, for example, relying on complex sample survey designs. With these designs, surveys can provide information about all members of the target population, not just those who are participating in a given RCT, or members of a particular health plan. As a result, health survey data can make unique contributions about generalizability of treatments and their impacts and about use of and expenditures for health services[9].

Electronic health records (EHRs) and medical chart review. Finally, it was noted electronic health records (and other technologies capturing real-time clinical treatment and outcomes) are important sources for RWD for a wide range of clinical settings throughout the world. The expansion of electronic data capture is essentially lowering the cost of the medical chart reviews that have been widely used in the past to produce specific information on the RW use of specific tests or drugs for particular conditions. EHRs—such as the UK General Practice Research Database-contain more detailed, longitudinal information including disease-specific symptoms at the personal level and should greatly expand the use of this type of information. However, transforming the information for research purposes requires high-end statistical analysis tools and remains a challenge[9].

These 6 data sources are echoed in publications from Quintiles and IMS Consulting. Very similar lists are suggested by National Pharmaceutical Council (NPC) and National

Information Center on Health Services Research and Health Care Technology (NICHSR) in the USA (Figure 2)[18].

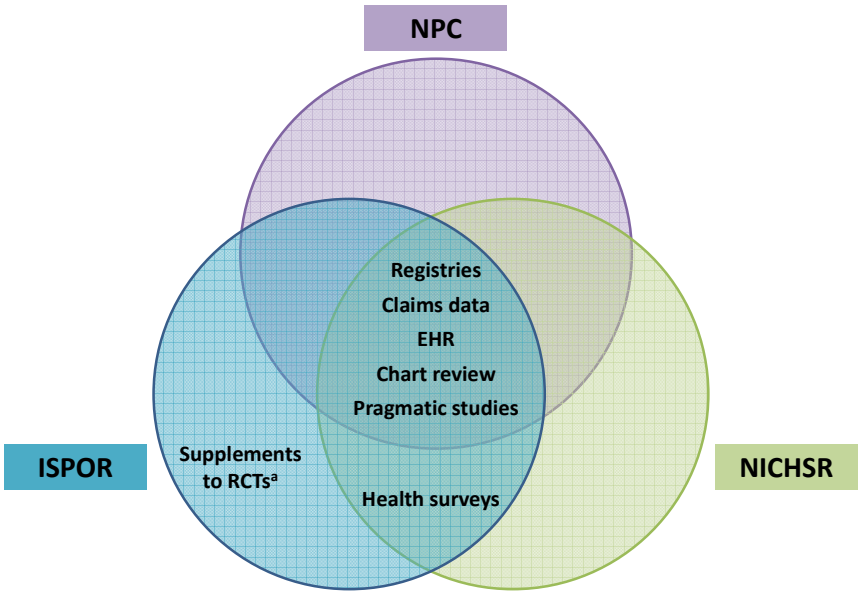

Figure 2. Venn diagram to illustrate the areas of agreement in the definition of real world studies across international organisations (ISPOR, NPC and NICHSR)[18].
[a)]Collection of PRO; resource use and cost data EHR

Very few bodies appear to employ a narrower definition of RWS than that from the ISPOR task force. The European Commission include the concept of no randomisation in their definition; although this is in reference to observational research, as opposed to RWD specifically (these terms are often used interchangeably). By deduction, this would exclude pragmatic studies from their definition. ISPOR's definition of observational research is more vague on this point, stating that care is not *typically* a result of randomisation (or other forms of patient assignment), presumably to allow the inclusion of pragmatic studies. The classification of pragmatic studies as a method of RWD collection could potentially be a point of contention. The ISPOR task force acknowledge that whether they are strictly RWS is open to debate. On the other hand, many international bodies group include them in their definition of RWS[18]:

- NPC, USA
- NICHSR[1], USA
  - The NICHSR appear to differentiate between large simple trials and pragmatic clinical trials, unlike other organisations which used the terms interchangeably. But they explain that some large simple trials are also pragmatic trials.

[1] The NICHSR are part of the US National Institutes of Health (NIH) and were set up at the National Library of Medicine to improve ". the collection, storage, analysis, retrieval, and dissemination of information on health services research, clinical practice guidelines, and on health care technology, including the assessment of such technology."

- Large simple trials: retain the methodological strengths of prospective, randomised design, but use large numbers of patients, more flexible patient entry criteria and multiple study sites to generate effectiveness data and improve external validity. Fewer types of data may be collected for each patient, easing participation by patients and clinicians.
- Pragmatic trials are a related group of trial designs whose main attributes include: comparison of clinically relevant alternative interventions, a diverse population of study participants, participants recruited from heterogeneous practice settings, and data collection on a broad range of health outcomes.

- Patient-centred outcomes research institute (PCORI), USA
- PCORI implies that pragmatic studies are categorised as RWS through its announcement of a new research funding initiative for pragmatic trials ("More Support for Bigger, Longer Real-World Trials").

- Medicines and Healthcare products Regulatory Agency (MHRA), UK
- It could be inferred from the MHRA business strategies that pragmatic studies (utilising (Electronic health records - EHR) are considered to produce RWD.

- Farr Institute, UK
- It could be inferred from the programme for their industry forum meeting that pragmatic trials are included in their consideration of RWD collection.

To revisit the concept of observational research - it seems the main defining feature of observational research, common across publications, is that care is not dictated or mandated. That is, the investigator does not interfere with choice of the prescribed health intervention such that interventions are prescribed in the usual manner in accordance with the terms of the marketing authorisation. But it is not that simple, as there are inconsistencies internally regarding the definition of an intervention. Depending on local regulations, for example, blood tests and patient questionnaires may be considered interventional in some countries (particularly in Europe) but not in others[18].

4. THE ADVANTAGES OF REAL-WORLD DATA VS. RANDOMISED CLINICAL TRIALS DATA

RCTs are well recognized as the "gold standard" for evaluating treatment outcomes. They are designed to test a therapeutic hypothesis under optimal conditions in the absence of confounding factors: highly selected patients, optimal management conditions, and ideal settings; nevertheless their comprehensive exclusion criteria may produce studies in a narrow segment of the population only, leading to results with limited external validity. Groups which are often under-represented in RCTs include women, children, the very elderly ethnic minorities and those with multiple co-morbidities[16,19]. Thus, they provide information on *efficacy* under conditions very different from real life[19]. In other words, RCT findings are limited in the extent to which they can be extrapoled to reflect the treatment effects achievable at the population level (Figure 3). Outside the strictly controlled environment of the classical RCT, many factors can interfere with a therapeutic option's potential efficacy[11].

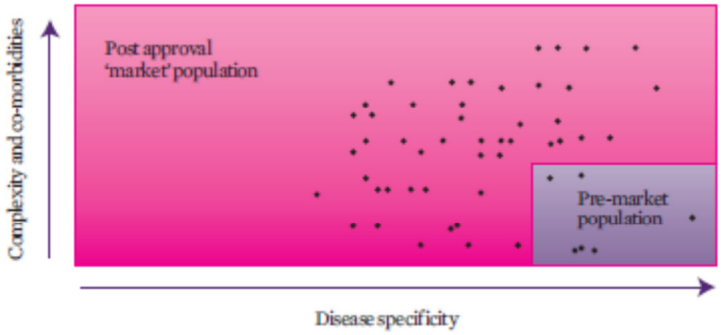

Figure 3. Scope of RWS vs. RCTs in the population[16].

In contrast, RWS assess *effectiveness* in large unselected populations, which include patients with comorbidities[20]. RWS have been described in a variety of ways. The European Working Group on Relative Effectiveness has defined RWS as a way to analyse medical data collected under real life conditions. RWS consider a more contextualised endpoint, this takes account of the constraints on outcomes imposed in normal clinical care by such factors as unavailability of diagnostic or monitoring tests, poor adherence to treatment and non-standard dosing or administration. In essence, they are conducted in everyday settings, and for this reason, they provide insights into the real life effectiveness of a medical condition/intervention[16,19](Table 2).

Table 2. Main differences between randomised clinical trials and observational research[21].

Randomised clinical trial	Observational studies and registries
Conducted to demonstrate efficacy and main safety profile of drug.	Conducted to demonstrate effectiveness of drug under conditions of routine clinical care and confirm safety profile. Evaluate especially rare events and potential safety signals.
Randomisation takes care of confounding factors (creates structural homogeneity).	Design and statistical analysis strategy should minimize influence of confounding.
Relatively short-term duration.	Allow long-term follow-up and investigation of chronic use. Investigate long-term safety.
Relatively small numbers with limited ability to detect safety issues with low incidence.	Allows large sample size.
Very restricted (homogeneous) patient population (low external validity).	Conducted in real-world patients with broad age range and comorbidity (good external validity).
Relatively low risk population for concurrent events.	Relatively high risk population for concurrent events.
Very good compliance as strict controlling and monitoring.	Unclear compliance – often only information about prescription – not actual adherence.
Usually one comparator (standard of care) or placebo.	Allows comparison of different treatments and different treatment practices across populations.
Strictly protocol driven.	Less influence on data quality and time points of data collection – driven by usual care practice. Allows investigation of unintended exposure (e.g. during pregnancy).
Often 100% source monitoring – excellent quality.	Restricted means of source monitoring.

At variance with RCTs, pragmatic trials are conducted in a routine care setting with heterogeneous patient populations and prolonged durations, which increase the likelihood of obtaining conclusions relevant to clinical practice[19]. Purely observational studies, which involve no artefact of intervention, may best reflect this real-world experience but are, themselves, burdened with methodological peculiarities[21].

The limitations of RWS are often intrinsically associated with their characteristic design[19]. Whether or not a study realistically represents real-life conditions can be unclear. A trial might involve intensive patient follow-up, yet include a broad population fairly representative of the true treated population. Conversely, an observational study can focus on outcomes in a highly-selected patient population, yet involve no clinical intervention beyond usual care. The challenge is to recognise and describe which elements of a study represent real-life, and to find a unified way of presenting them. Roche *et al.,* (2013) proposed a framework to classify different studies by design to assist those involved in the use conduct, review, and quality appraisal of therapeutic research, including patients, clinicians, policy-makers, and guideline developers (Figure 4)[22].

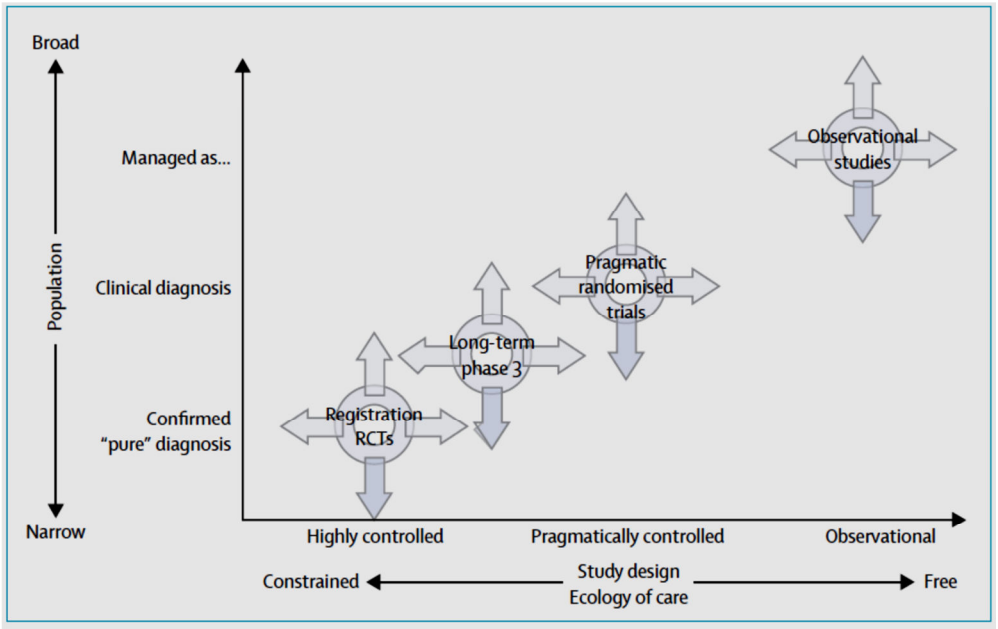

Figure 4. A conceptual framework for therapeutic research[22].
Studies are described in terms of their design or ecology of care (x-axis) and their population characteristics (y-axis), with each axis representing a continuum.

The framework classifies studies within a two dimensional real-life space bound by the study population (y-axis) and ecology of care (x-axis). The ecology of care axis categorises study interventions along a continuous scale (from highly-controlled efficacy RCT management and follow-up, at one end, to usual care at the other). The label between the two-pragmatically controlled—refers to controlled trials that are designed to resemble usual care in terms of intensity of follow-up and in terms of reference, studied, and concomitant treatments. The population axis categorises study populations along a continuum from those with a confirmed, pure diagnosis (denoting a highly-selected population with no interfering comorbidities, modifying treatments or risk factors) through to a so-called managed-as population (ie, managed as having a condition with or without a confirmed diagnosis). Neither of these characteristics on its own is sufficient to describe the validity or utility of clinical study results to real life[22].

Figure 4 illustrates typical positions of the most common study designs, but studies can be located anywhere within the framework depending on the specifics of their design. The origin of the two axes corresponds to trials with the highest internal and lowest external validity. The further a trial is positioned from the origin, the greater are its real-life attributes, conditioning its generalizability[22].

Comprehensive assessment of therapeutic strategies requires evaluation of both their efficacy under optimum conditions (high internal validity) and effectiveness in real-life populations and situations (high external validity). To ascertain the relevance of study findings to target populations and clinical decision making, studies must first be well

described in terms of patient selection and ecology of care. Only then can appropriate quality assessments be selected and undertaken[22].

5. DECISIONS IMPACTED BY REAL-WORLD DATA

RWD currently plays a prominent role in several contexts of the product lifecycle. It features during drug development (e.g. to determine natural history, define subpopulations with better benefit-risk profiles, inform the design of pivotal trials); within drug regulation activities (e.g. fulfilment of post-marketing commitments, conditional marketing authorisations and adaptive pathways, examining drug utilization and adherence to approved indications); and during reimbursement discussions (e.g. as inputs for resource use and effectiveness data for pharmacoeconomic modelling, relative effectiveness assessment, and marketing access agreements)[1,23] (Figure 5) (Table 3). Moreover, the assessment of the value of medicines and treatments in real-world settings may be made less resource intensive with RWD-based methodologies[8].

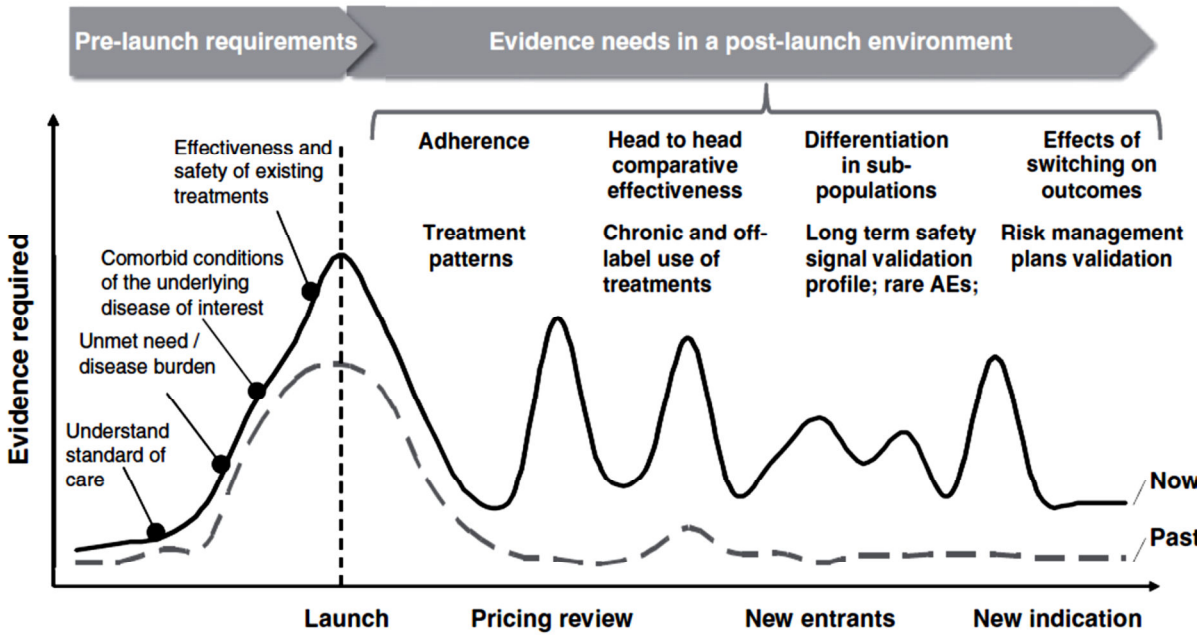

Figure 5. Examples of pre-launch and post-launch evidence requirements of therapies in a real-world setting[21].

Table 3. Variable activities supported by RWD across the product lifecycle[23].

Preclinical	Phase I-II	Phase III	Peri-Launch	Phase IV
Marketing Sizing	Market Landscape	Competitor Reconnaissance	Registries	Safety Surveillance
Unmet Need	Economic Burden	Patient Burden	Target Product Profile	Continuous Monitoring
Patient Profiling	Disease History	Treatment Patterns	Labelled Claims	Tailored Therapeutics
Early Modelling	Model Refinements	Endpoint Assessment	Global Value Dossiers	Health Technology Assessments
	Endpoint Development	Piggyback Evaluations	Pricing & Reimbursement	New Indications
	Instrument Validation			Comparative Effectiveness
				Risk Sharing Arrangements

In the view of many analysts and researchers, RWD has significant potential to improve the ways drugs are discovered and developed (Figure 6)[8]. In Portugal, there is no structured RWD collection still, but in framework of Decree-Law nr. 97/2015 of 1st June and implementation of national HTA agency, are being discussed the utility of registries and the use of RWD to access the outcomes of interventions[24].

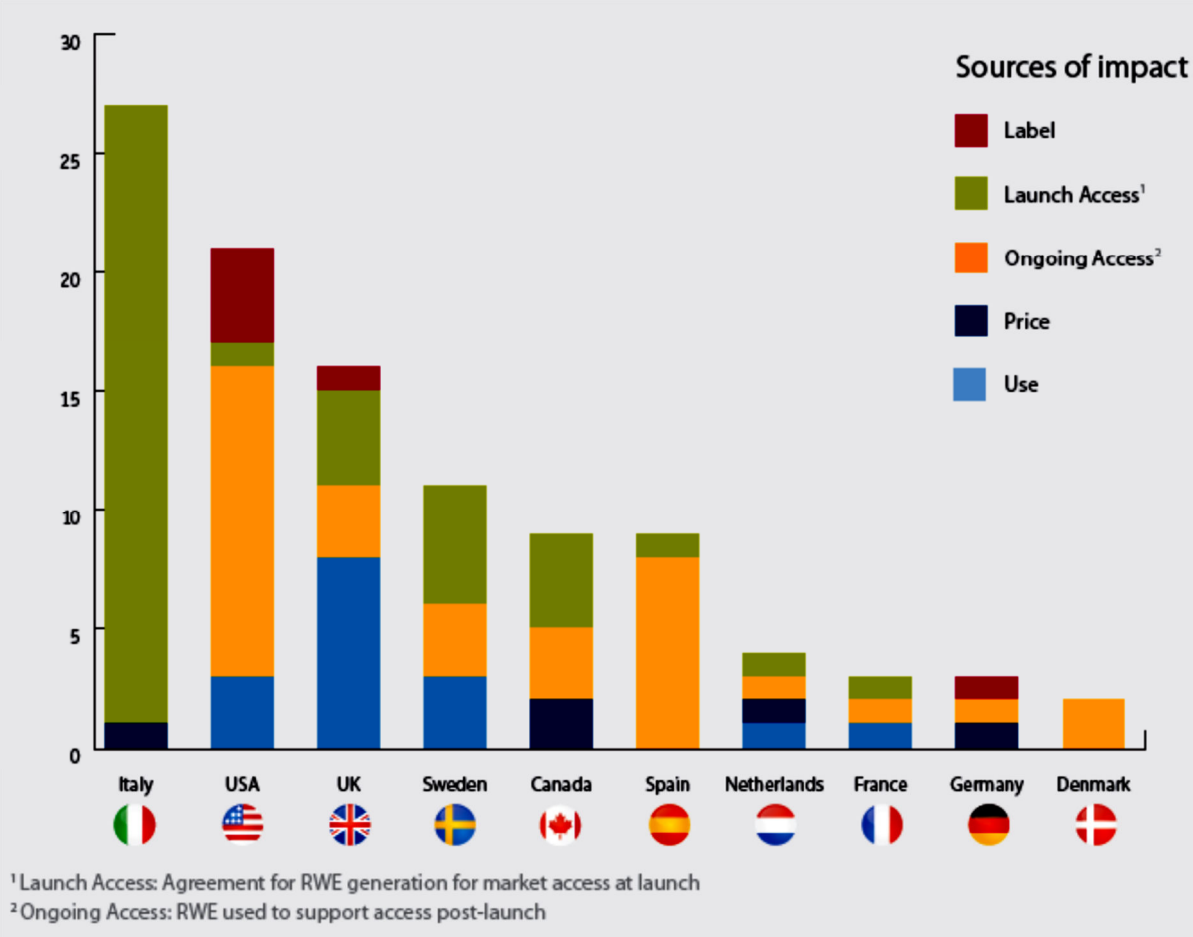

Figure 6. Examples of RWE applications in some countries[25].

The main driver behind the development of an EU-level approach to RWD appears to be the European Commission's push for the development of eHealth infrastructures and use of EHR. The European Commission has been particularly active in the development of methodological standards to facilitate the collection and use of patient data. The European Health Strategy for the 2008–2013 programming period has put emphasis on the development of eHealth infrastructures and on the funding of research projects aiming to promote the adoption of international terminology and coding standards to enable data sharing and international comparisons[8].

- **eHealth infrastructures:**

The term "eHealth" describes the "application of Internet and other related technologies in the healthcare industry to improve the access, efficiency, effectiveness, and quality of clinical and business processes utilized by healthcare organizations, practitioners, patients, and consumers in an effort to improve the health status of patients". eHealth comprises institutional structures, data architecture systems, competence centres and

legal frameworks. Competencies of eHealth authorities cover a range of eHealth instruments, including ePrescriptions, telehealth and patients EHRs system[8].

- **Electronic health records:**

An EHR is the longitudinal electronic record of an individual patient that contains or virtually links records together from multiple Electronic Medical Records (EMRs) which can then be shared across health care settings (interoperable). It aims to contain a history of contact with the health care system for individual patients from multiple organisations that deliver care[8].

Another important driver is the increased support for the development of EU-wide datasets and enhanced interoperability. Enhancing interoperability between European datasets constitutes part of the Strategy objectives. Cross-country research projects are actively supported by different EU programmes to link existing registries, develop new ones and pool resources, paving the way to more standardised strategies for the collection and use of RWD. These recent developments are creating new opportunities for research through improved data collection and enhanced interoperability; however they remain quite fragmented, potentially hindering the pace of scientific advances. Reflexions on data harmonisation, data linkage and interoperability are therefore taking place at the European level, aiming to give guidance on data harmonisation[8].

5.1 Real-World Data to building evidence for drug development and post-market studies

5.1.1 Drug development

RCTs have traditionally been the preferred setting for product development in the healthcare industry. As was discussed above, RWD can also be used to assess the efficacy of different medical treatments and inform drug development strategies. For instance, a research team including researchers directly affiliated with GSK and Novartis studied the relative efficacy of drugs used to treat Chronic Obstructive Pulmonary Disease (COPD) and the relationship between these data and the results of clinical trials, using data from the Optimum Patient Care Research Database. Another study sponsored by Novartis and called the European Cubicin Outcomes Registry and Experience project (EU-CORESM), is gaining access to a registry that gathers data from 118 institutions. The study considers the characteristics of the patient population and the relative efficacy of treatment for skin and soft tissue infections. The findings will also be used by the company for in-house research, going beyond the scope of the EU-CORESM study[8,26,27].

Case Study

- The Salford Lung Study

The Salford Lung Study is the world's first phase III pragmatic RCT in asthma and COPD, which aims to randomise over 7000 patients.

Patients are randomised to receive either a continuation of their usual treatment or a novel once-daily DPI containing a combination of a new inhaled steroid and a new LABA (fluticasone furoate/vilanterol (FF/VI; GlaxoSmithKline, Stockley Park, UK)) for 12 months.

After randomisation, patients receive "usual" care for 12 months by their own general practitioner (GP), practice nurse and community pharmacist. Effectiveness and safety data are monitored and collected in near-real time using an electronic health record, minimising the number of patient visits required.

GPs prescribe as usual, patients order and collect repeat prescriptions in their usual way, and collect their study medication from their usual community pharmacist, which allows assessment of real-world medication adherence in terms of number of prescriptions delivered to the pharmacy and the number dispensed to the patient.

There are yet no study results but the researchers believe that the creation of an effectiveness study environment in Salford serves as a benchmark for other initiatives, including pharmacovigilance and phase IV studies, to collate data from primary and secondary care. They anticipate that initiatives such as this will reshape the future of clinical trials and meet the demand for value-based medical evidence[20].

5.1.2 LONG-TERM OUTCOMES OF AN INTERVENTION

Case study

An example of medium-scale project using a disease-specific database can be found in a study using data from 870 patients to assess long-term outcomes of transcatether aortic valve interventions (TAVIs) based on the UK TAVI registry, which has been set up to capture the outcomes of all such procedures executed in the UK. The study, one of the first of its kind to concentrate on a mid-to long-term time horizon, tracked survival and mortality rates for the interventions at 30 days, 1 year and 2 years after the event.

It found that while a substantive proportion of these high-risk patients were deceased within the first year, overall the survival rates were encouraging[8,28].

5.1.3 PHARMACOVIGILANCE

The European Union (EU) put forth a new legislation on pharmacovigilance in July 2012. The legislation has the overall objective to improve the safety of use of medicines in Europe and through a more proactive approach to risk minimization planning and post-marketing follow-up[28,29]. **Table** 4 shows examples of risk management plans as suggested by European Medicines Agency (EMA) to ascertain and evaluate benefit and risk of specific treatment, treatment specific characteristics and the information needed to address a specific study question[21].

Table 4. Risk management plans to ascertain and evaluate benefit and risk[21].

Type*	Main characteristics	Potential study aims	Information needed for analysis
I.Passive surveillance	Spontaneous reports received throughout the world (WHO, FDA AERS, etc.), routine PV	Signal generation	Number of reported adverse events (AEs)
II. Stimulated reporting	("Dear Doctor letter. . .")	Evaluation of safety signal	Number of reported AEs
III. Active surveillance	– Sentinel sites – Drug event monitoring – **Registry**	Evaluation of safety signal Safety and effectiveness study**	Safety outcome, treatment, appropriate confounders Disease outcome, treatment, appropriate confounders
IV. Comparative observational studies	– **Cross-sectional survey** – **Case-control study** – **Cohort study**	Evaluation of safety signal Effectiveness study on population level (RWE)**	Safety outcome, treatment, appropriate confounders Disease-outcome, treatment, appropriate confounders
V. Target clinical investigation	– Large simple trial	Safety and effectiveness study**	Disease outcome, safety outcomes, treatment, appropriate confounders
VI. Descriptive studies	– **Cross-sectional survey** – **Case-control study** – **Cohort study**	– Natural history of disease – Safety study – Drug utilization study	Disease outcome, appropriate confounders Treatment, severity of disease, age and gender, etc.

*Source: Guideline on Risk Management Systems for Medicinal Products for Human Use. EMEA, 2005

**Depending on design issues and information collected.

Bold indicates potential sources of RWE.

The new legislation puts a wider focus on continuous follow-up of both safety aspects as well as effectiveness from use in clinical practice spurring comparative effectiveness research. It involves stronger requirements on measuring the effectiveness of risk-minimization plans for the most important risks associated with new medicines. In parallel, the benefit/risk assessment (B/R) section of periodic safety update reports (PSUR) and risk management plans (RMPs) was also re-examined, which allowing more in-depth assessment of medicinal product B/R[28,29].

Each company has a system in place to collect and evaluate spontaneous reports of suspected adverse drug reactions (ADR). However, the spontaneous reporting system allows only the generation of safety signals and indicates where possible safety issues might be without quantification of the risk. Other data sources are needed to evaluate and validate such a signal further. The ADR system works well for rare and severe adverse events, but less for common morbidities. ADRs are usually underreported by primary care physicians and their ascertainment is also not done according to standardized criteria and therefore relatively subjective and imprecise. In addition, the estimation of reporting rate is usually not possible because the denominator (population exposed) is unknown und therefore relative safety cannot be assessed with any validity[21].

The new legislation had already spurred a new range of research, most specifically with respect to the obligatory post-authorisation follow-up studies (e.g. Post-Authorisation Safety Studies [PASS]). PASSs can either be clinical trials or non-interventional studies; they are any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk-management measures. PASS studies have certainly been carried out before, but with the mandatory assessment post marketing has created a wealth of new research activity in the area and search for credible data sources to respond to the new requirements[29]. These developments in tandem result in a clear shift towards continuous assessment of benefit as well as risk after a product is on the market in Europe. Sources of good quality RWD are essential for companies to meet regulatory authority expectations[28].

Case Studies

Several of the cases examined are concerned with post-market drug risk assessment. Such cases have used RWD to gain an in-depth understanding of specific issues, including the long-term effects of different treatment options on a determined patient group, such as those registered in a disease-specific registry[8].

It was also identified occasions in which studies have drawn on large national datasets to assess the impact of drugs or medical treatments. These included a Danish study that evaluated the net clinical benefit of new oral anticoagulants versus no treatment in a "real-world" atrial fibrillation (AF) population. The study used a long-term database covering all Danish patients discharged with AF over ten years (between 1997 and 2008), looking at patients' clinical histories, including pharmacotherapy, and premorbid risk stratification scores for stroke/thromboembolism. The analysis was further facilitated by linking the existing dataset to the unique personal identifier and Danish biobanks in order to assess the effects of three drugs compared to usual treatment and inform healthcare decision making. Studies at the national level can, then, draw on databases linked across multiple identifiers and databases (depending on the maturity of the e-infrastructure of the individual countries)[8,30].

There are also examples of cross-border initiatives offering added dimensions by including a cross-national set of patients. The studies building on the EU-ADR database for example used eight databases in four European Countries (Denmark, Italy, Netherlands and the UK) where both clinical information and drug prescriptions are recorded for large-scale drug safety monitoring. The database contains information about 30 million patients. The studies looked at drug safety across a range of diseases including acute myocardial infarction; acute renal failure; anaphylactic shock; bullous eruption; and rhabdomyolysis[7,31].

A further example is supplied by the VAESCO (Vaccine Adverse Event Surveillance and Communication) project which has supported studies in the areas of vaccine safety surveillance. This study involved seven databases from European countries (Italy, Spain, Finland, UK, Sweden, Norway, Denmark and the Netherlands), covering at least 26.67 million patients. Its aim was the development of vaccine safety and best practices, evaluation of strategies and new methods and to facilitate data collection through common aims and standards, and to provide information on vaccination safety[8].

5.2 Real-World Data in healthcare service delivery

Healthcare delivery decisions at the individual and system levels increasingly incorporate evidence from data analytics. RWD can be used to support personalised decisions on treatment options. These options are then tailored to the patient's specific genotypic

characteristics and outcome probabilities. In other examples, data are incorporated into studies investigating questions related to health services coverage, quality or costs with a view to informing national or regional healthcare delivery strategies[8].

5.2.1 Real-World Data for assisting doctors and patients in choosing between treatment options

In some cases RWD and big data analytics are synthesised for initiatives involving personalised medicine and which require treatment decisions to be based on the individual characteristics of the patient. These cases use large datasets on treatment outcomes[8].

Case studies

The EuResist project is an integrated European system for computer-based clinical management of antiretroviral drug resistance. Algorithms processing genotypic information across a multinational database are used with other genetic and response indicators in order to determine the best course of treatment for individuals with HIV infection. The initiative aims to develop a system capable of predicting how patients are likely to respond to a specific method of treatment and consequently recommend a certain treatment out of a portfolio of options. In pursuit of this aim, the project builds on databases of genotypic information, which are combined with data on drug resistance[8,32].

5.2.2 Analysing Real-World Data to optimise the efficiency of healthcare services delivery

RWD analytics are particularly useful in supporting innovative ways to improve and optimise healthcare delivery.

Case studies

One potential area for innovation is that of expanding the potential range of healthcare services by aggregating data for decision-support and supporting telemedicine, as illustrated by the strategy for home care implemented in Southern Denmark. In this case, the new system was set up with the aim of improving outcomes for chronically ill patients. The strategy includes linking data across healthcare databases to create a holistic view of each patient; but also creates a platform that can integrate data from home monitoring and telemedicine applications and offer access to different healthcare professionals that can use the data to support their decisions. Furthermore, the automation of processes supports trends toward process optimisation and an efficient

use of time, while the business intelligence and analysis potential of the linked database may offer commercial value to the region[8].

In other cases RWD analytics has been leveraged to optimise current processes in healthcare delivery and limit associated costs, for instance by reducing the number of UK patients that have to be readmitted to hospital with Chronic Obstructive Pulmonary Disease (COPD) following their discharge. In this case, the computing assets of the National Health Service (NHS) enabled the analysis of multiple types of standardised patient and treatment data. The analysis supported the optimisation of the treatment process for patient outcomes and cost implications for hospitals[8].

Studies assessing healthcare delivery also include research investigating the evidence on the uptake of existing services and their delivery, for instance the effect of uptake of cardiac rehabilitation (CR) treatments on survival. Working with the database hold by private insurance Achmea, Van Engen *et al.* (2013) looked at this relationship in the Netherlands, and were able to demonstrate that despite the efficacy of the CR treatment, most Dutch patients did not receive this type of care[8,33].

Furthermore, the data analytics allowed the researchers to make recommendations about populations that should be specifically targeted by CR treatment initiatives, such as women, patients with long travelling distances to the nearest CR provider and patients with comorbidities[8].

RWD has also supported studies focusing on evaluating the quality of care. Franzke *et al.* (2009) collected data on patients with acne. This research allowed the capture of raw data and aspects of subjective patient experience and socioeconomic factors reported by patients with acne vulgaris. The data were then used to analyse the patients' trade-offs in choosing between doctor prescribed medication and the acquisition of medical products through self-medication[8,34].

An example of a Portuguese registry to optimise the efficiency of healthcare services delivery, is the Reuma.pt (Rheumatic Diseases Portuguese Register), which includes patients with rheumatoid arthritis(RA), ankylosing spondylitis(AS), psoriatic arthritis(PsA), juvenile idiopathic arthritis(JIA), systemic lupus erythematosus and several other rheumatic diseases. The ultimate goal is to register all rheumatic patients treated with biological agents in mainland Portugal, Madeira and the Azores, ensuring effective monitoring of treatment indication, efficacy and safety. The Reuma.pt is also registering comparative cohorts of patients with RA, AS, PsA and JIA treated with classical immunomodulatory agents[35].

5.2.3 Assessing the cost-effectiveness of medical treatment using Real-World Data

RWD is also being used to inform decisions related to the burden of medical treatment costs. For example, the databases maintained in the Swedish national and Italian regional healthcare systems have been used to assess the burden of costs related to cardiac diseases or cancer (e.g. Lothgren *et al.*, 2013; Roggeri *et al.*, 2013)[8,36,37].

Case Studies

Lothgren *et al.* (2013) have simulated cost implications per patient and examined the budget implications of different drugs used by patients with bone tumours. While the researchers could not directly access the relevant data, they triangulated available sources to estimate cost burden per patient and at the system level in Austria, Sweden and Switzerland. They thereby determined the drug with the lowest administration and collateral costs[30].

Roggeri *et al.* (2013) used a set of Italian regional databases (administrative databases of seven local healthcare units located in four different regions: Veneto, Toscana, Abruzzo and Puglia), linked with socio-economic datasets to assess the direct healthcare costs and resource needs associated with acute coronary events. Included in the study was information on demographic characteristics, prescriptions of drugs reimbursed by the national health system, hospital discharge records, outpatient visits and diagnostic-therapeutic procedures[31].

6. USE OF REAL-WORLD DATA AND REAL-WORLD EVIDENCE IN EUROPE: STATE OF THE ART

The European economy is still undergoing its worst economic health crisis in years and while governments are undertaking measures to foster growth after the financial crisis, regulators and payers are raising their requirements in order to ensure safe, effective, cost-effective and affordable medicines to its population. The focus during these past years has been on affordability and Europe has been forced to make tough decisions in its health care sector. A number of reforms have been initiated and implemented to try to improve on public efficiency such as health care delivery. These reforms, combined with a greater cost-consciousness amongst payers, have driven an increased requirement of RWE to better understand the consequences of the introduction of new medicines into the European markets[29].

RWD collection and use for reimbursement activities, such as relative effectiveness assessment, risk-sharing agreements and pharmacoeconomic analysis was the most noted actual context[1,34,38]. As payers demand for knowledge on drug utilization studies, real-life safety and clinical effectiveness to inform payment decision increases, so does the need for RWD. This evidence, in turn, helps payers to "better understand the outcomes of various treatments and only pay for those which are most beneficial to society"[1,39].

The second most recurring actual context for RWD collection and use was for regulatory activities. The theme most frequently mentioned within this context relates to the role of RWD in fulfilling post-marketing commitments. For example, RWS can be designed to collect information on long-term safety and effectiveness as part of phase IV, post-marketing safety and pharmacovigilance commitments[1,29].

Collection and use of RWD during drug development was the third most-mentioned actual context. RWD is used, amongst other things, to help drug developers study the natural history of disease, define patient populations for clinical trials, standardize outcome measurements, define sub-populations for treatment, understand treatment patterns both pre- and at product launch, and, as previously-stated, long-term safety and effectiveness outcomes[1].

Another context that received equal mention was the use of RWD in drug utilization studies to investigate, for example, drug dosing in clinical practice, patient compliance, standard of care and treatment flows in different clinical contexts[1,29].

6.1 REAL-WORLD DATA IN HEALTH CARE DECISIONS

Decisions about the deployment of health resources are taken by 2 subjects: by physicians for the individual patient and by public health policy makers on a population level (governments, national health insurance providers and payers)[40,41]. Healthcare decisions preferably should be evidence-based and/or evaluated but reality shows that many decisions need to be taken on the basis of imperfect evidence and with uncertainty about the outcome of decisions. Evidence about the real-world can best be obtained from the real-world practice[40]. The use of RWD to monitor safety, measure outcomes and assess comparative effectiveness is increasing by healthcare provider, health plan and regulatory agency decision makers across the healthcare continuum[32].

In general terms, the policies on RWD collection and use differ per stakeholder group, in part due to the different goals/mandate such stakeholders groups have[1]. Payers must balance the need to provide improved health outcomes and access to new technologies with budgetary considerations. Clinical trials developed for regulatory purposes may be insufficient to resolve payer uncertainty. To physicians/researchers: techniques and tools to analyse data for RWE have become increasingly widespread and accessible to physicians. Physicians are now able to answer an increasing number of important health services and policy questions without the considerable expense, length of time, and complication of conducting high-cost experimental studies. Industry views RWD collection as an additional opportunity to demonstrate the value of medicines, for both the patient and the health system. It may also provide new opportunities for industry to work with payers to advance novel approaches to pricing and reimbursement[15].

Payers and HTA bodies believe that traditional approach of the drug development plan is deficient in that it is no longer sufficient to know if a new drug or technology is efficacious; the nature of the global healthcare marketplace means that it is essential to know how it performs in networks, communities, countries and populations as well as when it should be used and why it may be preferred to other treatments[33].

Traditionally, RWD has been collected prospectively in Europe by recruiting patients and/or health care providers to respond to specific sets of questions. In an era where there is the interest to interfere as little as possible when collecting health information from real-world health care practice, other ways of generating the evidence are being further. With an increased demand for RWD by multiple stakeholders, and a demand to generate critical evidence within a shorter time-frame and at a more cost-effective manner, retrospective data collection has become a more attractive form of generating RWE. Europe as a region has substantial potential to become an important area for this type of research activities with a long history of collecting patient-level data[29].

For more sophisticated RWD, linked patient-level data representing entire populations and their complete care flow throughout the health care system is more and more critical. In the UK, the Ministry of Health, together with the EMA did an important effort to pave the way for one important data source widely used today. The Clinical Practice Research Datalink (CPRD) is a database developed through linkage of patient-level data from various parts of the NHS health care system into one entire database. CPRD has managed to set up a system providing access to its data to all stakeholders by licensing the data under certain premises. By allowing for this transparency, CPRD has also become scrutinized by many researchers and hence accepted by most parties[29].

A region where there are great opportunities for more advanced RWD generation is the Nordic region. All Nordic countries have national and population-based health registers in place since the 1950's to which there is mandatory reporting of patient-level information. Some key strengths with these data sources are that they represent the entire population of 25 million inhabitants in the region, different data sources can be linked at an individual patient-level through unique patient identifiers and that the data are very rich and longitudinal. Moreover, given the greater focus on patient outcomes and personalized medicine, the Nordic region has universally adopted EMR in its health care systems as a result of decades of providing a strong source for RWE[29].

Some European countries have various great regional data sources, others are developing systems that allow for continuous access and use of rich patient-level data, in some these cases regulators and HTA agencies already using RWD to decision-making[25,29]. To highlight markets' individual characteristics, imshealth® created an RWE assessment scale based on supply and demand. Data supply and demand frameworks were each scored out of five and application was scored out of ten to reflect the importance of observing RWE demand in practice. This reveals major differences in RWE impact, with countries scoring between 2 and 11 of a potential 20 (Figure 7). The maximum score of 11 reflects that no country has the ideal conditions for RWE use in a scalable manner and highlights RWE's infancy. Lower scores indicate that RWE is relatively less available or more costly to generate with less consistent or transparent use in decision making. But even in markets with lower scores, RWE is still relevant[25].

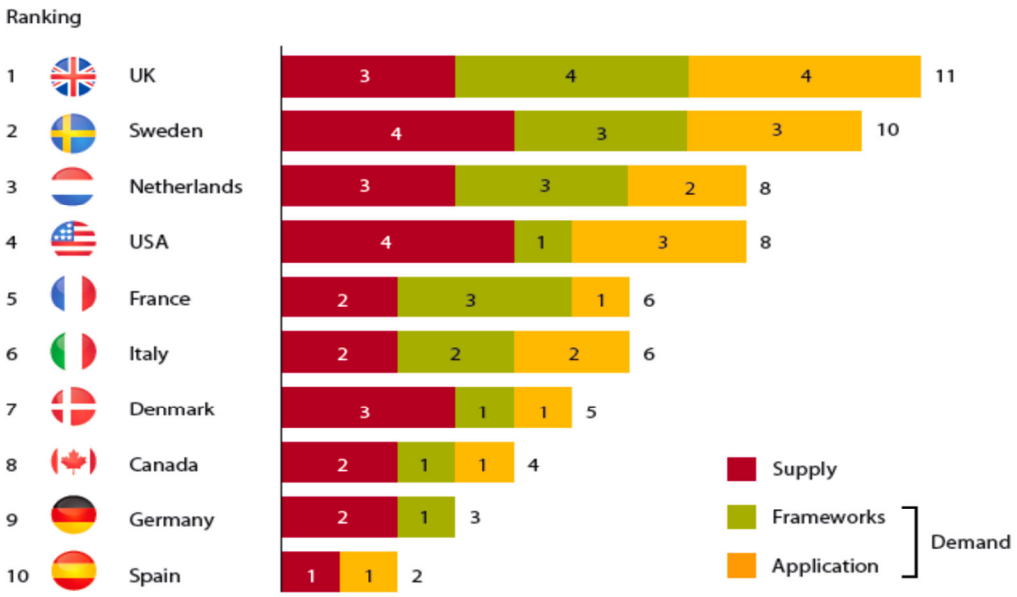

Figure 7. RWE market impact scores (out of 20)[25].

UK is closest to the ideal because RWE is used in systematic review for most evaluation processes (HTA, reimbursement, clinical guidelines). Stakeholders can disseminate RWE directly to prescribers, and RWE-enabled payment-for-performance contracts encourage appropriate prescribing. Even the UK can go further: for example, RWE-enabled prescribing indicators are still limited. Conversely, countries like Denmark and Spain lack clearly defined roles for RWE in decision frameworks[25].

In terms of application – where RWE has informed decisions – all countries are distant from the ideal. Consistent, transparent use of RWE in decision making is lacking across therapeutic areas and patient populations. Case studies from the UK suggest the most extensive application, given the number, variety, and breadth of resulting decisions relative to the entire health system. Conversely, in countries such as Germany, public case studies of RWE application are rare[25].

Combining the strengths in frameworks and application with strong patient-level databases, the UK becomes the highest scoring market. In the UK primary care datasets are long-standing and high quality, supporting over 1,000 peer-reviewed research papers. These are being transformed into a wider linked dataset, the CPRD under government leadership[25].

Spain ranked last based on lack of patient-level data and RWE use outside of a few specific regions. Spain has regional pockets of extensive electronic data capture but the lack of translation into research datasets limits its ability to generate RWE. National HTA approaches are under development but have yet to explicitly address RWE use in evaluation. Different case studies of RWE use could be identified at the regional level

particularly in relation to access, though the extent to which medicine use was really impacted was limited[25].

Data presented by Lilly (2014) showed that Portugal has in Europe tail of RWD availability (Figure 8); in contrast, France, Italy, Netherland, Belgium and Nordics have a good integrated RWD collection and stakeholders considered RWE an essential tool[35].

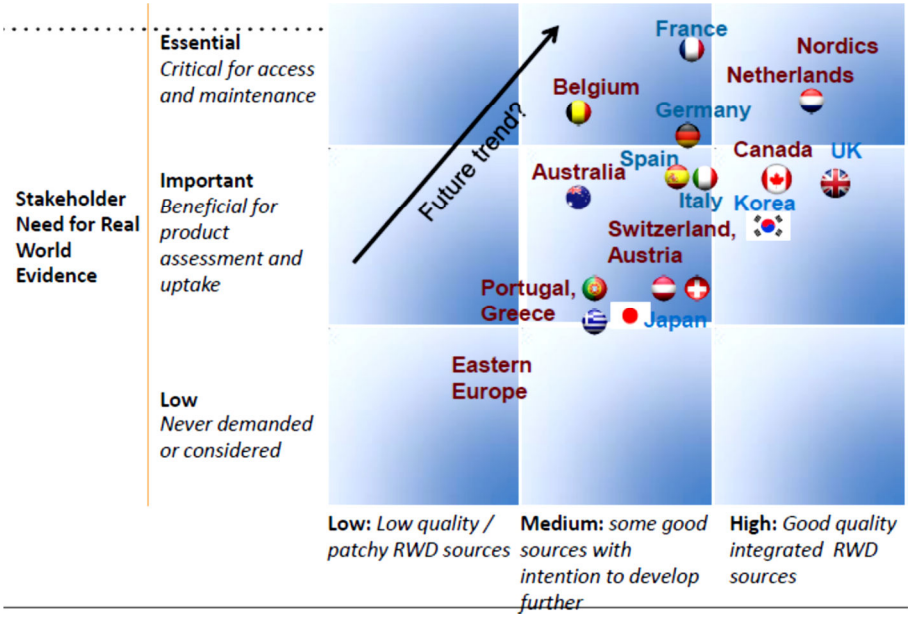

Figure 8. Availability of RWD[35] .

We are just in the beginning of a new era for Europe to thrive its opportunity to make use of data sources available across the region.

6.1.1 IMPLICATIONS IN ASSESSMENT OF THERAPEUTIC VALUE

The therapeutic value can be defined in terms of positive patient-relevant endpoints and relevant levels of effectiveness, efficacy and safety[17]. Knowledge of the therapeutic value brought a new drug is a core element supporting treatment decisions. By comparing a new drug with the best available treatment option, it can be deemed an added therapeutic value if it demonstrate a relevant level of therapeutic advantages[17,42].

Among different stakeholders, perceptions of the value of a medicine may differ in terms of evidentiary criteria needed for adoption. Patients are likely to value a medicine that prevent or slow the progression of disease or those that can demonstrably improve QoL by alleviating symptoms. For physicians, value could be perceived as “moving the needle” on some clinical surrogate endpoint with which they are familiar. For example, a specific change in mmHg systolic blood pressure or a particular change in haemoglobin A1C may

be sufficient for clinicians to feel a new treatment is worthwhile. But for payers, the definition of value is somewhat elusive and differs across/within countries[33].

According European Parliament's Committee on Environment, Public Health and Food Safety, the main tools used to estimate added therapeutic value (ATV) is **Relative Efficacy/Effectiveness Assessments** (REA)[17]. REA is the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions. The High Level Pharmaceutical Forum investigated the data availability to conduct relative effectiveness assessments. It was concluded that there is no clear consensus as to whether clinical trials yield efficacy or effectiveness information. All data on pharmaceuticals yield information that is somewhere on an efficacy/effectiveness spectrum, as illustrated in Figure 9 which is a simplified presentation of the spectrum. As a general rule, conventional clinical trials tend more to the efficacy side of the spectrum. The term effectiveness is used differently in EU Member States, which does not correspond with the High Level Pharmaceutical Forum definition. While some Member States use it to describe what is actually happening in real-life (which is always theoretical to a certain extent), others stated to use it exclusively to describe clinical trials that are as far as possible to the effectiveness side of the spectrum. According to these Member States, this gives the best estimate of what happens in real-life. There is no clear consensus on the interpretation among EU Member States[43].

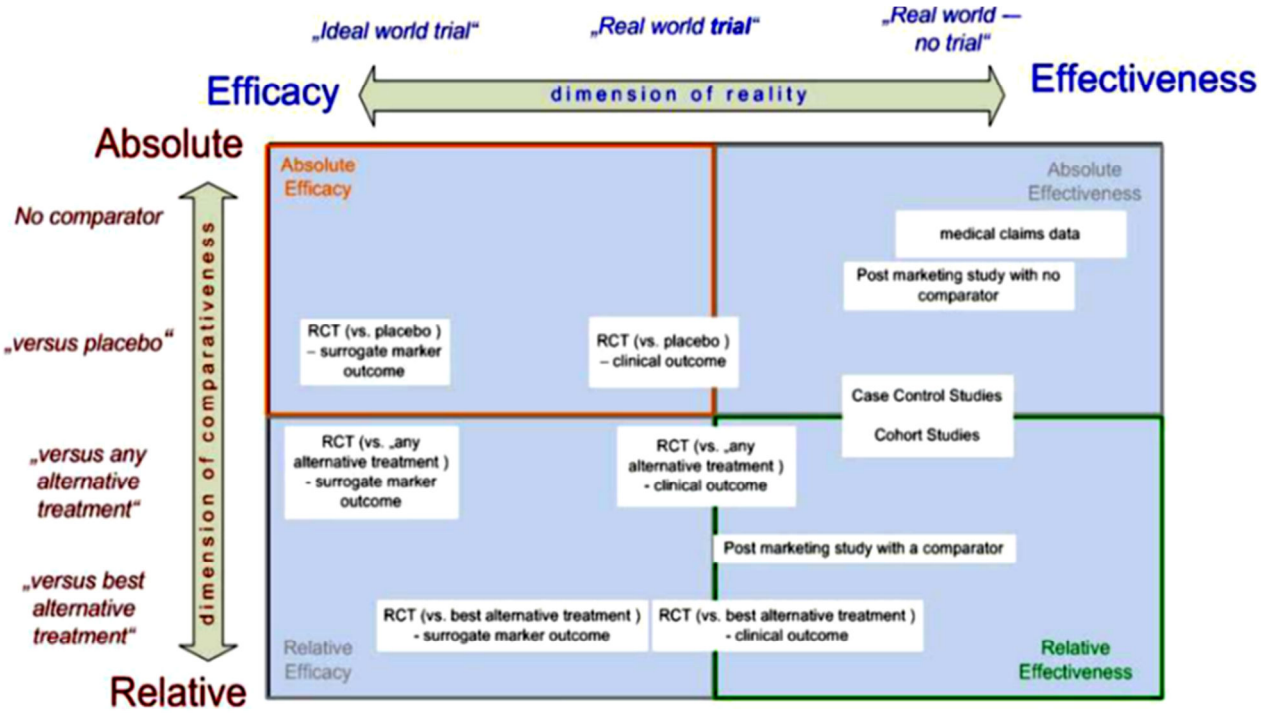

Figure 9. Efficacy/effectiveness spectrum[43].

The added therapeutic value of new medicinal products can be assessed at different stages during the manufacturing and distribution processes. In broad terms, there are two important moments when the clinical assessment can play a role: prior to the authorized entry of the medicine onto the market (**marketing authorisation phase**); and when the pricing of a new medicine and its reimbursement is determined (**pricing and reimbursement phase**)[17].

In practice however, the ATV assessments (through REA) are often conducted at the stage of pricing and reimbursement of the medicine, rather than prior to its authorised entry onto the market [17].

It acknowledged that differences between the objectives and priorities of different national health care systems may create differences in the way in which health-care interventions will be evaluated relative to one another and differences in relative effectiveness valued. In a survey of 27 member states in 2007, however, it was found that little distinction is currently made in member state assessments between efficacy and effectiveness. Member states mostly relied on relative efficacy data to inform their HTA and felt that there was inadequate effectiveness data available[38]. The ATV is not the only aspect considered by national authorities when assessing new medicines: its cost, budgetary impact and the quality of evidence used for the ATV assessment are also important considerations. A multi-disciplinary assessment that is often used and referred to is HTA, which encompasses a systematic evaluation of the wider aspects and issues related to the introduction of a new medicine or drug. HTA is conducted by interdisciplinary groups using analytical frameworks drawing on a variety of methods, with the main purpose of informing technology related policymaking in health care. The REA and ATV remain the central element of HTA, but cost-effectiveness in particular is seen as an important element to complement the REA[17].

HTA agencies generally refer to a comprehensive evidence base that combines data from several sources when assessing the clinical effectiveness of health interventions. Therefore, non-RCT evidence is also considered when performing health technology assessments[1]. Recently, the conducting of pragmatic RCTs within EHR databases providing an assessment of the comparative effectiveness in a randomised method. Patients are recruited at the point of care, randomised among routinely available interventions and then followed unobtrusively using the electronic health care database. The EHR database can be used to identify patients with criteria of inclusion. After eligibility review by the clinician and informed consent, patients are then randomised. Study participants are then followed for treatment and for major clinical outcomes using the EHR data. The randomisation ensures that baseline differences and confounding is reduced[44].

Moreover, in instances when there are uncertainties regarding the safety and effectiveness of new medications, additional RWD may be requested at the time of initial

reimbursement which would need to be collected within an agreed-upon time period. The collected RWD would then be used for reassessment of clinical effectiveness at the end of this period. These arrangements are often classified as Market Access Agreements (MAA's), Coverage with Evidence Development (CED) schemes, or Payment for Performance (P4P) schemes[1].

Several HTA agencies adhere to a hierarchy of evidence that places non-RCT data, such as observational studies data, at a lower level than RCT data. As a result, RWD is regarded as inherently being of lower quality thus conclusions made based on RWE are regarded as more circumspect. Clinical effectiveness is thus rarely solely determined on the basis of RWE. Causality is also not determined on the basis of RWE. Nonetheless, it has been noted in several documents that collection and use of RWD allows for timely generation of valuable evidence. In fact, the use of automated outpatient pharmacy data, electronic health records by physicians, and applications on smartphones by patients, can provide real-time health data. This significantly reduces the time needed to gather sufficient RWD for relative effectiveness studies. Moreover, several authors mentioned that the use of EHR, pragmatic clinical trials, claims databases and existing patient registries for RWD generation is more cost-effective in comparison to setting up RCT's. For example, the European Alliance for Personalised Medicine refer to the company Handle my Health which has the ability to aggregate patient data from multiple health smartphone applications ("apps") into one data packet before sending it to the MHRA in the United Kingdom for real-time verification of data, potentially in the context of early access to medicines schemes. Another example concerns the recently-published findings of a RWS by PatientsLikeMe, demonstrating that lithium did not affect amyotrophic lateral sclerosis. RWD for this study was self-generated by patients of the PatientsLikeMe community and preliminary results were published in peer-reviewed journal after only 9 months from study initiation[1].

It is important to note that all guidelines provided by HTA agencies does not dictate what sort of RWD data should be collected, the RWS design, the data collection tools to be used, or the statistical analysis methods to be used[1]. Some of these guidelines stated that RWE is a "nice to have" as a supplement for evidence in economic evaluations, but is not required. More specifically, they acknowledged the usefulness of RWD in:

- Sourcing country-specific resource use and costs;

- Estimating natural history and baseline risks in actual clinical practice, therefore supporting the extrapolation of RCT data and facilitating modelling beyond the time horizon of the RCT;

- Sourcing country-specific QoL data;

- Estimating long-term outcomes, especially treatment-related (i.e. true effectiveness and safety);

- Sourcing true compliance estimates;

- Identifying real-world treatment pathways and comparators;

- Providing evidence for a patient population that is broader than that of the RCT, hence enhancing the generalizability and transferability of the results (e.g. patient with co-morbidities or concomitant therapies);

- Further validating model assumptions and performance in a real-world setting[45].

Even so, in recent years has been an increasing interest in incorporating RWD/RWE in HTA. One of these examples are presenting below.

Case study

Inclusion of RWE in HTA

"Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis"[46,47].

Percutaneous vertebroplasty (PVP) is a minimally invasive surgical procedure in which bone cement is injected into a fractured vertebra. Percutaneous balloon kyphoplasty (BKP) is a variation of this approach, in which an inflatable balloon tamp is placed in the collapsed vertebra prior to cement injection.

The objective of this review was to systematically evaluate and appraise the clinical effectiveness and cost-effectiveness of PVP and BKP in reducing pain and disability in people with osteoporotic vertebral compression fracture (VCFs) in England and Wales.

Results showed that for people with painful osteoporotic VCFs refractory to analgesic treatment, PVP and BKP perform significantly better in unblinded trials than optimal pain management (OPM) in terms of improving QoL and reducing pain and disability. However, there was as yet no convincing evidence that either procedure performs better than operative placebo with local anaesthetic (OPLA) with data from two high-quality trials. It can be argued that these procedures should not be undertaken unless the patient has failed to respond to a facet joint injection.

It is possible that BKP and PVP may lead to reductions in mortality and at different levels of effect; however, this possibility was derived from registry data (from USA and Germany) and without information on the causes of death in these cohorts, and in the absence of randomisation, it was not possible to conclusively establish a causal link. There were no data to analyse whether or not OPLA would also be associated with mortality

benefits. If such benefits exist then the cost per quality-adjusted life-year (QALY) gained of the interventions compared with OPM would be low.

Some questions remains without answer:

Can it use the observational data available from the US and Germany to estimate mortality differences between treatments for osteoporotic VCFs?

Can it use bias adjustment methods to pool both randomised and observational (even after propensity adjustment) data on mortality?

What impact do mortality differences have on the cost-effectiveness of PVP and BKP vs. non-invasive management?

6.1.2 THE CHALLENGE OF OBTAINING REAL-WORLD EVIDENCE

Although the potential of RWD use seems quite clear, it was revealed barriers that restrict further development towards its full exploitation:

- the absence of common standards for defining the content and quality of RWD (absence of common terminology, incomplete datasets, lack of data quality assurance systems);
- methodological barriers (absence of standards for RWD analysis and for data linkage) that may limit the potential benefits of RWD analysis;
- privacy concerns expressed predominantly by clinicians and patients and binding data protection legislation which can be seen to restrict access and use of data;
- governance issues underlying the absence of standards for collaboration between stakeholders active in the field of RWD, and limitations of incentives for data sharing[8].

The complexity of data collection underscores the fact that the level of evidence required in any circumstance will relate to the question at hand. It is important to recognize the variable quality of data (whether prospective or retrospective, or experimental or observational) and the expectations across regulators, payers, provides and patients[9,13]. This diversity arises because of differing priorities. Obtaining early insights into these needs is fundamental to design an efficient RWE strategy[14].

The challenge of meeting both regulatory and payer requirements is being recognized. Efforts are underway to streamline regulatory and payer processes and reduce the complexity. Two examples include the contribution of regulatory assessment reports to HTAs and initiatives to promote early dialogues:

1. The European network for Health Technology Assessment (EUnetHTA) initiated collaboration between the European regulator and HTA bodies with the aim to improve the contribution that regulatory assessment reports – the so-called European Public Assessment Reports (EPARs) - can make to the assessment of relative effectiveness of medicinal products by HTA bodies. As a result, the templates for preparing EPARs were revised to better address the needs of health technology organizations. Even the regulators and HTAs acknowledge that understanding a broad range of needs is crucial[14].

2. Shaping European Early Dialogues for health technologies (SEED) is an international project financed by the European Commission from October 2013 to August 2015. The SEED Consortium, led by the French National Authority for Health, is composed of 14 European HTA agencies. The aim of the SEED project is to conduct pilots on early dialogues between its member HTA agencies and manufacturers of health technologies (pharmaceuticals and medical devices) whose products are currently in the development stage. In total, 10 early dialogues are planned, with seven focused on drugs and three on medical devices. Early dialogues allow companies developing health products to meet with European HTA agencies in order to present their development plan for the product in question, and to ask specific questions relative to their plan. The objective of the SEED early dialogues is to reduce the risk of production of data that would be inadequate to support the company's future reimbursement request[13].

Prospective observational studies and interventional trials allow researchers greater control over the completeness and quality of RWD, but at increased time and cost. A recent phenomenon is the dramatic increase in the number of very large global prospective observational studies. Twenty-nine industry sponsored observational studies of over 5,000 patients were started in the period 2009-2011 compared with 65 in the period 2012-20143. Such "elephant" studies are indicative of sponsors' recognition of the common questions across markets, the need for increased sample size for greater statistical study power, and more centralized decision-making to streamline real-world research programs[13].

6.1.3 LOOK INTO THE FUTURE

The RWD activities are expected to increase by 25 % in the next years. Most of these activities are studies which have safety and effectiveness objectives and to a lesser extent drug utilization and health economics and the most common therapeutic areas are: oncology, cardiovascular and metabolic disorders. Pharmaceutical companies are conducting more and more epidemiological studies to prepare dossiers for market access (disease understanding, unmet needs, population targeting), it face big challenges for the

coming years especially in EU and there is an increase need for local regulatory knowledge. There's still need to increase awareness for the importance of RWS and the impact it has on the patient's life[48].

The issue of obtaining relative effectiveness data is highly recognized, and efforts are underway to find solutions. Several recent initiates, pilot programs and public-private partnerships to develop methods and systems for using RWD generated by the healthcare system had been established. For example the EU-based Innovative Medicine Initiative (IMI) program "GetReal". It is a public private consortium consisting of pharmaceutical companies, academia, HTA agencies and regulators, patient organizations and subject matter experts. The goal of GetReal is to develop new ways of incorporating real-life clinical data into drug development. The benefits of this are manifold – not only will it help pharmaceutical companies take better decisions during drug development, it will aid healthcare decision makers when deciding how best to grant patients access to a new treatment[21,49].

Among other things, the project will analyse existing processes and methodologies for HTA. It will also generate a decision-making framework to help pharmaceutical companies design drug development strategies. The framework would include ideas for the design of trials and studies capable of providing information on the real world effectiveness of medicines, including relative effectiveness[49].

The project also aims to develop tools that will allow different stakeholders in drug development and approval to test different mathematical models in their decision making and assess their impact. It will create a network of regulators, HTA organisations, companies, academics, healthcare professionals, patients and other societal stakeholders. This is important because the challenges faced by the pharmaceutical industry, regulators and other healthcare decision makers are linked[49].

By bringing together all key stakeholder groups (namely industry, academia, regulatory agencies, HTA bodies, reimbursement agencies, healthcare budget holders, and patient groups) to share their insights and know-how, GetReal would help to generate a consensus on best practice in the timing, performance and use of real-life clinical studies in regulatory and reimbursement decision-making. It will also help to create a strong platform for the communication of results and for future discussions in this important area[49].

7. CONCLUSIONS

In the last years has been discussed the promise of RWD. A number of analysts and academics have signalled its potential to contribute to improved health products and outcomes. Advances in computing allow collecting, share, analyse and use large quantities of data routinely at a relatively low cost – as never before. The increased use of new technologies in the healthcare sector has changed the ways in which patient level information are collected, stored and used. In this context, RWD can be used in conjunction with RCTs and other medical data to provide insights into real-world clinical outcomes. RWS conventionally include a larger, broader study population than RCT's, implying that they are sufficiently empowered to significantly capture heterogeneity of treatment effects in clinical practice. RWS are often conducted over a longer time horizon than RCT's and as such their results can be more accurately extrapolated to future effects when compared to RCT results. The ability of RWD to address knowledge gaps presented by RCT-generated evidence was the also recognised as advantage. For example, pragmatic clinical trials by design can be used to identify drug-drug interactions, overdosing or other forms of inappropriate use of medications. RWE is also a valuable source of safety and effectiveness data in exceptional circumstances where RCT's are not ethical (e.g. narcotic abuse) or feasible (e.g. for the urgent reimbursement of a novel medication to treat a life-threatening disease). In more general terms, the generalisability of results of RWE contributes to filling what has become to be known as the "efficacy-effectiveness gap. RWD also allow for assessment of long-term effects and rare serious adverse effects, owing to the larger number of patients for whom data is conventionally available and the wider range of health outcomes measured when compared to RCT's[1,8,9,50].

In fact, the use of automated outpatient pharmacy data, electronic health records by physicians, and applications on smartphones by patients, can provide real-time health data. This significantly reduces the time needed to gather sufficient RWD for relative effectiveness studies. Several authors mentioned that the use of electronic health records, pragmatic clinical trials, claims databases and existing patient registries for RWD generation is more cost-effective in comparison to setting up RCT's[1].

It was also identified factors limiting the potential benefits driven from RWD analysis. The liability of RWD to different form of biases (i.e. selection bias, information bias and confounding bias) was the most recurring disadvantage. Retrospective or prospective observational or database studies do not meet the methodological rigor of RCTs, despite the availability of sophisticated statistical approaches to adjust for selection bias in observational data (covarate adjustment, propensity scores, instrumental variables, etc.). Observational studies need to be evaluated rigorously to identify sources of bias and

confounding, and adjusted for these prior to estimating the impact of interventions of health outcomes. Observational or database studies may also require substantial resources. Several of authors went on to indicate that, as a result of biases, the determination of causality based on RWD should be done with caution[1,9,21].

The poor quality of RWD available was too mentioned disadvantage. Incomplete or missing data was the specific disadvantage highlighted in relation to poor quality of RWD. This pertained to, among other things, databases with incomplete information ("gaps") on certain collected elements, the absence of outcomes representing "mild" outcomes, or missing lab data. The phenomenon of incomplete data can be related to the type of healthcare database; for instance, claims databases inherently lack information on clinical disease severity and lifestyle habit. On the other hand, electronic healthcare records may also have data gaps on clinical outcomes or have incorrectly-coded medical diagnostic information. On a similar note, several authors have noted that despite the presence of many different sources of RWD, such as electronic healthcare records and administrative claims databases, the majority of these databases have not been established to collect information for research purposes. For example, EHRs capture data on symptomatic outcomes of interest, but have little information on mild symptoms. Researchers therefore need to remain aware of different types of data sources and their corresponding limitations when initiating RWS's[1,8].

Another important disadvantage that received little mention is the availability of RWD and RWE at the time of important decision-points in the product lifecycle. For instance, at the stage of reimbursement, payers often require data on the real-world relative effectiveness of new interventions that is usually not yet available pharmaceutical industry[1].

The lack of standardization of RWD collection methods and definitions of terms, as well as the lack of harmonization (regionally and internationally) of required RWD data is frequently considered practical obstacle[1,8].

Another issue is the ambiguity regarding the applicability of RWE to decision-making. Due to several factors such as the lack of consensus among stakeholders on the value of RWE and lack of guidance on using RWE in decision-making, ambiguity remains on how RWE should be used decision-making processes. The recurrent political consideration of RWD refers to the need for increased collaboration among stakeholders on a number of issues. Firstly, it has stated that agreement must exist between HTA agencies and regulatory agencies as to evidence needs RWD should fulfil; phase IV, post-marketing studies conducted for regulatory purposes can provide very useful insights for questions on relative effectiveness relevant for reimbursement decisions. Therefore, more dialogue needs to take place on harmonizing data needs from these two stakeholder groups.

Secondly, it also states that key stakeholders (patients/ patient organizations, regulatory agencies, HTA agencies, pharmaceutical industry, payers/insurers and academia) should come together as co-designers of projects when identifying RWE needs and designing RWS's[1,33].

In conclusion, the collection of RWD represents an important way forward to determine the value of medicines. However, for it to proceed in a comprehensive fashion, we need a reality check on several important methodological and practical issues. Detailed methodological guidance for the collection of RWD needs to be produced. Also HTA and regulatory agencies need to engage in more discussion about the types of data required and the decisions that will result[51].

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