

Real World Evidence

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Impact on Regulatory Decision Making

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List of Abbreviations

ADAPT-SMART	Accelerated Development of Appropriate Patient Therapies, a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes
ADDIS	Aggregate Data Drug Information System
CCG	Clinical Commissioning Group
CHMP	Committee for Medicinal Products for Human Use
CIRS	Centre for Innovation in Regulatory Science
CKD	Chronic Kidney Disease
CPRD	Clinical Practice Research Datalink
COPD	Chronic Obstructive Pulmonary Disease
CT	Commission de la Transparence (French Transparency Commission)
EC	European Commission
EMA	European Medicines Agency
EHR4CR	Electronic Health Records for Clinical Research
EMIF	European Medical Information Framework
EPAR	European Public Assessment Report
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
FORCE11	Future of Research Communications and e-Scholarship 11
GBA	Gemeinsamer Bundesausschuss (German Joint Federal Committee)
GDPR	General Data Protection Regulation
GKV	Gesetzliche Krankenversicherung (German Statutory Health Insurance)
HAS	Haute Autorité de Santé (French National Authority for Health)
HRQoL	Health-related Quality of Life

HTA	Health Technology Assessment
i~HD	European Institute for Innovation through Health Data
ISPOR	International Society for Pharmacoeconomics and Outcome Research
IMI	Innovative Medicines Initiative
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (German Institute for Quality and Efficiency in Health Care)
LDH	Lactate Dehydrogenase
MAPPs	Medicines Adaptive Pathways to Patients
MARS	MPS IVA registry
MHRA	Medicines and Healthcare Products Regulatory Agency
MPS	Mucopolysaccharidosis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICHSR	National Information Center on Health Services Research
NIH	National Institute of Health
NIHR	National Institute for Health Research
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PASS	Post Authorization Safety Studies
PAES	Post Authorization Efficacy Studies
PCORnet	Patient Outcomes Research Network
PEM	Prescription Event Monitoring
PNH	Paroxysmal Nocturnal Hemoglobinuria
POC	Proof of Concept
PRIME	PRiority MEDicines
PRO	Patient-reported Outcomes

R&D	Research and Development
RCT	Randomized Clinical Trial
RMP	Risk Management Plan
RWD	Real World Data
RWE	Real World Evidence
SAWP	Scientific Advice Working Party
SmPC	Summary of Product Characteristics
UNCAM	Union Nationale des Caisses d'Assurance Maladie (French National Health Insurance Fund)
US	United States

1. Introduction

In recent years, the pharmaceutical space has been faced with a number of major challenges for innovative drug development. On the one hand all stakeholders in this dynamic environment as for example regulators, health technology assessment (HTA) bodies, or payers were heavily committed to efficiently manage strong budget pressures in the national healthcare systems of virtually all developed countries worldwide. On the other hand pharmaceutical companies were faced with a significant loss of earnings due to sequential waves of patent expiries of blockbuster drugs developed in the nineties of the last century, the so called patent cliff. [1] Due to the massive pressure in the system to deliver new and effective medicines faster to the patient, the pharmaceutical community is essentially working on new ways to expedite the development and market access of affordable but also profitable drugs. This is one of the major reasons why there is currently a paradigm shift ongoing, which continuously undermines the previously accepted scheme to develop new innovative medicines: The use of real world evidence (RWE) as part of the HTA and regulatory decision making. [2, 3, 4]

For the pharmaceutical companies it turned out that this paradigm shift bears some immediate risk for the reimbursement value of newly launched medicines as new capabilities in the companies needed to develop quickly to support the required value propositions of the medicines. However, and this is more the focus of this master thesis, there are certainly intriguing opportunities emerging which are associated with a new development paradigm, especially from a patient perspective, as the utilization of real world data (RWD) puts the treated patient in every-day life at the center of the data analysis. This is in contrast to the still widely accepted internal validity of the randomized controlled clinical trial (RCT) which usually analyses an extremely homogenous population of patients barely reflecting the real world. [5] Especially in the regulatory space it is a common perception that the RCT is still considered the gold standard for evidence generation of new medicines. However, the mindset has begun to change. The overall goal of the regulating stakeholders, namely regulatory agencies, payers, and HTA bodies, is to efficiently manage the translation of new scientific findings into medicines that meet current standards of safety and efficacy, are available to patient earlier than in the past, and are affordable (also refer to figure 1). This has proven to be a major challenge, balancing expectations of patients and securing sustainability in the public healthcare systems which suffer under the pressure of an increasingly older population.

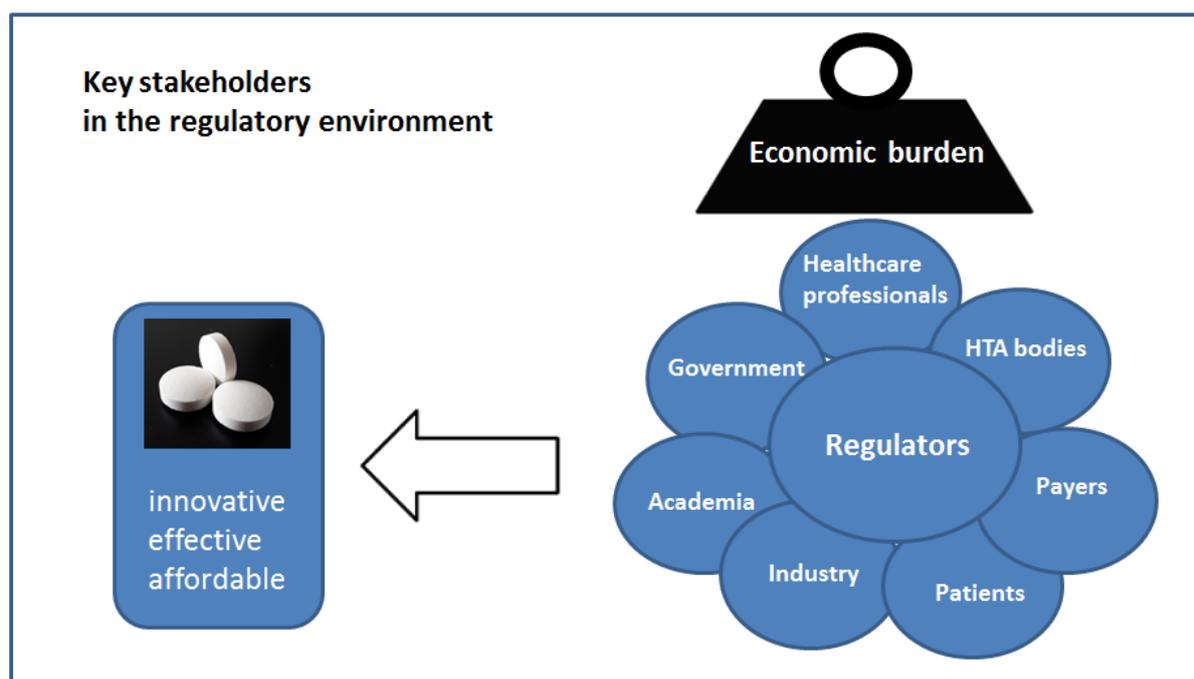


Figure 1: Key stakeholders in the current regulatory environment. The economic pressure in the national healthcare systems weighing on all stakeholders to provide affordable medicines that meet current scientific standards is constantly increasing.

Considering this complex and dynamic environment, the objective of this master thesis is to analyze the emerging role of real world evidence in the regulatory space and its impact on regulatory decision making. After providing some fundamental definitions, this master thesis will analyze the current applications of real world evidence in the drug development process and lifecycle. It will further touch on

- the regulators' viewpoint on this topic,
- describe current regulatory tools making use of real world evidence,
- refer to a set of intriguing case studies where real world data has been used for decision making,
- analyze the associated major drawbacks and how these could be addressed,
- and provide detailed conclusions and a final outlook.

For the sake of comprehensiveness, this thesis will focus on the pharmaceutical space in the European Union (EU). However, the author is confident that the majority of conclusions in this analysis can be transferred to other major regions worldwide.

2. Essential Definitions

2.1 Real World Data and Real World Evidence

There is still a certain level of discussion in the expert community about the definitions of real world data and real world evidence. The founding of the International Society for Pharmacoeconomics and Outcome Research (ISPOR) task force has helped to advance a common understanding in the field. The primary objective of the ISPOR task force is to develop consensus guidelines on good practice standards for outcomes research, and by doing so establish a framework to assist health care decision makers in using real world data with emphasis on coverage and payment decisions. [6] For the objective of this master thesis, reference is made to the definition given by ISPOR and the EU Innovative Medicines Initiative (IMI) Get Real project (refer to section 5.4 for more details on IMI GetReal):

Definition of the term *real world data*: [7]

Real world data is described as an “umbrella term for data regarding the effects of health interventions (e.g. safety, effectiveness, resource use etc.) that are not collected in the context of highly-controlled RCTs. Instead, real world data can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data. Data collected include, but are not limited to, clinical and economic outcomes, patient-reported outcomes (PRO) and health-related quality of life (HRQoL). Real world data can be obtained from many sources including patient registries, electronic medical records, and claims databases.”

More specifically, there are six sources of real world data defined by the ISPOR: [7]

- Supplements to traditional registration RCTs aiming at collecting e.g. PRO data, HRQoL data.
- Pragmatic clinical trials based on prospective, randomized assignment of patients involving a larger and more diverse real world patient population.
- Registry studies defined as prospective, observational cohort studies of patients with a specific disease and/or receiving a specific treatment.
- Claims databases or administrative data that can be retrospective or real time, usually used for retrospective longitudinal and cross-sectional analyses of patient, group or population outcomes.

- Health surveys which are conducted to gather descriptions of health status and well-being, e.g. health care utilization, treatment patterns from representative individuals out of groups of patients, groups of providers or individuals in the general population.
- Electronic health records (EHRs) and medical chart reviews in databases that contain detailed, longitudinal data, e.g. disease specific symptoms at patient level.

There is still some debate in the real world scientific community whether pragmatic trials should be regarded as real world data due to the fact that pragmatic trials are based on external randomization. [7] ISPOR acknowledges that one could argue about the real world nature of pragmatic trials from a rather strict perspective. However, the majority of experts in the field consider pragmatic trials as being part of the real world data sources. The definition of pragmatic trials used by the US National Information Center on Health Services Research (NICHSR) is somewhat intuitive and provides additional clarification together with bullet point number two in the above list: [8, 9] Pragmatic trials are a related group of trial designs “whose main attributes include the 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.”

By way of comparison the definition of the term real world evidence can be considered rather straight forward: [7]

“Real World Evidence is the evidence derived from the analysis and/or synthesis of real-world data.”

To summarize, the community is still debating about the common definitions of real world data and related terms. However, during recent years a fairly clear picture has evolved. The vigorous discussions around these terms reflect the dynamics currently associated with this area of pharmaceutical development.

2.2 Efficacy versus Effectiveness

Two terms which are extremely important for the discussion around real world data are the terms efficacy and effectiveness of a medicine. Even in expert literature and amongst different countries these terms are used in an ambiguous fashion. In the context of this master thesis, the following common understanding of IMI GetReal is considered adequate. [7]

The term *efficacy* is considered to be “the extent to which a healthcare intervention produces a therapeutic effect as compared to a placebo under ideal conditions, i.e. the highly controlled conditions of RCTs”. In RCTs, randomization and additional measures are applied to reduce the naturally occurring bias. These trials can be used to statistically prove a causal relationship between an intervention and the studied endpoints. In contrast, the term *effectiveness* of an intervention is considered to be associated with “its health benefits in routine clinical practice, which stands for real world studies”. [7] In such studies, multiple variables like concomitant medication and comorbidities are introduced and may significantly influence the patient’s outcomes. Effectiveness studies usually include a minimum of two active comparators and no placebo, e.g. comparing an intervention with the current standard of care.

2.3 The Efficacy – Effectiveness Gap

A topic which is an intensive matter of discussion among experts and which is of high relevance for this master thesis is the so called efficacy – effectiveness gap. There are many examples in pharmaceutical research that show a certain level of discrepancy between the outcome of efficacy determination under ideal conditions and effectiveness determination under usual circumstances of health care practice. [8] Knowing that regulators mostly rely on pure efficacy analyses for licensing decisions this may create significant consistency issues if one is confronted with a medicine which is prone to the efficacy – effectiveness gap. Obviously, such a medicine may be highly efficacious under ideal RCT conditions, however lack effectiveness in the real world, or vice versa. This may have severe consequences in both ways as either one loses promising therapies never reaching the clinical practice or, even more dramatic, patients will be exposed to interventions that will not fulfil expectations nourished by RCTs. Finally, the real world is the environment where it counts for the every-day patient. This is one of the driving factors why this topic is extremely important and why it is considered highly relevant for future sustainable success in the healthcare environment. [10] There are intriguing examples where positive RCT data could not be reproduced in the real world, one of which is the well-known rimonabant case. [8, 11, 12] Due to the fact that the rimonabant case has been evaluated in numerous publications it will not be discussed in further detail in this master thesis. On the contrary, there are also numerous examples where real world data has proven highly useful to show additional value of a new medicine. Therefore, the emphasis of this master thesis will be on discussing new opportunities for

healthcare decision making which emerge from the use of real world data and which may help to avoid cases like rimonabant in the future.

2.4 The Access-versus-Evidence Conundrum

For quite some time now clinical trials have been used to show efficacy and safety for a new medicine. These were deemed acceptable by regulatory authorities granting the marketing authorization. The RCT setting has usually been regarded as the gold standard by regulatory authorities for obtaining a marketing authorization and for demonstrating equal or superior effects of the new drug compared with the standard of care. [13] However, this paradigm has started to shift. Previously, pharmacovigilance and drug safety were key drivers of collecting real world data, usually in the frame of post marketing obligations and surveillance (also refer to section 3.2). Compared to the RCT setting, where the studied populations are intentionally homogenous and limited, the real world will include different types of patients who were not included in the RCT like e.g. children and adolescents, elderly, pregnant women, or patients with concomitant disease. Further, the number of patients simply increases dramatically in the real world leading to the fact that rare safety signals which will not be detected in the RCT can be observed in the real world. These circumstances are dramatic upsides for using real world data for pharmacovigilance purposes. [14] As previously observed in the past, the shift of a paradigm in pharmaceutical development has again been driven by safety concerns. Therefore, using real world data for drug safety purposes is widely accepted nowadays.

Based on the above, it appears an essential question to explore the current situation for real world data usage, especially in the regulatory space when it comes to the granting of the initial marketing authorization. Indeed, there is a lot of substantial discussion ongoing and many stakeholders hold different views on this topic. This master thesis will examine the obstacles and opportunities of all involved parties and will bid to provide a holistic outlook where the journey might lead. However, one thing that is important to clarify from the beginning: The regulators are confronted with a so-called access-versus-evidence conundrum, or more simply spoken the chicken-egg problem. [15] Real world data may well be valuable for decision making in certain situations, also during drug development and initial registration, however access to real world data before the medicine is approved and launched to the real world cannot be generated. This represents a vicious circle. The community is working on

tools to overcome this access-versus-evidence conundrum by using new approaches (refer to chapter 5); however the core of this issue seems to be difficult to tackle.

2.5 Brief Summary of Chapter 2

Organizations like ISPOR and IMI have been working intensively on defining the framework of real world data and evidence. There is still remaining discussion in the expert community but a reasonable level of common understanding has been reached. Phenomena like the efficacy - effectiveness gap and the access versus evidence conundrum, which can have a tremendous effect on the success of a medicine during its lifecycle, are important factors and under constant debate (also refer to figure 2).

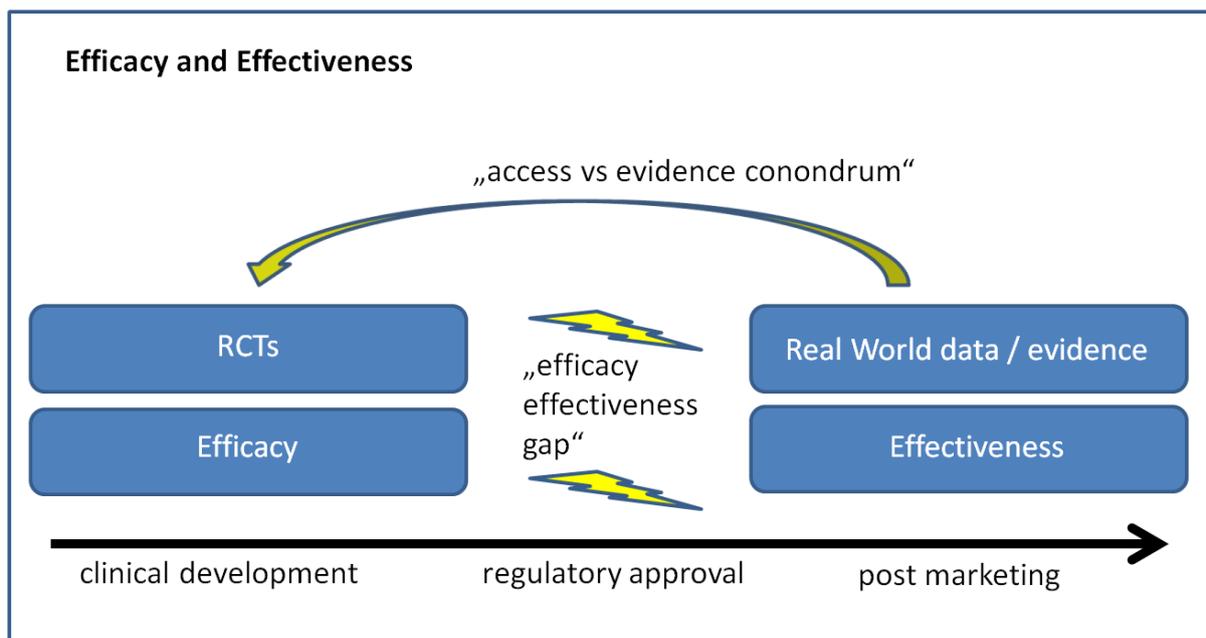


Figure 2: Schematic visualization of the efficacy-effectiveness gap and the access-vs-evidence conundrum. Efficacy - effectiveness gap: Efficacy determined in RCTs may not always be predictive for the effectiveness of a medicine in the real world. Access-vs-evidence conundrum: Strictly spoken, real world data can only be obtained after marketing authorization when the drug is launched in the real world. Therefore, the usage of real world data of the same drug cannot be used for its marketing authorization procedure.

3. Real World Data – Current Areas of Impact

Decision makers in the healthcare environment altogether have the following major goals:

- The development and implementation of treatment strategies that improve patient outcomes and
- improving the efficiency in the healthcare system.

These objectives can be achieved by constantly optimizing the current system and developing new mechanisms to identify more efficient interventions for the future. In this context and in the context of the efficacy – effectiveness gap (refer to section 2.3), the usage of real world data can be a promising approach to address the most urgent healthcare needs. All involved stakeholders as regulators, HTA bodies, or pharmaceutical companies are using real world data up to a varying extend already today for their decision making; however there is great potential to extend the current activities. [16] The following chapter will summarize the opportunities which arise from the usage of real world data with focus on the pre- and post-authorization phase during drug development.

3.1 Research and Development

According to experts in the field, the usage of real world data has a significant strategic component during pharmaceutical research and development (R&D). Pharmaceutical developers can use real world data to better design their R&D programs with regards to a more efficient development of drug candidates into firstly effective and secondly reimbursable medicines. This is particularly important in the light of the concept of stratified medicine which gains more and more importance over time as previous blockbuster approaches by big pharma seem to be a phased out model. [17, 18, 19] Stratified medicine is focusing on the identification of subgroups of patients with distinct mechanisms of diseases or common responses to treatments. This allows the development of treatments that are efficacious in a particular subset of patients. Ultimately, the vision of stratified medicine is to ensure that the right patient gets the right treatment at the right time. Real world data can increase the effectiveness of clinical trials by supporting the identification of the most appropriate sub-populations benefiting from the new treatment which may help to reduce time and costs in clinical trial budgets and to define the prospective value of the medicine as early as possible. Currently, real world data is mostly used to define which information is

attributable to the patient, to the medicine, or to the disease. In other words, what is the basic epidemiology and what are the patient's characteristics. [20]

An intriguing example how analyses in the real world can give rise to new developments is the poor adherence to treatments in the diabetes field. It has been shown in numerous pro- or retrospective observational studies, e.g. analyzing health records or patient surveys, that though adherence is associated with beneficial outcomes it is often poor in the real world. [21] Reasons for low adherence are extremely diverse and include age, social and psychological factors, education, a lack of understanding of the long-term benefits of treatment, ineffective communication between physician and patient, adverse outcomes such as weight gain, failure of clinicians to modify interventions appropriately, or the complexity of the medication regimen. As a consequence, strategies to counteract poor adherence should include educational initiatives, improved communication between physician and patient, reminder systems, and a reduction in the complexity of the prescription regimen. Concerning the latter, companies have specialized on the development of targeted solutions by e.g. placing once or twice yearly injectable devices under the skin. [22] These devices release the medicine in a controlled manner to adjust plasma glucose levels and are largely independent from the daily supervision by the patient or physician. The hope is that by using such devices, low treatment adherence as being one of the main factors leading to poor glycemic control in diabetic patients, can effectively be mitigated and help to reduce increased risk of hospitalization and severe cardiovascular complications in the real world.

Interestingly, real world analyses are increasingly used to determine whether a medicine shows the same effect in real life as compared to a clinical trial. Many investigators are using pragmatic trial designs to pursue that goal. One of the most prominent examples in this field is the Salford lung study which is discussed in section 6.1 of this master thesis.

As indicated above, there can be numerous uses of real world data across the medicine lifecycle. In a workshop recently held by the Centre for Innovation in Regulatory Science (CIRS), experts in the field coming from different competent authorities, academia and industry discussed and concluded that companies are using real world data for the following areas in the field of research and development: [23]

- Discovery of drug pathways, inform disease area and precision medicine strategies
- Estimation of unmet medical need, profiling of target populations

- Optimization of trial design
- Quantification of disease burden
- Development of evidence plans, value dossiers, value propositions
- Determination of treatment patterns
- Management of supply chain and inventory
- Uncovering new indications

The following list of activities involving real world data were concluded from representatives of regulatory agencies:

- Evidence generation for new molecular entities, fixed dose combinations, new indications and extension of indications, especially for rare and life-threatening diseases
- Adaptive licensing and conditional marketing authorizations
- Pharmacovigilance and drug safety analysis
- Verification of dosing
- Analysis of subpopulations

The first bullet point from the regulators list referring to evidence generation definitively supports the view that a change of the previous mindset has begun. However, it needs to be specified that evidence generation based on real world data is usually only accepted by regulators in situations when evidence through RCTs cannot be generated due to other limiting factors (also refer to chapter 4). With regard to the above, an intriguing case study in section 6.3 of this master thesis describes the extension of an indication of an orphan drug based on registry data in the EU.

3.2 Real World Data Driving Pharmacovigilance

Many new developments in healthcare were driven by drug safety considerations. In principle, this is also applicable for the use of real word data in regulatory decision making. Pharmacovigilance and drug safety are key drivers of gathering real world data already today. This is due to the fact that in the real world, safety signals will be observed which cannot be detected in the RCT environment. In the real world the number of patients exposed to the new medicine increases rapidly and this will enable to detect even very rare adverse events, especially in the long term. [14, 24] Furthermore, patients who wouldn't have been eligible

for the restricted RCT setting will be exposed with the new medicine, e.g. pediatric patients, elderly, pregnant women and patients with concomitant disease. These exposures usually unveil additional types of adverse events which may contribute to the maturation of the safety profile of the concerned medicine. These mechanisms are widely accepted throughout the regulatory institutions worldwide.

With regards to post-marketing surveillance, as soon as a new medicine obtains approval its performance will be monitored in the real world. In the EU guideline on good pharmacovigilance practice, several tools are mentioned to gather information on marketed products including post authorization safety studies (PASS) and post authorization efficacy studies (PAES). [25] As for example the design of a PASS could be interventional or non-interventional, most of the PASSs are expected to be non-interventional real world type studies. The appropriate methods applied for analyses in PASSs could be e.g.

- Prescription event monitoring (PEM)
By using PEM, specific patients concerned by an adverse event can be identified through electronic health records or automated health insurance claims. PEM is usually applied to monitor drug safety in the immediate after launch phase.
- Registries
Patient registries may be useful to analyze e.g. the effectiveness of a medicine in heterogeneous populations, deviating dosing, or specific variables associated with patient subpopulations. In section 5.6 of this master thesis more information on registries can be found.
- Observational studies
A number of observational study designs are especially useful in validating signals from spontaneous reports, active surveillance programs or case series, e.g. the cross-sectional study design, the cohort study design, or the case control study design.

In section 6.2, a case study describes the outcome of an EU article 31 safety referral concerning metformin containing medicinal products in which conclusions were drawn largely based on real world data. Many of the products concerned by this referral were in the market place since decades. The final outcome of the referral led to the revision of the labeling of the concerned products. In this specific case the targeted population could be extended to enable a wider use of metformin as first line treatment.

3.3 Real World Data Driving Market Access

Another current key driver of gathering real world data besides post marketing drug safety is associated with HTA and reimbursement. Pricing and reimbursement is still a matter of national assessment involving the HTA bodies and payers on a country level. The most commonly known institutions are e.g.: [26]

- UK
The National Institute for Health and Care Excellence (NICE), associated with two major budget holders in England, the National Health Service (NHS) and the Clinical Commissioning Groups (CCGs).
- France
The Haute Autorité de Santé (HAS) fixing the reimbursement rate in cooperation with the Commission de la Transparence (CT) and Union Nationale des Caisses D'Assurance Maladie (UNCAM).
- Germany
The Gemeinsamer Bundesausschuss (GBA) supported by the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) and the Gesetzliche Krankenversicherung (GKV) Spitzenverband negotiating the reimbursed price based on the outcome of the additional benefit assessment of the medicine.

It is obvious that the system is complex and heterogeneous throughout the EU. An increasing number of countries are assessing the relative effectiveness of a new intervention compared to standard of care and are using the results as a basis of their decision on pricing and reimbursement. The objective of such activities is the determination of the added benefit or value of a new medicine. As many countries established a reference-pricing-based model for new medicines which did not show additional benefit, the effectiveness assessment by HTA bodies has a major impact on the commercial success of a medicine in the market. More and more, real world evidence is adding to a successful market access by enhancing the value proposition of a new intervention. [27] In essence, real world evidence can be considered as the basis for new pricing strategies that incorporate patient reported and clinical outcomes. It is increasingly acknowledged by HTA bodies and payers that real world data may provide useful evidence on whether a specific treatment is worth a higher price than the standard of care due to the fact that if the final clinical outcomes will be significantly improved this may ultimately reduce the overall budget of the healthcare system. As health economic arguments

gain increasing importance, payers intensify their focus on showing true value of the medicine, e.g. whether the patient can get back to work quickly or if home care is required. Appropriate real world data can provide these insights. [28, 29]

To summarize, by gathering suitable real world data, evidence can be generated to demonstrate that an intervention addresses an unmet medical need in a cost effective manner. In section 6.4 of this master thesis, a case study describes how a new-of-its-kind model of conditional coverage in the UK uses real world registry data to demonstrate clinical effectiveness and to support sustained reimbursement.

3.4 Brief Summary of Chapter 3

Currently, the most common area of impact of real world data in the pre-authorization phase of a medicine is to support research and development programs with regard to information attributable to the patient population or disease of interest. The previous and still current major drivers of real world data generation are post marketing purposes as for example safety analyses for pharmacovigilance applications and market access considerations for the sake of determining the added benefit of a new medicine (also refer to figure 3).

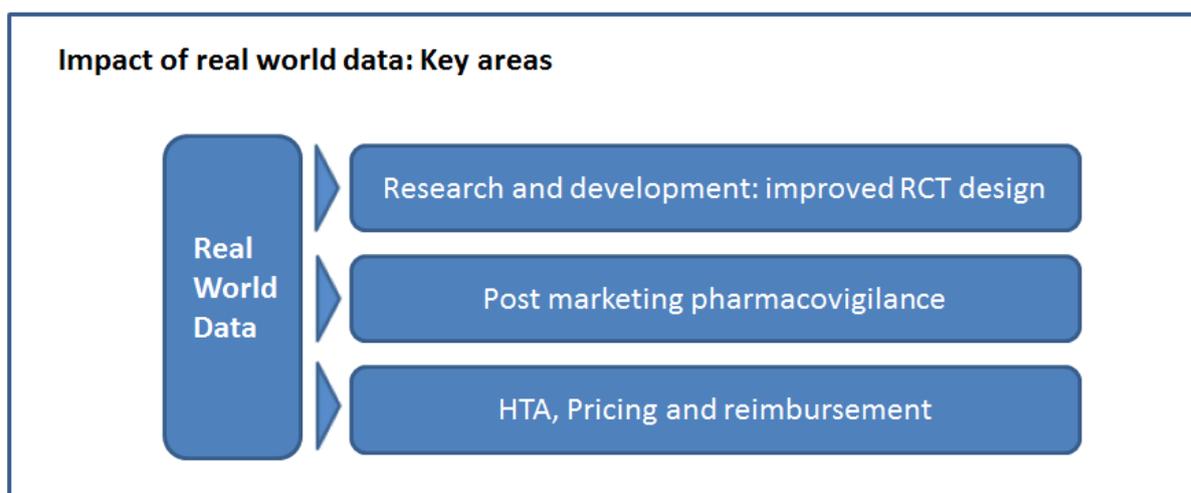


Figure 3: Key areas of impact of real world data use during the lifecycle of a medicine. In the pre-authorization phase real world data is primarily used to improve the design of classical RCTs. Major drivers of real world data generation are post-marketing applications like pharmacovigilance and market access.

4. The Regulator's Viewpoint

The European medicines regulatory network includes the European Medicines Agency (EMA), the national competent authorities of the EU countries and the European Commission (EC). The objective of this network is to apply the current scientific and regulatory standards to protect and promote the health of all citizens and animals in the EU. The network serves a population of over 500 million people, the world's third largest population after China and India, and is pursuing a joint strategy built around specific priority areas. One of these priority areas is the support of new medicines development in areas which address key needs of the public health. [30] A recent and prominent example of such key measures is the introduction of PRIority MEdicines (PRIME), a scheme intended to bring together the expertise of all EMA scientific committees for the efficient support of the development of promising innovative medicines. The use of real world data is an important topic of the strategic approach of PRIME and associated tools. This will be described in more detail in chapter 5 of this master thesis.

As the EMA is taking a central role in driving the strategy of national regulators throughout the EU, this master thesis will mainly focus on the analysis of the position of the EMA with respect to the utilization of real world data from a regulator's viewpoint. In the EMA's annual report from 2016, the agency emphasizes the importance to "harness the power of big data". The EMA's executive director Guido Rasi puts forward that efforts are underway to "better understand how a medicine performs when used in real life by doctors and patients" and how big data could "support regulatory decision making throughout its (the medicines) lifespan". [15]

With regard to post-marketing data, once a medicine has entered the market, the EMA and EU national competent authorities continuously monitor the benefit risk profile of a medicine in real life. One of the key tools in this respect is the maintenance of the risk management plan (RMP). [31] Regulatory risk minimization measures originating from this continuous monitoring can result in the adaptation of the product information, the addition of new contra-indications, or even suspension or withdrawal of a medicine from the market. In 2016, over 300 medicines were concerned by an update of the product information based on new safety data, thus enabling healthcare professionals to take more informed decisions when prescribing those medicines. [15]

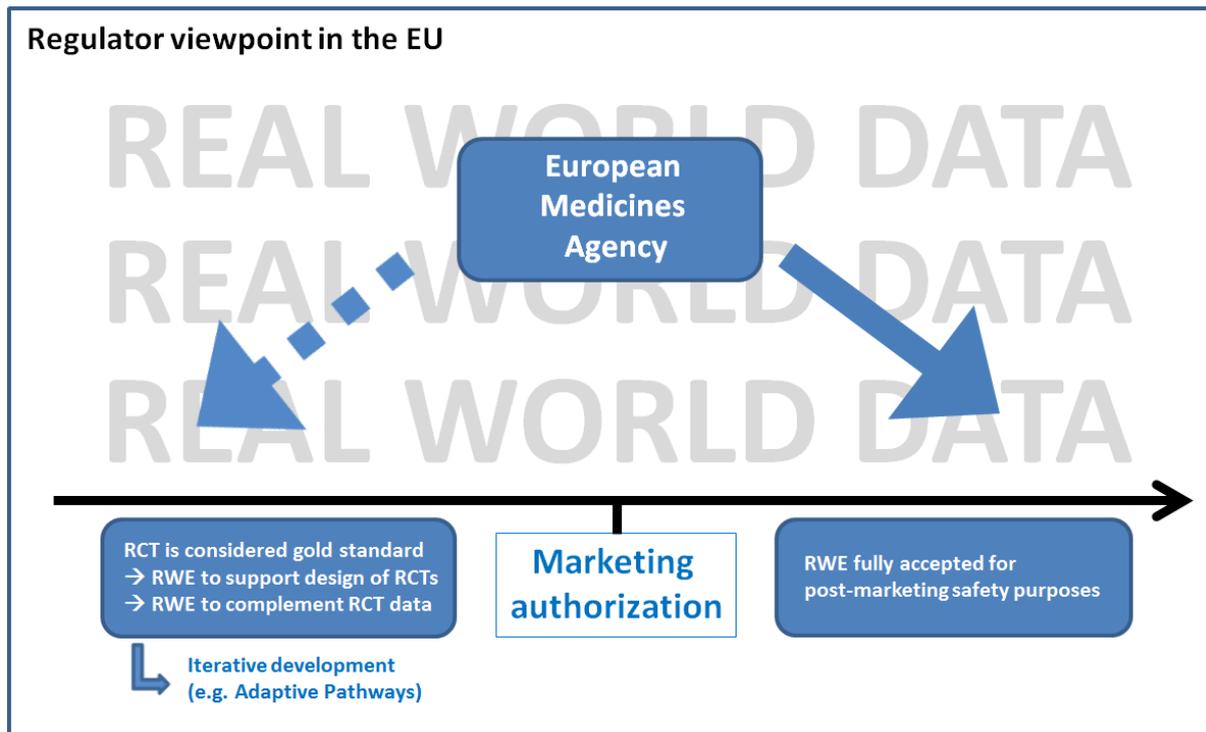


Figure 4: The current position of the EMA with regard to use of real world data. The EU regulators are using real world data analysis for post marketing purposes on a regular base. During the pre-approval phase, the EMA is driving the use of real world data as a complement to traditional RCTs. Recently, several tools to establish this strategy have been implemented, e.g. the Adaptive Pathways scheme.

With regards to usage of real world data for licensing purposes, the EMA is referring to significant progress in exploring innovative regulatory approaches in cooperation with additional healthcare stakeholders. Mainly, EMA is referring to the Adaptive Pathways which will be discussed in this master thesis in more detail in section 5.2. The idea of the Adaptive Pathways is to license a medicine in a progressive manner, initially the medicine being authorized in a restricted population of patients, potentially using the conditional approval procedure. In 2016, eight medicines received a recommendation for conditional marketing approval. [15] This licensing tool is available to facilitate early approval and patient access to promising medicines that address specific unmet medical needs. The concept of real world data use for and after conditional marketing approval is strongly emphasized by the EMA (also refer to section 5.2 for further details). Once conditional marketing approval has been granted the medicine could be expanded into wider or additional indications based on real world data as evidence increases in the market over time. Hans-Georg Eichler, EMA Senior

Medical Officer, comments on this topic: “Adaptive Pathways is a response to problems which have long existed in medicines regulation but have grown more acute in recent years. One such problem is the access-versus-evidence conundrum (also refer to section 2.4): on the one hand, there are patients today with serious illnesses for whom time is of the essence, while on the other there are patients in the future for whom complete knowledge of benefits and risks will be paramount”. [15] In the EMA’s 2016 annual report, emphasis lays on the agency exploring ways to improve the knowledge and use of real world data. Two major workshops have been organized recently to advance the commitment in this field: The workshop on big data (November 2016) and on patient registries (October 2016). Both of these initiatives will be discussed in sections 5.5 and 5.6. The EMA states that while currently “real world data is primarily used in the post-marketing phase, there is a growing focus on their use throughout a medicine’s entire lifespan.” The agency further states that “difficulties remain in accessing these data and methodological challenges associated with their integration and analysis”. [15]

To summarize, the EMA is a major driver in the field of real world data and evidence. A number of promising initiatives are underway to catalyze discussions, the development of new perceptions and mindsets, and the creation of new opportunities for the registration of medicines which tackle a high medical need in a specific disease area. The agency is aware of the fact that the access-versus-evidence conundrum needs to be addressed. However, the previous paradigm for the registration of new medicines only melts down slowly. Most of the proposed tools are based on previously existing regulatory mechanisms (refer to chapter 5). Overall, the regulators appear open for discussion and opportunities; however they still seem to be hesitant up to a certain level to acknowledge full usefulness of real world data which can be explained by a number of concerns brought forward and discussed in more detail in chapter 7 of this master thesis (also refer to figure 4).

5. Innovative Regulatory Initiatives Using Real World Data

Referring to the conclusions of the previous chapter summarizing the regulator's viewpoint, in the following an analysis of the initiatives currently underway in the EU to expedite the development of new medicines will be presented to better understand the current regulatory landscape. The impact of real world data for evidence generation in these tools is significant and reflects the clear commitment of the EMA to improve the previous development paradigm. There are numerous opportunities for pharmaceutical developers to participate, e.g. in tailored regulatory mechanisms making use of real world approaches, and in science driven initiatives with multiple expert stakeholders discussing intensively the strengths and weaknesses of real world data approaches to gain a common understanding about what is considered feasible.

5.1 PRIME

PRIME is a scheme under coordination of the EMA to further intensify scientific and regulatory support with the aim to improve development activities and with the aim to enable accelerated assessment of promising new medicines. The participation in PRIME is voluntary and the sponsor has to apply while meeting certain eligibility criteria. [32] The criteria are the same as for the accelerated assessment. Medicines eligible for the scheme should

- target conditions with unmet medical need for which no satisfactory method of diagnosis, prevention or treatment exists, or if such a method exists, the medicine will be of a major therapeutic advantage, and
- demonstrate the potential to address the unmet medical need, e.g. by introducing new methods of therapy or by improving existing therapies.

The data available at the time of PRIME application should demonstrate the potential of the new medicine

- to bring a major therapeutic advantage to patients in a specific indication by improving the clinical efficacy in a meaningful manner,
- to have an impact on the prevention, onset and duration of the disease,
- or improve the morbidity and mortality of the disease.

PRIME is intended to catalyze the early, continuous and strengthened regulatory interaction between the sponsor and the EU regulatory network. The objective is to generate robust data packages and to make the medicines development as efficient as possible in the shortest possible timeframe. As part of PRIME, the EMA will provide advice to the sponsor about the overall development plan and, more specifically, about possible routes of authorization for the medicine in question. If the medicine fulfills certain criteria, the EMA may propose to follow the Adaptive Pathways approach. The Adaptive Pathways has the potential to gradually extend the targeted patient population by using evidence from the real world (refer to the next section). However, the Adaptive Pathways may not be suitable for all medicines eligible to PRIME and vice versa. PRIME could be the entrance ticket to Adaptive Pathways if the envisaged development plan shows potential to benefit from real world evidence but this route does not represent an automatism.

PRIME is one of the key new features supporting early patient access to medicines in the EU. It can be considered as an overarching scheme for expedited early regulatory support for promising new medicines. Even if PRIME is not specifically dedicated to the generation and usage of real world data it represents an important mechanism in a set of complementary tools to expedite the regulatory process in general. All these tools such as PRIME, Accelerated Assessment, Conditional Marketing Authorization, and Compassionate Use are not mutually exclusive and increasingly incorporate the generation of real world data. PRIME also clearly highlights where the major focus of the EMA lies: Expedited access to innovative medicines addressing a high unmet medical need.

5.2 Adaptive Pathways

Adaptive Pathways is defined as a prospectively planned, iterative approach in bringing new medicines to the market. The iterative development plan will target a well-defined, rather narrow population which most likely will benefit most from the new treatment. Subsequently, iterative phases of evidence generation also including real world data will follow. This may lead to adaptations of the marketing authorization by extending the initial indication or by adding new indications. [33] As a result, and based on more extensive clinical trial and real world data, the target population may grow and expand. The Adaptive Pathways scheme is based on three fundamental principles. Each of the three elements should be included in the scheme:

- Implementation of an iterative development plan, either by
 - the stepwise approval from an initial restricted patient population to an increasingly expanded population (most likely less severe patients or additional indication), or
 - the Conditional Approval based on surrogate endpoints and subsequent confirmation of the benefit risk balance
- In advance identification of areas where clinical trial data could be appropriately supplemented by real world evidence.
- Participation of patient and HTA bodies in discussing the development program of the new medicine to increase the probability that the medicines will be covered by national healthcare systems.

This master thesis puts emphasis on the second bullet point above which explicitly mentions the prospectively planned contribution of real world data to the evidence generation.

The use of the Conditional Marketing Authorization in the Adaptive Pathways is encouraged by the EMA to allow prospective planning of confirmatory post-authorization studies. A Conditional Marketing Authorization may be granted when the risk benefit of the product is positive, unmet medical needs are addressed, however the data set is not comprehensive but it is likely that the sponsor will be able to fill the data gap. [34]

An Adaptive Pathways pilot program has been successfully concluded in July 2016. Since then, the EMA has continued to accept applications in the context of the EMA's Parallel Scientific Advice with HTA bodies (refer to the next section). During the pilot phase, the following case reports of real world data were submitted by different sponsors: [35]

- Use of existing disease registries.
- Single arm studies for rare diseases compared with outcomes concluded from disease registries.
- Open label salvage studies in patients without remaining treatment options to expand the initial indication.
- Post-authorization drug registries for analyses concerning effectiveness, long-term outcomes, drug utilization, patient related outcomes, and time to treatment failure.
- Linking drug registries to risk-sharing schemes for reimbursement.

In December 2016, the EMA held a workshop with numerous Adaptive Pathways stakeholders such as regulators, HTA bodies, payers, academia and pharmaceutical companies. [34] It was noted during the workshop that there is the necessity for more varied sources of evidence to support RCTs which for the time being remain the best tool for measuring the effects of medicines. However, RCTs cannot be used in all cases, e.g. when data are limited, treatments are urgent, or patient groups are small. One of the key questions discussed at the workshop was whether “regulators can still maintain the highest standards of benefit risk assessments. In this regard, many of the discussions around Adaptive Pathways have centered on the proposal to increase the use of real world data in the evaluation of new medicines and what this could mean for patients.” It was further noted that there is a need to be absolutely concise concerning the strengths and limitations of the real world data and how this data could be used to most efficiently support data from RCTs. Rosa Giuliani, a member of the EMA’s Healthcare Professional Working Party and oncologist by training, acknowledged the importance of RCTs. However, she mentioned that “patients enrolled in cancer trials are not truly representative of patients she sees in the clinic. Many patients with cancers who suffer from other conditions, for example, will find themselves excluded from trials for both cancer and the other conditions that they may have. Furthermore, it is estimated that by 2030, 70% of all cancer diagnoses will be for elderly patients, a population routinely excluded from many trials. Real world data can therefore play an important role in plugging the gaps in knowledge and dealing with uncertainty in treatments with new medicines.”

5.3 Parallel Scientific Advice

The Parallel Scientific Advice, also called Parallel Consultation, is a tool to stimulate discussions between pharmaceutical sponsors and healthcare decision makers which was recently developed under the lead of the EMA and the European Network for Health Technology Assessment (EUnetHTA). [37] Products eligible for parallel scientific advice should bring added benefit to patients by

- A new mode of action in the targeted indication,
- AND address a life-threatening or chronically debilitating disease,
- AND address an unmet medical need in situations where no alternative treatments are available or only unsatisfactory treatments are available.

Since classical scientific advice is more focusing on needs of the regulatory agencies to provide approval for marketing authorization, Parallel Scientific Advice is intended to bring together requirements and views from regulators and HTA bodies with the aim to facilitate marketing authorization, market access, successful reimbursement, and pricing. As HTA bodies are looking more and more into robust methods to assess relative effectiveness of new medicines in routine clinical practice to support their decision making, the impact of real world data in this context is gaining importance. The relative effectiveness of an intervention is usually defined as “the extent to which an intervention does more good than harm, when compared to one or more intervention alternatives for achieving the desired results and when provided under the routine setting of health care practice (i.e. real world setting)”. [38]

Due to the fact that RCT based efficacy data is associated with drawbacks to determine relative effectiveness of a medicine, HTA bodies worldwide are currently exploring the opportunities of the usage of real world data to supplement the evidence for a medicine in the relative effectiveness assessment. However, as HTA is still a primarily national duty in the EU, the level of harmonization in this area cannot be compared with the level of harmonization in the regulatory field. [38] With regards to real world data usage, a common policy how to handle alternative evidence generation is lacking. This is certainly important in view of the increasing number of conditionally approved drugs, especially in the oncology and orphan space. EUnetHTA may represent the appropriate platform to bring forward discussions on policy alignments.

The aim of Parallel Scientific Advice is to establish a single platform for advice from regulators and HTA bodies before initiation of pivotal clinical trials to support marketing authorization, reimbursement and post licensing evidence generation. The intention is to have a “maximum gain” by the optimization of opportunities for mutual understanding and problem solving between regulators and HTA bodies. [37] It will be interesting to see how views of the HTA bodies will influence the views of the regulators over time as cooperation in the Parallel Scientific Advice increases between the different stakeholders which may significantly impact the acceptance of real world data for decision making also on the regulator’s side.

5.4 IMI Projects

The Innovative Medicines Initiative (IMI) is a joint public-private partnership sponsored by the Directorate General Research and Innovation of the European Commission. Members of IMI include pharmaceutical companies, academia, HTA bodies, regulators, and patient organizations. [39] It is part of the Horizon 2020 program of the European Commission to fund research and innovation. IMI is intended to improve the competitive environment in the European pharmaceutical research space. One of the objectives of IMI is to reduce research bottlenecks in the development of new medicines. Under the umbrella of IMI, several projects were initiated which are compelling from a real world data perspective. These projects will be described in the following.

5.4.1 MAPPs and ADAPT-SMART

The Medicines Adaptive Pathways to Patients (MAPPs) scheme was brought forward by IMI and seeks to enhance access to beneficial treatments for the right patient groups at the earliest appropriate time in the product life span. [40] MAPPs is investigating opportunities to optimize and potentially shorten steps in the current medicines life cycle. In essence, it has a comparable spirit as the EMA Adaptive Pathways scheme. MAPPs is defined as a multi-stakeholder approach in the development and evaluation of new medicines and promotes an outcome based healthcare approach as a key contributor in the future. In order for outcomes-based healthcare to succeed, MAPPs requires the knowledge of the performance of an intervention, both at the population level and at the individual patient level. The objective of MAPPs is to expand the healthcare toolbox complementing RCT data with real world information.

Accelerated Development of Appropriate Patient Therapies, a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes (ADAPT-SMART) is the enabling platform for the coordination of MAPPs activities by IMI and will support projects investigating MAPPs tools and methodologies. [41] Hans-Georg Eichler, Senior Medical Officer at the EMA, and project leader of ADAPT-SMART, pointed out at the project kick off meeting that MAPPs/ADAPT-SMART will rely on evidence generation through the entire treatment life span of a medicine. He added his personal view that “in the long term, we will see a growing number of products and research questions that can’t be addressed in the conventional RCT. If our attitude is RCT or die, we won’t succeed”. Solange Rohou, Senior Director EU

Regulatory Affairs and Policy at Astra Zeneca, and ADAPT-SMART deputy project leader highlighted at the same meeting that the regulatory environment in the EU is lagging behind the new advanced therapies coming to the market. She added that “the current RCT may not be the only way to address these new therapies in many cases” and that some “of the conventional R&D models of industry may no longer be viable within the current regulatory pathway, and a flexible pathway that measures the performance of a new therapy over its entire lifecycle would not only address patient needs, but also benefit society as a whole.” [41]

5.4.2 GetREAL

GetREAL is an IMI project which started in the year 2013. The objective of GetREAL is to foster the development of new methods to generate real world evidence and to determine how the collection and synthesis of real world data could be implemented earlier in pharmaceutical R&D and in the healthcare decision making process. [42] To achieve these goals, GetREAL is investing in a multitude of areas, e.g:

- Collaborating with key stakeholders in medicine development to assess the acceptability and usefulness of real world evidence and to further refine analytic approaches of real world data sets.
- Studying the scientific validity of real world evidence trial designs and analytical approaches to better inform pharmaceutical R&D and healthcare decision makers on their potential for use in assessment of effectiveness.
- Identifying the operational challenges of performing real world evidence studies early in the medicine development process and developing practical solutions to better inform their planning and delivery.
- Identifying and sharing best practice in evidence synthesis and predictive modelling of different types of data to estimate effectiveness of medicines.

The IMI GetREAL project has developed several tools to enhance the implementation of real world evidence in the planning of pharmaceutical development programs:

- RWE Navigator

The RWE Navigator is considered an educational tool for a variety of users. It is intended to support the identification and definition of the so-called effectiveness issues of a trial design. Effectiveness issues may prevent demonstrating relative

effectiveness of new medicines in a real world based trial. For the trial sponsor it is key to identify the main effectiveness issues prior initiation of the trial and to adapt the trial design accordingly. The RWE Navigator also provides guidance to specific types of appropriate analyses and study designs using real world evidence. [43]

- **PragMatic**

The PragMatic tool was designed to educate trial teams about possible consequences of more pragmatic trial design options. It provides support when handling challenges during trial protocol evaluation on generalizability, validity, precision, stakeholder acceptability and operational feasibility. PragMatic is intended to stimulate the design of randomized pragmatic trials for which experience in executing these kinds of trials is still limited. [44]

- **Aggregate Data Drug Information System (ADDIS)**

ADDIS is a data management and analytical tool to support evidence based decision making in healthcare. It is a structured database of clinical trial results that combines and summarizes the results of individual trials and assesses trade-offs between favorable and unfavorable effects of a treatment. ADDIS uses state-of-the-art methods for evidence synthesis of aggregated data useful in network meta-analysis and network meta regression and supports the researcher to set up a structured benefit risk analysis. [45]

- **Sure-Real**

Sure-Real is a simulation and interactive visualization tool to determine the impact of alternative evidence generation strategies in clinical trial design using real world evidence. The tool is intended to visually design and explore multiple trial scenarios during the creation of evidence development plans. The Sure-Real platform includes the timeline designer, the patient experience manager and the population manager which allow managing the underlying data by introducing modifications. The updated results and metrics are shown on a visual interface. [46]

5.5 The EMA Big Data Workshop

In November 2016, the EMA has called a big data workshop due to the fact that the recent advances in sophisticated computational technologies combined with the expansion of health and biological data are considered to provide unparalleled opportunities for the public health sector; however the EMA saw the need to clarify possibilities and challenges regarding the

exploitation of big data to support medicine development and regulatory decision making. The workshop with numerous stakeholders from regulatory, HTA, academia and industry was intended to stimulate a discussion on this topic. [47]

The overall amount of health care data is immensely increasing every day. The data can be generated from a population level, individual patient level, health or disease data, traditional health measurements, social media, longitudinal data on patient's experiences and many other sources. With these massive amounts of data comes along a more or less unstructured storage in poorly organized repositories. As a consequence, the data can therefore be considered more or less inaccessible or at least difficult to access for scientific precision purposes. [47] Furthermore, big data is noisy and may be prone to missing data sets as well as known or unknown bias. It will be important to understand whether or not the conclusions from big data are of causal nature or based on coincidence. Many challenges associated with big data also apply to real world data. At the workshop it was discussed how these difficulties could be overcome by using common data models like the Observational Medical Outcome Partnership (OMOP) or the Sentinel data models (also refer to section 7.1).

Key conclusions of this workshop were formulated by Guido Rasi, Executive Director, EMA: "The regulatory tools should be put in place to enable use of big data analytics in the regulatory context, so that we are ready to take full advantage of the value of this type of evidence. [...] Data access and use should be for the common good and should not be commercialized. [...] EMA will continue to engage with its regulatory partners and with stakeholders to promote an open and forward-looking vision, aligning the regulators with advances in technology." [47]

5.6 Registries

Patient registries have been defined as an organized system that uses observational study methods to collect uniform data in order to enable the evaluation of specified outcomes for a population characterized by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes. In other words, a patient registry is a collection of standardized information for one or more purposes about a group of patients who share a condition or experience. Registries are considered to be an extremely promising approach to access large amounts of observational real world data in a structured manner. [48]

Despite the fact that high quality registries represent a tremendous asset to the evaluation and monitoring of medicines for public health benefits, a number of challenges were recently observed associated with using existing registries or building new registries to support the assessment during the marketing authorization process. Due to these observations, the EMA has started the patient registry initiative in 2014. After a one year pilot phase and a multi stakeholder workshop in October 2016, the EMA has published a strategy paper on patient registries in May 2017 further defining the mandate of a registry cross committee task force. [49] In essence, the EMA puts forward that several factors including the lack of coordination, harmonized protocols, data sharing and long term sustainability have led to inefficient use of existing registries. The registry initiative is intended to establish an EU wide network to facilitate the collaboration between registry coordinators, healthcare professional organizations, academic institutions, or users of the registry data like e.g. regulators, HTA bodies, or pharmaceutical companies.

The EMA has defined a number of arguments as to why the registry as a tool supported by the registry initiative is of major importance. Those specific arguments which are considered important in the context of this master thesis are listed in the following: [49]

- Patient registries provide observational data from the real world that may contribute to medicines benefit-risk evaluation during the marketing authorization process and post-authorization, depending on the disease area.
- In certain areas, small numbers of patients or events evoke complex demands on medicines evaluation. In such cases RCT data may be limited or unfeasible to collect. The initiative should be supportive in gathering high quality, harmonized registry data that may contribute to the evaluations.
- The registry initiative should enable discussions at an early stage in the authorization procedure to increase use of existing patient registries.
- In such cases where no suitable registry exists to support an authorization procedure, the registry initiative should facilitate the creation of a new registry based on standard methodological approaches to ensure wider downstream applicability.

The EU registry initiative emphasizes the commitment of the EMA to intensify the usage of observational real world data, not only for post marketing purposes, but also for purposes

during the marketing authorization phase by supplementing RCT data or by compensating the lack of data in situations where it is not feasible to perform RCTs.

5.7 Brief Summary of Chapter 5

There are numerous initiatives in the EU to foster the usage of evidence generated from real world. In principle, these initiatives can be divided into mechanisms that are based on iterative clinical development applying existing regulatory procedures and especially targeting medicines that address a specific high unmet medical need, the arrangement of symposia with key stakeholders to foster the discussion of topics with specific interest, or experimental initiatives to enhance the progress of observational research from a more technical point of view (also refer to figure 5).

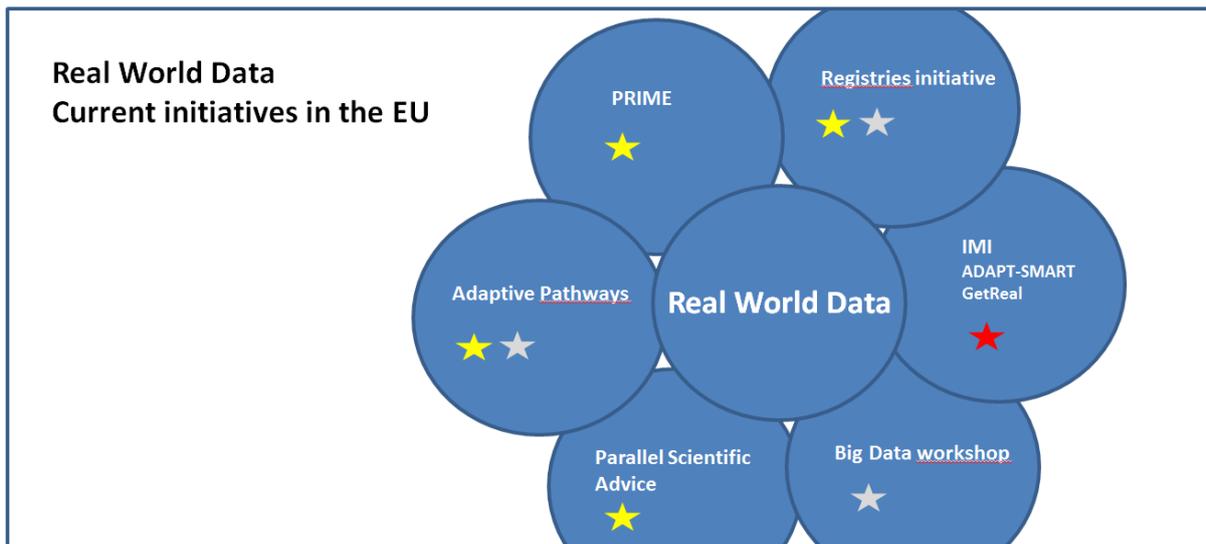


Figure 5: Current initiatives to support the use of real world data in the EU. Regulatory mechanisms using innovative approaches are marked in yellow, workshops with specific interest in grey, programs to enhance observational research in red.

6. Real World Data Case Studies

In this chapter, a number of intriguing case studies from the recent past are presented to provide an understanding at which level the healthcare decision makers in the EU are prepared to accept data from the real world. Reference is made to

- an impressively large pragmatic trial which replicates evidence from registration RCTs,
- an article 31 referral procedure in which real world analyses were used to take final decisions,
- an orphan drug which obtained an extension of the indication based on registry data, and
- a case of conditional reimbursement until registry data will confirm the real world effectiveness of the medicine.

6.1 The Salford Lung Study – A Pragmatic Trial

The Salford lung study is considered a landmark study in the real world space. The study was conducted to examine the safety and effectiveness of a new combined fluticasone-furoate/vilanterol treatment in chronic obstructive pulmonary disease (COPD). Sponsor of the study was the company Glaxo Smith Kline (GSK) in partnership with several local institutions in the greater Manchester area, e.g. NorthWest EHealth, the University of Manchester, the Salford Royal NHS Foundation Trust, hospitals, general practitioners and community pharmacy staff. [50] The study is considered the first digitally enhanced, prospective, pragmatic, open-label, parallel-group, randomized phase III real world effectiveness trial which included a large real world population of patients in a setting of everyday clinical practice. The study was conducted in Salford/UK because of the high prevalence of COPD in this community which is served by a single hospital and an established integrated electronic medical record system, connecting both primary and secondary care. The local pharmacies also collaborated in this trial to allow patients to collect study medication from their usual community pharmacy. Researchers from the University of Manchester have developed an electronic health records system which could be used to conduct and extend the study in near real time. The database system integrated the patient's everyday interactions with general practitioners, pharmacists and hospitals and allowed the safety monitoring of the patients with only minimal intrusion into everyday life. [50]

The strategy behind the design of the study was to maintain the scientific rigor comparable to a RCT by using randomization and active controls; however, the study was intended to be as close as possible to everyday clinical practice due to minimal exclusion criteria, endpoints relevant to patients and healthcare decision makers, as well as an usual care comparator arm in which treatment could be influenced by the treating physician. The inclusion criteria were as simple as: Age above 40 years, a general practitioner's diagnosis in COPD, the patient being on a maintenance therapy and exhibiting the ability to give consent. Any other concomitant disease, smoking, or social history was not impacting the eligibility of the patient. [51]

The authors of the Salford COPD study concluded that in patients with COPD and a history of exacerbations, a once-daily treatment regimen of combined fluticasone-furoate and vilanterol was associated with a lower rate of exacerbations than in usual care, without a greater risk of serious adverse events. Another comparable Salford trial analyzed the management of symptomatic asthma. The authors of the Salford Asthma study concluded that in patients with a general practitioner's diagnosis of symptomatic asthma and treated with maintenance inhaler therapy, initiation of a once-daily treatment regimen of combined fluticasone-furoate and vilanterol improved asthma control without increasing the risk of serious adverse events when compared with optimized usual care. [52, 53]

The COPD trial enrolled 3161 patients in total, the Asthma trial enrolled 4725 patients in total.

Overall, the Salford lung trials demonstrate the feasibility of well designed, large, randomized pragmatic trials with a design closer to everyday clinical practice than conventional RCTs and with a conclusive outcome. The trials confirmed the previously obtained results from RCTs. There were significant logistical challenges which could be overcome in this specific setting. In summary, the Salford trials are promising examples how pragmatic approaches in clinical trial design may develop and contribute to the evidence generation of medicines in the future.

6.2 Metformin in Renal Impairment – Article 31 Referral

Metformin is an active substance in the group of biguanides which is indicated since decades to treat insulin dependent type 2 diabetes mellitus. It is one of most prescribed oral anti-diabetics and considered first line therapy in the EU. The molecular mechanism by which

metformin induces its effects is still not fully understood. The main effect on blood sugar is thought to be mediated by its inhibition of hepatic gluconeogenesis. [54]

In the past, the use of metformin in patients with diabetes and renal failure was not harmonized throughout the EU with contraindications in patients with different stages of moderate renal failure depending on the country and national product. This safety labeling was based on a potential risk of lactic acidosis in patients with moderate or severe renal impairment. The EMA considered the labeling of metformin to be re-evaluated because many patients in this population with renal impairment may not have been able to benefit across the EU from the benign effects of metformin. Therefore, in 2016 the EMA initiated a referral procedure under article 31 of Directive 2001/83/EC to achieve an EU wide consensus on this topic. [55]

After review of the available data, the CHMP concluded that the efficacy of metformin to reduce blood glucose in the population with moderate renal impairment was confirmed. With regards to the safety in the population in question, a number of important studies were analyzed. Among those two large meta-analyses including data back until 1950 were considered, a retrospective observational cohort study in type 2 diabetes patients with end stage renal disease using metformin despite contraindication, and two studies using the UK Clinical Practice Research Datalink (CPRD) as a reference. The CPRD is a governmental, not-for-profit research service in the UK, jointly funded by the NHS National Institute for Health Research (NIHR) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA). The objective of the CPRD is to provide anonymized primary care records for public health research. [56]

One of the studies using CPRD analyzed if diabetic patients on metformin have an increased risk of lactic acidosis at different levels of renal impairment in comparison with patients on metformin and normal renal function. [57] The primary outcome of the study was defined as lactic acidosis based on the CPRD read code. The study included 77.601 metformin treated patients between the years 2007 and 2012. The authors concluded that there is no difference in the incidence of lactic acidosis in patients with normal, mild, moderate or severe renal impairment. The same conclusions were made by the authors of the second study using the CPRD which was conducted totally independent from the first study. [58] The second study analyzed lactic acidosis defined by either CPRD read code or an elevated record of plasma

lactate as the primary outcome. The study included 223.968 patients treated with metformin. In the EMA assessment report the following is noted: “In both studies, no significant difference between the rates of lactic acidosis in patients with normal, mild or moderate renal impairment were found, especially when taking into account the wide confidence intervals observed in both studies. Some trends for correlation between lactic acidosis rates and declining renal function could be noticed; however both studies did not adjust for comorbidities between the CKD stages, making it thus impossible to compensate for confounding effects. Accordingly in the study by Richy, a clear increase of confounding conditions associated with lactic acidosis and declining renal function was found, which indicates that there might be other reasons unrelated to metformin in the increasing incidence of lactic acidosis in increasing renal impairment.”

The final conclusion in this referral procedure was that the possible increased risk of lactic acidosis in patients with diabetes and moderate renal impairment could be “sufficiently minimized”. Appropriate changes were requested to the Summaries of product characteristics (SmPCs) and package leaflets including a revised dosing recommendation, additional monitoring of renal function before and during treatment, and updated warnings and precautions. [55]

Overall, this referral case study demonstrates the importance of observational data including real world patient related outcomes for the evaluation of safety concerns of marketed products. It is important to note that this data can support labeling changes including a revision of the indications or contraindications as part of an EU wide referral, even for a well-established product which is in clinical use since many decades.

6.3 Eculizumab – Extension of Indication

Eculizumab, a monoclonal antibody manufactured by the company Alexion and marketed under the tradename Soliris, is registered in the EU as an orphan drug for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). [59] PNH patients have a reduced median survival of approximately 15 years from diagnosis. PNH is associated with multiple serious morbidities, several of which are potentially life threatening. The common clinical manifestations of PNH are hemolytic anemia, venous thrombosis and deficient hematopoiesis. In 2013, the treatment with eculizumab was considered to be the most expensive therapy with treatment costs of up to 600.000 EUR per year and per patient. [60]

The clinical development program which was designed to investigate the use of eculizumab as a treatment for patients with PNH is based on one pivotal randomized, blinded, placebo controlled trial (TRIUMPH study) and a non-comparative supportive trial (SHEPHERD study). Due to the design of the TRIUMPH study, the indication included the following restriction: “Evidence of clinical benefit of eculizumab in the treatment of patients with PNH is limited to patients with history of transfusions”.

In April 2014, Alexion submitted a type II variation to extend the indication from patients with a prior history of transfusions to patients with and without a prior history of transfusions. The extended indication still falls within the previous orphan designation. The variation was approved by EMA one year later. [61]

The approval by the EMA was based on a prospective, observational study using data from a PNH registry. The primary objective from the PNH registry was to collect data to

- evaluate the safety related to the use of eculizumab, and
- characterize the progression of PNH as well as clinical outcomes, morbidities and mortality in patients treated with or without eculizumab.

The primary endpoint in the registry was the change in lactate dehydrogenase (LDH) from baseline up to 6 months between eculizumab treated patients with no history of transfusion and never treated patients with no history of transfusion, reported as absolute changes in LDH values from baseline up to 6 months and LDH values at 6, 12, 18 and 24 months. [61]

A total of 1547 patients were enrolled in the PNH registry. The registry was designed to enrich the population for patients more likely to require a transfusion in the six month period. Prior submission of the variation, the possible use of the data from the PNH registry in patients without a history of transfusion was discussed with the Committee for Human Medicinal Products (CHMP) via protocol assistance. The Scientific Advice Working Party (SAWP) agreed with the proposal to use the data from the PNH registry in a type II variation with the aim to update the indication of eculizumab. The conclusions in the EPAR were the following: “The efficacy of eculizumab is shown in patients with PNH independently of prior transfusions who present with hemolysis and display relevant clinical symptoms. The data presented are supportive of the amendment. The indication of PNH is therefore amended as follows (bold was added, strikethrough was deleted):

Eculizumab is indicated in adults and children for the treatment of patients with PNH. Evidence of clinical benefit of eculizumab in the treatment of patients with PNH is limited demonstrated to in patients with history of transfusions hemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history.”

This case study is a convincing example how real world data can be used to extend indication claims under very specific conditions. Given the challenges of the disease and the previously demonstrated efficacy of eculizumab in the disease, a prospective randomized controlled study including a non-treatment group was not feasible. Therefore, data from the PNH registry was considered appropriately supportive to extend the target population.

6.4 Elosulfase Alfa – Conditional Reimbursement

Elosulfase alfa, marketed by the company BioMarin under the tradename Vimizin, is indicated as an orphan medicinal product for the treatment of the Morquio A syndrome and approved in the EU since the year 2014. Morquio syndrome is a rare inherited metabolic disorder and manifests primarily as a progressive skeletal dysplasia involving the spine which is the major cause of morbidity and mortality in these patients [62, 63]. Further symptoms are hearing and vision loss, heart valve abnormalities and pain. Morquio syndrome, also referred to as mucopolysaccharidosis (MPS) type IV, is caused by a genetic aberration leading to a deficiency of the enzyme N-acetylgalactosamine-6-sulfatase, for which elosulfase alfa is a recombinant substitute and usually given by weekly intravenous infusion. As the treatment is not a cure, infusions will have to be given for the entire patient’s lifetime. Elosulfase alfa is the only medicine available specifically targeting the Morquio syndrome. [64]

The elosulfase alfa case is an intriguing example how real world data could be required in the future to manage market access and coverage of innovative high cost interventions. In the UK, the NHS has negotiated with the marketing authorization holder a conditional five year fixed fee agreement which was the first of this kind in the UK. The agreement includes a managed access scheme for patients and an effectiveness monitoring to confirm the benefits of elosulfase alpha in clinical practice before further funding decisions will be taken. [65] The following points are part of the managed access agreement:

- A protocol that defines the clinical criteria for starting and stopping treatment with elosulfase alfa, e.g. patients must have a confirmed diagnosis including confirmed enzymatic testing and mutation analysis.
- The assurance from the marketing authorization holder to collaborate with the MPS Society and NHS England to collect patient's anonymized data and support the MPS IVA registry (MARS registry). The main objectives of the registry are:
 - Characterization and description of the MPS IVA population, including the heterogeneity, progression and natural history of the disease.
 - Evaluation of the long term effectiveness and safety of elosulfase alfa.
 - Support of the MPS IVA medical community with the development of recommendations for monitoring subjects to optimize patient care.

The data in the registry will be used by NICE to perform an effectiveness review five years after publication of the access agreement.

The conditional nature of the coverage was justified by the NHS assessment as the medicine is considered to improve specific aspects of the quality of life of the patients, however long term benefits were uncertain. Furthermore, the drug was considered expensive with an estimated cost of approximately 400.000 pounds per year and per patient. [66] Important to note that if NICE would not confirm elosulfase alfa in the five year review, patients would have to discontinue NHS covered treatment with the medicine.

With regard to the managed access contract between the marketing authorization holder and the NHS, Barbara Hakin, NHS National Director, pointed out: “This agreement will enable us to start treating people with this debilitating condition, assess whether this treatment provides real benefits in the long term and, assuming it does, then continue to provide it in a sustainable way. This drug is not a cure but it can have benefits for patients, though long-term outcomes remain uncertain. NICE was right to highlight the very high list price, which would have a disproportionate impact on the availability of other treatments. “ [67]

This case study shows how real world data could be used in the future to provide periodic demonstration of effectiveness in clinical practice with the objective to maintain coverage by payers. It also shows that payers may be willing to justify coverage of expensive cutting edge medication in specific situations when the medical need is high and when effectiveness in the target population is confirmed at regular intervals.

6.5 Brief Summary of Chapter 6

The case studies discussed in this chapter demonstrate the feasibility of a large pragmatic trial confirming conclusions drawn from previous RCTs (Salford lung study), how real world data is used to take decisions in a safety referral of a medicine which is marketed since many years (metformin containing products), the extension of an indication based on real world data in a situation of high unmet medical need (eculizumab), and how periodic confirmation of real world effectiveness could be used to maintain sustainable coverage of a medicine (elosulfase alfa, also refer to figure 6).

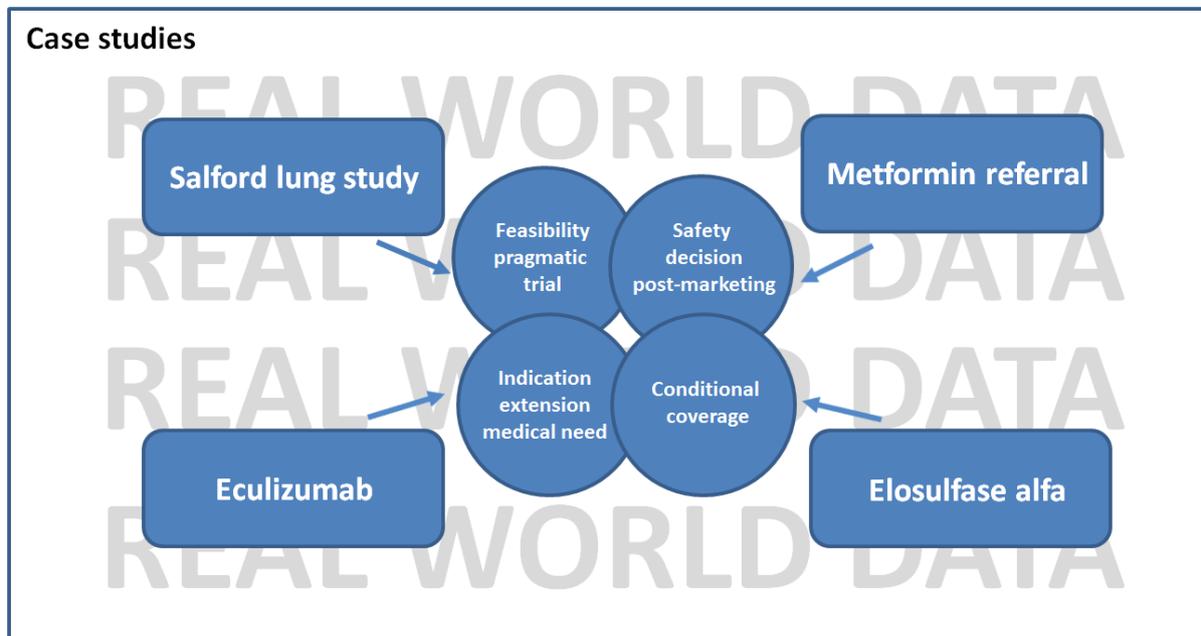


Figure 6: Case studies analyzed in this master thesis. The examples emphasize current applications of real world data in the design of large pragmatic trials (lung study), the regulatory safety and labeling decision making (metformin and eculizumab), and the pharmacoeconomic decision making (elosulfase alfa).

7. Key Challenges Associated with Real World Data

The amount of health and biological data is increasing every day at an incredible pace. In parallel, the computational technologies to gather and analyze these massive amounts of data are getting more and more sophisticated which generates unprecedented opportunities for potential users of real world data. However, despite the obvious opportunities there are still a number of challenges to be addressed before stakeholders will be able to benefit from the entire wealth of the available information. In many cases, the data was stored for other purposes but not for systematic healthcare research. This leads to fact that the data is noisy, many sets of data may just be missing, and different databases one would like to analyze with a common goal are simply not technically compatible.

In the following, the current major challenges and mitigation strategies related to real world data analysis are discussed.

7.1 Data Access

The real world data one would like to analyze is not necessarily the property of the own organization. The most insightful data is usually captured at healthcare providers, hospitals or academia, all of them not having the primary interest or resources to perform targeted observational research. Accessing the data also may require purchasing information from commercial organizations or approaching federal institutions like the CPRD (see also section 6.2). A large number of companies appear on the scene promoting easy access to electronic health records, registries, administrative healthcare data, or survey data from countries all over the world. Consequently, as the topic currently increases in awareness, the number of companies specializing in the targeted access to real world data will probably even multiply in the short run. [68]

Still, there may be hurdles in creating access to the appropriate data for a specific purpose. As a consequence, experts in the field emphasize that the building of networks and collaborations across the community is vital to the success of the observational research project. Interestingly, experts emphasize that it may be preferable to have a science based approach including public and private expert collaborators instead of proprietary access to data sources. The outcome may be a rather collaborative environment developing new technologies and standards, finally driving the sharing of knowledge. [69] An excellent example for such

collaboration is the IMI Electronic Health Records for Clinical Research (EHR4CR) which has officially ended in 2016; however currently embarking on several follow up initiatives. EHR4CR has involved 35 academic and private collaborators, among those ten pharmaceutical companies. The project also included eleven hospitals in France, Germany, Poland, Switzerland and the UK. As a result, the EHR4CR has developed a scalable platform utilizing de-identified data sets from hospital electronic health records. The platform is intended to enhance protocol feasibility assessment, patient identification for recruitment, clinical data exchange, and safety reporting. According to EHR4CR, all activities were done in full compliance with the ethical, regulatory and data protection policies of the participating countries. [70, 71] The European Institute for Innovation through Health Data (i~HD) has emerged out of the EHR4CR project. i~HD is a not-for-profit organization to develop and promote best practices in the governance, quality, semantic interoperability and uses of health data, including its reuse for research. An important role of i~HD is to provide independent governance oversight with regard to clinical research platforms and their expanding networks of hospitals. [72]

To summarize, it becomes obvious from the above mentioned examples that the generation of public-private partnerships is essential to fruitfully facilitate data access and foster the generation of new policies and standards in this highly agile area of medical research.

7.2 Data Diversity

As mentioned above and in section 5.5 of this master thesis, the risk with big data of any kind is that it may be generated in a comparably unstructured fashion and stored in poorly organized repositories. As a consequence, it appears to be rather unusable for precision research purposes. Experts in the field point out that to maximize the opportunities in public health, any data generated in the real world should be F-A-I-R as brought forward by the principles of the Future of Research Communications and e-Scholarship (FORCE11) initiative: [73]

- Findable

Data are assigned a globally unique and eternally persistent identifier and described by rich metadata.

- Accessible
Data are retrievable by their identifier using a standard communication protocol while the protocol is open, free, and universally implementable.
- Interoperable
Data use a formal, accessible, shared, and broadly applicable language.
- Reusable
Data have a plurality of accurate and relevant attributes and are released with a clear and accessible data usage language.

The principles by FORCE11 illustrate the pressing need to agree on common denominators on a worldwide level to be able to leverage synergies from different data sources. This topic leads directly to another technical issue concerning big data which is touching on the integration of data from various sources for the purpose of a common analysis. Initiatives like the Observational Health Data Sciences and Informatics (OHDSI) collaborative are trying to overcome this barrier by striving to bring out the value of observational health data through large scale analytics. Under the umbrella of the OHDSI, the Observational Medical Outcomes Partnership (OMOP) common data model was developed which allows for the systematic analysis of disparate observational databases. [74] The concept behind OMOP is to transform data from disparate databases into a common format and a common representation. This step enables a subsequent systematic analysis using a library of standard analytic routines. The OMOP approach can be useful if one would like to commonly analyze differing observational databases which were intended for essentially different purposes, e.g. comparing a database including electronic medical records aimed at supporting every day clinical practice with a database including administrative claims supporting the insurance reimbursement processes. The analyses may have implications in safety monitoring, comparative effectiveness research, clinical research and health economics by providing answers to the following questions:

- What happened to these patients? (clinical characterization)
- What will happen to a specific patient? (patient level predictions)
- What are the causes for the observed effects? (population level effect estimation)

In the EU, IMI is running the European Medical Information Framework (EMIF) project. EMIF has adopted the OMOP common data model and is currently mapping several electronic health records databases. The objective is to build an integrated information

framework for consistent re-use and exploitation of available patient-level data. The underlying platform will leverage data on approximately 40 million European adults and children by aggregating healthcare databases and cohorts from Denmark, Italy, Netherlands, UK, Spain, and Estonia and it is designed to be representative of different types of existing data sources, e.g. population-based registries, hospital-based databases, cohorts, and national registries. [75, 76]

The US FDA currently has access to several big data sources from the Sentinel initiative and the Centers for Medicare and Medicaid Services. These currently cover more than 200 million patients in the United States. Through the Sentinel platform which also uses a common data model like OHDSI, access to administrative data from different health insurance sources can be provided including demographics, time under observation, hospital and doctor visits and pharmacy dispensing. These data can be complemented by data from electronic health records. Currently, the focus of Sentinel is to obtain information on the safety of approved medical products. However, the FDA is engaged in promoting synergies and identifying opportunities for the broader use of Sentinel together with US research networks like the National Institutes of Health (NIH) Collaboratory Distributed Research Network and the Patient Outcomes Research Network (PCORnet). [77]

The above mentioned initiatives are no doubt extremely ambitious and promising and only just about starting to leverage the potential of real world data analysis. However, important to note that a recent investigation from OHDSI emphasized the bias which may be inherent to observational study design and which is an everlasting criticism with regard to outcomes reported from real world data. OHDSI suspected a bias towards reporting of statistically significant exposure-outcomes pairs with a p-value below 0.05. It was suggested that this may be due to e.g.: [78]

- Observational study bias
 - Selection bias

Selection bias can occur when the study population is not a random selection from the target population. As a result the recruited population may not be representative. To best avoid this bias, the objective should be to achieve a maximum participation rate in order to obtain a representative cross-section of the target population.

- Information bias
Information bias results from false or inexact recording of study relevant individual parameters and can be caused by measurement error, misclassification of categorical variables or interviewer bias. These factors can be partially influenced by good study planning or standardized interviews.
- Confounding
A confounder could be a risk factor for the disease under study, which is associated with the exposure of interest, but is not part of the causal pathway between exposure and the end point. Observational studies are usually evaluated with regression models. The potential confounders should be incorporated in the model as explanatory risk factors.
- Publication bias
Publication bias occurs when the publication of research results depends not just on the quality of the research but also on the hypothesis tested, and the significance and direction of effects detected. [79]
- p-hacking
Also termed “specification searching”, is the manipulation of research results through data mining with the aim to artificially reduce the p-value below 5%. [80]

To tackle these issues, an intensified discussion is required throughout the entire observational research community with the aim to identify or develop reliable methods for data analysis and to enable usage of observational big data for regulatory decisions.

7.3 Data Privacy

The opportunities lying in the analysis of real world data are manifold. However, privacy concerns can be a critical barrier to making progress in this field. As mentioned at the recent Big Data EMA workshop: “BIG data brings BIG opportunities but also BIG responsibilities”. The aggregation of real world data from diverse sources requires the implementation of complex and more comprehensive databases. This continuously growing complexity comprises an increased risk to privacy. Therefore, the privacy practices put into place for real world data analyses need to be able to protect patients and companies. [47]

According to surveys, the majority of patients is supportive of medical records research. Also patient groups have expressed the willingness to share data if the purpose is to advance research or to support the treatment of other patients. In the EU Nordic countries, mandatory health registries have been established with wide acceptance throughout the population. In these countries, consent to usage of patient data is interpreted as a part of a contract for receiving free healthcare. Ethical review boards are established to supervise that the data is handled appropriately and that the patient's privacy is maintained. It has been shown that communication to adequately address privacy concerns in the public has rendered the general perception more positive. Therefore, appropriate information needs to be channeled to those concerned groups which may have a risk of misinformation or requiring additional education. It will be key to adequately communicate on the opportunities and risks of data sharing, inform patients about how their data is going to be used safely in the planned analyses, and what the benefits will be for all stakeholders by doing this observational research. [81]

A milestone in regulating data privacy in the EU is the recently adopted General Data Protection Regulation (GDPR). It will become enforceable in May 2018. The primary objective of the regulation is to give control to citizens over their personal data and to simplify the legal regulatory environment for international business. The regulation applies to all companies processing the data of subjects residing in the EU, regardless of the company's location. Organizations in breach of GDPR can be fined up to 4% of the annual global turnover or 20 million EUR, whichever is greater, e.g. for not having sufficient consumer consent to process private data sets, for not having the records in order or for not notifying the supervising authority as well as the data subject about a data breach. Importantly, data clouds will be part of the GDPR enforcement. The conditions for consent have been strengthened as the subject consent must be obtained in an intelligible and easily accessible form using clean and plain language. The withdrawal of consent must be as easy as giving consent. The rights for the subjects themselves have also been expanded. With GDPR, the subject has the right to obtain confirmation as to whether or not personal data concerning the subject is currently being processed, where it is processed and for what purpose it is processed. Further, the subject has the right to obtain a copy of the concerned personal data free of charge. [82]

In summary, the measures under GDPR should significantly enhance data transparency and subject empowerment. Overall, GDPR is intended to provide increased accountability to

increase public trust. The regulation is therefore considered to be an effective tool to help improve the design of studies and the quality of data.

7.4 Brief Summary of Chapter 7

The key challenges associated with real world data are mainly based on their largest advantage: huge amounts of data sets from patients in every day clinical practice. There are significant efforts ongoing to mitigate risks with regard to data access, data diversity, and data privacy. These initiatives can originate from public or private sponsors or a combination of both. In essence, it is obvious that a mutual effort has to be done to leverage the wealth of real world information which should mainly be based on scientific collaborative interactions acknowledging the need for legal accountability and transparency (also refer to figure 7).

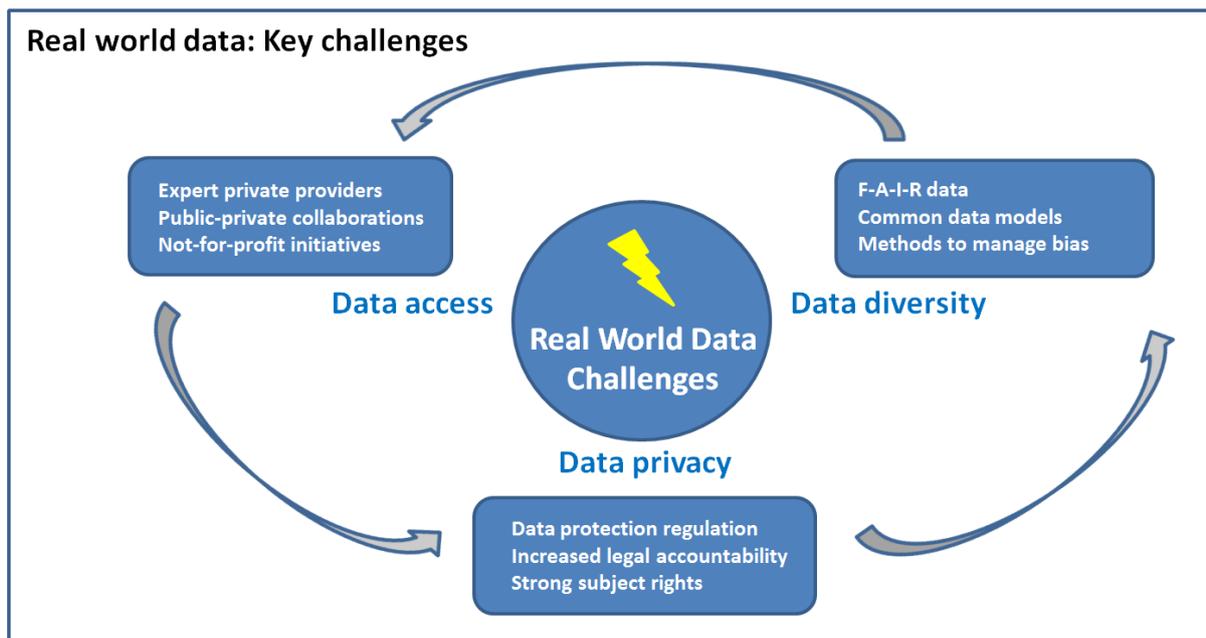


Figure 7: Key challenges associated with the use of real world data. The risks with real world data usage are mainly relating to data access, data diversity, and data privacy. The observational research community has embarked on numerous mitigation strategies involving public-private collaborations as well as legal accountability and transparency.

8. Final Conclusions and Outlook

This master thesis provides an in depth analysis concerning real world data and its penetration into the current regulatory space in the EU. The major conclusions drawn from this analysis are (also refer to figure 8):

1. There is still significant discussion ongoing in the expert community concerning the basic definitions of the terms real world data, efficacy and effectiveness; however an overall common understanding has been reached by initiatives especially from organizations like ISPOR and IMI which provide an appropriate working basis.
2. There are meaningful current applications of real world data during the lifecycle of a medicine, e.g. to inform the R&D process in the light of stratified medicine or to confirm if a medicine's effect can be translated in every day medical routine. The key drivers of real world analysis are still post-marketing safety surveillance and market access considerations.
3. The EMA exhibits a strong commitment to create an innovative path forward in this field and to support promising new approaches. Guido Rasi, EMA Executive Director, summarized the regulator's position at the end of a workshop on big data in November 2016: "The tools and data described in this workshop will not replace randomized clinical trials, but will improve clinical trials and also complement trial data, supporting decision-making on medicines. Regulators need to better understand how to use these types of information to support future decision-making and must be able to differentiate between causality and coincidence." [47]
4. Numerous regulatory initiatives are ongoing to foster further development of innovative approaches for the utilization or analysis of real world data during the registration of a new medicine. These mechanisms are focusing on interventions which address a specifically high medical need or situations where the feasibility of classical RCTs is limited.
5. There are case studies available representing intriguing examples where beneficial usage of real world evidence has been reported and from which one can estimate even more opportunities in the future. The cases presented in this master thesis include the first large pragmatic trial, an EU safety referral, the extension of an orphan indication based on registry data, and the conditional coverage of a specialty high cost medicine.

6. The limitations on the use of real world data are intensively discussed in the community and concern mostly data access, data diversity, and data privacy. Numerous initiatives have been initiated to mitigate these limitations. Taking into account the amount of these initiatives, it gets obvious how agile this field currently is and how intensively the community is working on interdisciplinary approaches to overcome the main challenges and provide answers for the future to leverage the opportunities.

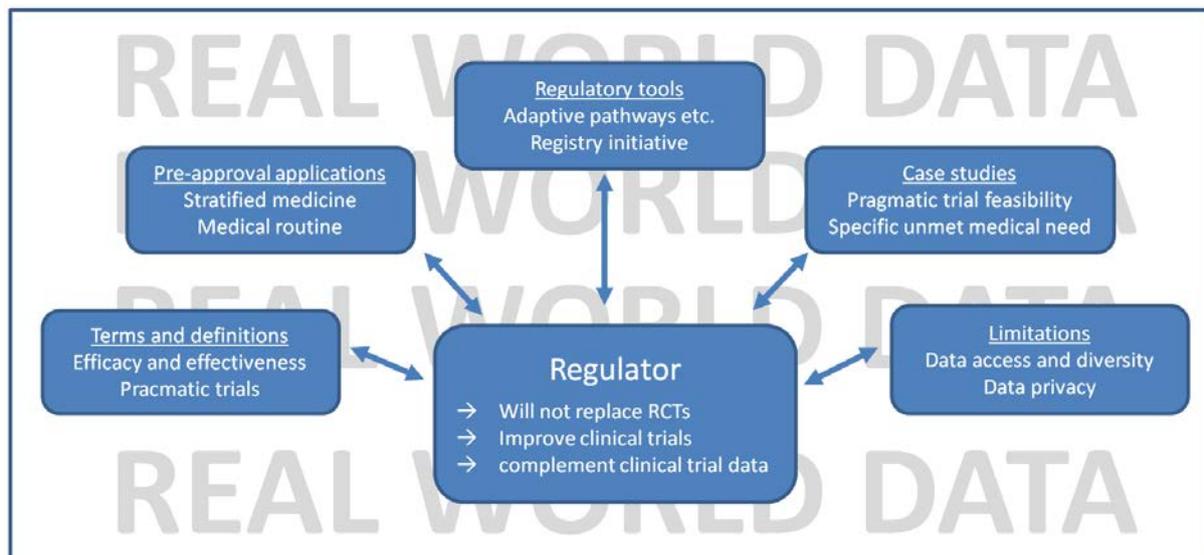


Figure 8: Analysis of the regulatory environment with respect to real world data. Numerous factors and activities influence the current regulatory opinion in the EU. The actual EMA position can be described as follows: Real world data will not replace traditional RCTs but improve clinical trial design and complement clinical trials in the decision making process.

To summarize, there are many initiatives and discussions ongoing in the regulatory and pharmaco-economic area to support the application of real world evidence in the decision making processes. It is the author's perception that many stakeholders are extremely committed to move this topic forward; however the tools and strategies still require some further attention from all involved parties to enable full leverage of the potential of real world data synthesis for evidence generation. This is probably where the next steps have to take place and where the common understanding needs further amplification. There are numerous tools available or under further development to increase precision of observational research. These will, if consistently applied, increase the trust into the obtained outcomes. The

feasibility of large pragmatic trials has recently been demonstrated with comparable results to previous RCTs. The community is aware of the drawbacks of real world data usage and mitigation strategies are under development. To make the next steps, further official guidance from the regulators and associated institutions is eagerly awaited. It should be clarified by the regulators which data and analyses are considered appropriate to make subsequent product claims. As an example, in the US the FDA has recently published guidance on how to use real world evidence in the registration of medicinal devices. This guidance needs to be expanded to medicinal products and the EMA should follow the FDA and publish clear guidance to enable next level discussions. [83]

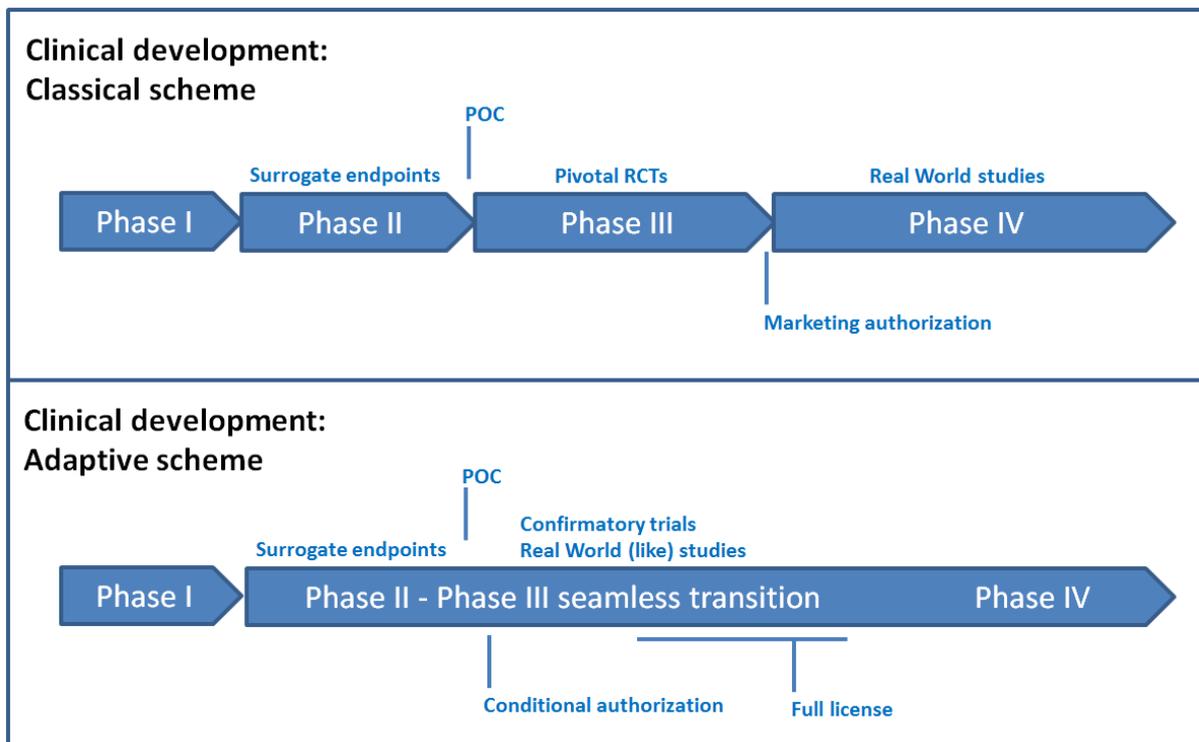


Figure 9: Schematic overview comparing classical clinical development with the innovative adaptive scheme. Sponsors developing promising medicines that address a high unmet medical need may reduce substantially the time to (conditional) authorization and patient’s access based on a launch shortly after clinical proof of concept (POC). Real world evidence can play a crucial role to support the full license and will be available significantly earlier compared to the classical approach.

Another area of specific interest is the growing interaction between regulators and HTA bodies at European level, catalyzed by the EMA and the EUnetHTA. For reimbursement decisions, HTA bodies are under tremendous pressure by payers and patient organizations to conclusively show relative effectiveness and added benefit of a medicine in every day clinical practice. The HTA bodies increasingly rely on data from the real world to meet these objectives. The more they interact with regulators and the more both parties influence each other, e.g. in the Adaptive Pathways scheme, the more one can expect a common understanding on key positions. This could nourish obvious discussions on the commonalities and differences of the acceptability of real world data for the decision making processes. Currently, we have more or less two separate systems: On the one hand the regulatory environment with the regulatory agencies as the major decision makers basing their decisions on efficacy considerations; on the other hand the pricing and reimbursement environment with the HTA bodies and payers as the major decision makers basing their decisions to an increasing degree on relative effectiveness considerations. At the end of the Big Data workshop, Guido Rasi stated that “the knowledge generated from large data sets and new computing technologies is as relevant for the work of HTA bodies as it is for regulators” and “the boundary between regulators and HTA bodies may be naturally dissolved by the coming wave of evidence”. [47] Consequently, one could argue that regulators and HTA bodies are currently approaching each other and the topic of real world data use could serve as a catalyst in the discussions due to the fact that there is increasing interest on both sides.

Taking together the above, the following highly relevant questions arise: Which data is essentially crucial to deserve a marketing authorization? Should it be data demonstrating that the medicine is efficacious in an extremely controlled environment, like in the past, or should it be data illustrating that the medicine has a high likelihood to show effectiveness in the real world? Finally, both aspects may have to be taken into consideration. However, from a patient’s and payer’s perspective the latter is certainly the key argument which puts even more weight on pharmaco-economical aspects. As a consequence, the importance of the real world component may gradually increase in the future even in earlier phases of the medicine’s life cycle. One potential scenario could be that “pragmaticness” of the pivotal trials in medicine development may increase over time. Alternatively, the regulators may request one RCT and one large pragmatic trial instead of two separate RCTs for the registration of a new medicine. Many scenarios are possible and it is unclear where the system will exactly migrate.

In case of promising innovative medicines addressing a specifically high unmet medical need, the clinical development will most probably move away from strict exploratory and confirmatory phases to more seamless adaptive trial designs with conditional approval and market entry early after clinical proof of concept based on surrogate endpoints (also refer to figure 9). [84] Real world data is expected to play a much more prominent role earlier in the development compared to the classical approach. Whatever is going to be applied in the future, it is obvious that the regulatory community has started to question previous paradigms and things have begun to move.

Further crucial questions that arise from the above are the following: Why are regulators and HTA bodies located in two separate silos? How close can we bring registration and value requirements together, with regard to real world data and beyond? In principle, the combined analysis of a matched submission dossier by regulators and HTA bodies could be feasible. However, the reimbursement space, in contrast to the regulator's space, is dominated by national country specific budgetary interests and the level of EU harmonization of HTA bodies is comparably low which currently still prevents a joint evaluation at HTA level. [85] The founding and acceptance of EUnetHTA has been a step towards reduced fragmentation, but the HTA environment is lagging behind and further commitment is required to drive harmonization among national bodies. However, the enhanced interaction between regulators and HTA bodies to support iterative pharmaceutical development may help to harmonize not only the views between regulators and HTA bodies but also between HTA bodies across the EU. The short-term vision by the EU commission is to have an increasing level of cooperation between EU HTA bodies on procedures concerning medical, economic, and ethical aspects, with primary focus on a mutual recognition process in the assessment of relative effectiveness, as budgetary processes are considered much more difficult to harmonize. [86, 87] Vytenis Andriukaitis, EU commissioner for Health and Food Safety, pointed out during the EC-EUnetHTA forum in October 2016 that “the commission has supported voluntary cooperation on HTA for more than 20 years [...] Now it is time to take the next step to build a permanent, sustainable mechanism for EU cooperation on HTA [...] avoiding duplication in the assessment of the same product or intervention”. [88] Ultimately, a long-term vision that is supported by the conclusions in this master thesis, may be to drive the development of a combined regulatory and HTA institution in the EU which takes decisions concerning both efficacy and effectiveness parameters of the new medicine based on a submission dossier

enriched by pragmatic and real world data. Consequently, the combined agency could provide a marketing authorization as well as a recommendation on the eligibility of an EU wide reimbursement status (refer to figure 10). The fact to liberate synergies in this extremely complex environment would certainly be appreciated by many stakeholders and contribute to the expedited access to new medicines. The development of a common understanding how to integrate real world data most efficiently in the registration and market access activities may help building a bridge between regulators and HTA bodies and enhance further harmonization at EU level.

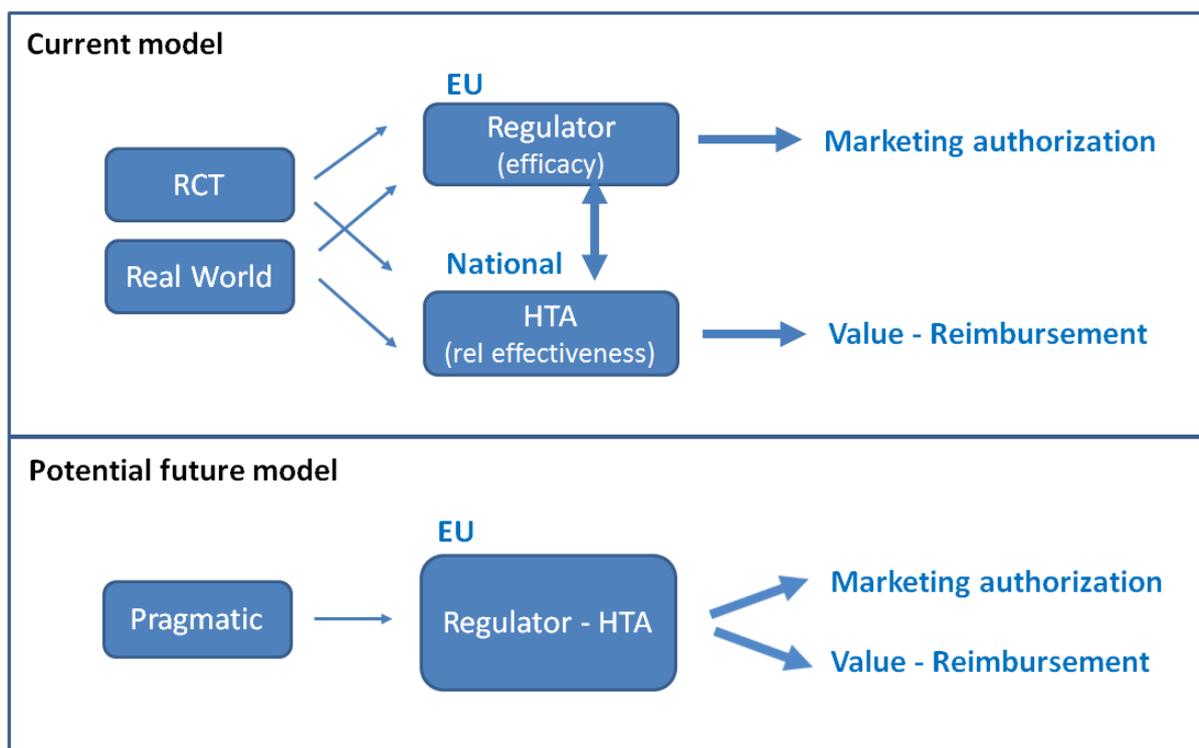


Figure 10: Schematic comparison of simplified models concerning interactions between regulators and HTA bodies, current and future. Today, regulators mostly rely on RCTs and supportive real world data for decision making. The interaction with HTA bodies is of increasing importance. It is discussed in this master thesis if the environment could change into a system where pragmatic trials may be acceptable for both marketing authorization and value recommendations, provided by a single European institution incorporating efficacy and effectiveness considerations.

To conclude, in this master thesis it could be demonstrated that real world data already has a significant impact on regulatory processes which are in place today. The strongest current impact was identified on post-marketing surveillance and complementation of pre-registration RCTs. Further, numerous tools are brought forward by the regulators to develop and implement new procedures based on evidence from the real world to strengthen real world impact earlier in the medicine's lifecycle. These are especially targeting situations when the medical need is high with the overall goal to expedite the pharmaceutical development and the patient's access to innovative medicines. Other expert initiatives have the objective to enhance the discussion on the utility and development of real world data synthesis, and how the observational research community could best use these insights. Considering all these activities and projects underway, especially with regard to the recently strengthened cooperation between regulators and HTA bodies, it can be estimated that the impact by real world data will increase in the near future not only on the regulatory, but on the overall healthcare decision making processes across the entire medicine's lifecycle. Potential synergies between regulatory and HTA related decision making may even intensify the harmonization of processes concerning market authorization and market access at the European level.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Ort, Datum

Unterschrift