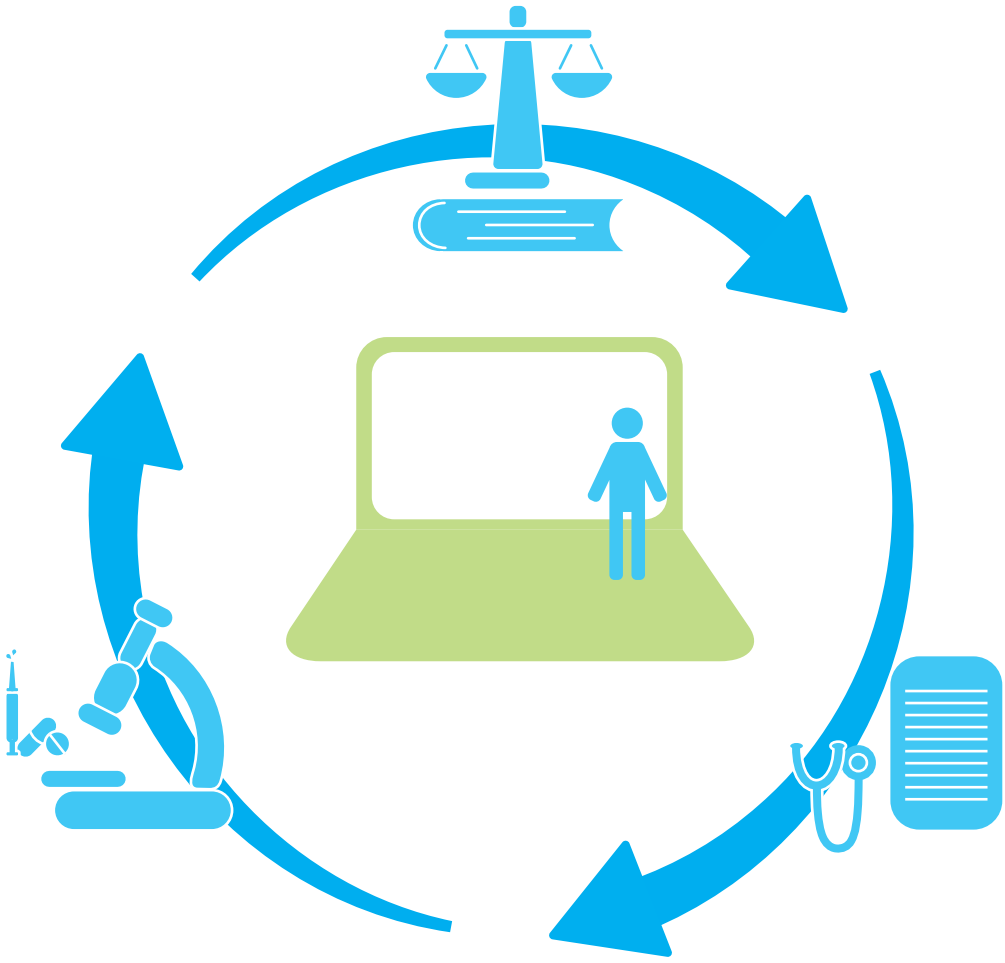
RARE DISEASE REGISTRIES:

A MUST FOR REGULATORY DECISION MAKING

Carla Jonker



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The studies presented in this thesis have been conducted under the umbrella of the Regulatory Science collaboration between the Dutch Medicines Evaluation Board (CBG-MEB), PedNet Haemophilia research Foundation and the Julius Center for Health Sciences and Primary Care of UMC Utrecht. The CBG-MEB is dedicated to ensure that licensed medicinal products during their whole life-cycle have a positive benefit-risk. This role requires intensive collaboration with academic and clinical partners in order to develop new assessment and decision-making methods, to engage with the clinic and to strengthen regulatory science. This PhD thesis aims to go beyond its scientific merits as such by delivering science, learnings and insights to promote public health.

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RARE DISEASE REGISTRIES:

A must for regulatory decision making

Registers van zeldzame ziekten: een must voor regulatoire besluitvorming (met een samenvatting in het Nederlands)

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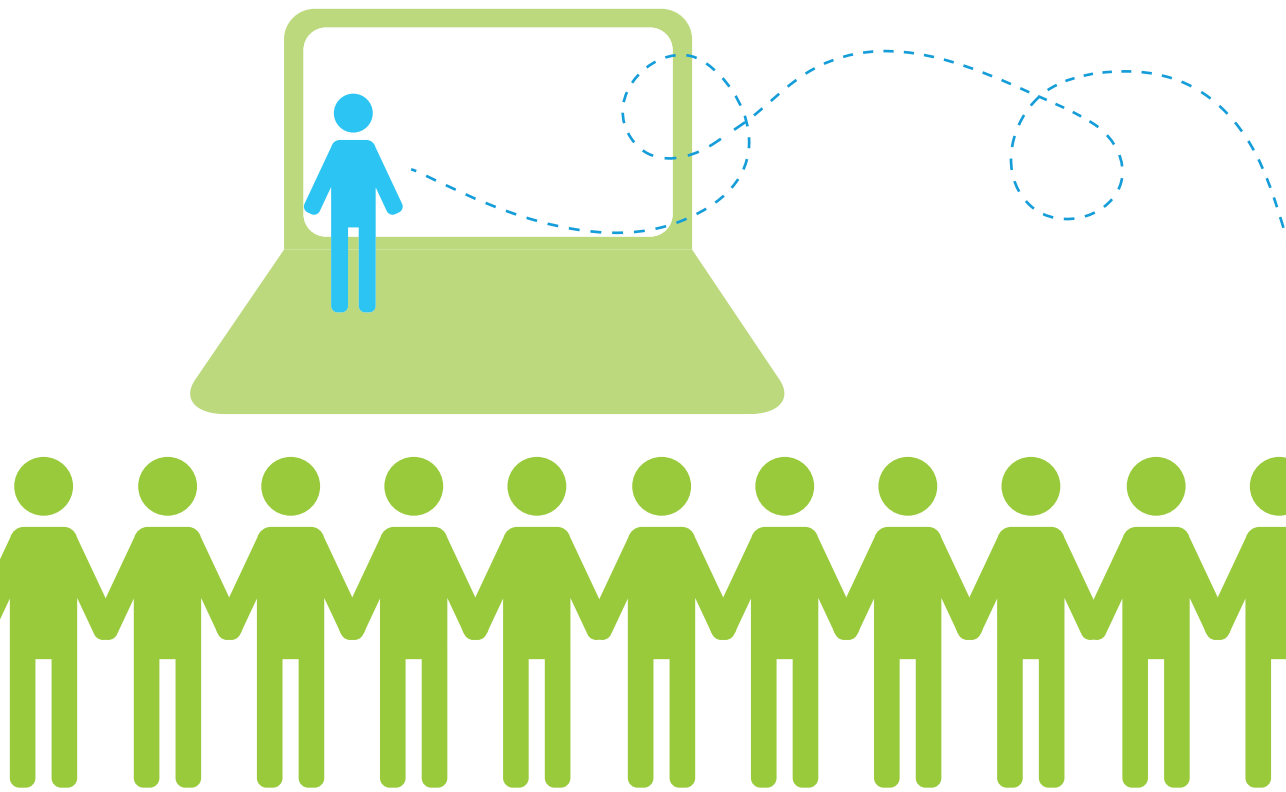

Chapter 1
General introduction

General introduction

Before a new medicine can enter the market, regulatory authorities assess if the balance between efficacy and safety is positive. Randomized controlled trials are the gold standard for the assessment of drug effects, because of its potential to prevent bias. A disadvantage of randomized trials is the limited applicability of the, unbiased, results to daily practice, notably because they often include selected (usually younger, with limited co-morbidity). Thus, such studies focus mainly on assessment of efficacy and shorter-term safety rather than real-life effectiveness and long-term safety.[1] For rare diseases with a chronic nature, it can be a challenge to perform randomized controlled trials with an adequate sample size and sufficient duration of follow-up to robustly determine treatment outcomes. As a result the knowledge about a medicinal product for the treatment of a rare disease is often incomplete and data on relevant longer-term outcomes are often lacking at the time of marketing authorisation. Different stakeholders (patient groups, regulatory, clinicians, scientists, industry and payers) have recognized the value of disease registries to learn about the natural course of (especially rare) diseases following standard of care and to monitor long-term collection of safety data to complement data collected in randomized controlled trials.[2]

First registry

The start of registries in the clinical setting seems to be the establishment of a leprosy registry in Norway in 1856, both for health care and research purposes. In Norway physicians collected detailed case histories on all leprosy patients. The knowledge obtained through the leprosy registry played a significant role in the control of the disease, the evaluation of trends in prevalence and had a great impact on the developments in disease control.[3]

Rheumatology

More recent examples of registries that played a major role to learn more about the disease and treatment thereof are rheumatology and haemophilia registries. Since the 1960s rheumatology registries have been set-up because the randomized controlled trials for biologic disease-modifying anti-rheumatic drugs insufficiently addressed the long-term safety of this new class of medicinal products.[4] Little was known about the background rates of serious outcomes such as infections and malignancies, what made it difficult to decide what the safety of the biological agents would be.[5] Especially in the case of children with juvenile idiopathic arthritis, a rare condition, more outcome data was needed to understand the effects of long-term treatment with immunosuppressive agents as well as the development of comorbidities.[5] Registries were able to provide data on longer drug exposure, greater number of patients, pregnancies during biologic therapies and patients with various risk profiles.[4]

Haemophilia

In the case of haemophilia, registries date back to the era of the human immunodeficiency virus (HIV) epidemic in the 1980s as a result of the infusion of

contaminated blood products with HIV and hepatitis C.[6] After the introduction of recombinant products in 1992 inhibitor development is the most important outcome measured in registries for patients with haemophilia.[7] The role of registries is acknowledged by the World Federation of Haemophilia (WFH), and the European Association for Haemophilia and Allied Disorders (EAHAD). EAHAD recommends the establishment of national haemophilia registries as one of the European principles of haemophilia care.[8] One of the oldest registries is the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO), they established a national data-base (NHD) in 1978. The aims of the UKPHDO are to improve haemophilia care, to advance the education of professionals in the knowledge of haemophilia and other inherited bleeding disorders and their treatment and to promote research.[9]

Mycophenolate mofetil

Already in the first year of existence of the Committee for Human Medicinal Products for human use (CHMP), the CHMP described the use of registry data in the regulatory decision-making process. In 1996 mycophenolate mofetil in combination with ciclosporin and corticosteroids was approved for the indication "prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants".[10] For the assessment of mycophenolate mofetil, data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS registry) were used as a historical control.[11]

Gaucher disease

The first product registry used in regulatory decision-making process is the Gaucher registry. This registry is initiated by the company Genzyme and entry of patients is predominately determined by the prescription of a specific drug, imiglucerase.[12-13] In the Gaucher registry, data is collected from patients with Gaucher disease, independent of disease severity or treatment status.[12] Data from the Gaucher registry provided sufficient evidence for the indication "treatment of long-term enzyme replacement therapy in patients with chronic neuronopathic (Type 3) Gaucher disease".[14] Despite the impressive amount of data collected, shortcomings of the Gaucher's registry were that no information was collected related to the safety or treatment-associated adverse events and the question remained whether all Gaucher disease phenotypes were represented in this registry.[13] Although the Gaucher Registry was not restricted to patients treated with imiglucerase, due to the mandated creation of product registries for alternative treatment options, patients switching from one treatment to another were often lost for follow-up.[15]

Review of factor VIII products

In 2013 data collected by the PedNet and Rodin study group were published.[16] These data were later confirmed by the UKHCDO and FranceCoag studies.[17-18] For the Pharmacovigilance Risk Assessment Committee (PRAC) these results were the reason to start a referral procedure, which is a request on behalf of the European Union to conduct a scientific assessment of a particular medicine or class of

medicines and is one of the strongest tools the PRAC has to review whether the benefit/risk balance of a medicine is still positive. In the Rodin study about a third of all the children developed factor VIII inhibitors against their medicine, which reduces its benefit and makes bleeding more likely. This is a known risk for all factor VIII products but the authors of the study concluded that children given so-called second generation full-length recombinant factor VIII products were more likely to develop antibodies than those given a third generation recombinant product.[16] An increase in inhibitor formation was not seen with other recombinant or plasma-derived factor VIII products. The outcome of the PRAC referral, which took ten months to complete, was that the benefits of treatment with second generation full-length recombinant factor VIII products continue to outweigh their risks in previously untreated patients. The product information was updated to reflect the study results.[19] While some uncertainties on the observational nature of the study were expressed, a combined analyses of these three large cohort studies confirmed the trend of an increased risk of inhibitor development in PUPs for one recombinant product.[20]

Regulatory context

The publication of the Rodin study initiated this thesis. At the time any medicinal product is approved, the knowledge about the effectiveness in daily practice and safety is limited.[1] Especially in the field of rare diseases the sample size to perform meaningful randomized controlled trials is small. Pre-licensure clinical studies on often selected patients are not powered to identify uncommon or rare adverse reactions.[21] Therefore post-authorization studies are needed to assess the effectiveness and safety of medicines. Registries are one of the options described in the Guideline on good pharmacovigilance practices (Figure 1).[22]

Guideline on good pharmacovigilance practices (GVP)
Module VIII – Post-authorisation safety studies (Rev 3)

Registries

A registry is an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure. A registry can be used as a data source within which studies can be performed.

Entry in a registry is generally defined either by diagnosis of a disease, prescription of a medicinal product, or both (patients with a certain disease treated with a defined medicinal product, defined active substance or any medicine of a defined class of medicinal products). The choice of the registry population and the design of the registry should be driven by its objective(s) in terms of outcomes to be measured and analyses and comparisons to be performed.

Registries are particularly useful when dealing with a rare disease, rare exposure or special population. In many cases, registries can be enriched with data on outcomes, confounding variables and effect modifiers obtained from a linkage to an existing database such as national cancer registries, prescription databases or mortality records.

Depending on their objective, registries may provide data on patient, disease and treatment outcomes, and of their determinants. Data on outcomes may include data on patient-reported outcomes, clinical conditions, medicines utilisation patterns and safety and effectiveness. It is acknowledged that on occasion, registries may be the only opportunity to provide insight into efficacy aspects of a medicinal product. However, observational registries should not normally be used to demonstrate efficacy. Rather, once efficacy has been demonstrated in randomised clinical trials (RCTs), patient registries may be useful to study effectiveness in heterogeneous populations, effect modifiers, such as doses that have been prescribed by physicians and that may differ from those used in RCTs, patient sub-groups defined by variables such as age, co-morbidities, use of concomitant medication or genetic factors, or factors related to a defined country or healthcare system.

Where adequate data are already available or can be collected, patient registries may be used to compare risks of outcomes between different groups. For example, a case-control study may be performed to compare the exposure to the medicinal product of cases of severe adverse reactions identified from the registry and of controls selected from either patients within the registry or from outside the registry. Likewise, a cohort study may be embedded in a registry. Case-only designs may also be applied (see VIII.App 1.1.2.4.).

Patient registries may address exposure to medicinal products in specific populations, such as pregnant women. Patients may be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires. Simple cohort studies may measure incidence, but, without a comparison group, cannot evaluate any association between exposures and outcomes. Nonetheless, they may be useful for signal amplification particularly for rare outcomes. This type of registry may be very valuable when examining the safety of an orphan medicinal product authorised for a specific condition.

Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 3)

Figure 1. Description of a registry in the guideline on good pharmacovigilance practices (GPV)

Registry data can be collected either in disease or product registries.[23]
Disease registries are often created by public organisations such as academia or medical research associations of health care professionals or patients. They may have different objectives, such as to describe the natural history of a disorder, to monitor the efficacy or safety of treatments. For example in subpopulations (e.g. geriatric patients) for which pre-authorisation data are limited, registries can be used to describe the impact of a

disease on patients' health and quality of life or to identify patients suitable for (studies on) new treatments. Irrespective of the original aim pursued by the registry, the data collected may also be useful to support the regulatory evaluation of benefits and risks of medicines. For disease registries the entry is determined by the diagnosis of a disease, in product registries by the prescription of a specific drug. In general, disease registries gather insights on clinical outcomes of conditions in patients receiving different treatments, rather than on the outcomes of a specific treatment, and they may support a wider range of study designs, e.g., controlled designs without an external data source. They are also generally better integrated into health care systems and are therefore more likely to be sustainable and provide long-term follow-up data on patients.[2] For example, in the field of lysosomal storage disorders two companies independently set-up a product registry to collect data to enable an annual reassessment of the benefit/risk profile of their product.[15] The added values of both registries are increased knowledge about the effect of enzyme replacement therapy on clinical outcomes in females and paediatric patients, but can also lead to a better understanding of the natural course of the disease.[24-25] However, because of the lack of collaboration between the two product registries, after more than ten years of experience important questions are still not answered. This is due to fragmentation of data, lack of quality and completeness of data and the impossibility to compare different treatments.[15]

Patient registry initiative

In 2015 the European Medicines Agency (EMA) set up the initiative for patient registries.[26] The goal of the initiative is to make better use of existing registries to support their contribution to the benefit-risk evaluation of medicinal products.[27] At time of the start of the patient registry initiative there were a number of challenges such as coordination between ongoing initiatives at the national and international level; harmonised protocols, scientific methods and data structures; data sharing and transparency and sustainability of a registry. To address these problems the patient registry initiative promotes dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries (Figure 2). They organised a number of disease-specific workshops with stakeholders, including registry owners, patients, regulators, reimbursement bodies, employees of pharmaceutical companies and health technology assessment bodies. The participants of these workshops gave recommendations on the use of registries in the disease areas cystic fibrosis, multiple sclerosis, chimeric antigen receptor T-cell therapy, haemophilia and cancer therapies based on genetic and molecular features. The main recommendations included the topics core data elements, informed consents, governance, data sharing and interoperability. For each workshop the EMA published a report on their website.[26]

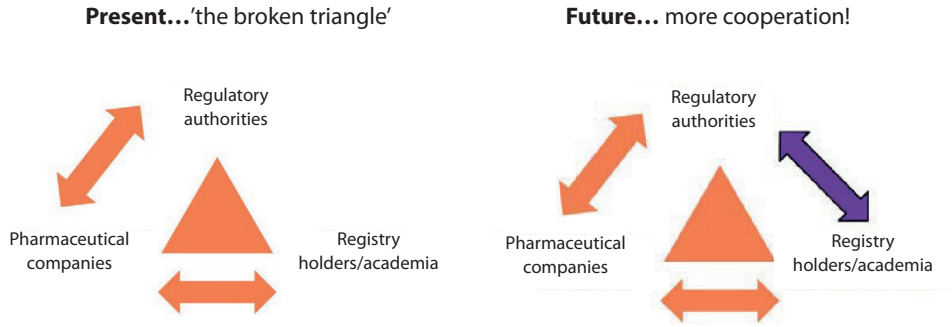

Figure 2. 'Broken Triangle' barrier to better use of patient (disease) registries.
Source: Nicola Ruperto, PRINTO

Research aim and outline of the thesis

The aim for this thesis is to investigate the value of registries for regulatory decision-making. The field of haemophilia has been used as a case study, because of the long-term follow-up of patients included in haemophilia registries. The studies reported in this thesis highlight how registries are used in the regulatory decision-making process and discuss what the direction will be for the use of registries in this context.

We started to investigate what the experiences were with registries for medical products approved by the CHMP. **Chapter 2** provides an overview of all registries that have been proposed for all new medicinal products, which were approved in the European Union between 2007 and 2010. We reviewed the frequency, the type, and the reason for requiring a registry. **Chapter 3** shows the results of a review on whether registry studies for new medicinal products indeed were performed as agreed at time of approval.
We continue the thesis with data available from the PedNet registry. In the PedNet registry data are collected from children with haemophilia, who are followed from birth onwards. The aim of the registry it to enable studies on side effects and outcome of treatment. All newly diagnosed patients with haemophilia A or B with a factor VIII or IX activity below 25%, born from 1 January 2000 and treated in one of the participating centres are eligible for inclusion.[28] In **Chapter 4** outcome data of the PedNet registry are compared with a number of clinical trials. The clinical guideline that describes the requirements for the performance of clinical trials in the field of haemophilia A was the starting point for this investigation.[29] In **Chapter 5** we studied whether a disease registry, the PedNet haemophilia registry, could serve as a suitable alternative to clinical studies to investigate the safety of a recombinant factor VIII product in previously untreated patients with severe haemophilia A.
The problems described in **Chapter 2 and 3**, the opportunities identified in **Chapter 4 and 5** and the experience gained over time with the patient registry initiative hopefully lead to a better understanding of the key elements of registries. Little is known, about whether stakeholders find the key elements: collection of comment data elements, data quality and governance aspects important and feasible

in the context of registries. In collaboration with the patient registry initiative a survey was set up among industry and other stakeholders on what matters for the capturing of data in registries in the field of rare diseases for regulatory decision-making. The results of this survey are presented in **Chapter 6**.
In **Chapter 7** the main findings of these studies and results are discussed in the light of the benefits and the challenges to use registry data for regulatory decision-making.
And finally in **Chapter 8** the main findings of these studies are summarized.

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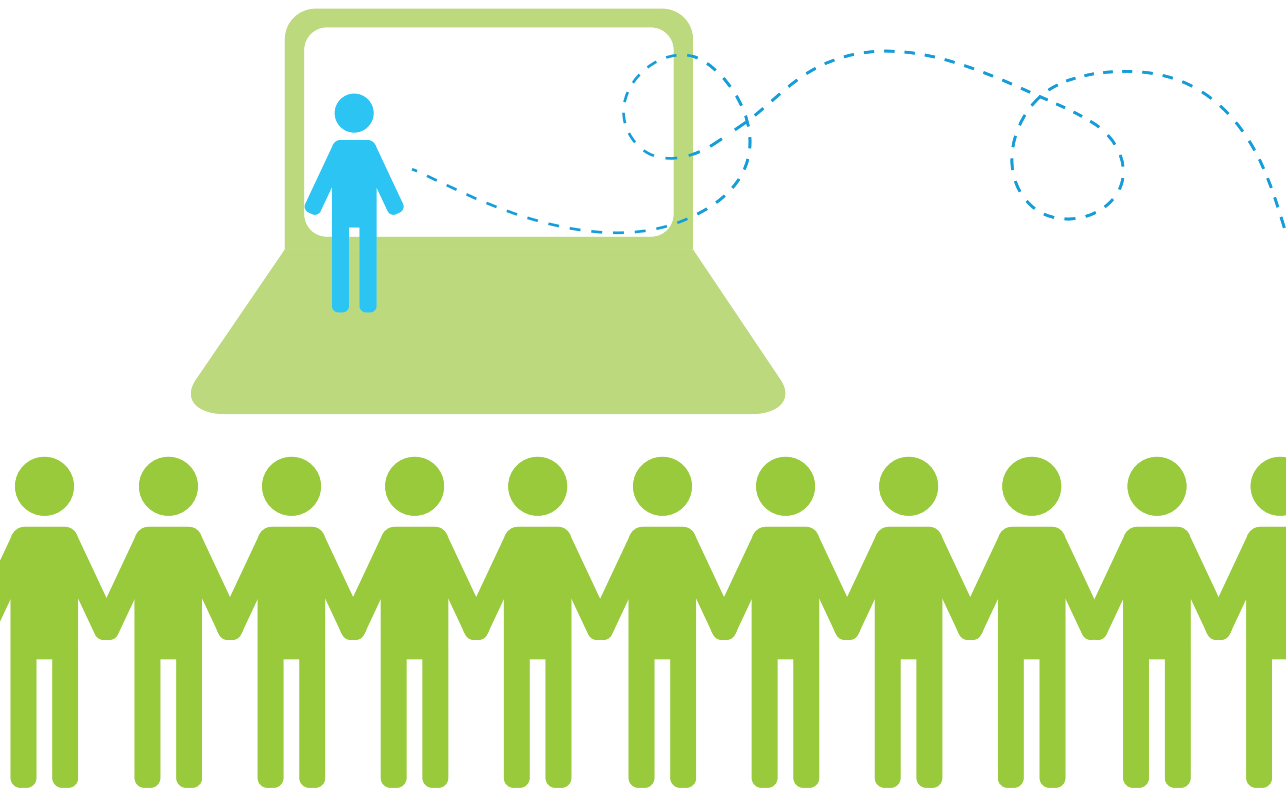

Chapter 2
Registries supporting new drug applications

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Abstract

Purpose
Knowledge of the benefits and risks of new drugs is incomplete at the time of marketing approval. Registries offer the possibility for additional, post-approval, data collection. For all new drugs, which were approved in the European Union between 2007 and 2010 we reviewed the frequency, the type, and the reason for requiring a registry.

Methods
The European Public Assessment Reports (EPARs), published on the website of the European Medicine Agency were reviewed for drugs approved by the Committee for Medicinal Products for Human Use. We searched for key characteristics of these drugs, including therapeutic area (ATC1 level), level of innovation (the score is an algorithm based on availability of treatment and therapeutic effect), and procedural characteristics. In addition, we identified if these registries were defined by disease (disease registry) or exposure to a single drug (drug registry).

Results
Out of 116 new drugs approved in the predefined period, for 43 (37%), one to six registry studies were identified, with a total of 73 registries. Of these 46 were disease registries and 27 (single) drug registries. For nine drugs the registry was a specific obligation imposed by the regulators. The level of innovation and the orphan status of the drugs were determinants positively predicting post-approval registries (OR 10.3 (95% CI 1.0-103.9) and OR 2.8 (95% CI 1.0-7.5); respectively).

Conclusions
The majority of registries required by regulators are existing disease registries. Registries are an important and frequently used tool for post-approval data collection for orphan and innovative drugs.

Introduction

Evidence regarding benefit and especially risks of drugs is still limited by the time they are approved by regulatory agencies. Therefore, regulators require additional evidence regarding safety and real-world effectiveness throughout the remainder of the drug's life-cycle.[1] In some situations, companies are required to provide data from randomized controlled trials in order to establish remaining uncertainties about the benefits and risks of new drugs. Once approved, the number of patients exposed to the drug will be much larger, long-term data will become available and safety concerns that could not be detected during clinical trials may be identified. Hence, data collected post-authorization are critical for learning more about the benefit-risk balance of new drugs. The Food and Drug Administration (FDA) in the USA and the European Medicine Agency (EMA) in Europe have developed extensive guidance for industry indicating how to address identified and potential safety concerns and how to deal with missing data.[2, 3] These pharmacovigilance activities focus on monitoring real-life clinical use, including the systematic collection of observational data in registries. Data collected post-approval through these registries can be used to complement pre-registration study data to address existing knowledge gaps, e.g. missing data regarding children, use during pregnancy, and effects of long-term treatment. A registry can be used as a data source for other studies, such as studies to measure the effectiveness of risk minimization measures and drug utilization studies.[3]

In Europe, the Committee for Medicinal Products for Human Use (CHMP) is responsible for the scientific evaluation and approval of drugs for use within the European Union. Increasingly more drugs have been approved based on limited data sets during the last decade, e.g. 30 drugs were conditionally approved between 2006 and June 2016.[4] Earlier we have shown that this trend has not necessarily lead to more safety issues.[5] For many of these drugs, registries have been proposed to fill the knowledge gap.

Although registries are suggested and approved as a tool for post-approval collection of additional data for new drugs, it is currently unknown how often this tool is being used, for how many and what type of drugs, and what the rationale is to for requesting a registry. Therefore, the goal of this study was to assess the frequency and the reasons for requesting post-approval registries in Europe and to examine the type of registries (drug or disease). Further we investigated, whether registries had been imposed by the regulatory authority as a specific obligation or had been 'spontaneously' promised by a company in order to address remaining uncertainties on drug benefits and risks. We examined the rationale (e.g. safety concerns or long term efficacy) underlying the decision to set up a registry. Additionally, we explored what drug characteristics (e.g. ATC-code, level of innovation and size of pre-approval safety population) and procedure-related determinants (e.g. type of procedure or the existence of an orphan status) predicted a post-marketing registry to be included in a drug dossier.

Key points

- One third of all drugs approved in Europe, between 2007 and 2010, were coupled with a requirement for a registry, mainly with the purpose of providing additional data due to safety concerns.
- The majority of these registries are existing disease registries.
- For orphan and innovative drugs registries are an important tool for post-approval data collection.

Methods

We performed a retrospective review of drugs approved by the CHMP in the European Union.

Data source

We identified drugs that were approved by the CHMP between 1 January 2007 and 31 December 2010 from the European Commission's Community Register (http://ec.europa.eu/health/documents/community-register/html/index_en.htm). Only drugs approved on the basis of a full application dossier for a new active substance and biosimilars were included in the dataset. The date of approval is defined as the date of publication of the European decision.

Primary outcome

The aim of the study was to investigate the frequency and reason for a requirement for a post-approval registry study to complement the marketing authorization dossier of new drugs. Scientific and regulatory information was collected from the European Public Assessment Reports (EPARs), which are accessible through the EMA website (www.ema.europe.eu). The requirement to set up a registry was identified from the Risk Management Plan (RMP) summary of the EPAR. In this summary safety specifications, proposed pharmacovigilance and risk minimisation activities are recorded. We included all registries that were mentioned in the EPAR. A registry is defined as an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure.[3] We excluded studies with a single research question collecting data from one or more electronic health records database. In line with Bouvy et al., we also excluded non-interventional, open-label, prospective short-term observational studies (2 years or less).[6] These studies were considered to be designed for a specific research question rather than a long-term study in a registry where routine clinical data are collected systematically. Both registries recorded as a specific or imposed obligation conform annex II of the Marketing Authorization and those required to investigate a safety concern are included. If more details were needed or if the information in the EPAR was not conclusive, data were obtained from the RMPs and study reports, which were retrieved from the

database available at the Medicine Evaluation Board (MEB). Data were extracted by CJ, all data were systematically checked by PM or MK to ensure accuracy of extracted information. Any discrepancies were resolved in discussion with CJ, MK and PM.

Characteristics of registries, drugs and procedures

We retrieved a number of relevant characteristics of the identified registries. First, we identified in the dossier the primary goal for requiring the registry; e.g. to address safety, effectiveness or pregnancy outcomes. Second, we ascertained whether the specified outcome was defined by the disease (disease registry) or exposure to a single product or drug (drug registry). Drug registries could also include a class of drugs, but in our data set only single-drug registries were identified.

To identify determinants for requiring a post-approval registry, we identified characteristics related to the nature of drug and the nature of the procedure that we hypothesized could influence the decision to require a registry. First, the therapeutic area was classified using the anatomical main group of the Anatomical Therapeutic and Chemical code (ATC-1 level, http://www.whocc.no/atc_ddd_index). Second, the type of molecule was categorized as either a small molecule, vaccine or biosimilar, in accordance with the European legal definitions.[7] Third, we classified the level of innovation of a new drug using an algorithm developed by Motola et al.[8] Drugs were classified based on a sequential assessment of the availability of alternative treatment options for a particular disease and the therapeutic effect they had demonstrated in clinical studies, both as assessed at the time of approval. The algorithm graded drugs based on these considerations as (A) important, (B) moderate or (C) modest innovations, or as 'mere' pharmacological/technological innovations.[8] Consequently, drugs classified as important innovations target diseases where treatment is not available and have demonstrated major benefits on clinical endpoints or established surrogate parameters.[9]

Fourth, we determined the size of the safety population; the total number of subjects exposed to the drug for any duration in the clinical development program before approval. Finally two procedural characteristics were identified; orphan drug and registration type (standard, under exceptional circumstances or receiving conditional approval) as defined in the Notes to Applicant.[10]

Statistical analyses

Univariate and multivariate logistic regressions were applied to identify, which key drug and procedural characteristics were independent determinants of the requirement for a post-approval registry. Characteristics that were potentially associated with inclusion of a registry in the dossier ($p<0.1$) were included in the multivariate model. In the final model, only characteristics reaching a significant level of $p<0.05$ were considered as statistically significantly associated with the primary outcome.

Table 1. Key characteristics of 73 registries

	All registries N (%)
Total	73 (100%)
Primary goal	
Safety	39
Safety & Effectiveness	7
Pregnancy	27
Disease	46 (63%)
Drug	27 (37%)
Number of registries per drug	
None	73
One	29
Two	6
Three	4
More than four	6
Registry imposed	
Yes	9 (12%)
No	64 (88%)

Results

Between 1 January 2007 and 31 December 2010, 116 new drugs (new active substances and biosimilars) were approved in Europe by the CHMP. A total of 73 registries were included in the RMPs of 43 (37%) of these newly approved products. For 29 of these new drugs, there was a post-approval requirement for a single registry and for 14 drugs there was a requirement for between two and six registries (Table 1), implying that for 73 new drugs there was no need for a registry. For only nine drugs registries were imposed by the CHMP. For drugs subjected to a registry the size of safety population ranged between 94 and 13,000 patients; 15 drugs had an orphan status and 13 drugs were approved under exceptional circumstances or were conditionally approved (Table 2, and Supplementary Table 1 for individual drugs).

The primary goal of 39 of the 73 registries was to collect safety outcomes, in seven cases, it was to collect safety outcome and real-world effectiveness data; and in 27 cases, it was to collect data on potential birth defects when the drug orphan status and 13 drugs were approved under exceptional circumstances or were conditionally approved (Table 2, and Supplementary Table 1 for individual drugs). was taken during pregnancy. The most common aims of these registries were to increase knowledge on identified and potential risks or information that was missing – especially pregnancy outcome – at the time of approval.

Table 2. Key characteristics of new drugs approved[1] with and without registries 2007 – 2010

	All drugs N (%)	Registry[2] N (%)		Univariate	Multivariate
		Yes	No		
Total	116 (100)	43 (37)	73 (63)	OR (95%CI)	OR (95%CI)
Drug characteristics Therapeutic area (ATC 1 level)					
A	12 (100)	5 (42)	7 (58)	1.9 (0.5;7.5)	
B	12 (100)	3 (25)	9 (75)	0.9 (0.2;4.0)	
J	26 (100)	12 (46)	14 (54)	2.3 (0.8;6.7)	
L	29 (100)	13 (45)	16 (55)	2.2 (0.8;6.2)	
Other[3]	37 (100)	10 (27)	27 (73)	Ref	
Type of molecule					
Biological	30 (100)	15 (50)	15 (50)	1.5 (0.4;5.3)	
Small molecule	71 (100)	22 (31)	49 (69)	0.7 (0.2;2.1)	
Vaccine	15 (100)	6 (40)	9 (60)	Ref	
Level of innovation[4]					
A: important	7 (100)	6 (86)	1 (14)	**16.0 (1.7;147.1)**	**10.3 (1.0;103.9)**
B: moderate	42 (100)	18 (43)	24 (57)	2.0 (0.8;4.9)	1.2 (0.4;3.5)
C: modest	23 (100)	7 (30)	16 (70)	1.2 (0.4;3.6)	0.8 (0.2;2.6)
Pharm/Tech	44 (100)	12 (27)	32 (73)	Ref	Ref
Size of safety population[5]					
Median (range)	1549 (94-13,000)	1002 (9413,000)	1811 (11910,257)	1.0 (1.0;1.0); p=0.11	
Procedural characteristics					
Orphan medicinal drug[6] (yes)	26 (100)	15 (58)	11 (42)	**3.0 (1.2;7.4)**	**2.8 (1.0;7.5)**
CA[7] and EC[8] registration (yes)	23 (100)	13 (57)	10 (43)	**2.7 (1.1;6.9)**	1.7 (0.6;5.0)

P<0.05 in bold type face, * all determinants with p<0.1 were included in the multivariate analyses

[1] Date of approval is date of publication of European Decision
[2] A registry was promised in the European Public Assessment Report (EPAR, as part of the RMP)
[3] Therapeutic area classified using the anatomical main group of the Anatomical Therapeutic and Chemical Code. All drugs that are not classified as A (alimentary tract and metabolism), B (blood and blood forming organs), J (anti-infectives for systemic use) or L (antineoplastic and immunomodulating agents) are classified as other.
[4] The drug is an important, moderate, modest of pharmacological or technological innovation
[5] Size of safety population is the number of patients that have been analysed in the safety analysis (initial application, in EPAR)
[6] The drug has an orphan status
[7] The drug was given a conditional approval (CA)
[8] The drug is approved under exceptional circumstances (EC)

We identified 27 (37%) drug registries that were set up by companies to monitor use and outcomes of their drug specifically. Only patients using these specific drug are enrolled into these registries. The use and outcomes of treatment with a drug is monitored in 46 (63%) disease registries, in which patients will be enrolled with a specific diagnosis or disease, irrespective of the drug(s) they are using. Examples of disease registries are the Swedish and German rheumatology registries Antirheumatic Therapies In Sweden (ARTIS) and Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT), in which safety data is collected in patients with rheumatoid arthritis for the recently approved drugs abatacept, certolizumab, golimumab and tocilizumab.[11] Similarly, for three filgrastim biosimilars, safety and immunogenicity are collected in the Severe Chronic Neutropenia (SCN) European registry. The SCN registry monitors clinical progress and treatment and adverse events for patients with SCN, regardless of their therapy.[12]

A specific kind of registry is the pregnancy registry. Of the 27 identified pregnancy registries, 11 were set up specifically to monitor the impact on offspring of a specific drug taken during pregnancy. In the remaining 16 cases, data were collected from existing pregnancy registries; e.g. for darunavir, etravirine, maraviroc, raltegravir and telbivudine pregnancy outcome data are collected from the Antiretroviral Pregnancy Registry. This is an existing pregnancy registry, set up in 1989 for pregnant women who are exposed to antiretroviral drugs, intending to generate early signals of teratogenic effects associated with prenatal exposure to antiretroviral products.[13] The registry enrolls human immunodeficiency virus infected patients through their health care providers (http://www.apregistry.com/).

We identified registries that were imposed by the CHMP for only nine drugs, suggesting that registries are specific measures taken in the framework of the marketing authorization. Six of these drugs (amifampridine, canakinumab, idursulfase, mecasermin, rilonacept, and tocofersolan) were approved under exceptional circumstances, because at the time of approval no comprehensive data on the safety and efficacy under normal conditions of use could be provided. Two drugs (both pandemic influenza vaccines) had received a conditional approval, this means that the company will be required to provide confirmative data in a short timeframe, and one drug (lenalidomide) had a regular approval.
Four of the imposed registries were set up with the aim to collect safety and real-world effectiveness data: amifampridine (symptomatic treatment of adults with Lambert-Eaton myasthenic syndrome); canakinumab, rilonacept (both for the treatment of patients with severely symptomatic cryopyrin-associated periodic syndromes (CAPS)); and idursulfase (for the treatment of patients with Hunter syndrome). Three registry studies set up for, respectively, mecasermin (treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency); lenalidomide (for the treatment of multiple myeloma), and tocofersolan (vitamin E deficiency due to digestive malabsorption in paediatric patients with congenital chronic cholestasis or hereditary chronic cholestasis) focused on the collection of safety data.

Pregnancy registries were imposed for two (adjuvanted) pandemic influenza vaccines. Safety during pregnancy (e.g., risk of birth defects) was unknown at the time of marketing approval, due to the lack of evidence in pregnant women. The regulatory authorities designated the lack of a pre-registration data as important missing information, considering that pregnant women are an important target population for these vaccines as influenza is likely to cause more severe illness in pregnant women.[14] It is noteworthy, though, that the applications for the pandemic influenza vaccines and rilonacept are now withdrawn in the European Union, all three for commercial reasons.

Determinants for registries

We explored if specific drug or procedural characteristics were associated with whether a registry was imposed by the regulatory authority or the initiative of the applicant. We used logistic regression to examine this issue. In the univariate analysis, level of innovation (important innovation OR 16.0 (95% CI 1.7-147.1)), orphan drug (OR 3.0 (95% CI 1.2-7.4)) and approval under exceptional circumstances or conditional approval (OR 2.7 (95% CI 1.1-6.9)) (for all $p<0,05$), were associated with initiation of a registry. In the multivariate analysis, drugs considered as having an important level of innovation (OR 10.3 (95% CI 1.0-103.9) and orphan drugs (OR 2.8 (95% CI 1.0-7.5) (both $p<0,05$) remained significantly associated with registries. Therapeutic area, type of molecule and size of safety population were not associated with a registry included in the marketing dossier.

Discussion

Our study indicates that for one third of new drugs approved between 2007 and 2010, a commitment was made to perform studies in one or more registries to address remaining uncertainties of the drug's effects at the time of approval. The goal was primarily to collect further safety data (39 registries, 53%), or impact of drug use during pregnancy (27 registries, 37%) and only seven registries (10%) collected data on both safety and drug effectiveness. Only for nine out of 43 drugs, the registry was explicitly requested (imposed) by the CHMP as a specific obligation in the framework of the marketing authorization; the rest were proposed by the applicants. The majority of the registries involved were from existing disease registries (43 out of 73, 59%), implying that data collection was already ongoing and that a - sometimes only historical - control group may be available.

In a large proportion of new drug approvals registries are planned for the post-approval period, suggesting that regulators and/or companies feel a need to collect 'real world' data to supplement incomplete knowledge at time of approval. This may not be a surprising development in an era of increasing availability of electronic health data.[15-16] The main reason for 'real world' data collection is to address remaining safety concerns as well as generate data in low exposure groups notably pregnant women. This reflects the EU Pharmacovigilance legislation introduced in 2012. The legislation and the establishment of the Pharmacovigilance Risk Assessment Committee focus on all aspects of the risk management of drugs for human use[17], including the assessment of the risk

of adverse reactions, while taking the therapeutic effect of the medicine into account. With regard to pregnancy data, in 2002 the FDA issued an amendment describing the requirement for the collection of pregnancy data through registries.[18] A recent review concluded that these type of registries remain an important tool to collect safety data in the absence of randomized controlled trial data on pregnant women.[19] Moreover, the FDA did accept registries for regulatory purposes in the evaluation of medical devices and is exploring further ways to use real-world data in support of drug applications.[20]

Two-thirds of the registries are existing disease registries, which is the approach promoted by EMA's Cross-committee Task Force on Registries. This is an initiative of the European regulators to facilitate better use of existing registries for the assessment of product safety and efficacy in daily clinical practice.[21] An example of a disease registry set up and exclusively sponsored by one company are the following two orphan drugs. The first registry is for amifampridine which also includes patients who do not use amifampridine.[22] The second registry is the Hunter Outcome Survey, in which patients with Hunter syndrome who are treated with enzyme replacement therapy are included.[23] The majority of patients however, received the drug marketed by the company. Recently, this approach was criticized by Hollak et al., who expressed a strong preference for disease registries to collect data, analyzed by independent statisticians, supervised by patients, health-care professionals and other relevant stakeholders, and to be launched early in the development of orphan drugs to obtain natural history data.[24] We support this recommendation for a disease registry that is owned by an independent party. This guarantees that data of all drugs used can be included, thereby enabling future comparative analyses, which is in the interest of the patients and may be an instrument to control the price of drugs. Still, a third of all registries collect data on a single product, this limits their usability for continued learning.

Innovative drugs require more often a registry. These drugs fulfil unmet medical needs of patients eagerly awaiting these drugs. Innovative drugs are often 'first-in-class' drugs with a new mechanism of action, where the full benefit-risk profile - and in particular evidence about safety - may not be complete at the time of approval. Four out of seven (57%) of the innovative drugs in this study were authorized through a conditional approval or an approval under exceptional circumstances, emphasizing that the data were limited at the time of marketing authorization. In addition, orphan drugs status by itself was an independent determinant for an approval with a registry in this study. This may be partly due to the large number of existing disease registries available in orphan diseases[25] and is in line with our finding that in most cases data will be collected from existing disease registries. Earlier we have shown that higher levels of innovation or approval under exceptional circumstances/ conditional approval are not related to more safety issues post-approval.[5, 9] Registry studies are considered valuable to increase our understanding of drug effects, especially for these drugs where the knowledge is incomplete at time of approval.

Our study has some limitations. The information about registries is retrieved from EPARs, published on the website of the EMA at the time of authorization. We used a more narrow definition of registries than described in the Good Vigilance Practices 3; i.e. 'Any organised collection of data on patients all or not exposed to a specific drug may be considered a registry according to the Good Vigilance Practice (GVP) definitions'. We excluded five studies in electronic health records (secondary data analyses) and seven open-label short term (2 years or less) observational studies that could be considered to have met this wider definition. These studies were designed, however, for a specific research question rather than being intended for long-term monitoring of patients in a registry with routine systematic collection of clinical data. These studies had not been acknowledged in the regulatory review as a registry study. One observational study proposed for roflumilast, which was not acknowledged as a registry in the regulatory review, could be considered as a registry according to our more narrow definition. In sensitivity analyses, the addition of this 'registry' did not materially change our findings. Important innovations remained associated with a registry required at time of approval, although orphan drug status lost significance in the multivariate model (data not shown). Registries promised at a later stage in the drug life-cycle might have been missed, and observational or effectiveness studies not designated as registries were not taken into account. These last sources may be less suitable for e.g. orphan drugs or for drugs exclusively used in a hospital setting. We observed that the rationale for the choice between the collection of data via a registry versus any other type of pharmacovigilance activity, such as post-authorization safety studies or a retrospective cohort study in a database is not clearly described in the EPAR. The rationale for a registry should follow from the benefit-risk discussion of the drug, meaning that 1) it is indisputable which data are still needed to complete the understanding of the benefit-risk profile of a drug and 2) that these data can be retrieved from a registry during the post-marketing phase.

Future studies should focus on the outcome of these planned registries in terms of studies actually undertaken post-launch and the impact they may have had on the knowledge of the benefit-risk ratio of a drug, e.g. through changes in the drug labelling or through published findings in the literature. Challenges such as standardized protocols with clear objectives and endpoints, standards for data completeness, coding of data, the possibility to link register data to external data and timelines for providing data are needed to share information between registry owners, companies and regulators.[26] Post-approval studies in Europe and the USA to address safety, respectively efficacy uncertainties at time of approval are, however, disappointing because recent reviews of such studies indicated that not many issues were resolved.[27-28] Reported delays in setting up imposed registries do not provide reassurance that these may provide timely information.[6]

Finally, we graded the innovation of a drug at time of approval. Clearly, the level of innovation may be subjective and time-dependent. In a previous study we have compared drugs classified using the Motola algorithm with some other classifications

(Canadian Human Drug AdvisoryPanel and Prescrire International) and found a poor correlation.[9] No system, however, can be considered as a 'gold standard',[9] and we thus used two reviewers to grade drugs according to the transparently predefined criteria in the algorithm. Indeed, over time, with the registration of new drugs or alternative treatments becoming available, the value of drugs considered innovative at the time they were initially approved may diminish. Because in our study we looked for determinants of registries proposed at time of approval, such diminishing valuation of a drug after approval does not impact our study results.

We conclude that in one third of the newly approved drugs, a registry is required to provide additional data because of safety concerns. Most of these drugs were drugs with an important level of innovation and orphan drugs, for which there is high medical need. The majority of the registries involved are existing disease registries, implying that data collection is already ongoing and that a control group for comparison may be available.

Conflict of Interest

The authors declare no conflict of interest.

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Supplementary table

Active substance	Date of approval	Therapeutic Area (ATC-code)	Producttype	Level of innovation
abatacept	21-may-07	L04AA24	biological	C: modest
amifampridine	23-dec-09	NO7 XX05	small molecule	B: moderate
aztreonam lysine	21-sep-09	J01DF01	small molecule	B: moderate
betaine anhydrous	15-feb-07	A16AA06	small molecule	C: modest
canakinumab	23-oct-09	L04AC08	biological	A: important
certolizumab pegol	1-oct-09	L04AB05	biological	Pharm/Tech
darunavir	2-feb-07	J05AE10	small molecule	A: important
denosumab	26-mei-10	M05BX04	biological	C: modest
eculizumab	20-jun-07	L04AA25	biological	B: moderate
eltrombopag	11-mar-10	B02BX05	small molecule	B: moderate
eslicarbazepine acetate	21-mai-09	N03AF04	small molecule	Pharm/Tech
etravirine	28-aug-08	J05AG04	small molecule	B: moderate
filgrastim (Zarzio)	6-feb-09	L03AA02	biological	Pharm/Tech
filgrastim (Ratiograstim)	15-sep-08	L03AA02	biological	Pharm/Tech
filgrastim (Nivestim)[1]	8-jun-10	L03AA02	biological	Pharm/Tech
golimumab	1-oct-09	L04AB06	biological	Pharm/Tech

Size of safety population	Orphan drug and approval	Primary goal for registry and if imposed	Drug or disease, incl. number of registries
2778	Regular	Safety & pregnancy	Disease 6
282	Orphan & Exceptional approval	Safety & effectiveness Imposed	Disease 1
373	Orphan & Conditional approval	Safety	Disease 1
140	Orphan & Regular	Safety	Drug 1
104	Exceptional approval	Safety & effectiveness Imposed	Drug 1
2367	Regular	Safety	Disease 4
1783	Conditional approval	Pregnancy	Disease 1
13000	Regular	Pregnancy	Disease 1
716	Orphan & Regular	Safety	Drug 1
422	Orphan & Regular	Safety & pregnancy	Disease and drug 2 and 1
1694	Regular	Pregnancy	Drug 1
1041	Conditional approval	Pregnancy	Disease 1
316	Regular	Safety	Disease 1
541	Regular	Safety	Disease 1
183	Regular	Safety	Disease 2
2758	Regular	Safety & pregnancy	Disease 3

Supplementary table continued

Active substance	Date of approval	Therapeutic Area (ATC-code)	Producttype	Level of innovation
human papillomavirus vaccine[1]	20-sep-07	J07BM02	vaccine	Pharm/Tech
icatibant	11-jul-08	C01EB19	small molecule	B: moderate
idursulfase	8-jan-07	A16AB09	biological	B: moderate
influenza virus surface antigens	2-mai-07	J07BB02	vaccine	Pharm/Tech
lacosamide[1]	29-aug-08	NO3AX18	small molecule	Pharm/Tech
lenalidomide[1]	14-jun-07	L04AX04	small molecule	B: moderate
maraviroc	18-sep-07	J05AX09	small molecule	A: important
mecasermin[1]	3-aug-07	H01AC03	small molecule	B: moderate
meningococcal group A, C, W-135 and Y conjugate vaccine	15-mar-10	J07AH08	vaccine	Pharm/Tech
nicotinicacid / laropiprant[2]	3-jul-08	C10AD52	small molecule	Pharm/Tech
pandemic influenza vaccine (h1n1) (split virion, inactivated, adjuvanted)[3]	23-mar-10	J07BB02	vaccine	Pharm/Tech
pandemic influenza vaccine (h1n1) (split virion, inactivated, adjuvanted)[3]	8-jun-10	J07BB02	vaccine	Pharm/Tech
plerixafor	31-jul-09	L03AX16	small molecule	C: modest
prasugrel[1]	25-feb-09	B01AC22	small molecule	Pharm/Tech

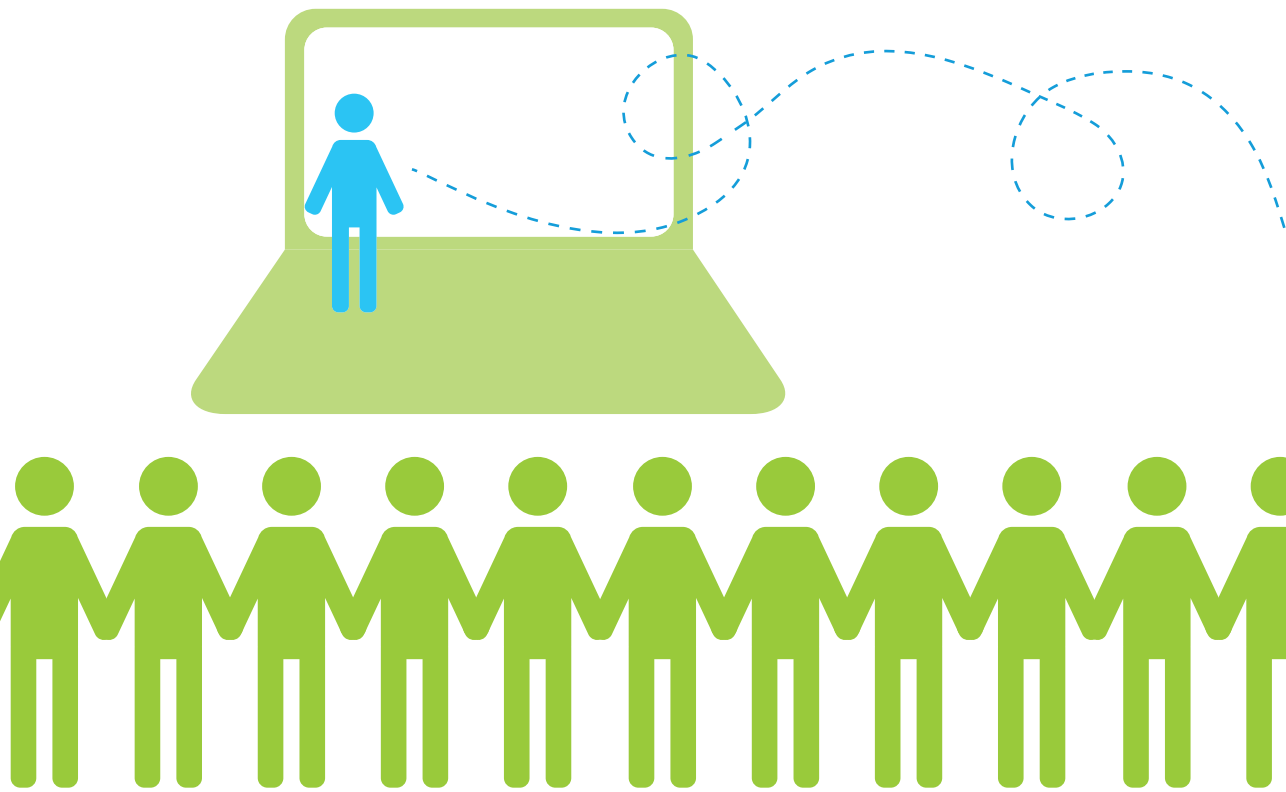
Size of safety population	Orphan drug and approval	Primary goal for registry and if imposed	Drug or disease, incl. number of registries
16142	Regular	Pregnancy	Drug 2
962	Orphan & Regular	Safety	Drug 1
108	Oprhan & Exceptional approval	Safety & effectiveness Imposed	Disease 1
646	Exceptional approval	Pregnancy	Drug 1
1338	Regular	Pregnancy	Disease 2
353	Orphan & Regular	Safety Imposed	Drug 1
840	Regular	Safety & pregnancy	Disease and drug 1 and 1
1516	Oprhan & Exceptional approval	Safety Imposed	Drug 1
6745	Regular	Pregnancy	Disease 1
2552	Regular	Pregnancy	Drug 1
3456	Conditional approval	Pregnancy Imposed	Drug 1
1020	Conditional approval	Pregnancy Imposed	Drug 1
1161	Orphan & Regular	Safety	Disease 1
8656	Regular	Safety	Disease 3

Supplementary table continued

Active substance	Date of approval	Therapeutic Area (ATC-code)	Producttype	Level of innovation
prepandemic influenza vaccine (h5n1) (surface antigen, inactivated, adjuvanted)	29-nov-10	J07BB02	vaccine	Pharm/Tech
raltegravir	20-dec-07	J05AX08	small molecule	A: important
rilonacept[1,3]	23-oct-09	L04AC04	biological	A: important
romiplostim	4-feb-09	B02BX04	biological	C: modest
rufinamide	16-jan-07	N03AF03	small molecule	A: important
sapropterin	2-dec-08	A16AX07	small molecule	B: moderate
telbivudine	24-apr-07	J05AF11	small molecule	B: moderate
tocilizumab	16-jan-09	L04AC07	biological	C: modest
tocofersolan	24-jul-09	A11HA08	small molecule	B: moderate
ulipristal	15-mai-09	G03AD02	small molecule	Pharm/Tech
ustekinumab	16-jan-09	L04AC05	biological	B: moderate
velaglucerase alfa	26-aug-10	A16AB10	biological	Pharm/Tech
vernakalant hydrochloride	1-sep-10	C01BG11	small molecule	Pharm/Tech

1. Details were obtained from the Risk Management Plans (RMP) and study reports, retrieved from the database available at the Medicine Evaluation Board (MEB).
2. The company decided to voluntarily withdraw the marketing authorisations. This followed the CHMP recommendation to suspend the marketing authorisations of this product.
3. The company decided to voluntarily withdraw the marketing authorisation for these products for commercial reasons. The products had never been placed on the market in any country of the European Community.

Size of safety population	Orphan drug and approval	Primary goal for registry and if imposed	Drug or disease, incl. number of registries
3983	Regular	Pregnancy	Disease 1
899	Conditional approval	Pregnancy	Disease 1
614	Orphan & Exceptional approval	Safety & efficacy Imposed	Drug 2
271	Orphan & Regular	Safety & pregnancy	Drug 6
1978	Orphan & Regular	Safety& pregnancy	Disease 2
647	Orphan & Regular	Safety & effectiveness	Drug 1
1491	Regular	Pregnancy	Disease 1
2439	Regular	Safety & Pregnancy	Disease 4
167	Exceptional approval	Safety Imposed	Drug 1
3560	Regular	Pregnancy	Drug 1
2266	Regular	Safety & pregnancy	Disease 3
94	Orphan & Regular	Safety & effectiveness	Disease 1
883	Regular	Safety	Drug 1



Chapter 3
Drug registries and approval of drugs:
Promises, placebo or a real success?

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Abstract

Purpose
As part of the approval process, regulatory authorities often require post-authorization studies that involve patient registries; it is unknown, however, whether such registry studies are adequately completed. We investigated whether registry studies for new drugs were performed as agreed at time of approval.

Methods
This study reviewed protocols and follow-up reports for 73 registry studies that were proposed for 43 drugs approved by the Committee for Medicinal Products for Human Use in Europe in the period 2007 to 2010.

Results
The data-lock point of January 1, 2016, was taken to allow a 5-year follow-up period for each drug after approval. At that time, 2 studies (3%) in registries had been finalised, 19 registries (26%) had not enrolled any patients, and 52 studies (71%) were ongoing. The median enrolment was 31% (Interquartile range [IQR], 6-104) of the required number of patients for 41 registry studies that had a predefined sample size, 30% (IQR 2-101) for non-imposed registries, and 61% (IQR 18-144) for imposed registries.

Implications
Enrollment of patients into post-approval registries is poor, although the results for imposed registries seem better. Currently, registries only have a limited impact on resolving gaps in the knowledge of a drug's benefits and risks at time of marketing authorization.

Introduction

Approval is a discrete moment in the lifecycle of a drug, after which the drug typically becomes widely available to the public. However, full knowledge regarding the drug's benefits and risks is not complete at this point. For some drugs, regulators and industry may agree on collecting further clinical data through additional trials or observational studies. There is a trend to expand the collection of clinical research data into more "real-life" data settings like patient or drug registries. Registries, or registry studies, may be deemed necessary if, at the time of approval, the benefits, but especially risks, are not completely understood. Registries may be either newly developed as a consequence of a decision by the regulatory agency (eg, European Medicines Agency [EMA]) as a "new registry" or "registry studies" can be performed in existing disease registries or other databases. Regulators may even impose a registry as a specific obligation to address a particular concern with respect to either safety or efficacy, in the framework of the marketing authorization. Moreover, the EMA has proposed in its adaptive pathways project to use registry data to generate post-approval data in more extended patient populations while giving an early license in a restricted population.[1] However, some criticism was raised with respect to this option because it is considered that industry does not always fulfill its post-approval commitments in a timely fashion.[2-4] The most recent review of post-approval studies agreed with the US Food and Drug Administration showed that 5 to 6 years after approval, 20% of these studies had not started patient inclusion, 25% were delayed or ongoing, and only 54% had been completed.[5]

Evidence is lacking from Europe whether it is realistic to expect that this kind of early approval (with "real-world" registry data being provided post-approval) is effective. Therefore, we reviewed for drugs approved between 2007 and 2010 by the Committee for Medicinal Products for Human Use in Europe. We previously reported that for 43 (37%) of 116 drugs approved in this period, 73 studies in registries had been proposed.[6] The present study investigated if the planned number of patients had been enrolled, the results are made publically available and if the registry studies provided evidence that affected the known benefit-risk balance.

Methods

The European Public Assessment Reports (EPAR), which are publicly available via the EMA website (http://www.ema.europa.eu/ema/) were investigated for scientific and regulatory information of these 43 drugs that had been approved in Europe by the Committee for Medicinal Products for Human Use between 2007 and 2010 and where a commitment was made to perform at least 1 study in a registry. The period 2007 to 2010 was chosen to allow at least a 5-year follow-up for each drug after approval. This approach is in line with the time for submitting a renewal application (ie, the obligatory re-evaluation after 5 years of the risk-benefit balance of any new medicinal product after its initial approval).[7] The lead author (C.J.J.) reviewed the statistical analysis

plan of the registry study protocol to determine whether target enrollment was achieved. The Mann-Whitney U test was used to test if enrolment differed between imposed and non-imposed registries and between disease and product registries. In addition, we evaluated what impact the data had on the drug's benefit risk balance (ie, a change in the product label) after 5 years. To this end, EPAR updates were reviewed by using the term "registry" or the name of the registry or registry study to find evidence that these data were mentioned in the EPAR irrespective of whether they led to updates of the drug labeling. All data were systematically checked by 2 of the authors (P.G.M.M. or M.S.C.K.) to ensure accuracy of extracted information. Any discrepancies were resolved in discussion with 3 of the authors (C.J.J., M.S.C.K. and P.G.M.M.)

PubMed was searched if the protocols or findings of the registry or registry studies had been published in a peer-reviewed journal to investigate if translation of knowledge had occurred from registry owners and industry to health care professionals and the scientific community. Search terms included the generic name of the drug and the term "registry" or the name of the registry or study as recorded in the EPAR. The status of the registry with respect to statistical analysis plan and enrollment was retrieved from the study reports submitted to the Dutch Medicines Evaluation Board; the data lock point was January 1, 2016.

Results

Of the 73 identified registry studies 9 (12%) were imposed by the regulatory authority as a specific post-approval obligation.[6] The remaining 64 registries were proposed voluntarily by companies and agreed with by the regulatory authority. At the data-lock point of January 1, 2016, two registry studies (3%) had been finalised[8], 52 studies (71%) were ongoing. In 19 registries (26%) no patients were enrolled. Reasons for not enrolling any patients were: withdrawal of the drug from the market (4 [of which 2 registry studies had been imposed], the drug was not reimbursed (1), the data were collected through other pharmacovigilance activities (2), there was no (recorded) use of the drug in the at risk population (pregnant women) (3), and for 9 registries the reason could not be retrieved from the data submitted to the agency. The planned number of patients to be included was described in the statistical analysis plan of 41 registry studies (56%) and for the imposed registry studies this was known for 7 out of 9 registry studies (78%). The figure shows the percentage of patients enrolled in registry studies with a predefined number of patients to-be-enrolled in the statistical analysis plan. The median enrolment in these 41 registry studies was 31% (interquartile range [IQR] 6-104) of the required sample size; 30% (IQR 2-101) for non-imposed registries and 61% (IQR 18-144) for imposed registries. (P = 0.46). The median enrolment in product registries was 50% (IQR 1-119) and 28% (IQR 11-93) in disease registries (P = 0.74).

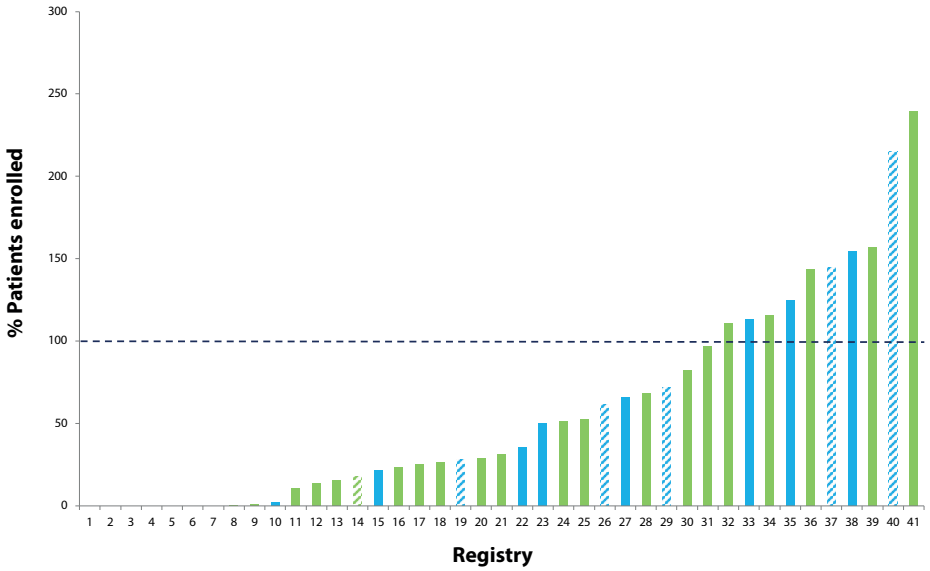

Figure 1 Percentage of patients enrolled in registry studies with a predefined number of patients to-be-enrolled in the statistical analysis plan. The bars indicate the percentage of patients enrolled from those planned to-be-enrolled in registry studies (data lock point is 1 January 2016). The green bars indicate the disease registries, the blue bars the product registries and the striped bars the registries that were imposed. Note that for 32 registries the percentage could not be calculated due to missing numbers.

For 6 drugs, data from the registry studies were published in a follow-up EPAR published on the EMA website.[9-14] In addition, for 2 products these data led to changes in the Summary of Product Characteristics (ie, the drug label). The first drug is eculizumab;at the time of approval, a single pivotal study supported the benefit-risk of eculizumab in patients with paroxysmal nocturnal hemoglobinuria but only in patients who had undergone transfusion previously.[9] The registry study data then confirmed that a positive benefit-risk applied to all patients with paroxysmal nocturnal hemoglobinuria irrespective whether they had a previous transfusion . The second drug that led to a label change was the influenza A (H1N1) pandemic vaccine, for which the results of the registry study conducted in pregnant women (an important hitherto not studied population) showed that the vaccine was not associated with an increased risk of adverse pregnancy outcomes.[10] The 4 other registry studies reported in EPARs complemented the limited datasets at time of approval confirming the benefit risk balance at this time point, thus not requiring any label changes. Two registries (Psoriasis Longitudinal Assessment Registry and the Icatibant Outcome Survey) for ustekinumab and icatibant, respectively provided reassurance that no new safety signals emerged.[11-12] Registry data indicated that longer treatment of romiplastin did not lead to unexpected immunogenicity.[13] Finally, the US Cystic Fibrosis Foundation Patient Registry provided controlled long-term effectiveness data for aztreonam lysine, it reported a better outcome of aztreonam-treated patients with respect to hospitalization.[14]

Data from 11 registry studies (15%) were published in peer-reviewed journals.[8,15-24] For 4 registry studies these data were only published for the baseline characteristics of the patients enrolled[15-16] and/or the enrolment process were described.[17-18] Five articles published baseline data and interim data after 1 year[19] or after > 1 year of treatment.[20-23] Publications with data generated in a registry of pregnant women receiving the pandemic vaccine provided evidence on absence of risk, which (as described earlier) is also reflected in the Summary of Product Characteristics.[8] Data from pregnant women with Gaucher disease suggest that continuing treatment during pregnancy may be appropriate.[24]

Discussion

The present study, including 73 post-approval studies in registries imposed or agreed on by the Committee for Medicinal Products for Human Use, showed that 5 years after approval only 2 registry studies (3%) had been finalised[8] and that 19 registries (26%) had not enrolled any patients. Of the 41 registry studies with predefined sample sizes, enrolment was poor (median inclusion 31% for all registry studies), albeit that inclusion for imposed registry studies seemed better (61% versus 30% enrollment for non-imposed registry studies).

In 2012, pharmacovigilance legislation was implemented to enable regulators to protect the public from emerging safety issues not only at the time of approval of a drug but throughout a drug's life cycle. The impact on industry is that a clear legal framework for post-authorization monitoring has been established. Regulators can now take action if industry does not complete its post-approval studies.[25] Our study was performed on drugs approved before the new pharmacovigilance legislation came into force. This approach was taken to allow registries to mature, considering among others the delay in "real-world" use of a drug after approval due to sometimes protracted reimbursement negotiations. Obviously, we cannot dismiss the possibility that the new pharmacovigilance regulation may have had an impact on the performance of registries. Two studies focusing on more recent imposed registry studies (albeit with inherently shorter follow-up periods than our study and one being a study from the United States) however, found similar results of slow recruitment.[26-27] What we add is that even with longer follow-up periods, recruitment in registries remains poor and that imposed registry studies (a regulatory tool that is likely to have been used more frequently since the new pharmacovigilance legislation) may perform better than non-imposed ones. The exact reasons for poor recruitment were not easily identifiable in our study. For 9 registries no reason was provided for the lack of or poor enrollment. To improve enrollment, for the future, more attention is needed on the feasibility to conduct a registry; for example, whether an existing registry is available. It is important that this factor has been explored by both industry and the regulatory authority beforehand.[28]

Finally, EMA promotes making use of existing disease registries.[28] These registries have the advantage of having already shown the ability to recruit and follow

up patients. These registries usually have extensive track records of generated valuable health care knowledge beyond specific effects of a drug of interest, and may provide historical or contemporaneous control data. Product registries, conversely, may have the advantage that industry sponsors pay data monitors to ensure quality and validity of data entered into the registry. In contrast, disease registries are often created by academic investigators, where quality control may be limited due to limited resources. These differences may impact accrual rates and success of the studies performed in registries. Interestingly, data from our study suggested, however, that product registries achieved higher enrollment rates.

Our study also showed that for a few drugs only, the data generated from registries were published on the EMA website or in peer-reviewed journals. Only 8 out of 73 registry studies reviewed in the presentstudy were published in the European Union electronic Register of Post-Authorisation, but it should be kept in mind that this Register was launched in November 2010, while our study period was 2006-2010.

Once a drug is approved, it will be used usually by much larger numbers of patients than studied pre-approval. Safety and/or efficacy data generated in the registry or real-world setting can only translate into knowledge for prescribers and other health care professionals, if such data are made publicly available. Although, it is challenging to study the exact impact of registry data to the knowledge of benefits and risks of any drug, the knowledge obtained thus far through registries seems limited. Results of 6 registries were mentioned in EPAR updates only, of which 2 (eculizumab and influenza A [H1N1] pandemic vaccine), resulted in changes in the label. A small proportion of registry studies was published in the peer review literature. Our results on poor performance of registry studies ties in with the work of Vermeer et al,[29], who found that only one fifth of all uncertainties described in Risk Management Plans were resolved 5 years after marketing authorization]. Importantly, Hoekman et al.[30] showed that most post-marketing obligations were eventually completed but often with substantial delay. We appreciate the work done so far by regulators to be more transparent[31] and swiftly publish information on their developing knowledge of the benefits and risks of drugs. Our results suggest, however, that more effort is needed from all stakeholders.

Poor performance of post-approval registry studies challenges the real-world evaluation of, for example, rare cancer drugs that require further data to complement the knowledge on drug benefits and harms after approval. To improve the knowledge of new drugs, the value of registries does not only depend upon recruitment, but also upon quality and completeness of the data collected; some articles suggest that improvements need to be made in this context as well[32-33]. Post-approval registries are, however, just one part of the real-world evaluation, the poor performance of studies in these registries challenges the authorization of drugs. This situation can only be improved if regulators are explicit about data that are needed and what the consequences will be if data are not timely delivered.

Conclusions

Five years after approval only 2 (3%) of 73 registry studies had been finalised, 19 registries (26%) had not enrolled any patients, and 52 (71%) were ongoing. Enrollment for imposed registries seemed better, but overall inclusion rate was poor. Registries have had only a limited impact on resolving gaps in the knowledge of a drug's benefits and risks at time marketing authorization. It is important to be careful with broadening the use of post-marketing studies as a means of resolving uncertainties about benefits and risks after marketing authorization.[30]

Acknowledgements
The following can be added: C.J.J., M.S.G.K. and P.G.M.M. participated in the literature search, study design, data collection and figure creation. All of the authors participated in the interpretation of the data and the preparation, review, and approval of the manuscript.

Conflicts of interest
The authors have indicated that they have no conflict of interest regarding the context of this article.

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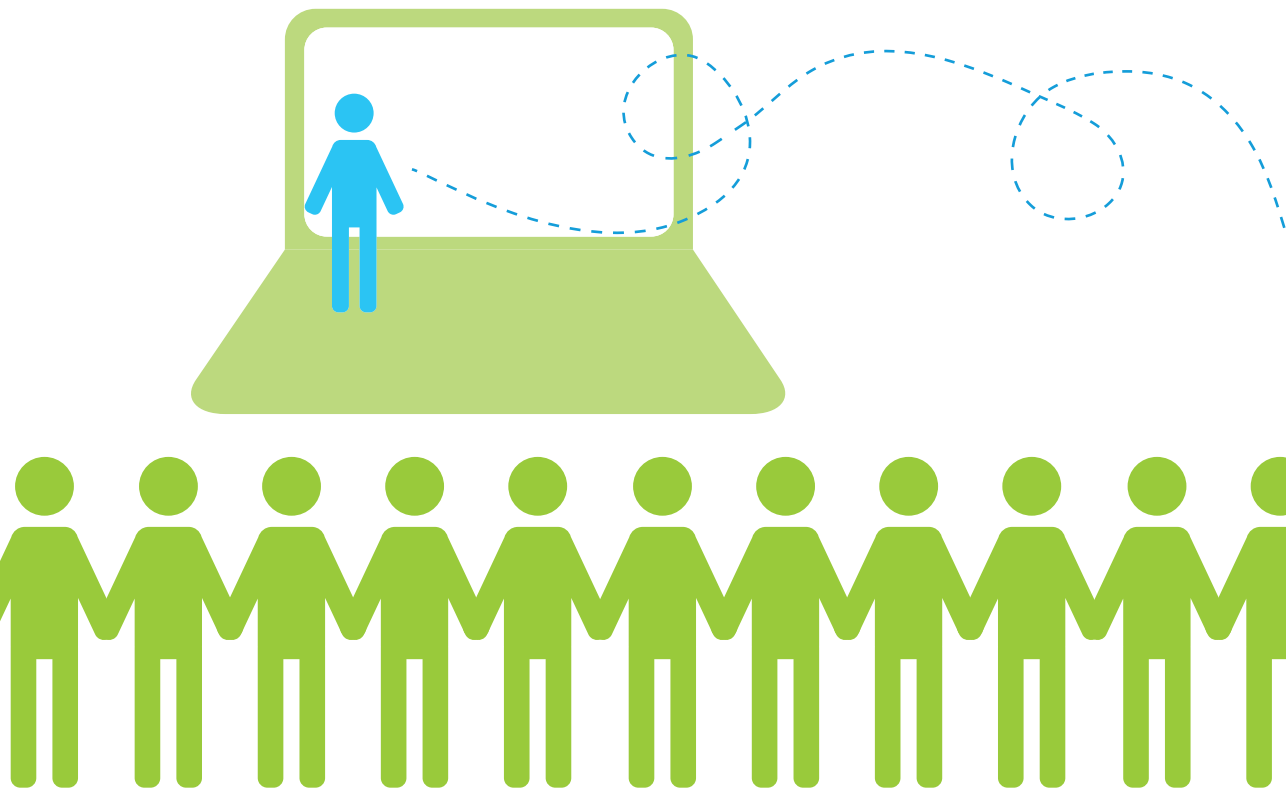

Chapter 4
Clinical trials and registries in haemophilia: Opponents or collaborators?
Comparison of PUP data derived from different data sources

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H. Marijke van den Berg
Anneliese Hilger

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Abstract

Introduction
The "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products" (ClinGL) provides the requirements for the performing of clinical trials (CTs) for marketing authorization in Europe. The number of eligible previously untreated patients (PUPs) for CTs might be difficult to meet because of the concurrent development of FVIII concentrates, and additional data sources must be explored.

Aim
The extent to which CTs and the PedNet registry met relevant parameters, identified in the ClinGL, as well as inhibitor incidences were investigated in patients from both sources.

Methods
Anonymized data of eight CTs in 369 PUPs performed from 1987 to 2009 were compared with each other and with 632 PUPs (born 2000-2009) from PedNet.

Results
Clinical trials in PUPs performed for marketing authorization were too heterogeneous in their investigated parameters; therefore, a comparison of single factor concentrates was not possible. Data collection in PedNet met relevant parameters required for PUPs in accordance to the ClinGL. The overall inhibitor incidences were comparable (CT=30.9% vs. PedNet=30.6%) when only severe Haemophilia A (HA) patients from both data sources were considered.

Conclusions
Previously performed CTs in PUPs were divergent, which prevented a direct comparison of outcomes. However, this study demonstrated that data from CTs and carefully designed registries may complement each other in the establishing of sufficient safety information for single products to improve clinical insights and support regulatory decisions.

Introduction

Haemophilia A (HA) is an X-linked bleeding disorder that leads to a reduced synthesis of factor VIII (FVIII) and therefore to the need of treatment with an exogenous factor. FVIII purified from blood is referred to as plasma-derived (pdFVIII), in contrast to biotechnologically manufactured recombinant FVIII (rFVIII).[1,2] Successful treatment with substitution of the missing protein is challenged by the development of anti-drug antibodies (inhibitors).[3-5] Inhibitors occur in approx. 30% of previously untreated patients (PUPs) with severe HA, generally within the first 50 exposure days (EDs).[6-8] HA is a rare disease detected in 1:5000 male births. From 2.5 million males that are annually born in the European Union (EU)[9] approximately 500 are born with HA. Half of them exhibit the severe form of the disease. Greater than 50% of these newborns with severe HA have a negative family history for HA[10,11], and their disease will likely only be diagnosed during bleeding with a need for immediate therapy. This further reduces the number of potential PUPs to be included in CTs.

The clinical development programme for most FVIII products on the EU market followed the previous Guideline on the clinical investigation of recombinant factor VIII and IX products[12], where studies in previously treated patients (PTP), but no PUP studies were required for marketing authorization (MA). The Paediatric Regulation, which came into force in the EU in January 2007, was developed to ensure that medicines for use in children were of high quality, ethically researched and authorized appropriately. This led to the establishment of the Paediatric Committee (PDCO) at the European Medicines Agency (EMA), which is responsible for the compliance of studies performed in children as delineated in the paediatric investigation plans (PIPs). In consequence, the Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (ClinGL)[13] was revised and published 2012. The CT concept was updated to strengthen the investigation in the paediatric population and the requirement to perform PUP studies was included.

Many new factor concentrates are currently in development or apply for MA[2,14,15], but the number of PUPs for recruitment into CTs may be difficult to achieve in an appropriate timeframe. Therefore, other data collection systems such as registries should be explored whether they can be used to supplement data derived from CTs.[16] The following research questions were pursued to investigate the comparability of different data sources:

1. Are CTs in PUPs, performed in the context of MA for factor concentrates, comparable?
2. What are the parameters required in the ClinGL for regulatory PUP studies?
3. How do CTs and a registry perform in terms of data collection in PUPs?
4. Is the inhibitor development observed in CTs and PedNet comparable?

Material and Methods

Material

Data sources

Clinical trials: Data of clinical trials were anonymized and consolidated into a confidential database (PEI-DB) that was established as part of the ABIRISK project (www.abirisk.eu) and is located in the Paul-Ehrlich-Institut. Data from PUPs and minimally treated patients (MTPs) were used for this evaluation. The PEI-DB summarizes relevant variables from CTs that were identified, presented and approved at the ABIRISK Variable Definition Workshop in October 2012.

PedNet: The PedNet haemophilia registry is a collaboration of haemophilia centres that was established in 2004 (www.pednet.eu, www.clinicaltrials.gov trial no: NCT02979119). All PUPs with severe HA born between 2000 and 2009 (Cohort I) were selected for this analysis for consistency with the performance period of CTs (e.g., treatment and assays). Cohort I was followed until January 2016. Participating centres collected the anonymized data, which were submitted using web-based case report forms (CRFs).[17]

Parameters

The following key parameters were investigated to analyse the comparability of CTs with each other: differentiation and inclusion of PUPs/ minimally treated patients (MTPs), disease severity, observational period, definition of (high-titre) inhibitor, inhibitor test schedule, and inhibitor test assays. Parameters to be performed in PUP studies were identified in the Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products.[12] CT protocols were reviewed to identify whether key parameters to analyse efficacy and safety focussing on immunogenicity of factor VIII products in PUPs were collected in accordance to the ClinGL. The same evaluation was performed for the PedNet protocol.

Methods

Statistics

Survival curves were created for all inhibitors and high-titre (>5 BU/ml) inhibitors[18] using the Kaplan-Meier method. Time to event was defined as the time from first ED to the last ED prior to the first positive inhibitor test or, if not positive, when the subjects reached 50 EDs. Subjects who did not reach 50 EDs were right censored at the number of their last documented ED. Only patients from CTs with FVIII:C <1% were chosen for reasons of comparability. Survival curves were compared using the log-rank test and Gehan-Breslow-Wilcoxon test.

Results

1. Are CTs in PUPs, performed in the context of MA for factor concentrates, comparable?

There were 8 CTs performed between 1987 and 2009 in a total of 369 PUPs and MTPs. The number of patients per CT varied between 16 and 97, with 3 CTs investigating >50 patients. A total of 71 MTPs was included in 3 CTs. One CT enrolled PUPs with all severities of HA, but patients in most CTs exhibited FVIII:C ≤ 2%. The definition of severity using clinical performance was possible in one CT, which allowed enrolment of patients with FVIII:C levels >2%. The intended observational period (follow-up) ranged from 9 months to "100 EDs or 5 years, whichever comes first". The time from first ED of the first patient until the last ED in the last patient (trial period) varied between 28 and 85 months. Inhibitor testing procedures used different assays and sampling schedules (Table 1).

2. What are the parameters required in the ClinGL for regulatory PUP studies?

The ClinGL, which came into effect in 2012, covers the performance of clinical investigations pre- and post-MA. The first part of the ClinGL includes instructions for the design of clinical concepts and general aspects regarding efficacy and safety are compiled. Definitions of severity and treatment status were determined, and recommendations for the performance and timing of inhibitor tests are presented. The most important patient characteristics that must be documented are also included. Section 6.5 of the ClinGL provides details of the performance of clinical investigations in PUPs and describes how PUP studies should be integrated into the general concept. Annex I provides an overview of this general concept. Annex II of the ClinGL identifies the most relevant data to collect on efficacy and safety in PUPs. Table 2 presents an overview of the identified relevant parameters for CT in PUPs.

3. How do CTs and the PedNet registry perform in terms of data collection in PUPs?

The here presented analysis focused on the completeness of documentation of parameters for safety, efficacy and follow-up. Review of the CT dossiers revealed that most of parameters required by the ClinGL from 2012 were investigated in the earlier performed CTs, but not all parameters were consistently introduced in all studies. Data collection for the PedNet follows a single protocol, and every parameter that is part of the study protocol is documented in all PUPs (Table 3).

The identified parameters for proper analysis of immunogenicity primarily apply to inhibitor testing, which should be performed at defined time points: before first exposure, between ED 10 and 15 and at ED 50. Inhibitor testing before first exposure was required in 7 of the 8 CTs, and half of the CTs demanded inhibitor tests at ED 10-15 and ED 50. Inhibitor testing when a suspicion of inhibitor development arose was only formally demanded in 3 of the 8 CTs, as well as confirmation of a positive test result.

Table 1. Comparison of clinical trials performed in the frame of marketing authorization between 1987 and 2009.

CT	1	2	3	4	5	6	7	8
PUPs [n]	38	73	97	16	18	19	29	8
MTPs [n] (EDs)	--	--	--	--	12 (1-4 ED)	12 (1-4 ED)	--	47 (1- 3 ED)
Definition of severity	severe, moderate, mild	<2%	< 2%	<2% or by judgement of the principal investigator	≤ 2%	≤ 2%	≤ 1%	≤ 2%
Number of patients with severity defined by FVIII:C								
<1%	11	54	52	5	26	23	22	17
≤2%	10	19	45	6	4	8	7*	38
>2%	17	--	--	5	--	--	--	--
Number of patients with severity defined by clinical performance								
severe	16	73	97	12	30	31	29	17
moderate	16	--	--	1	--	--	--	--
mild	6	--	--	3	--	--	--	--
Not available	--	--	--	--	--	--	--	38
Intended observational period	9 month	100 ED or 5 years	50 ED or 5 years	100 ED or 5 years	2 years and ≥20 ED	2 years and ≥20 ED	50 ED or 2 years	75 ED or 3 years
Trial Period [month]	28	85	36	28	42	38	58	66
Definition of an inhibitor	--	≥ 0.6 BU at Central Lab	≥ 0.6 BU at Central Lab	> 0.6 BU	≥ 0.6 BU at Central Lab	> 0.6 BU at Central Lab	> 0.6 BU in 2 following tests	≥ 0.6 BU at Central Lab, confirmed by 2nd sample
Definition of a high titre inhibitor	--	> 10 BU	> 5 BU	--	> 5 BU	> 5 BU	--	> 5 BU
Inhibitor test schedule	Dimfficacy	prior the first infusion and then every 3 month	week 2, month 1, month 3, q3 month for 2 years	prior 1st infusion, then every 3 month	q3ED to 20 ED, q10ED to 50ED or every 3 month	q3-4 ED to 10 ED, q10 ED to 50 ED	q3-4 ED to 20 ED, q10 ED to 100ED	5±1 ED, 10±1 ED, 15±1 ED, 20±1 ED, every 10±3 EDs
Inhibitor test assay	--	Bethesda	Bethesda + ELISA	Bethesda	Nijmegen	Nijmegen	Nijmegen	Nijmegen

* 7 patients had a FVIII:C level ≤1%

Table 2. Parameters to be documented pre- and post-marketing authorization from the general section and for PUPs according to the Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (ClinGL).

Parameters	ClinGL Page (Line)
Immunogenicity	
Inhibitor testing immediately before first exposure, at ED 10-15, ED 50 and if there is any suspicion of inhibitor development.	18 (19-22), 6 (16-17), 7 (10-11)
Confirmatory measurement of a positive test result	7 (27-29)
Validated testing to be performed in a Central Laboratory	7 (25-26)
Nijmegen modification of Bethesda assay	7 (25)
Inhibitor thresholds are ≥0,6 BU for a low-titer, > 5 BU for a high-titer	7 (30)
Inhibitor tests to be performed, when FVIII level has reached baseline	7 (32)
Screening and documentation of conditions influencing FVIII inhibitor measurements (e.g. chronic viral infections (e.g. HIV, HCV) or Lupus coagulants)	7 (33-34)
Efficacy	
Clinical efficacy (FVIII consumption, physician´s assessment of response in treatment of major bleeds) Clinical efficacy of treatment (prophylaxis, on demand)	18 (17-18) 6 (3-4)
Pharmacokinetic data (incremental recovery, half-life, AUC, clearance)	6 (1-2), 7 (39)
Safety	
Vital signs (blood pressure, heart rate, temperature)	18 (23-24)
Adverse events	6 (6)
Hypersensitivity to heterologous proteins	6 (20-22)
Follow-up	
50 PUPs for 50 EDs started pre-MA	11 (44), 12 (1)
100 PUPs for 100 EDs post-MA	12 (1-2), 18 (25-27)
Patient characteristics	
Treatment status: never been treated with clotting factor	11 (37-38)
Severe hemophilia as <1%	7 (24)
Ethnicity, family history, life style, general health status, infection status, type of FVIII gene mutation, reason for treatment, treatment start date, kind of treatment (on demand, prophylactic, continuous infusion)	7 (14, 15, 35-38)

The PedNet protocol does not require inhibitor testing before first exposure. Inhibitor testing is advised at least every 5 EDs during the first 20 EDs and every 3 months thereafter until 50 EDs. A confirmative assessment is required in cases of positive test results. Most of the CTs (7 of 8) used a central laboratory, whereas inhibitor testing for PedNet was performed in the local laboratories of the participating centres using the Nijmegen modification of the Bethesda assay. This assay was only used in half of the CTs. An inhibitor is characterized as a test result ≥0.6 Bethesda Units (BU), and an increase in this value to >5 BU indicates a high-titre inhibitor. This definition was found in half of the examined CT protocols. A cut off value for positivity ranging from 0.3 to 0.6 BU was used in local laboratories in PedNet.

Clinical efficacy was assessed using documentation of FVIII consumption and assessment of the response in the treatment of major bleeds. These assessments were performed in all CTs and the PedNet.
The identified parameters for analyses of the safety of products, besides the development of inhibitors, included adverse events (AEs) and vital signs, especially blood pressure, heart rate and temperature. The documentation of AEs was mandatory in all CTs, and 7 of 8 CTs also recorded vital signs. Besides the monitoring of inhibitor development, no AEs or vital signs were documented in the PedNet, but these data were collected in the local data collection systems of participating centres under supervision of the attending physicians.

Follow-up varied in CTs; the duration was at least 50 EDs or until inhibitor development in 5 of 8 CTs, and 3 of 8 CTs collected data in a minimum of 50 PUPs. PedNet required documentation up to 75 EDs or until inhibitor development for all PUPs included in the registry.

4. Is the inhibitor development observed in CTs and PedNet comparable?
Kaplan-Meier curves were developed to correlate inhibitor occurrence with documented EDs for severe (<1% FVIII:C) HA patients (Figure 1). Inhibitor development occurred in 54 of 198 severe CT patients and 186 of 617 PedNet PUPs. Data from 12 CT and 16 PedNet patients were excluded due to limited information. High-titre inhibitors were diagnosed in 26 CT PUPs and 128 PedNet PUPs. Two CT (0.5%) and 6 PedNet patients (0.9%) developed inhibitor after ED 50. Thirty-one percent of severe patients in CTs was not followed until ED 50, and therefore, these data were right censored in comparison to 2% from PedNet.

Comparison of survival curves using the log-rank test and Gehan-Breslow-Wilcoxon test revealed p-values of 0.67 and 0.47, respectively, which are not significantly different. Overall Inhibitor incidences at ED 20 were 25.9% (CTs) and 24.8% (PedNet). The overall inhibitor incidences at ED 50 were 30.9% (CTs) and 30.6% (PedNet). Eighty-seven percent (47 of 54) of inhibitors in CTs developed before ED 20, and the occurrence was 81% in PedNet (151 of 186). High-titre inhibitors were detected at ED 20 in 12.8% (CTs) and 16.8% (PedNet) of patients. Inhibitor incidences for high-titre inhibitors at ED 50 were 14.9% (CTs) and 21.0% (PedNet). Comparison of survival curves of severe patients with

Table 3. Overview of identified relevant parameters from the ClinGL and to what extent these parameters were collected in CTs and PedNet

Parameters for CTs in PUPs	Clinical trials	PedNet
Immunogenicity		
Inhibitor testing before first exposure	◔	○
Inhibitor testing at ED 10-15	◑	●
Inhibitor testing at ED 50	◑	●
Inhibitor testing if there is suspicion of inhibitor development	◔	●
Confirmation measure of a positive inhibitor test result	◔	●
Central laboratory	◔	○
Inhibitor titre in BU, using the Nijmegen modification	◑	●
≥ 0,6 BU = low titre, > 5 BU = high titre	◑	●
Clinical efficacy		
Factor VIII consumption	●	●
Physician's assessment of response in treatment of major bleeds	●	●
Safety		
Adverse events	●	○
Vital signs (blood pressure, heart rate and temperature)	◔	○
Follow-Up		
Follow-up for at least 50 EDs	◔	●
Follow-up of 50 PUPs	◔	▩[a]

black = parameter is collected, white= parameter is not collected, half-filled circle means, that in half of the CTs, the parameter is collected. [a] The follow-up of 50 PUPs in the PedNet is in general possible but depends on the real-life usage of the factor concentrate.

high-titre inhibitors revealed no significant differences with p-values of 0.13 and 0.18, respectively.

Inhibitor development in CTs and PedNet together revealed that 3.75% (9 of 240) inhibitors developed within the first 3 EDs and 7.5% (18 of 240) developed within the first 4 EDs. These same rates were observed for high-titre inhibitors, and 3.9% (6 of 154) developed within the first 3 EDs and 7.8% (12 of 154) developed within the first 4 EDs.

Discussion

1. Are CTs in PUPs, performed in the context of MA for factor concentrates, comparable?

The presented analysis demonstrated that protocols of CTs in PUPs were highly diverse, especially in number of patients, pretreatment conditions, severity definition, follow-up period and inhibitor test modalities. Inclusion of MTPs may impact study outcome via exclusion of patients who developed an inhibitor very early. The current investigation demonstrated that almost 8% of patients developed an inhibitor within the first 4 EDs. Further, inclusion of MTPs may cause doubts about the product that triggered inhibitor development. Limitation in the sensitivity of test systems for FVIII determination and additional severity classification options, for example clinical performance, resulted in trials where PUPs with FVIII levels >2% were included. This inclusion may have confounded the study results of inhibitor development (Table 1). The current ClinGL requires only patients <1% FVIII:C to harmonize inclusion criteria. This criterion is consistent with the Definitions in Haemophilia, which were developed and standardized by the ISTH Subcommittee on Factor VIII and Factor IX [18]. These definitions were recently updated and now include determinations for ED, which is stipulated as any infusion of a FVIII containing product in a 24-h period.[19] Clinical trials often required "50 ED or 3 years of follow-up, whichever comes first", which created differences in patient follow-up. On-demand patients may have reached only 10 EDs at the end of study period in some studies, and therefore, these patients remained at risk for inhibitor development. The variability of patient follow-up in PUP CT impaired comparisons between products. The frequency of testing increased in recent CTs and is more consistent with the period of highest risk for inhibitor occurrence.

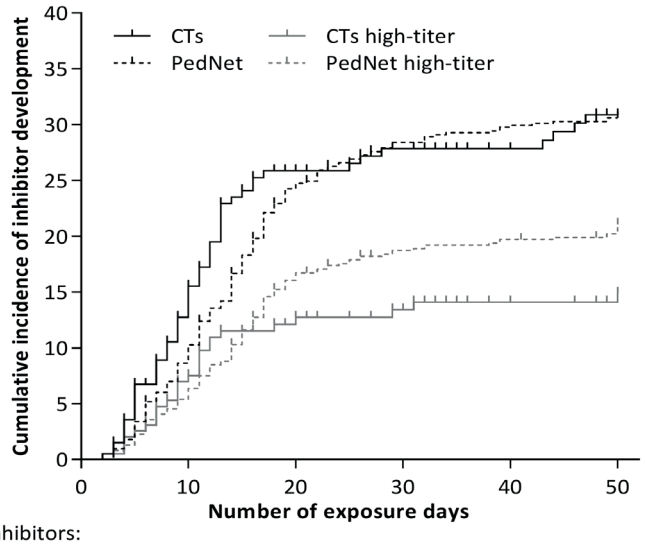
The choice of inhibitor test assays corresponded to the time the CT was performed. After introduction of the Nijmegen modification of the Bethesda test by Verbruggen et al. in 1995[20], all later performed CTs used this modified assay. Confirmatory testing of further samples is essential to monitor inhibitor development over time. This monitoring prevents over-estimation of transient inhibitors and may improve diagnosis and monitoring of low-titre inhibitors.[21] High variability in study protocols was detected depending on the period in which the CTs in PUPs were performed, which prevented a direct comparison of

outcomes. The revised ClinGL[13] requires that PUP studies be performed using a harmonized concept, in accordance with Paediatric Investigation Plans (PIP).

2. What are the parameters required in the ClinGL for regulatory PUP studies?
The ClinGL determines key parameters to be investigated in CTs in support of MA, including efficacy, safety focusing on immunogenicity, follow-up period and relevant patient characteristics. These parameters are the result of the collaboration of EMA internal and external experts, which began as a meeting in 2006 that focused on international standardization and harmonization of the requirements for CTs on FVIII.[22] The introduction of PUP studies was also based on the fact that PUPs are rare and vulnerable patients, and therefore, data in PUPs should be collected systematically.

There are many current ongoing initiatives to collect data and address open issues in haemophilia, such as the possibility of head-to-head product comparison. For example, the WFH is developing a World Bleeding Registry that uses a modular CRF as a comprehensive data collection tool for haemophilia treatment centres (HTCs).[23] ISTH SCC recently published a minimal dataset for the post-registration surveillance of new drugs in haemophilia.[24] A drafting process of the ClinGL has been initiated proposing at the European level to reconsider the CT requirements for PUPs and establish a minimum core parameter set for registries.[25]

3. How do CTs and the PedNet perform in terms of data collection in PUPs?
Before the ClinGL went into effect in 2012, there was no obligation to perform CTs in PUPs. A regulatory framework to demand a specific trial design was lacking. The clinical trial protocols of 5 CTs were drafted in the 1980s or early 1990s, when the relevance of specific parameters or concepts were not clear. One aspect is the ED concept to schedule inhibitor tests or the length of patient follow-up; another aspect is the use of the Nijmegen modification of the Bethesda test, which was introduced in 1995.[20] Testing for FVIII inhibitors prior to first exposure to treatment must be performed in CTs to obtain solid baseline data. The PedNet registry does not require baseline inhibitor testing before first exposure to a FVIII product because every PUP of the HTCs must be enrolled, including patients who may require immediate treatment. This omission may be critical, but the absence of baseline information must be balanced against the avoidance of PUP selection. Observed differences in the documentation of key parameters in CTs and PedNet are also based on the nature of the two data collection systems. CT protocols were heterogeneous because sponsors were free to choose endpoints and methods to investigate efficacy and safety in PUPs. The PedNet records real-life data using a standardized case report form. However, data collection after MA depends on the availability and use of certain products. Key parameters in PedNet are more uniformly collected than in the investigated CTs. Based on the nature of a registry, some aspects are not fulfilled by PedNet: for example, inhibitor tests were performed in the HTCs and not in a central lab, which might be critical regarding variability of test assays. However, a confirmatory test with a second sample following a defined procedure



Patients with inhibitors:						
All inhibitors						
CTs	0	29	47	50	50	54
PedNet	0	63	151	173	182	186
High-titer Inhibitors						
CTs	0	14	23	24	25	26
PedNet	0	39	102	114	120	128

Figure 1 Kaplan-Meier curves for inhibitor development in PUPs from CTs (solid lines) and PedNet (broken lines). A second analysis focusing on high-titre inhibitors was performed (grey lines). The table below indicates patient numbers for all inhibitors and high-titre inhibitors at the corresponding EDs.

in cases of a positive inhibitor result is obligatory for PedNet. AEs and vital signs were documented in the local HTCs, and AEs were reported via pharmacovigilance systems.

In principle, CTs are performed to prove that a new product is efficacious and safe to obtain MA, in case of haemophilia based on data coming from a limited number of patients. Disease registries are designed to collect reliable long-term data from all patients and all products in use. The present study demonstrated that well-designed and well-managed registries may be prepared to collect the required key parameters of the ClinGL. However, stratification of risk factors and the avoidance of bias may be challenging. The investigation of additional parameters may become relevant with new haemophilia treatment options.

4. Is the inhibitor development observed in CTs and PedNet comparable?
The present analysis revealed that the overall inhibitor incidence rate did not differ significantly in data from the PedNet and CTs (Figure 1). The inhibitors were detected slightly earlier in CTs, which may be based on more frequent inhibitor testing in

the first 20 EDs of patients with FVIII:C <1%. In a systematic review from Iorio and colleagues[6] a regression analysis demonstrated that more frequent testing for inhibitors was associated with a higher inhibitor detection rate, likely related to the increased recognition of transient inhibitors. Van den Berg and colleagues[26] recently stated that intensified screening for inhibitors over the last 20 years led to a more frequent detection of low-titre inhibitors, and high-titre levels were stable over time. This finding was based on registry data, but it was not mirrored by the outcome of CTs, which may be caused by the small number of patients per CT and the lack of adjustment for confounding factors. Analysis of only high-titre inhibitors revealed that the rate of high-titre inhibitors was lower in CTs compared to PedNet. Numerous factors, for example too short follow-up period, heterogeneity in patient population and differences in dosing regimen, may influence inhibitor rate detection. Whether a follow-up of 20 EDs was sufficient to calculate inhibitor incidences was discussed[27], but the here presented results support a follow-up of 50 EDs for a valid assessment because of the variation of 13-19% for PUPs who develop an inhibitor between ED 20-50. Consequent data collection in registries may lead to a sufficient number of patients treated with the same product to allow relevant calculations and comparison; CTs performed before 2012 could not fulfil this aspect. The analysis also revealed that the inclusion of MTPs in CTs may influence the outcome due to early inhibitor development within the first 4 EDs prior to enrolment.

Conclusion

This investigation revealed that CTs with PUPs performed in the past for MA purposes were not sufficiently designed to allow comparisons between products. This analysis exemplarily demonstrated that the PedNet collected data according to the parameters and conditions required by the ClinGL. The results of inhibitor development were comparable regardless of the differences in data collection of both sources, especially when focusing on patients with severe HA.

The restriction in patient availability has been controversially debated for decades.[28] An international workshop organized by the European Medicines Agency (EMA) was held in 2015 to investigate whether haemophilia registries can provide valuable data for regulatory purposes.[29] One of the outcomes of this workshop was that the reporting structures from registries to regulators must be developed as well as the possibility for registries to demonstrate an appropriate quality assurance level of data entry and maintenance. Several large-scale epidemiological studies and a randomized controlled trial were published[10,11,30-35] and intensively discussed with the result that it is difficult to conclude statistically significant outcomes for single products. Ideally, a randomized controlled CT allowing for head-to-head comparison of all products would be a favourable solution to assess inhibitor development in PUPs. However, all RCTs in a rare disease, such as haemophilia, will be underpowered or take >5 years, which makes this design very difficult to pursue. Neither legal nor regulatory frameworks are available to follow this idea because MA must be based on individual data packages derived for single products.

The ClinGL demands that a harmonized concept be followed, but research in clinicaltrials.gov revealed that planned and already recruiting PUP-studies were different in essential parameters, such as the inclusion of MTPs or the exclusion of patients with a known family history of inhibitor development. CTs performed before 2012 mostly recruited patients in central Europe and United States, but some of the present CTs are searching for patients in countries outside these regions. Whether this strategy will impact future study results must be critically evaluated.[36,37] Concepts for CTs and PedNet follow different strategies to investigate inhibitor development in PUPs; CTs aim for data collection for a single product in a limited time period, and a disease registry, such as PedNet, collects longitudinal data in patients and has a consistent enrolment of PUPs. Data collection in registries reflects real-life use of factor concentrates, which may allow comparison between products. Further harmonization of data collected in CTs and registries is needed to avoid methodological constraints and differences in design and realization.[38] Clarification of the legal ownership of registry data (or patient data in general) and access to these data must be addressed to improve clinical insights and support regulatory decisions.[29] Data derived from registries should not be regarded as opponents to CTs but as important complementary data sources after MA.

Urgent work needs to be done now: there must be agreement on the core dataset that should be collected from registries, and this dataset must be approved by regulatory agencies. Accreditation of registries on at least the European level to demonstrate an agreed excellence in design and management should be determined. Strategies must be developed for data sharing between academia, regulators, companies and other stakeholders.

Author contribution

C. Keipert wrote the article, provided data from the PEI-DB and analysed the data; C.J. Jonker wrote the article and provided data from the PedNet. H. M. van den Berg and A. Hilger participated in discussions and reviewed the article. All of the authors had full access to the data and participated in the design of the analysis, discussion of results and revising the draft manuscript.

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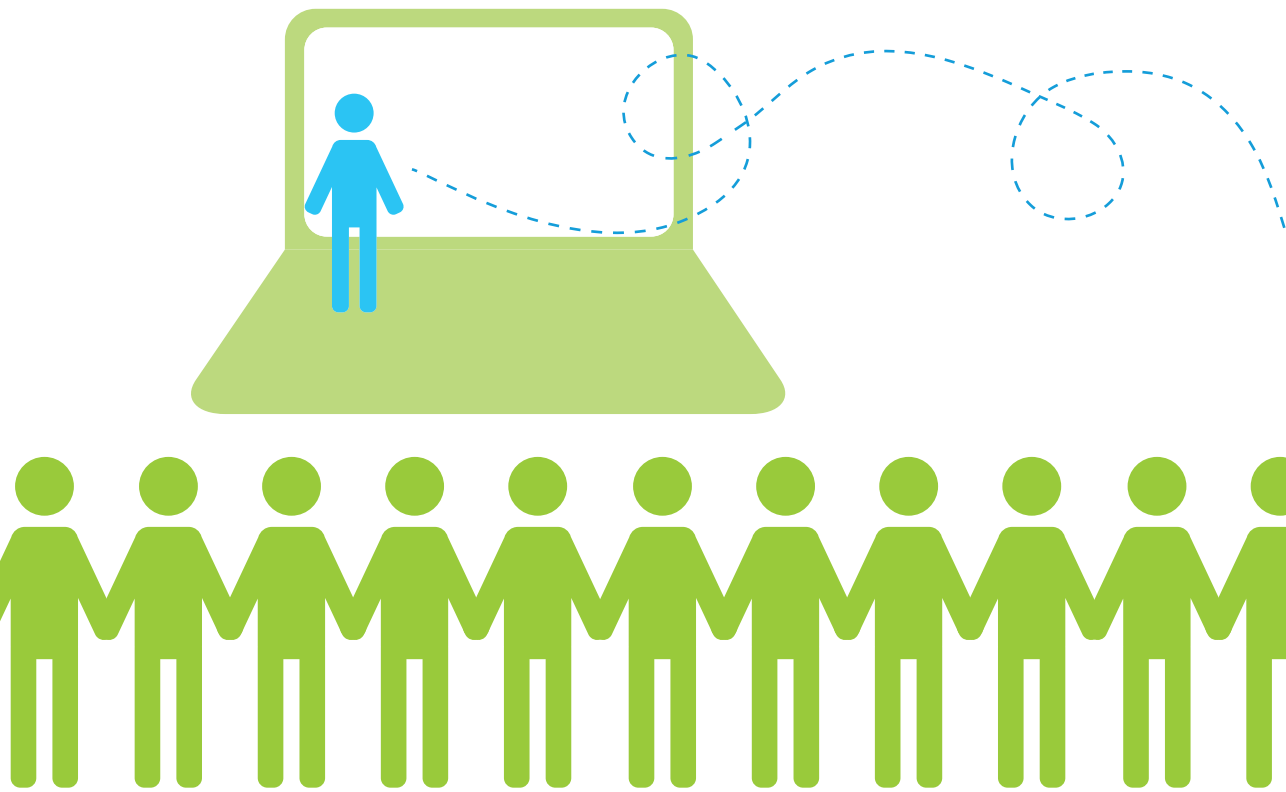

Chapter 5
Inhibitor development in previously untreated patients with severe haemophilia;
A comparison of included patients and outcomes between a clinical study and a registry-based study

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Abstract

Aim
The aim of this study was to investigate whether a disease registry could serve as a suitable alternative to clinical studies to investigate safety of orphan drugs in children.

Methods
We used individual patient data from Previously Untreated Patients (PUPs) with severe haemophilia A from the factor VIII (rAHF-PFM)-clinical study and the PedNet registry. The primary outcome was the patient characteristics at entry and the difference in inhibitor development between the clinical study and the registry-based study at 50 exposure days.

Results
Clinical study patients more often had a positive family history of inhibitors (31% vs 10%) and a high-risk F8 genotype (82% vs 63%). In the clinical study 41/55 (75%) and in the registry-based study 162/168 (96%) patients reached 50 exposure days. Inhibitors developed in 16 of the 41 patients in the clinical study (39%) versus 44 of the 162 patients in the registry-based study (27%); 7 patients (7%) versus 28 patients (17%) had high-titre inhibitors. The risk of developing an inhibitor during the first 50 exposure days was similar (HR 1.04; 95% CI 0.56 – 1.94), when adjusted for family history of inhibitors, F8 gene mutation and intensive treatment at first exposure.

Conclusion
In the registry-based study patient numbers and completeness of follow up were higher. The risk of developing an inhibitor to a single product was comparable. Although, the sample size of this study was too small to conclude on differences in high or low titre inhibitors, this suggests that a registry could serve as a more suitable source for evaluation of high titre inhibitors in the setting of factor VIII deficiency.

Introduction

In the field of orphan diseases clinical trials are inherently small and relatively often use non-randomized study designs.[1-2] Disease registries may be a reasonable alternative for small, single-arm clinical studies to evaluate safety and efficacy of a drug. A great benefit of registries is that they include 'real-life' patients, and are suited for monitoring safety and beneficial effects over a longer period.[3] Within the regulatory field, the Patient Registry Initiative of the European Medicine Agency is exploring the use of patient registries. This initiative supports a systematic approach for a better use of registry data for the benefit-risk evaluation of medicines, mostly post-marketing.[4-5] To retrieve high quality registry data, key aspects are a comprehensive enrolment of patients, avoidance of selection bias, collection of essential core data and completeness of data.[5]

Haemophilia A is a rare disease, with a prevalence of 1:5000 new-born males, for which single-arm clinical studies have supported market approval of (recombinant) clotting factors that replace the deficient factor VIII.[6] In various registries, patients with haemophilia are closely monitored for the occurrence of antibodies against administered clotting factor; so-called 'inhibitors'. The occurrence of inhibitor development in previously untreated patients (PUPs) has been reported to be as high as 25-35%.[7-8] There is an ongoing debate as to whether plasma products might be associated with a lower risk of inhibitor development in comparison to recombinant products.[7, 9-10] Different inhibitor incidences between individual recombinant products have also been published.[7-9,11] Major limitations to the interpretation of results from previous clinical studies were due to differences in study design, patient selection and a short follow-up.[12] Recently, data from historic clinical studies were investigated. These data proved unsuitable for comparing immunogenicity between products, due to differences in study design, diversity in enrolled patient populations, and small numbers of included patients.[13] Lately, a number of new factor VIII products has been licensed, and many new products are being developed.[14] To investigate the occurrence of inhibitor development for these products, it might be difficult to recruit sufficient PUPs in clinical studies in an appropriate time frame. This knowledge has recently led to a change in the guideline for the investigation of factor VIII products. To retrieve long-term safety data in PUPs, core data elements should be collected in patient registries rather than in small clinical trials.[6]

To investigate whether a registry-based study could serve as a reasonable alternative for a single-arm clinical study, we evaluated inhibitor development in PUPs with severe haemophilia A using the same recombinant FVIII product in a clinical study and a registry-based study. We selected the factor VIII (rAHF-PFM)-clinical study, because the study was performed in the same time frame as the data collected in cohort I of the PedNet registry.

Methods

Study design

In previously untreated patients (PUPs) with severe haemophilia A using factor VIII (rAHF-PFM), we compared the development of anti-factor VIII antibodies (inhibitors), using individual patient data from the factor VIII (rAHF-PFM) PUP-clinical study and the PedNet registry. We checked all core data elements required in the guideline for regulatory PUP studies, and compared core data elements relevant for patient characteristics and inhibitor formation in the two study populations.

Data sources

The clinical study: Factor VIII (rAHF-PFM) PUP-clinical study

The factor VIII (rAHF-PFM) clinical study was a prospective clinical study including 55 patients treated with human recombinant FVIII octocog alfa from 24 haemophilia centres (www.clinicaltrials.gov trial no: NCT00157157)[15]. The participants in this clinical study received a specific intervention (human recombinant FVIII octocog alfa) according to the protocol created by Takeda. The first patient entered the study on 1 April 2004 and the last patient exited on 11 September 2009. Takeda provided the individual patient data of this clinical study to us after they had been fully anonymized. In line with the definition used in the PedNet study, patients that received 1-4 infusions of rAHF-PFM before entering the study were defined as Previously Untreated Patients (PUPs).

The registry-based study: PedNet Haemophilia Registry

As of January 2018 the PedNet Haemophilia Registry had included 1035 patients with severe haemophilia A (factor VIII activity at baseline percentage <1%) from 31 haemophilia centrs (www.pednet.eu, www.clinicaltrials.gov trial no: NCT02979119).[16-17] To provide a contemporaneous comparison to the clinical study, we selected all PUPs treated with human recombinant FVIII octocog alfa who were born between 2000 and 2009. Participants included in the registry received the intervention (human recombinant FVIII octocog alfa) as part of their routine medical care according to the protocol created by PedNet. For this analysis we used the follow-up data available in January 2018. Sixty-one PedNet patients were selected from six centres that also participated in the clinical study. Due to privacy regulations we obviously did not have access to e.g., initials or date of birth to verify whether a patient was included both in the clinical study and in the registry. We matched patients on the factors F8 genotype mutation (yes/no), family history of inhibitors (yes/no) and treatment intensity (yes/no). In total 70 (2x35) matched patients matched on these three factors. Importantly, 35 matched patients from the PedNet registry were from centres that did not participate in the clinical study. Thus, this excludes the possibility of an overlap of patients from the clinical study and the PedNet registry.

Data

We extracted core data elements of the PUP populations from the clinical study and the registry as listed in the guideline.[6] For this study we selected the key patient characteristics of age, gender, type of haemophilia, severity of haemophilia (<1% factor VIII activity), family history of haemophilia (yes/no), family history of inhibitor development (yes/no), product, F8 gene mutation (high risk/low risk), and intensity of treatment at first exposure (yes/no). A high-risk F8 gene mutation was defined as genotypes with large deletions, nonsense mutations, and intron inversions. A low-risk F8 gene mutation was defined as genotypes with small deletions and insertions, missense mutations, and splice-site mutations.[15, 17] Intense treatment at first exposure was defined as an episode of treatment with factor VIII for a bleed or surgery on at least five consecutive days.

In addition, we collected the duration of treatment (number of exposure days and calendar days) and the number of patients followed until exposure days 20 and 50.

Outcome parameter

The primary outcome was the percentage of patients developing clinically relevant inhibitors to factor VIII (rAHF-PFM) up to 20 and up to 50 exposure days. A clinically relevant inhibitor is defined as at least two independent positive inhibitor tests with decreased in vivo recovery of factor VIII levels. For the registry laboratory results are used from the individual laboratories (according to the used inhibitor assay and their cut-off level)[17], and from a central laboratory for the clinical study.[15] High-titre inhibitor was defined as a peak inhibitor titre of at least 5 Bethesda units per milliliter. Testing was performed at least every 5 exposure days during the first 20 exposure days and thereafter at least every 3 months until 50 exposure days were reached. The secondary outcome was time to (high/low) inhibitor development defined as the number of exposure days prior to the first positive inhibitor test. An exposure day was defined as a day with one or more infusions of factor VIII.

Analyses

We used descriptive statistics and Chi-square tests to compare the patient characteristics of the PUP populations in the clinical study and the registry-based study. Using logistic regression, we compared the percentage of patients developing an inhibitor up to 20 and 50 exposure days (ED20 and ED50) unadjusted and adjusted for potential confounders. In this study, we adjusted for family history of inhibitor development (yes/no), F8 gene mutation (high risk/low risk), and intensive treatment at first exposure (yes/no). We performed complete case analysis.
The time to inhibitor development was visualized with a Kaplan-Meier plot, censored at 50 exposure days. Cox regression was used to calculate crude and adjusted hazard ratios for inhibitor development, using the same potential confounders as in the logistic regression analysis. To make the groups comparable for the exposure, subjects were censored at 50 exposure days and subjects, who did not reach 50 exposures days, were censored at their last documented exposure day.

Results

Patients

In the clinical study 55 PUPs, and in the registry-based study 168 PUPs with severe haemophilia A were included. Core data elements were available in line with the EMA guideline.[6] The most important patient characteristics that must be documented were included in the clinical study and the registry-based study and are shown in Table 1. All patients were male and used the same recombinant factor VIII product rAHF-PFM during all exposure days. In the clinical study, 17/55 (31%) patients had a positive family history of inhibitors versus 16/168 (10%) in the registry. The number of patients with a high risk F8 gene mutation in the clinical study was 45/55 (82%) versus 105/168 (63%) in the registry-based study. In the clinical study 8/55 (15%) and in the registry-based study 29/168 (17%) patients received intensive treatment at first exposure.

Treatment period

In the clinical study 48 (87%) and in the registry-based study 164 (98%) patients received 20 exposure days, or developed an inhibitor within that period. Forty-one (75%) patients in the clinical study and 162 (96%) in the registry-based study reached 50 exposure days or developed an inhibitor (Figure 1 and Table 2).

Inhibitor development

In the clinical study 11 out of 48 patients (23%) and in the registry-based study 37 out of 164 patients (23%) developed inhibitory antibodies within 20 exposure days (OR 1.02 (95% CI 0.47 – 2.20)). When adjusted for family history of inhibitors, F8 genotype and treatment intensity the odds ratio was 0.56 (95% CI 0.22 – 1.43).

In total 60 patients developed inhibitory antibodies within the first 50 exposure days: in the clinical study 16 out of 41 (39%) and in the registry 44 out of 162 (27%). The odds ratio was 1.72 (95% CI 0.84 – 3.51). When adjusted for family history of inhibitors, F8 genotype and treatment intensity the odds ratio was 1.22 (95% CI 0.54 – 2.75). In the clinical study 7/41 (17%) patients developed a high-titre of antibodies while in the registry-based study this occurred in 28 of 162 patients (17%). Patients developed inhibitor antibodies after a median of 15 exposure days in the clinical study (Q1-Q3 10-22 EDs) and in the registry-based study after 14 exposure days (Q1-Q3 10-17 EDs) (Table 2). The time between first exposure day and inhibitor development was 5.5 months in the clinical study (Q1-Q3 3.5-10.3) and in the registry-based study it was 3.1 months (Q1-Q3 1.4-7.9).

The Kaplan-Meier graph shows the number of exposure days to inhibitor development (Figure 1). We did not observe any differences in inhibitor incidences of patients during the first 20 exposure days. However, after 20 exposure days the risk to develop an inhibitor was higher for patients in the clinical study.

Table 1. Patient characteristics

Characteristic	Factor VIII (rAHF-PFM) PUP-clinical study (N=55)	PedNet registry based- study (N=168)
Previous untreated patient[a] (PUP)	55 (100%)	168 (100%)
Factor VIII activity at baseline		
≤1%	53 (96%)	168 (100%)
>1 and ≤ 2%	1 (2%)	0
> 2%	1 (2%)	0
Age at first exposure (months, median, IQR)	9.0 (3.0-11.0)[b]	9.9 (5.3-13.6)
Family history of haemophilia		
Yes	NA	88 (52%)
No	NA	79 (47%)
Unknown	55 (100%)	1 (1%)
Family history of inhibitors		
Yes	17 (31%)	16 (10%)
No	35 (64%)	140 (83%)
Unknown	3 (5%)	12 (7%)
F8 genotype		
High-risk	45 (82%)	105 (63%)
Low-risk	10 (18%)	56 (33%)
Unknown	0	7 (4%)
Intensive treatment on first exposure days for ≥ 5 days		
Yes	8 (15%)	29 (17%)
No	47 (85%)	139 (83%)

Patients characteristics for patients from the clinical study and the registry-based study, using the same rFVIII product.
[a]In the factor VIII (rAHF-PFM) PUP-clinical study MTP's were defined as patients using the same recombinant FVIII product before the start of the clinical study, in this study we defined MTP's as patients that received any exposure day of another product before entering the study for rAHF-PFM.
[b]Age is defined in months at time of baseline (clinical study).

When using Cox regression analysis, the hazard ratio for inhibitor development was 1.52 (95% CI 0.86 – 2.69) for patients in the clinical study compared to those in the registry-based study. After adjusting for family history of inhibitors, treatment intensity, and F8 genotype the hazard ratio was 1.04 (95% CI 0.56 – 1.94).

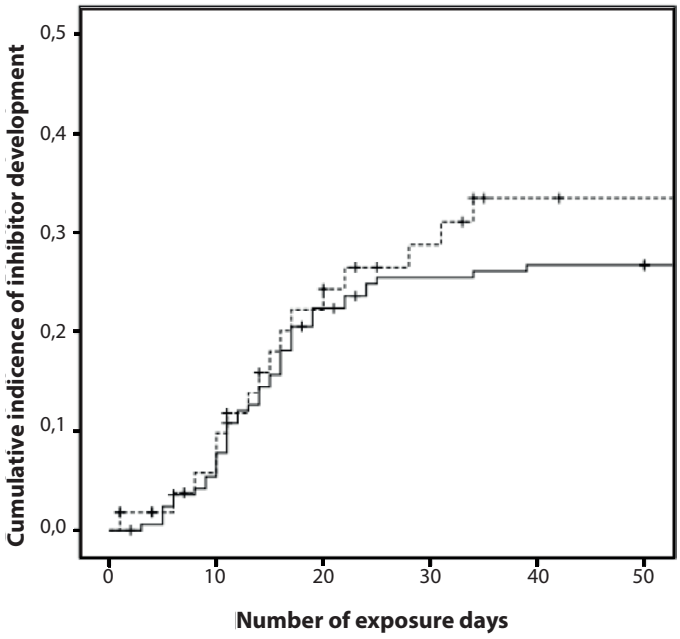
Discussion

At study entry patient characteristics were different between the clinical study and the registry-based study. In the clinical study the prevalence of family history of inhibitors was higher and more patients had a high-risk gene mutation. In the clinical study, only 75% of the 55 patients reached 50 exposure days. The follow-up in the registry-based study was more complete with 96% of all 168 patients reaching 50 exposure days. In the clinical study more patients developed an inhibitor, however, the percentage of patients that developed a high-titre inhibitor was comparable. The risk of developing an inhibitor during the first 50 exposure days was similar (HR 1.04; 95% CI 0.56 – 1.94), when adjusted for the main potential confounders.

This is, as far as we know, the first direct comparison of inhibitor development in PUPs, either participating in a clinical study or followed in a registry. Patients in both data sets were treated during the same time-period, between 2000-2009, and used the same recombinant factor VIII product. Both in the clinical study and in the PedNet registry, the core data elements collected were in line with the guideline.[6] Patients in the registry-based study were followed until January 2018, which led to a higher number of patients reaching 50 exposure days (96%), while this was only 75% for the clinical study. In a systematic review evaluating the incidence of inhibitor development in 24 published clinical studies in PUPs, only in 10 studies was the duration of the treatment longer than 50 exposure days.[18] In registries, the follow-up of patients is mostly longer, with >90% of the patients followed for more than 50 exposure days.[8-11] In the PedNet registry patients were followed for up to 1000 exposure days. Recently published data showed that 79% of all inhibitors developed within 20 exposure days and 18% between 20 and 50 exposure days.[16]

In the light of the discussion for the difference in risk rate for plasma and recombinant products, it is interesting that the inhibitor incidence found in both our data sets with a single recombinant FVIII product was similar to that reported for the plasma products in the SIPPET study.[10] It should be acknowledged though that small numbers and selection of patients are important factors that may have influenced the results reported here. Summary statistics of clinical studies have been published via meta-analyses and systemic reviews, comparing inhibitor rates.[12] The contribution of this paper is that we provide a direct comparison of individual data of a published clinical study and compare that to a study embedded in a disease registry. The completeness of the data illustrate that in the field of haemophilia a well-defined prospective registry could serve as a good data source to study long-term (safety) data of e.g., factor VIII products.

Figure 1. Kaplan-Meier curve for inhibitor development



Patients with inhibitor development	0	10	20	30	40	50
Clinical study	0	3	11	14	16	16
Registry-based study	0	9	37	42	44	44

Patients at risk	0	10	20	30	40	50
Clinical study	55	47	37	31	26	25
Registry-based study	168	157	127	120	118	118

Kaplan-Meier curves for inhibitor development in PUPs from a clinical study (broken line) and from a registry-based study (solid line). The table below indicates patients numbers with inhibitor development and the patient numbers on treatment at the corresponding exposure days. Patients not followed up to 50 exposure days are right-censored.

Table 2. Duration of treatment and inhibitor development in the Factor VIII (rAHF-PFM) PUP-clinical and the PedNet registry-based study

Outcome	Factor VIII (rAHF-PFM) PUP-clinical study (N=55)	PedNet registry based – study (N=168)
Number of patients (number, %)		
at ED20[a]	48 (87%)	164 (98%)
at ED50	41 (75%)	162 (96%)
Number of ED at inhibitor development (median, Q1-Q3)		
All	15 (10-22)	14 (10-17)
High-titre	13 (8-16)	14 (10-17)
Number of patients with inhibitor development (number, %)[b]		
at ED20	11 (23%)	37 (23%)
at ED50	16 (39%)	44 (27%)
Number of patients with inhibitor development[c] (number, %)		
Low-titre	9 (22%)	16 (10%)
High-titre	7 (17%)	28 (17%)
Time between first exposure day and inhibitor development (months, median, Q1-Q3)	5.5 (3.5-10.3)	3.1 (1.4-7.9)

[a]Exposure Day (ED) is defined as a calendar day during which one or more infusions were given, for the clinical study exposure prior to the start of clinical study was factored into the calculation of the exposure days.
[b]The percentage of inhibitor development up to ED20 or ED50.
The percentage is the number of patients with an inhibitor divided by the number of patients that reached ED20 or ED50.
[c]Inhibitor development up to ED50: All inhibitor: defined as the occurrence of at least 2 positive inhibitor titres combined with a decreased factor VIII recovery; High-titre inhibitor: defined as (at least) a peak inhibitor titre of at least 5 Bethesda units per milliliter. The percentage is the number of patients with an inhibitor divided by the number of patients that reached ED50.

An issue of clinical studies is the difficulty of recruiting PUPs with severe haemophilia A. In full cohorts such as FranceCoag Network, UKHCDO National Haemophilia Database and PedNet, more than 50% of the patients were diagnosed with a negative family history.[7-8,11] These patients are diagnosed after the onset of bleeding and therefore excluded from clinical studies. In unselected cohorts only 10% of the patients had a positive family history of inhibitors[19-20] and about 60% of the patients had a high-risk F8 genotype.[21] In the clinical study more patients had a positive family history of inhibitors and a high-risk F8 genotype; this might have increased the a priori risk of inhibitor development and reduces extrapolation to the general population.[22] The patient characteristics within the registry-based study seem to be more representative of 'real-life' patients from the described full cohorts above.

A limitation of this paper is that we compared data from only one clinical study and one registry-based study. We selected this clinical study because the number of patients included in that study was larger than other PUP studies and Factor VIII (rAHF-PFM) is widely used daily clinical practice and in patients included in PedNet. Further comparisons between different concentrates and different study and registry populations may strengthen our conclusions. Obviously, issues on study design, such as, duration of follow-up and inter-laboratory variations, may affect observed inhibitor formation. We, however, strongly believe that high titre inhibitors will usually be diagnosed accurately and that registries could substitute for clinical trials in the case of high titre inhibitors. Despite, the sample size of this study was too small to conclude on this, therefore using similar data standards, adhering to those standards and publishing these standards will make data more readily exchangeable between registry (and clinical) studies. In line with McGettigan et al. we think that the value of registries can be increased by clearly described operational proposals on patient registry data, quality assurance processes, governance and stakeholder communication.[5] This study thus illustrates that in the clinical study and the registry-based study the same patient characteristics and outcome parameters were collected, in line with the guideline.[6]

With all the new products that will be marketed, it is crucial that centres collect data on all PUPs with severe haemophilia and share their results.[23] Products can only be compared independently if data collection methodology is similar and includes all potential confounding factors.[23] The most important limitation of observational drug studies is that different products are given to patients with different a priori inhibitor risk.[24] Rather than performing single-arm PUP studies for separate products, a controlled study (thus comparing two products and adjusting for confounders) within a registry would, in our view, be feasible and may be more efficient.[25] We believe that further optimization may be achieved by performing randomized studies within registries.[25]

Conclusion

Our paper provides an example showing that patient characteristics were slightly different between a clinical study and a registry-based study. In the clinical study a higher percentage of patients developed an inhibitor. The number of withdrawals was higher in the clinical study, the completeness of the follow-up was better in the registry. This study indicates that registries like PedNet are potentially useful in assessing the inhibitor developments in treatments for haemophilia, and may serve as an alternative to uncontrolled clinical studies for evaluation of high titre inhibitors. Although the sample size of this study was too small to conclude on differences in high or low titre inhibitors. This paper contributes to the discussion for the use of registry-based studies to assess long-term safety data.

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Conflict of interest

All of the authors state that they have no financial or personal relationships that inappropriately influenced their role in this work. No funds for the content of this manuscript or the preparation of the manuscript were received by any of the authors.

Author contributions

C.J. Jonker wrote the manuscript and analysed the data. K. Oude Rengerink, A.W. Hoes, P.G.M. Mol and H.M. van den Berg participated in discussions and reviewed the article. All of the authors had full access to the data and participated in the design of the analysis, discussion of results and revising the draft manuscript.

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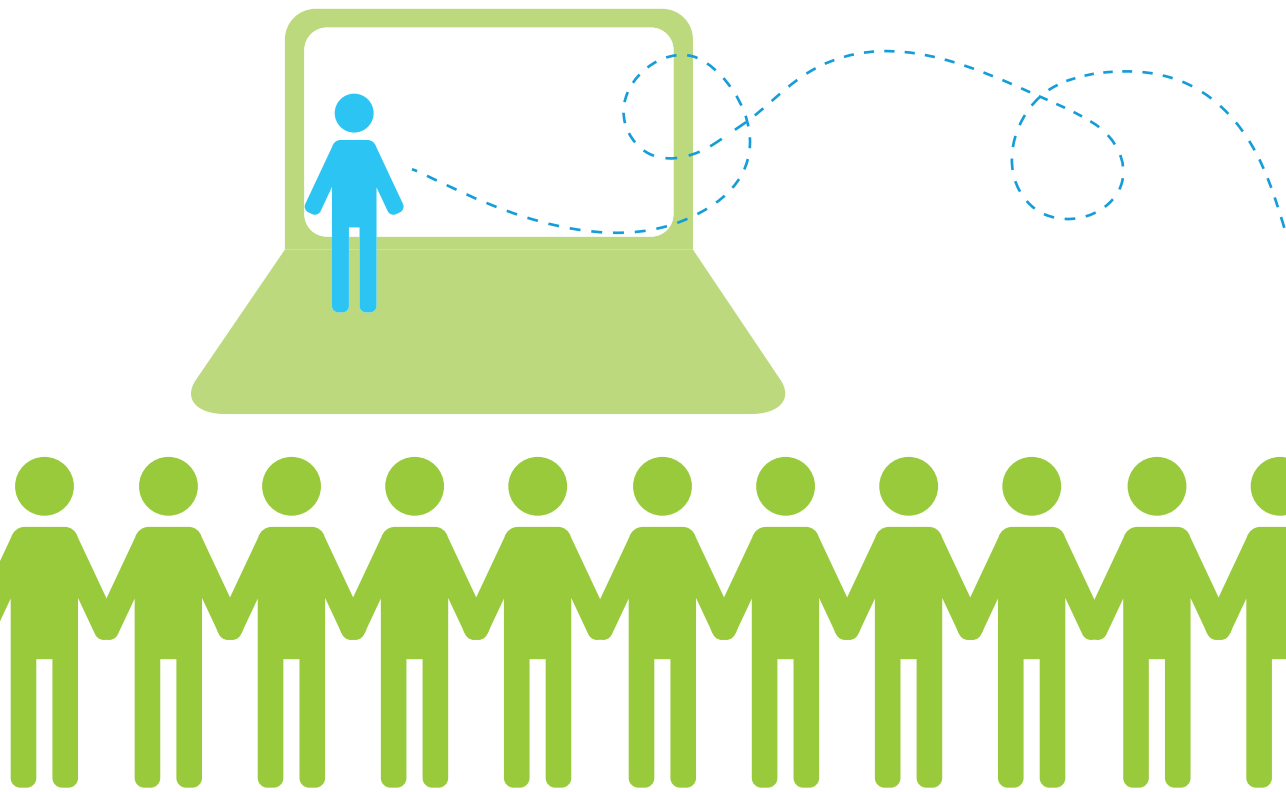

Chapter 6
Capturing data in rare disease registries to support regulatory decision making:
A survey study among industry and other stakeholders

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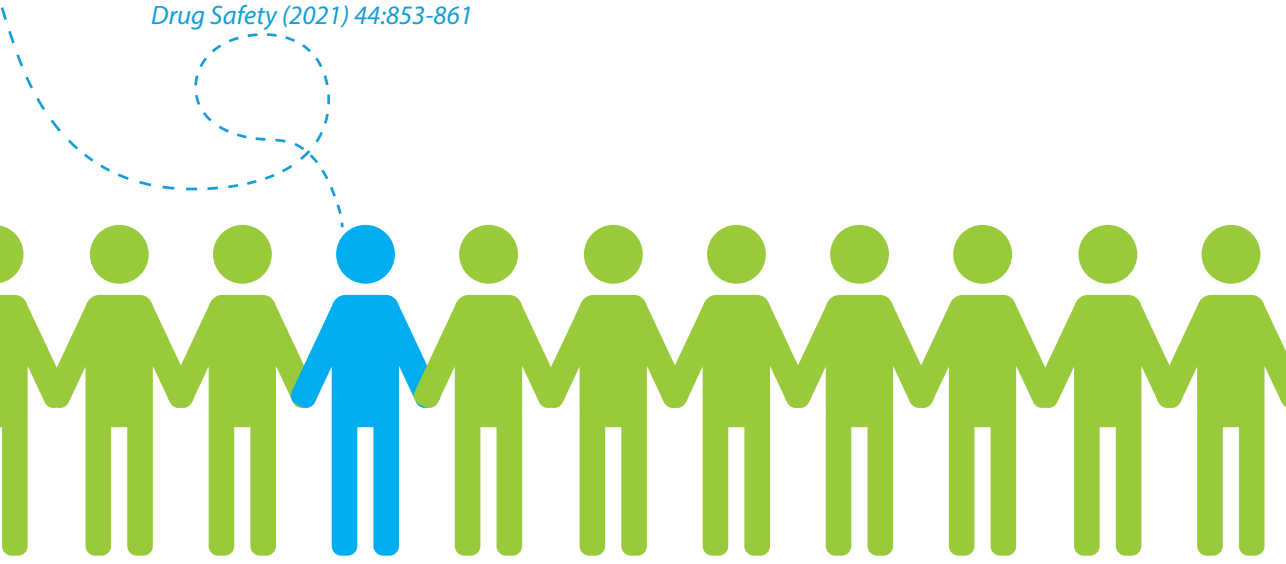

Abstract

Background
In rare diseases, registry-based studies can be used to provide natural history data pre-approval and complement drug efficacy and/or safety knowledge post-approval.

Objective
The objective of this study was to investigate the opinion of stakeholders about key aspects of rare disease registries that are used to support regulatory decision making and to compare the responses of employees from industry to other stakeholders.

Methods
A web-based survey was used to gauge the importance of (1) common data elements (including safety outcomes), (2) data quality and (3) governance aspects that are generic across different rare diseases. The survey included 47 questions. The data were collected in the period April-October 2019.

Results Seventy-three respondents completed $\geq$ 80% of the survey. Most of the respondents were from the industry (n=42, 57%). For safety data, 31 (42%) respondents were in favour of collecting all adverse events. For data quality, the respondents found a level of 30% reasonable for source data verification. For missing data, a level of 20% was considered acceptable. Compared to responders from industry, the other stakeholders found it less relevant to share data with industry and found it less acceptable if the registry is financed by industry.

Conclusions
This study showed that the opinion towards data and governance is well aligned across parties, and issues of data and governance on their own should not pose a barrier to collaboration. This finding is supportive of the European Medicines Agency's efforts to encourage stakeholders to work with existing registries when collecting data to support regulatory decision making.

Key Points

- A survey among industry and other stakeholders was used to investigate the key aspects of rare disease registries to support regulatory decision making.
- A set of demographics, clinical and medication-related data were identified that focused primarily on the disease of interest with much less emphasis on co-morbidities or adverse events.
- Compared to responders from industry, the other stakeholders found it less relevant to share data with industry and found it less acceptable if the registry is financed by industry.

Introduction

There is a large unmet medical need for effective treatments for the 30 million patients in Europe who suffer from one of 6000 to 8000 rare diseases.[1] The search for new treatments in rare diseases is challenging, owing to the small and heterogenous patient populations and often limited knowledge of the diseases' natural history.[2] Because of the scarcity of patients, and ethical concerns with denying beneficial active treatment, well-designed controlled clinical trials to assess the efficacy of a medicinal product and to detect serious adverse events can be difficult to perform.[3] Typically, marketing authorisation of therapies in rare diseases is therefore based on less evidence than for more common disorders. Consequently, post-marketing activities, such as registry-based studies, to further evaluate the effectiveness and/or safety of a new medicinal product are crucial in this patient population. Moreover, disease registries could provide data on the natural course of a disease, which may be used as a historical or external control to support a marketing application based on single-arm trial data. However, the contribution of registries to the knowledge of a new medicinal product is currently limited because of problems with the patient accrual rate, delayed start of patient inclusion, low data quality and missing data.[4-6]

In Europe, governance organisations are aware of these problems leading to the suboptimal use of registries and introduced efforts to improve the contribution of registries to assess risks and benefits of treatments. The European Medicines Agency (EMA) initiated the Patient Registry Initiative[7], with the main goal to make better use of existing registries to support regulatory decision making. Among other things, the Patient Registry Initiative organized meetings with stakeholders to discuss the importance of key elements of registries, including common data elements to be collected, data quality and governance aspects.[8] Attendees of these meetings were employees working in the pharmaceutical industry, regulators, academia, registry owners and patient representatives. Recently, the European Network for Health Technology Assessment (EUnetHTA) developed the Registry Evaluation and Quality Standards Tool (REQueST).[9] This tool assesses the quality of patient registries to support more systematic and widespread use of registry data in health technology assessments. In parallel, the European Reference Networks on rare diseases made recommendations to improve the quality of registries[10] and included similar key elements as identified by the Patient Registry Initiative.

The primary aim of this study was to quantify the opinion of stakeholders about key elements of registries as data sources for studies that support regulatory decision making in the field of rare diseases. The secondary aim was to assess whether the importance attached to these key elements differed between industry stakeholders vs others.

Methods

Study design and participants

We conducted a web-based survey among stakeholders familiar with the use of registries in a regulatory context. People known via the Patient Registry Initiative of the EMA and/or owners of registries who were identified via the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance were contacted. These people received a link to the survey via an e-mail and a reminder and could further disseminate the e-mail to people in their network. The survey data were collected during April–October 2019. Ethical approval was not necessary because of the nature of the study.

Outcome assessment

The survey was constructed in Qualtrics[XM] (a tool for online surveys, https://www.qualtrics.com) and included in total 47 questions (Electronic supplementary material [ESM]). The survey was created in an iterative process by members of the project team, and members of the EMA's Patient Registry Initiative. The survey questions were based on the themes of the workshops held at the EMA, i.e. common data elements, data quality and governance, and recurrent issues as described elsewhere.[8] In the survey, a registry was defined as "an organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure".[11]

In the survey, two questions were used to assess the characteristics of the responder and two questions were included about *registries in general*. The other questions concerned the three key elements of registries; i.e., 24 questions on *common data* elements that included aspects considered to be essential for the collection of demographic and baseline data, treatment and safety outcomes, and duration of follow-up; ten questions about *data quality* covering data entry, optimising and improving data quality, source data verification and missing data; and four questions about aspects of *governance*. As the intention of this study was to assess the importance attached to these key elements for the use of post-marketing studies, five questions were added about *registry-based studies*. A registry-based study uses a registry infrastructure for patient recruitment and data collection.[11] The survey contained three types of questions (1) multiple-choice questions where the respondent could choose one or more of the answer options (2) Likert scale questions with answer options from (1) very unimportant to (5) very important; and (3) a visual analog scale (VAS). The web-based version of the survey was pretested on functioning and content by seven persons working at the EMA and/or the Dutch Medicines Evaluation Board. After minor adaptations, the survey was distributed.

Analyses

Respondents who completed ≥ 80% of the survey were included in the analyses. Descriptive analyses were conducted and results of the multiple-choice questions and Likert scale questions are presented as number and percentage for all included responders and per stakeholder group (i.e. industry vs other stakeholders). The results of the VAS are presented as medians with the interquartile range (IQR). Differences in responses between industry and the other stakeholders were tested using Pearson X^2 tests or Mann-Whitney U tests for the outcomes measured using respectively multiple-choice and Likert scale questions/VAS scale questions. Given the large number of questions and subsequent tests performed, p-values < 0.01 were considered statistically significant. An element was considered important if ≥ 80% of the respondents gave it a score of important or very important. This cut-off has been used previously[12] and was used to separate "need to know" elements from "nice to know" elements. The same cut-off was used for the multiple-choice questions and the VAS. Data were analysed using IBM SPSS Statistics 20. Microsoft Excel 2010 was used for graphical presentation of results.

Results

There were 201 persons who opened the survey of whom 73 respondents (36%) completed ≥ 80% of the survey. The median time to complete the survey was 26 minutes (IQR 18-59). Most of them were employees of the pharmaceutical industry (n=42; 57%). The other 31 respondents were employees of European regulatory authorities (n=9; 12%), employees of health technology assessment agencies (n=5; 7%), owners of registries (n=5; 7%), patient representatives (n=3; 4%), physicians (n=2; 3%) or did not specify their role (n=7; 10%).

Overall results

General questions about registries

A minimal coverage of patients that in the respondents' view was needed to guarantee a minimal representation of the disease population for use of the registry to support regulatory decision making was 40% (median, IQR 28-60) (Fig. 1). For the geographical spread of the centres, most respondents considered it important to have centres within more than one country in Europe (92%) and to have at least more than one clinical centre (90%) that collects data (ESM).

Common data elements

Demographic data considered important to be collected in registries were sex (99%), vital status (93%), age (88%) and current pregnancy (86%) (Fig. 2 and ESM).

Data that need to be collected were clinical data (96% of respondents), treatment data (96%), laboratory data (90%) and patient-reported outcomes (PROs; 82%). For clinical data, the elements considered important were (first date of) diagnosis,

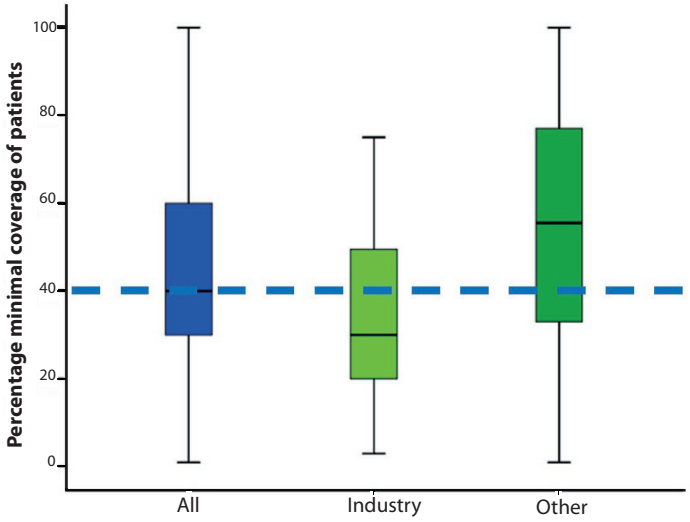

Figure 1. Percentage of *minimal coverage of patients* that in the respondents' view is needed to represent the disease population by stakeholder group (all, industry, other stakeholders).

severity of the disease, physical function, organ damage and confirmation of the diagnosis; for treatment data, the medical product (93%) and the intervention (86%); for laboratory, blood tests (88%) and biomarkers; (86%); and for PROs, the validated disease questionnaires (82%). Sixty-one percent of the respondents would collect a limited set of baseline data only or found co-morbidity data collection not necessary. Most respondents reported to base the diagnosis on clinical practice guidelines (73%) and the confirmation on a doctor's recorded diagnosis (80%) [ESM].

Respondents indicated that for the medication used to treat the disease of interest, the dosage (96%), the substance (90%), the reason to stop or to switch to another product (89%), and the start and stop date (84%) should be captured (Table 1). Information on non-pharmacological interventions should be captured according to 89% of the respondents. Seventy-four percent of the respondents would collect no or a limited set of data only for medicinal products used to treat co-morbidities (ESM).

Respondents considered the following data about pregnant women to be of key importance; the exposure to any medication during pregnancy (90%), the outcome of the pregnancy (90%), the trimester during exposure (84%) and the follow-up of teratogenic events (84%) (Table 1). Less than half of the participants (44%) would collect details of medication use of the partner, either before or during pregnancy (ESM).

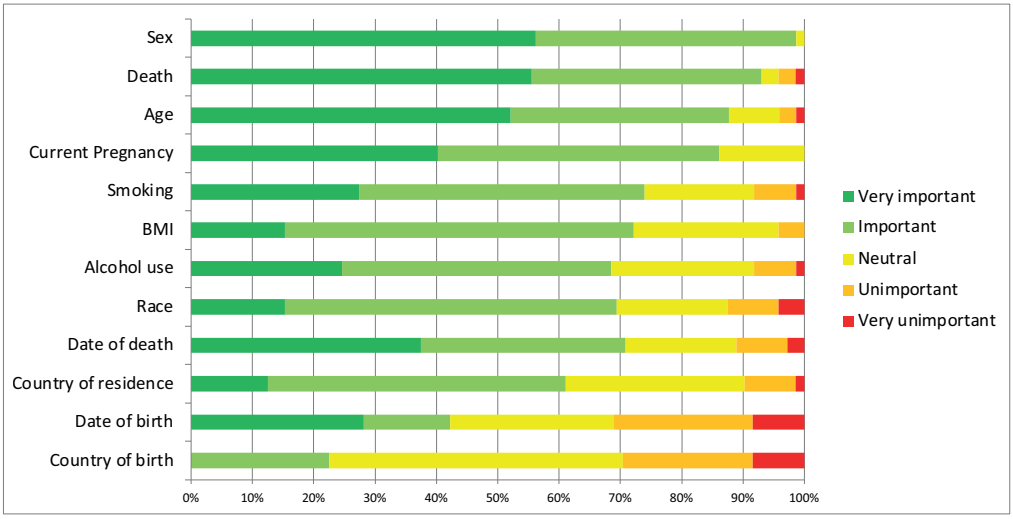

Figure 2. Results of the importance attached to the collection of various *demographic data*. *BMI* Body mass index

Treatment outcomes that the respondents found important to collect pertained to clinical (97%), treatment (96%), laboratory (89%) and PRO (86%) data. Respondents would base the efficacy outcomes primarily on clinical practice (73%), EMA guidelines (69%) and evidence-based literature (69%), but these scores did not reach the predefined 80% threshold. A doctor's recorded diagnosis (81%) was considered most relevant for confirmation of endpoints. Seventy-eight percent of the respondents indicated that only validated endpoints should be used. The majority of respondents thought that endpoints measuring disease progression should be monitored at least quarterly (43%) or twice a year (31%) [ESM].

Table 1. Number (percentage) of respondents (all, industry and other) that considered the *common data elements*-related questions important[a] with p-values of Pearson X^2 tests for differences between industry and the other stakeholders

	All (N=73)	Industry (N=42)	Other (N=31)	P-value
Medication: which of the following details with regard to the medicinal product to treat the disease of interest should be captured?				
Dosage	70 (96)	40 (95)	30 (97)	0.74
Substance name	66 (90)	40 (95)	26 (84)	0.10
Reason for stop/switch to other product registered	65 (89)	39 (93)	26 (84)	0.22
Start- and stop-date	61 (84)	35 (83)	26 (84)	0.95
Duration of the treatment	49 (67)	25 (60)	24 (77)	0.11
ATC[b] classification	33 (45)	14 (33)	19 (61)	0.02
Pregnancy: if women of childbearing potential are captured in the registry, how important is the collection of the following data if a woman becomes pregnant?*				
Exposure during pregnancy[1]	64 (90)	42 (100)	22 (76)	<0.01
Outcome of pregnancy[1]	64 (90)	40 (95)	24 (83)	0.20
Trimester during exposure[2,3]	58 (84)	36 (88)	22 (79)	0.61
Follow-up teratogenic events[1,4]	58 (84)	35 (88)	23 (79)	0.26
Follow-up child[1,4]	55 (80)	34 (85)	21 (72)	0.12
Follow-up mother[2,5]	51 (75)	33 (80)	18 (67)	0.25
Birth weight[3,4]	43 (63)	23 (58)	20 (71)	0.06
Safety outcomes: which adverse drug events should be collected?				
Adverse events of special interest	47 (64)	27 (64)	20 (65)	0.98
Serious adverse events	45 (62)	24 (57)	21 (68)	0.36
All adverse events	31 (42)	18 (43)	13 (42)	0.94
For *adverse events potentially related* to medicinal products the following should be recorded*				
Severity of the event	71 (97)	41 (98)	30 (97)	0.97
Duration of the event	62 (85)	34 (81)	28 (90)	0.74
A causality assessment[2]	61 (85)	38 (90)	23 (77)	0.30

[a] An element was considered important if >80% of the respondents gave it a score of important or very important. [b] ATC classification - Anatomical Therapeutic Chemical classification.
* Question assessed using a Likert scale. See ESM 3 for additional figures of all answers to the Likert scales.
[1] Two missing from the respondents from the other stakeholders; [2] One missing from the respondents from industry; [3] Three missing from the respondents from the other stakeholders;
[4] Two missing from the respondents from industry; [5] Four missing from the respondents from the other stakeholders.

For safety outcomes, 64% of the respondents indicated to collect adverse events of special interest, 62% serious adverse events, and 42% all adverse events. In the case of a reported adverse event, all elements were considered important to record; severity (97%), duration (85%) and, if applicable, causality assessment (85%) (Table 1).

Fifty-four percent of the respondents indicated that the duration of the follow-up of a patient should be 1-5 years. During follow-up, use of a medicinal product (89%), whether a patient was lost to follow-up (88%) and the underlying reason (82%) should be captured (ESM).

Data quality

According to the respondents, data were currently mostly entered into registries through web-based platforms (46%) and imported from electronic health records (34%). Data should be entered, in order of preference, by trained staff (75%), treating physicians (60%), patients themselves (58%), or a study coordinator (42%). Data entry was preferred at the time of the actual patient visit (75%) [ESM]. To improve data quality, it was considered of prime importance to have collection instructions (96%), use appropriate software (94%), have well-trained staff (94%) and use standard terminology (90%). To minimise missing data, respondents indicated the value of automated queries (97%), maximising data import from electronic health records (92%) and the use of mandatory fields (90%) to be important. For the improvement of consistency and/or accuracy, alerts (94%) and missing fields over time (80%) were considered important. Annual regular checks (78%) were strongly preferred over random checks (17%) [ESM].

Respondents indicated that to ensure data quality, 30% (IQR 10-54) of source data should be verified and up to 20% (IQR 10-25) of missing data for the key values could be acceptable (Fig. 3 and 4).

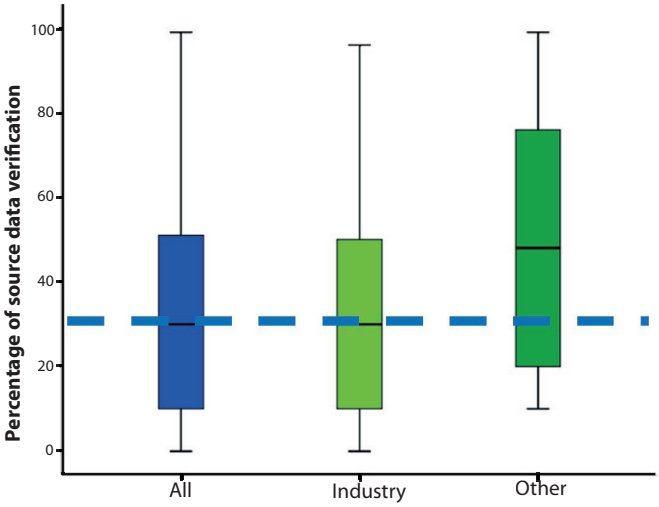

Figure 3. Percentage of source verification needed that is acceptable by the respondents by stakeholder group (all, industry, other stakeholders)

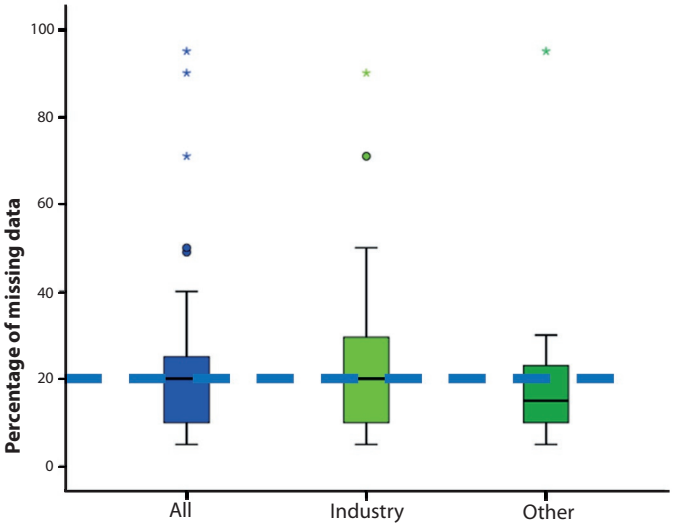

Figure 4. Percentage of missing data that is acceptable by the respondents by stakeholder group (all, industry, other stakeholders)

Governance

The availability of a central contact point (96%) and data sharing across countries (86%) were considered important. Most respondents considered it relevant for regulatory decision making that registry data are shared with regulatory authorities (94%) and academic centres (85%). Additionally, most respondents found it acceptable that registry data are financed by regulatory authorities (92%) or academia (83%), but less so by pharmaceutical companies (78%) or patients (53%) (Table 2). Moreover, respondents indicated that 92% (IQR 81-100) of the registry data should be FAIR (Findable, Accessible, Interoperable, and Reusable; Table 2).

Registry-based studies

Regarding registry-based studies, respondents found it important that a common study protocol is available in the case of a multi-centre registry (92%) and to have the registry-based study protocol recorded in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance database (84%). The primary objective (97%), the secondary objective (90%) and a statistical analysis plan (85%) should be predefined in a study protocol. The respondents suggested that missing data, analysis strategy, bias, treatment discontinuation, confounders and effect modifiers should all be addressed in the statistical analysis plan. To perform a randomised study in the context of registry-based studies was considered less essential (i.e. selected by 61% of the respondents) [ESM]).

Industry vs other stakeholders

In six of the 47 questions, a statistically significant difference was observed between industry and the other stakeholders. The coverage of patients needed to guarantee a minimally acceptable representation of the disease population within the registry was lower for respondents from industry than for respondents from other stakeholders (30% [IQR 20-50] vs 56% [IQR 32-78], $p < 0.01$) (Fig. 1). Compared with the group of other stakeholders, respondents from the industry found the exposure to any medication during pregnancy more important to register (100% vs 76%, $p < 0.01$) (Table 1); would use evidence-based literature less often for selecting the common data elements about the disease; i.e., 52% vs 84%, $p < 0.01$ (ESM); rated the possibility to request additional information from a treating physician as more important (86% vs 52%, $p < 0.01$); found it more relevant to share data with pharmaceutical companies (90% vs 45%, $p < 0.01$); and found it more acceptable if the registry is financed by pharmaceutical companies (95% vs 53%, $p < 0.01$) (Table 2).

Table 2. Number (percentage) of respondents (all, industry and other) that considered the *governance*-related questions importanta with p-values of Pearson X^2 tests for differences between industry and the other stakeholders

	All (N=73)	Industry (N=42)	Other (N=31)	P-value
How important are the following statements about data sharing in relation to governance of a registry?*				
Availability of a central contact point	70 (96)	41 (98)	29 (94)	0.25
Data sharing across countries	63 (86)	36 (86)	27 (87)	0.75
Data linkage to other data sources	55 (75)	33 (79)	22 (71)	0.07
Request for additional information, if needed by external stakeholders	52 (71)	36 (86)	16 (52)	<0.01
How relevant is it for regulatory decision-making that registry data are shared with…?*				
Regulatory authorities[1]	68 (94)	39 (95)	29 (94)	0.69
Academic centres[1]	61 (85)	36 (88)	25 (81)	0.18
Pharmaceutical companies[1]	51 (71)	37 (90)	14 (45)	<0.01
How acceptable is it that a registry is (partly) financed by….. if the data are to be used by regulators:*				
Regulatory authorities[2]	66 (92)	37 (88)	29 (97)	0.20
Academia[2]	60 (83)	38 (90)	22 (73)	0.12
Independent stakeholders[2]	57 (79)	32 (76)	25 (83)	0.29
Pharmaceutical companies[2]	56 (78)	40 (95)	16 (53)	<0.01
Patients[2]	38 (53)	26 (62)	12 (40)	0.11
FAIR: Findable, Accessible, Interoperable, and Reusable - How important is it that the data of the registry should be FAIR?[1]				
(median, IQR)	92 (81, 100)	92 (81, 100)	95 (82, 100)	0.89

IQR interquartile range
[a]An element was considered important if >80% of the respondents gave it a score of important or very important
*See ESM 4 for additional figures of all answers to the Likert scales
[1]One missing from the respondents from industry
[2]One missing from the respondents from the other stakeholders

Discussion

This study indicated the key aspects in terms of common data elements, data quality and *governance* for rare disease registries that were important (rated important or very important by ≥ 80% respondents) to stakeholders. A set of demographics, clinical and medication-related data were identified that focused primarily on the disease of interest with much less emphasis on co-morbidities or adverse events. Respondents considered that 30% of source data verification and 20% of missing data would provide acceptable levels of data quality. Regarding governance, availability of a central contact point and the ability to share data with regulatory authorities was considered important for disease registries to support regulatory decision making in the setting of rare diseases. Regarding registry-based studies, thorough epidemiological and predefined research protocols were expected, with less emphasis on the need for randomised designs. There were few differences between the industry and the other stakeholders. With regard to governance aspects, the other stakeholders found it less relevant to share data with industry and found it less acceptable when a registry is financed by industry.

A core common data set is essential for the interoperability of registries to allow the exchange of data.[13] Previously, a set of common data elements was released by the European Platform on Rare Disease Registration.[14] This set included date of birth, sex, and vital status. Our study confirmed the importance of collecting these elements and additionally identified that the stakeholders find it important to collect data on pregnancy. Depending on the therapeutic area or patient population, the choice of key disease-related data elements may, however, differ.[15] To prevent inconsistency in the capturing of the elements, clear definitions need to be formulated.[13] In this context, the defined core data sets by the European Society for Blood and Marrow Transplantation Registry and the European Cystic Fibrosis Society Patient Registry can be used, which have been shown to support regulatory decision making.[16-19]

In our study, less than 50% of the respondents indicated that all adverse events should be collected. During one of the previous meetings organised by the EMA's Patient Registry Initiative, routine collection of adverse events was indicated to be a burden.[20] Most registries focus on the collection of serious adverse events and /or adverse events of special interest.[20] An example is the TREatment of ATopic eczema (TREAT) Registry that has the secondary objective to collect eye disorders and eosinophilia as specific types of adverse events.[21] Another example is the REGIMS Registry that aims to assess the incidence, type, and consequences of side effects of multiple sclerosis immunotherapies.[22] Requirements for post-approval safety data management are described in International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E2D and good pharmacovigilance practices module VI.[23-24] Companies have the obligation for solicited cases to perform an assessment of causality and submit the causally related adverse drug reactions to the relevant authorities.[25-26] While registries could be an important source to evaluate long-term drug effects including safety outcomes that are often incomplete at the

time of drug approval, the collection of such data within most disease registries does not allow a causality assessment in line with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidance.[27] If registries are used as a data source for post-authorisation safety studies, it should be clear what the expectations are with respect to adverse event collection and managing follow-up information, causality assessment and, where appropriate, reporting timelines. Registries should provide accurate, timely and follow-up data on serious adverse events to enable a causality assessment.

Good quality data is crucial for a thorough benefit-risk evaluation of medicinal products. According to the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidance for good clinical practice, clinical trials should be monitored to verify that reported data are accurate, complete and accounted for by source records.[28] Our survey study showed that responders considered a level of 20% acceptable for missing data. A threshold of 10% of missing data based on a sample of 200 patients of the registry data was suggested by participants of one of the EMA disease-specific registry workshops.[20] It is recognised that most patient registries will have at least some missing data. Approaches to minimise the amount of missing data should be considered as part of the registry protocol and analysis plan. However, no guidance is given on what proportion of data should be verified. It is acknowledged that even 100% source data verification does not guarantee that a 0% error rate can be achieved.[29] A risk-based approach in combination with reduced source data verification could be a good solution to verify the data.[30-32] Source data verification for 10% of the registry data were suggested by participants of one of the EMA disease-specific registry workshops.[33] This implies that the outcome of our study, laying the bar at 30% for data verification, may not be feasible in practice. The results of our survey could provide a starting point to discuss which and how much data should be verified to guarantee validity of the data to be acceptable to all potential stakeholders.

To our knowledge, this is the first study assessing on a larger scale the importance that stakeholders attach to key aspects of registries in the field of rare diseases for regulatory decision making. A limitation of the study is that of the 201 participants who received and opened the survey, 82 (41%) did not respond to any question. Forty-six participants (23%) finished after completing only a few questions and 73 (36%) completed $\geq$ 80% of the survey and were included in the analyses. Reasons for the drop-out are regrettably unknown, but 82 (41%) did not respond to any question. This suggests that problems related to navigating through the survey and its content are unlikely. Related to this is that it should be noted that the survey used in this study was pretested on functioning and content among a small number (n=7) of regulators only and that no formal validation procedures were applied. Although respondents were allowed to skip questions in the survey, for instance, if a question was unclear to the respondent or not applicable, it is possible that some questions have been interpreted differently between respondents. Additionally, the generalisability of our findings to a wider population

should be assessed in future studies because the individuals included in our study probably had a particular interest in registries having participated in the EMA workshops, or were connected to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, and only a small and heterogenous number of other stakeholders was included. Furthermore, we used a cut-off of 80% for the responses to indicate importance, both for the Likert scale and the multiple-choice questions. Although this cut-off level has been used previously[12], this could still be considered rather arbitrary.

Conclusions

This study showed that the opinion towards data and governance is well aligned across parties, and issues of data and governance on their own should not pose a barrier to collaboration. This finding is supportive of the EMA's efforts to encourage stakeholders to work with existing registries when collecting data to support regulatory decision making.

Supplementary information
The online version contains supplementary material available at https:// doi. org/ 10. 1007/ s40264- 021- 01081-z.

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Declarations

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Conflicts of interest/Competing interests
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Ethics approval
Not applicable.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and material
The data that support the findings of this work are available from the corresponding author on reasonable request.

Code availability
Not applicable.

Authors' contributions
CJJ, STdV, PMcG and PGMM were involved in the conception and design of the study; CJJ, STdV and PGMM conducted the analyses; and all authors contributed to the interpretation of the data. All authors reviewed and edited the manuscript. All authors have read and approved the final manuscript. All authors attest they meet the International Committee of Medical Journal Editors criteria for authorship.

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Attachments

Attachment 1. Questions and answers options used in the survey

Question	
Registries in general	
1. What do you believe is a minimal coverage of patients (% of the disease population) needed to guarantee a minimal representation of the disease population for use of the registry to support regulatory decision-making?	
2. The geographical spread of the registry network is a key factor for understanding treatment practices and outcomes across the EU. How important is it that registry data originate from	
Common data elements	
1. How important is the collection of the following demographic data? Age; Date of birth; Death; Date of death; Gender; Race; Country of birth; Country of residence; Body Mass Index (BMI); Current pregnancy; Smoking; Alcohol use	
2. What kind of BASELINE data should be collected for the disease of interest?	
3. What kind of BASELINE clinical information should be collected? First date of diagnosis; Objective confirmation of the diagnosis; Severity of disease; Organ damage; Physical function	
4. Depending on the disease, what kind of BASELINE laboratory / diagnostic data should be collected? Blood tests; Genetic data; Biomarkers; Imaging data	
5. What kind of BASELINE treatment data should be collected? Medicinal product (including self-prescribed); Intervention, e.g. surgery	
6. What kind of BASELINE patient reported outcomes data should be collected? Quality of Life Questionnaire, e.g. SF 36; Validated patient disease specific questionnaires	

	Answer options
	VAS score from 0 to 100%
	Multiple-choice: • At least more than 1 patient care / clinical center • All the centers from the country • More than 1 country in Europe • Countries worldwide including USA
	5-point Likert scale ranging from (1) very unimportant to (5) very important
	Multiple-choice: • Clinical • Laboratory / diagnostic data • Treatment • Patient reported outcomes
	5-point Likert scale ranging from (1) very unimportant to (5) very important
	5-point Likert scale ranging from (1) very unimportant to (5) very important
	5-point Likert scale ranging from (1) very unimportant to (5) very important
	5-point Likert scale ranging from (1) very unimportant to (5) very important

Question	
7. Would you collect the same common data elements for co-morbidities and if no, why not?	
8. The common data elements about the disease that need to be captured should be based on	
9. The confirmation of the diagnosis should be based on	
10. MEDICATION Which of the following details with regard to the medicinal product to treat the disease of interest should be captured?	
11. For co-morbidities would you collect any data about medicinal products?	

Answer options
Multiple-choice: • Yes • No, a more limited data set, please explain • No, not needed, please explain
Multiple-choice: • Validated (national) clinical practice guidelines • EMA scientific guidelines • FDA guidance documents • Evidence-based disease literature • Daily clinical practice
Multiple-choice: • Doctor's written diagnosis • Hospital disease codes • Relevant genetic tests • Relevant biomarkers
Multiple-choice: • Substance name of the medicinal product • ATC classification • Start- and stop-date medicinal product • Duration of the treatment • Reason for stop/switch to other medicinal product registered • Dosage
Multiple-choice: • Yes • Yes, a more limited set • No

Question	
12. INTERVENTION If a non-pharmacological intervention takes place, what should be captured?	
13. PREGNANCY If women of childbearing potential are captured in the registry, how important is the collection of the following data if a woman becomes pregnant? Exposure to any medication during pregnancy; Trimester of pregnancy during exposure; Outcome of pregnancy; Birth weight; Follow-up mother with regard to perinatal complications; Follow-up child for functional or developmental deficits; Follow-up teratogenic events, considered to be associated with the medicinal product of interest	
14. In the case of pregnancy is it important to collect data from the partner?	
15. How important is the collection of the following data from the partner of the women who are pregnant? Exposure to medicinal product before pregnancy of the partner; Exposure to medicinal product during pregnancy of the partner	
16. TREATMENT OUTCOMES What data should be collected? Clinical; Laboratory / diagnostic data; Treatment; Patient reported outcomes	
17. EFFICACY OUTCOMES The criteria for the ENDPOINTS should be based on	
18. The confirmation of the endpoints should be based on	

Answer options
Multiple-choice: • Intervention, e.g. surgery, radiotherapy • Start - and stop date intervention • Duration of the intervention • Reason for stop/switch to intervention • Not applicable
5-point Likert scale ranging from (1) very unimportant to (5) very important
Multiple-choice: • Yes, please explain • No, please explain
5-point Likert scale ranging from (1) very unimportant to (5) very important
5-point Likert scale ranging from (1) very unimportant to (5) very important
Multiple-choice: • Validated (national) clinical practice guidelines • EMA scientific guidelines • FDA guidance documents • Evidence-based disease literature • Daily clinical practice
Multiple-choice: • Doctor's written diagnosis • Hospital disease codes • Relevant genetic tests • Relevant biomarkers

Question	
19. How important is it to use validated endpoints only?	
20. To be able to monitor disease progression, how often should endpoint parameters be assessed (at least)?	
21. SAFETY OUTCOMES Which adverse drug events should be collected?	
22. For adverse events potentially related to medicinal products the following should be recorded Severity of the event; Duration of the event; A causality assessment	
23. FOLLOW-UP VISITS How important is it to capture at each visit the following data: The use of a medicinal product at each visit; Patients lost to follow-up (definitely); Reason for lost to follow-up	
24. The minimal duration of follow-up of the patient should be	
Data quality	
1. How are the data entered in the registry?	

Answer options
5-point Likert scale ranging from (1) very unimportant to (5) very important
Multiple-choice: • Once a month • Quarterly • Twice a year • Once a year
Multiple-choice: • All adverse events • Serious adverse events • Adverse events of special interest (specific or anticipated problems) • Not applicable
5-point Likert scale ranging from (1) very unimportant to (5) very important
5-point Likert scale ranging from (1) very unimportant to (5) very important
Multiple-choice • 1 year • 1-5 years • 5-15 years • For life / as long as possible
Multiple-choice • Direct entry through web-based platform • Direct import from Electronic Health Reports • Manual data entry • Other, please explain

Question	
2. Who should be able to enter data in the registry?	
3. Once a patient has come for a visit, the frequency of data entry in the registry should be Immediately (at the time of the patient visit)	
4. How important are the following approaches to optimise data quality? Checking systematically data entry (double data entry); Standard terminology; Free text	
5. Source data verification - what percentage of the source data should be verified (source data verification is the process of ensuring that data accurately represents the source data from which it was derived?	
6. Missing data - what percentage of missing data of the key values is permissible?	
7. How important are the proposed measures to improve data quality? Training of data entry/management staff; Work instructions or standard operating procedures; Software with drop down menus, text prompts or flags; Audits; Manual checks at centres levels by monitors	
8. What is the importance of the following measures to minimise missing data? Mandatory fields; Creation of automated queries for missing data or unexpected values; Maximizing import of data from Electronic Health Records; Manual checks at clinical centre level by monitors	
9. How important are the following proposed indicators of quality to improve consistency and/or accuracy? To track changes in fields that will be previously entered; To measure number of missing fields over time; Creation of alerts if the input data is out of range	
10. How often should a quality check be done?	

Answer options
Multiple-choice • Only trained staff • Treating physician / investigator • Study-coordinator • Patient
5-point Likert scale ranging from (1) very unimportant to (5) very important
5-point Likert scale ranging from (1) very unimportant to (5) very important
VAS score from 0 to 100%
VAS score from 0 to 100%
5-point Likert scale ranging from (1) very unimportant to (5) very important
5-point Likert scale ranging from (1) very unimportant to (5) very important
5-point Likert scale ranging from (1) very unimportant to (5) very important
Multiple-choice • Event driven, e.g. at time of publication of data • Randomly • Regularly, e.g. every year

Question	
Governance	
1. How important are the following statements about data sharing in relation to governance of a registry? Data sharing across countries; Data linkage to other data sources; A central contact point available on behalf of the registry; Request additional information from treating physician, if needed by external stakeholders	
2. How relevant is it for regulatory decision-making that registry data are shared with? Regulatory authorities; Academic centers; Pharmaceutical companies	
3. How acceptable is it that a registry is (partly) financed by..... if the data are to be used by regulators: Regulatory authorities; Academic centers; Pharmaceutical companies	
4. FAIR: Findable, Accessible, Interoperable, and Reusable - How important is it that the data of the registry should be FAIR?	
Registry-based studies, to use the data to support efficacy and/or safety evaluation of medicinal products by regulatory authorities	
1. How important is it to be able to collect data under a common study protocol in a multi-registry study?	
2. How valuable is it to perform a randomized study in the registry, if the data are used to support efficacy and/or safety evaluation of medicinal products by regulatory authorities?	
3. How important is the registration of the registry-based study in a public register, like:ENCePP; EU Clinical Trials Register; ClinicalTrials.gov	
4. How important is it that the following elements are predefined in a registry study? Primary objective; Secondary objectives; Statistical Analysis Plan with clearly defined sample size; Identification of a control group; Randomization	
5. The statistical plan should include information about Analysis strategy; Confounders; Effect modifiers; Bias; Missing data; Treatment discontinuation	

	Answer options
	5-point Likert scale ranging from (1) very unimportant to (5) very important
	5-point Likert scale ranging from (1) very irrelevant to (5) very relevant
	3-point Likert scale ranging from (1) not acceptable to (3) acceptable
	VAS score from 0 to 100%
	5-point Likert scale ranging from (1) very unimportant to (5) very important
	3-point Likert scale ranging from (1) not valuable to (3) valuable
	5-point Likert scale ranging from (1) very unimportant to (5) very important
	5-point Likert scale ranging from (1) very unimportant to (5) very important
	5-point Likert scale ranging from (1) very unimportant to (5) very important

Attachment 2. Number (percentage) of respondents (all, industry and other) that considered the *common data elements*-related questions important[a] with P-values of Pearson X^2 tests for differences between industry and the other stakeholders.

	All (N = 73)	Industry (N = 42)	Other (N = 31)	P-value
The **geographical spread** of the registry network is a key factor for understanding treatment practices and outcomes across the EU. How important is it that registry data originate from				
>1 country in Europe	67 (92)	38 (91)	29 (94)	0.79
More than 1 centre	66 (90)	39 (93)	27 (87)	0.83
All centres in 1 country	26 (36)	12 (29)	14 (45)	0.29
Countries worldwide[1]	24 (33)	16 (39)	8 (26)	0.02
Common data elements - How important is the collection of the following **demographic data?**				
Gender	72 (99)	41 (98)	31 (100)	0.56
Death[2]	67 (93)	39 (93)	28 (93)	0.25
Age	64 (88)	37 (88)	27 (87)	0.42
Current pregnancy[2]	62 (86)	39 (93)	23 (77)	0.05
Smoking	54 (74)	31 (74)	23 (74)	0.93
Body Mass Index[2]	52 (72)	29 (69)	23 (77)	0.77
Date of death[2]	51 (71)	32 (76)	19 (63)	0.16
Race[2]	50 (69)	28 (67)	22 (73)	0.59
Alcohol use	50 (69)	27 (64)	23 (74)	0.82
Country of residence[2]	44 (61)	26 (62)	18 (60)	0.87
Date of birth[1,2]	30 (42)	19 (46)	11 (37)	0.88
Country of birth[1,2]	16 (23)	10 (24)	6 (20)	0.45

What kind of **baseline data** should be collected for the disease of interest?				
Clinical	70 (96)	41 (98)	29 (94)	0.39
Treatment	70 (96)	41 (98)	29 (94)	0.39
Laboratory	66 (90)	39 (93)	27 (87)	0,41
Patient reported outcomes	60 (82)	33 (79)	27 (87)	0.35
What kind of **baseline clinical information** should be collected?*				
First date of diagnosis	70 (96)	41 (98)	29 (94)	0.33
Severity of disease	70 (96)	40 (95)	30 (97)	0.89
Physical function	64 (88)	39 (93)	25 (81)	0.19
Organ damage	60 (82)	37 (88)	23 (74)	0.23
Confirmation	60 (82)	33 (79)	27 (87)	0.55
What kind of **baseline treatment data** should be collected?*				
Medicinal product	68 (93)	41 (98)	27 (87)	0.34
Intervention	63 (86)	37 (88)	26 (84)	0.57
Depending on the disease, what kind of **baseline laboratory / diagnostic data** should be collected?*				
Blood tests	64 (88)	39 (93)	25 (81)	0.29
Biomarkers	63 (86)	37 (88)	26 (84)	0.58
Genetic data	56 (77)	33 (79)	23 (74)	0.57
Imaging data	55 (75)	36 (86)	19 (61)	0.05

What kind of **baseline patient reported outcomes data** should be collected?*				
Validated disease questionnaire	60 (82)	37 (88)	23 (74)	0.11
Quality of Life Questionnaire	54 (74)	30 (71)	24 (77)	0.87
Would you collect the **same common data elements for co-morbidities** and if no, why not?[1]				0.45
Yes	28 (39)	16 (39)	12 (39)	
No, a more limited set	42 (58)	23 (56)	19 (61)	
No, not needed	2 (3)	2 (5)	0 (0)	
The common data elements about the disease that need to be captured should be based on				
Clinical practice guidelines	53 (73)	27 (64)	26 (84)	0.06
Evidence-based literature	48 (66)	22 (52)	26 (84)	<0.01
EMA scientific guidelines	45 (62)	29 (69)	16 (52)	0.13
Daily clinical practice	44 (60)	30 (71)	14 (45)	0.02
FDA guidance documents	17 (23)	13 (31)	4 (13)	0.07
The confirmation of the diagnosis should be based on				
Doctor's written diagnosis	58 (80)	32 (76)	26 (84)	0.42
Relevant biomarkers	51 (70)	31 (74)	20 (65)	0.39
Relevant genetic tests	47 (64)	29 (69)	18 (58)	0.33
Hospital disease code	43 (59)	24 (57)	19 (61)	0.72

[a] An element was considered important if ≥80% of the respondents gave it a score of important or very important. * Question assessed using a Likert Scale. See below for additional figures of all answers to the Likert scale. [1] One missing from the respondents from industry; [2] One missing from the respondents from the other stakeholders. Figure. Responses to each of the Likert scale options of the questions related to clinical data, laboratory data, and treatment and patient related outcomes data.

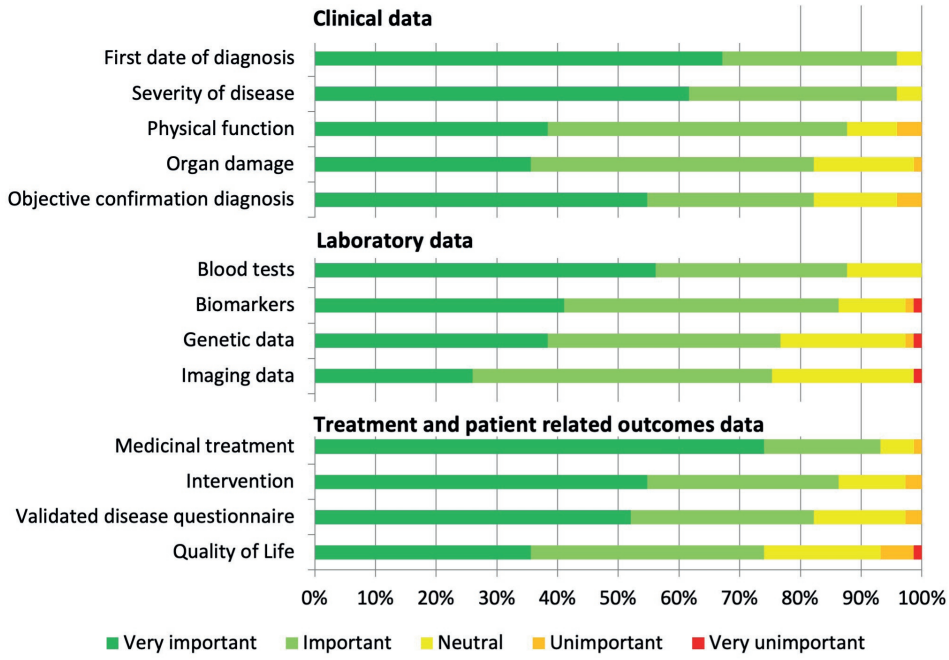


Figure 1. Responses to each of the Likert scale options of the questions related to *clinical data*, *laboratory data*, and *treatment and patient related outcomes data*.

Attachment 3. Number (percentage) of respondents (all, industry and other) that considered the *common data elements*-related questions important[a] with P-values of Pearson X^2 tests for differences between industry and the other stakeholders.

	All (N=73)	Industry (N=42)	Other (N=31)	P-value
Intervention If a non-pharmacological intervention takes place, what should be captured?				
Intervention	65 (89)	37 (88)	28 (90)	0.76
Start- and stop-date	54 (74)	30 (71)	24 (77)	0.56
Reason for stop/switch to other intervention	54 (74)	32 (76)	22 (71)	0.62
Duration of the intervention	35 (48)	18 (43)	17 (55)	0.31
For co-morbidities would you collect any data about medicinal products?				0.76
Yes	19 (26)	11 (26)	8 (26)	
No, a more limited set	50 (69)	28 (67)	22 (71)	
No, not needed	4 (6)	3 (7)	1 (3)	
In the case of pregnancy is it important to collect data from the partner[1]				0.08
Yes	31 (44)	22 (52)	9 (31)	
No	40 (56)	20 (48)	20 (69)	
How important is the collection of the following data from the partner of the women who are pregnant?*				
Exposure before pregnancy[1,2]	36 (51)	25 (61)	11 (38)	0.10
Exposure during pregnancy[1,3]	22 (32)	15 (38)	7 (24)	0.34
Treatment outcomes: What data should be collected?*				
Clinical[1]	69 (97)	41 (98)	28 (97)	0.17
Treatment[1]	68 (96)	41 (98)	27 (93)	0.12
Laboratory[4]	62 (89)	39 (93)	23 (82)	0.25
Patient reported outcome[1,2]	60 (86)	36 (88)	24 (83)	0.09
Efficacy outcomes: The criteria for the ENDPOINTS should be based on				
Clinical practice guidelines	53 (73)	29 (69)	24 (77)	0.43
EMA scientific guidelines	50 (69)	31 (74)	19 (61)	0.26
Evidence-based literature	50 (69)	25 (60)	25 (81)	0.06
Daily clinical practice	42 (58)	28 (67)	14 (45)	0.07
FDA guidance documents	19 (26)	14 (33)	5 (16)	0.10

The confirmation of the endpoints should be based on				
Doctor's written diagnosis	59 (81)	33 (79)	26 (84)	0.57
Relevant biomarkers	50 (69)	30 (71)	20 (65)	0.53
Relevant genetic tests	43 (59)	27 (64)	16 (52)	0.28
Hospital disease code	40 (55)	24 (57)	16 (52)	0.64
How important is it to use validated endpoints only?*				
	57 (78)	33 (79)	24 (77)	0.55
To be able to monitor disease progression, how often should endpoint parameters be assessed (at least)?[3,5]				0.03
Once a month	9 (13)	5 (13)	4 (13)	
Quarterly	30 (43)	14 (35)	16 (53)	
Twice a year	22 (31)	18 (45)	4 (13)	
Once a year	9 (13)	3 (8)	6 (20)	
Follow-up visits How important is it to capture at each visit the following data:*				
Use of medicinal product at each visit[2]	64 (89)	40 (98)	24 (77)	0.05
Patient lost to follow-up (definitely)[5]	63 (88)	37 (88)	26 (87)	0.25
Reason for lost to follow-up[2,5]	58 (82)	33 (80)	25 (83)	0.40
The minimal duration of follow-up of the patient should be[2]				0.33
1 year	6 (8)	5 (12)	1 (3)	
1-5 years	39 (54)	19 (46)	20 (65)	
5-15 years	7 (10)	5 (12)	2 (6)	
For life, as long as possible	20 (28)	12 (29)	8 (26)	

[a] An element was considered important if ≥80% of the respondents gave it a score of important or very important.
* Question assessed using a Likert scale. See below for additional figures of all answers to the Likert scale.
[1] Two missing from the respondents from the other stakeholders; [2] One missing from the respondents from industry; [3] Two missing from the respondents from industry; [4] Three missing from the respondents from industry; [5] One missing from the respondents from industry.

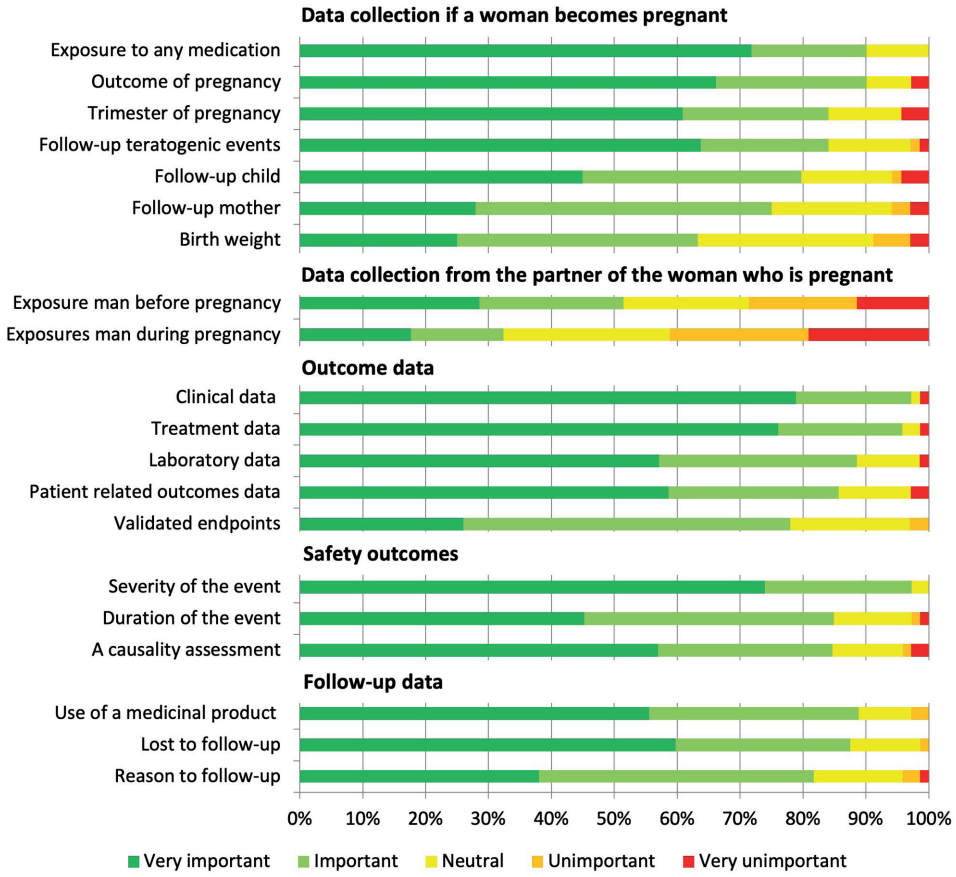


Figure 1. Responses to each of the Likert scale options of the questions related to *data collection if a woman becomes pregnant, data collection from the partner of the woman who is pregnant, outcome data, safety outcomes, and follow-up data.*

Attachment 4. Table. Number (percentage) of respondents (all, industry and other) that considered the *data quality*-related questions important[a] with P-values of Pearson X^2 tests for differences between industry and the other stakeholders.

	All (N=73)	Industry (N=42)	Other (N=31)	P-value
How are the data entered in the registry?[1,2]				**0.64**
Web-based entry	32 (46)	18 (45)	14 (47)	
Import from Electronic Health Report	24 (34)	12 (30)	12 (40)	
Manual data entry	7 (10)	5 (13)	2 (7)	
Other	7 (10)	5 (13)	2 (7)	
Who should be able to enter data in the registry?[2]				
Trained staff	54 (75)	30 (71)	24 (77)	0.56
Treating physician/investigator	43 (60)	23 (55)	20 (65)	0.40
Patient	42 (58)	25 (60)	17 (55)	0.69
Study-coordinator	30 (42)	22 (52)	8 (26)	0.02
Once a patient has come for a visit, the frequency of data entry in the registry should be*				
Immediately (at the time of the patient visit)[3]	54 (75)	31 (76)	23 (74)	0.72
How important are the following approaches to optimise data quality?*				
To use standard terminology[2]	65 (90)	38 (90)	27 (90)	0.79
Checking systematically data entry[2]	53 (74)	28 (67)	25 (83)	0.29
To use free text[2]	19 (26)	12 (29)	7 (23)	0.49
How important are the proposed measures to improve data quality?*				
Work instructions[2]	69 (96)	39 (93)	30 (100)	0.10
Software[2]	68 (94)	41 (98)	27 (90)	0.20
Training staff[2]	68 (94)	39 (93)	29 (97)	0.30
Audits[2]	58 (81)	34 (81)	24 (80)	0.31
Manual checks by monitors[2]	55 (76)	30 (71)	25 (83)	0.67
What is the importance of the following measures to minimise missing data?*				
Automated queries[2]	70 (97)	40 (95)	30 (100)	0.62
Maximizing import of data from Electronic Health Records	67 (92)	41 (98)	26 (84)	0.04
Mandatory fields	66 (90)	37 (88)	29 (94)	0.78
Manual checks[2]	52 (72)	28 (67)	24 (80)	0.43

How important are the following proposed indicators of quality to improve consistency and/or accuracy?*				
Creation of alerts if the input data is out of range[2]	68 (94)	39 (93)	29 (97)	0.68
To measure number of missing fields over time[2,3]	57 (80)	33 (80)	24 (80)	0.99
To track changes in fields that will be previously entered[2,3]	52 (73)	27 (66)	25 (83)	0.26
How often should a quality check be done?[2]				**0.78**
Regularly, e.g. every year	56 (78)	32 (76)	24 (80)	
Randomly	12 (17)	7 (17)	5 (17)	
Event driven	4 (6)	3 (7)	1 (3)	

[a] An element was considered important if ≥80% of the respondents gave it a score of important or very important.
* Question assessed using a Likert scale. See below for additional figures of all answers to the Likert scale.
[1] Two missing from the respondents from industry; [2] One missing from the respondents from the other stakeholders; [3] One missing from the respondents from industry.

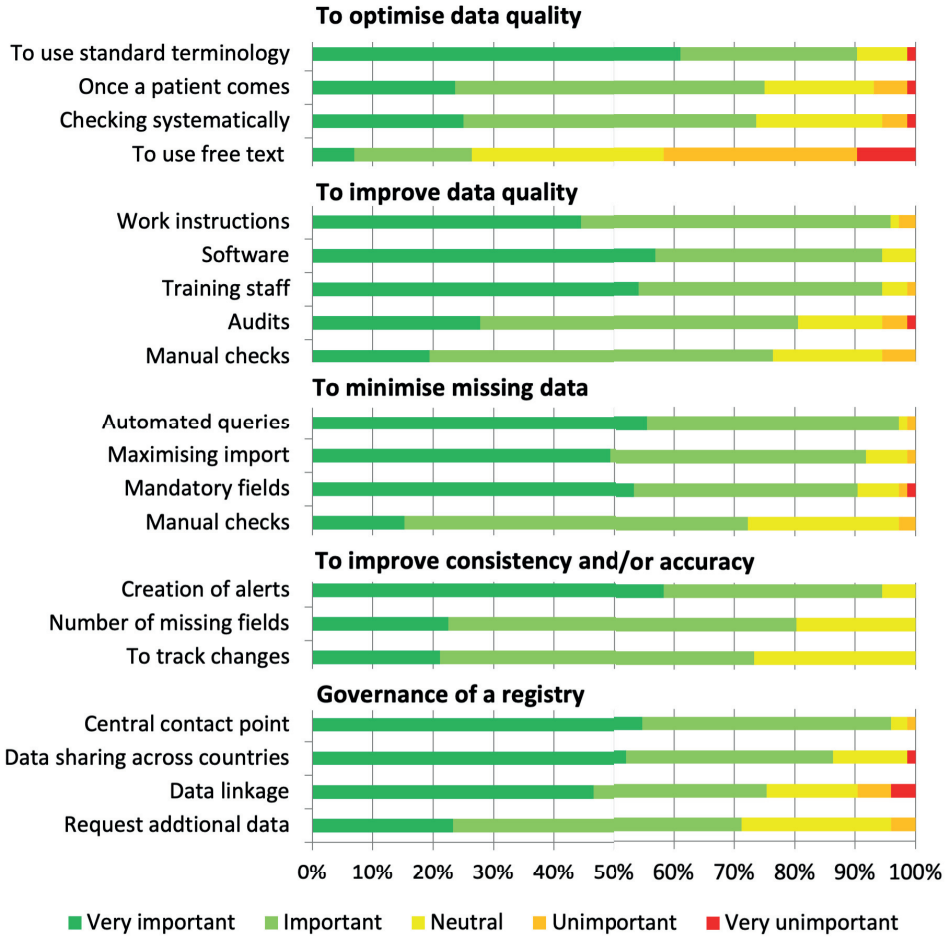


Figure 1. Responses to each of the Likert scale options of the questions concerning *optimise data quality, to improve data quality, to minimize missing data, to improve consistency and/or accuracy,* and *governance of a registry.*

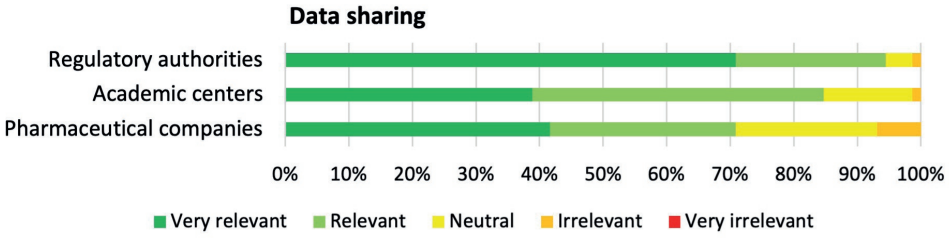


Figure 2. Responses to each of the Likert scale options of the questions related to *data sharing.*

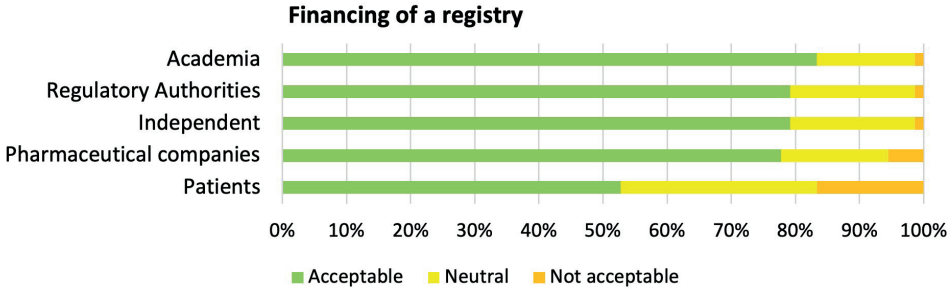


Figure 3. Responses to each of the Likert scale options of the questions related to *financing of a registry.*

Attachment 5. Number (percentage) of respondents (all, industry and other) that considered the *registry-based studies*-related questions important[a] with P-values of Pearson X^2 tests for differences between industry and the other stakeholders.

	All (N=73)	Industry (N=42)	Other (N=31)	P-value
How important is it to be able to collect data under a **common study protocol** in a multi-registry study?*				
	67 (92)	37 (88)	30 (97)	0.04
How valuable is it **to perform a randomized study in the registry**, if the data are used to support efficacy and/or safety evaluation of medicinal products by regulatory authorities?[1*]				
	44 (61)	21 (50)	23 (77)	0.07
How important is the registration of the registry-based study in a public register, like*				
ENCePP[2,3]	58 (84)	36 (88)	22 (79)	0.50
ClinicalTrials.gov[2,4]	55 (79)	32 (78)	23 (79)	0.97
EU Clinical TrialRegister[3,5]	52 (76)	28 (70)	24 (86)	0.42
How important is it that the following elements are predefined in a registry study?*				
Primary objective[1]	70 (97)	40 (95)	30 (100)	0.45
Secondary objective[3]	63 (90)	36 (86)	27 (96)	0.43
Statistical Analysis Plan[1]	61 (85)	33 (79)	28 (93)	0.22
Control group[1,4]	51 (73)	26 (65)	25 (86)	0.25
Randomization[1,4]	37 (53)	15 (38)	22 (76)	0.04
The statistical plan should include information about*				
Missing data[4]	69 (97)	41 (98)	28 (97)	0.95
Analysis strategy[4]	67 (94)	38 (90)	29 (100)	0.23
Bias[4]	66 (93)	39 (93)	27 (93)	0.18
Treatment discontinuation[4]	66 (93)	38 (90)	28 (97)	0.61
Confounders[3]	65 (93)	37 (88)	28 (100)	0.08
Effect modifiers[3]	63 (90)	36 (86)	27 (96)	0.28

[a] An element was considered important if ≥80% of the respondents gave it a score of important or very important.

* Question assessed using a Likert scale. See below for additional figures of all answers to the Likert scale.

[1] One missing from the respondents from the other stakeholders; [2] One missing from the respondents from industry; [3] Three missing from the respondents from the other stakeholders;

[4] Two missing from the respondents from the other stakeholders; [5] Two missing from the respondents from industry.

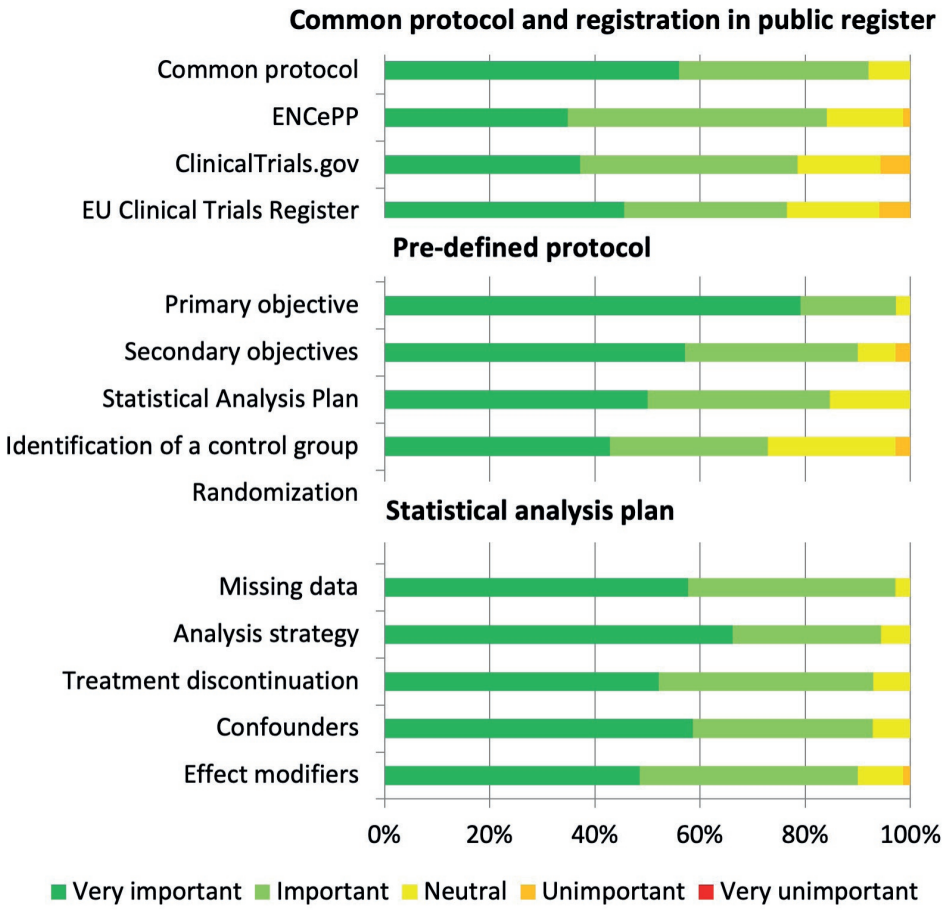


Figure 1. Responses to each of the Likert scale options of the questions related to *common protocol, registration registry-based study in a public register, pre-defined protocol,* and *statistical analysis plan.*

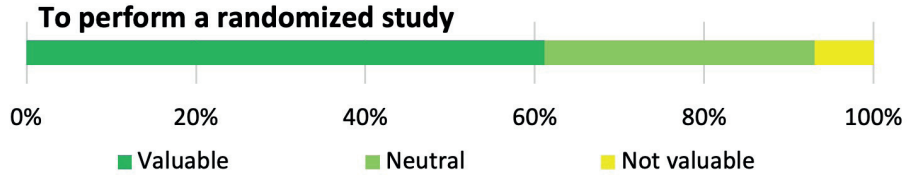
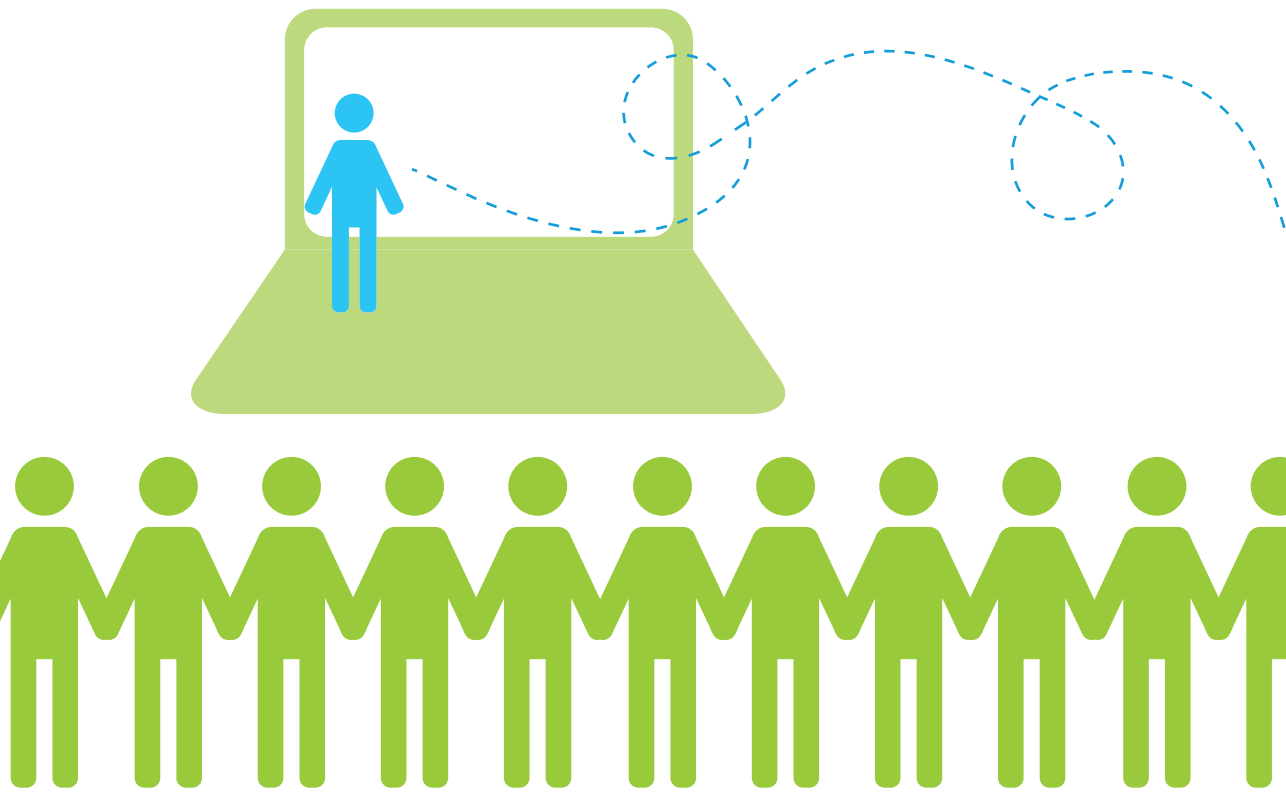


Figure 2. Responses to each of the Likert scale options to the question *to perform a randomized study.*



Chapter 7
General discussion

General discussion

The aim of this thesis was to investigate the value of registries in the regulatory decision making process for therapies in rare diseases. In general, registries are an important source for information on diseases, including standards of care, safety and effectiveness of treatments and long-term prognosis.[1] Registries are often categorized into disease and product registries. In a disease registry members are defined by a particular disease regardless of exposure to a specific medicinal product, other treatment or a particular health service. In contrast in a product registry data is collected from patients exposed to a specific medicinal product and are followed over time with the aim to evaluate the use, safety, effectiveness or another outcome of this exposure. Disease registries are generally better integrated into health care systems, may provide historical or contemporaneous control data and are therefore more likely to be sustainable and to provide long-term follow-up data on patients.[1] In this thesis we investigated post-approval registries requested by the Committee for Medicinal Products for Human use (CHMP) of the European Medicines Agency (EMA). Notably, we used haemophilia as a case study for the use of registries in rare diseases. The main findings of the studies included in this thesis are:

- In one-third of the newly approved drugs, a registry was required to provide additional data, mostly to provide data because of safety concerns. The majority (46 out of 73, 63%) of the registry studies were proposed in existing disease registries and in 37% (27 out of 73) a (new) product registry had to be developed. Most of the drugs involved were innovative and orphan drugs, for which there is high medical need.
- Five years after approval of the drugs, only 2 (3%) of 73 registry studies had been finalized, 19 registries (26%) had not enrolled any patients, and 52 (71%) were still ongoing. Enrolment of patients in new (mostly product) registries imposed by the regulatory authority as a specific post-approval obligation seemed to perform better, but the overall inclusion rate was poor.
- In the field of haemophilia registries we demonstrated that well-designed registries are important complementary data sources to clinical trials. Data derived from registries have been useful for safety information to support the regulatory decision process.
- In previously untreated patients with severe haemophilia A, using the same recombinant FVIII product, inhibitor development proved comparable in a single-arm clinical study and a registry-based study population. Moreover, in the registry-based study, patient numbers and completeness of follow-up were higher.
- The opinion towards data collection and governance is well aligned across relevant parties (including regulators, industry, registry holders, academia and patients) and these issues should therefore not pose a barrier to collaboration.

In the field of rare disease registries are acknowledged to be a useful tool to share data and to promote research, often in an international setting.[2] In the regulatory field, the EMA has set up the patient registry initiative and the Heads of Medicines

Agencies/EMA Task Force on Big Data to explore the opportunities and challenges posed by, respectively, registries and real world data in medicines regulation.[3-4] A main goal of the patient registry initiative is to increase the use of existing disease registries. Over the years we have seen a growing participation of the registry holders in the dialogue between regulators, industry and registry holders to understand the opportunities and limitations of disease registries. Nevertheless, interactions between regulators and registry holders should be improved further. There still exists a gap between regulators and registry holders about the value of disease registries to support regulatory decision making. More cooperation is needed to close the triangle between regulators, industry and registry holders. Importantly, the lack of legal contracts between regulators and registry holders is an obstacle for the exchange of data. In addition, there is a growing need to bridge data from the studies performed for medicinal products (which are typically limited to highly selected participants with limited comorbidity) in the context of a market authorization and data needed to predict the effects of the use of these products in daily practice. Examples are the data in understudied populations, such as children, elderly and pregnant women, which are usually not available from registration trials. These data will often be drawn from registries, especially in the field of rare diseases.

Based on the results presented in this thesis, several aspects and developments pertaining to (rare) disease registries warrant further discussion. In this chapter, first, some opportunities to improve data collection in disease registries will be presented and it will be argued why registries have particular value in the field of rare diseases. Second, with haemophilia as an example of a rare disease, assessment of long-term effects of therapies with gene therapy will be discussed. Third, important developments within the oncology field will be highlighted, which have a potentially large impact on the value of registries in oncology. Most notably, in the development of therapies for oncology there is a shift from "one-size-fits-all" cancer drugs to targeted treatments in small groups of patients.[5] In the changing field of therapies for oncology the potential of disease registries to quantify treatment effects in small patient populations will be outlined. Next, the impact of the General Data Protection Regulation on data sharing between stakeholders and, finally, the proposals to increase the use of disease registries in the regulatory decision making process are discussed.

Data collection in a disease registry

We have shown that registries are often used to answer questions of regulatory authorities, such as EMA, about the long-term safety and effectiveness of a new medical product.[6] Currently, however, the data provided by registries appears still inadequate to fully address the remaining uncertainties of medicinal products in the marketing authorisation process.[7-8] To improve the use of registries, points of interest are the collection of additional data elements, including adequate reporting of safety data.

Ideally all information that is captured in clinical trials about the efficacy and safety of a medicinal product would be captured in (rare) disease registries. Such registries should

be developed, funded and maintained independent from industry, to prevent any discussions on conflicts of interest. These disease registries, as the source for registry-based studies, should guarantee clinically relevant information on the course of the disease, have shown to be capable of collecting long-term data and should be freely exchangeable or accessible for analysis by third parties[9] However, the long list of data elements often needed for more specific regulatory questions will not align well with the original purpose and/or set-up of existing registries that are disease- or patient-oriented rather than focused on a medical product. It is essential to create a win-win situation whereby the data collected is beneficial for regulators, industry and registry holders alike. The regulators should be convinced that a registry could serve to identify not only patients using the medicinal products, but also control patients not using it, whereby crucial patient characteristics, including potential confounders (to adjust for possible differences in patient characteristics between users and non-users) should be available in the registry. The benefits for industry could be a faster recruitment of patients and limited costs. Registry holders could benefit from the enriched information in their registries because it increases their understanding of the complex natural progress of a rare disease, supports accelerated recruitment of patients in clinical trials to facilitate the development of new therapies and improves monitoring of current / standard care. Industry, registry holders and regulators should ideally liaise even before a medicinal product for (rare) diseases is in development. An essential condition for cooperation is agreement about the data to be collected and about the governance / data ownership of the registry. The common data set and the criteria for data quality and completeness should be known.[10] For data quality it is crucial to prevent missing data and to monitor the data actively and regularly. However, to achieve this, new (financial) incentives are needed to ensure the sustainability of rare disease registries.[9]

An important consideration is that, when industry performs a prospective study in a registry, data reporting should comply with the requirements for post-approval safety data management, as described in Guideline on good pharmacovigilance practices (GVP) module VI for safety reporting and in GVP VIII for post-authorisation safety studies.[11-12] For solicited cases, i.e., safety reports derived from organized data collection systems, companies have the obligation to perform an assessment of causality and submit the - causally related - adverse drug reactions to the relevant authorities.[13-14] This means that the company should have detailed information and follow-up data about the medical product in order to enable timely causality assessment. However, achieving complete coverage in registries on all adverse events remains very challenging. Obviously, registry holders could adapt data collection over time and add data on specific safety aspects, but even then a complete coverage of potential adverse effects is virtually impossible. It seems reasonable and as specified inthe International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E19, the safety outcomes can be recorded as defined in a study protocol of a registry study and this may be less comprehensive with regards to (well-known) non-serious adverse events.[15] This would reflect data collection in daily practice. In a registry the focus will be on, anticipated, specific safety outcomes related to the disease and the medication used

(e.g. inhibitor formation in haemophilia). A solution could be to (legally) formalize the cooperation between regulators and registry holders. This would give registry holders more responsibility for the content, quality and timing of reporting of (sometimes specific safety) data collected in registries and adapt the data collection when relevant.

Haemophilia: how to collect data on long-term effects of gene therapy?
For this thesis we took haemophilia as a rare disease case study. In chapter 4 and 5 we showed that, clinically relevant parameters described in clinical guidelines for factor VIII products can be collected in a registry. Importantly, we found that the follow-up of patients in a registry was more complete than in the available clinical study.[16-17] In the field of haemophilia, gene therapy products are available and promise a potential (and hopefully long-lasting) cure for both hemophilia A and B.[18-19] Main concerns for gene therapy, however, are its long-term safety and effectiveness. Although children would benefit the most form gene therapy, loss of effectiveness with time may be a major hurdle.[20] Long-term follow-up data from (electronic) registries and electronic health records offer the most cost-efficient way of collecting data on long-term effects of such therapies.[21] Clinical studies with many years of follow-up are not a realistic option.

If data are collected independent from industry, this helps to allow comparisons between different treatment regimens, products and gene therapy medicinal product and will reduce suspicion of commercial influences.[10] From our studies we learned that registries like PedNet are potentially useful in assessing inhibitor development in treatments for haemophilia and may serve as an alternative to clinical studies for evaluation of effectiveness, inhibitor development, and other safety signals. In addition to single-arm studies for separate products, or non-randomized comparisons of two therapies (taking confounding into account), randomized controlled trials (RCT) could be performed within these haemophilia registries. An example of such a registry-based RCT is the TASTE study that was performed to assess the effects of thrombus aspiration in myocardial infarction.[22] The primary outcome in this RCT within the SWEDEHEART registry was a composite of death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure. In this study patients were recruited, randomised and followed in the registry. Two years later the results of this cardiovascular study were confirmed by data of a standard RCT.[23] Not only in cardiovascular disease, but also in rare diseases opportunities should be explored further to perform an RCT within a registry.

The potential of disease registries for studies in oncology
The development of medicinal products for rare diseases has increased sharply in the last decades. In the United States (US) 40% of all new medicinal products approved since 2000 are orphan medical products.[24] In part, this is due to American and European legislation that provide incentives for development of orphan medical products. This is reflected in the field of oncology and haemato-oncology. In this clinical field there is a trend towards "orphanisation" of indications. Orphanisation is a term used to indicate the trend that common diseases are more responsive to targeted therapy in small

specific patient groups; thus claiming orphan drug benefits, which, unfortunately often results also in a higher pricing of the medical product. Consequently, in oncology, with originally a broad indication in large patient group, the number of medicinal products that is granted a marketing authorization, solely on the basis of a single arm study for a specific indication, is growing.[25-26] In the period 2009-2013 in eight of the 68 cases (12%) a new cancer indication was approved on the basis of a single arm trial.[25] In these trials, which often have a very small sample size, patients are treated with an experimental medicinal product for a new indication and then followed over time to observe their response.[27] The lack of a control group poses an important problem in interpreting the findings of these uncontrolled studies and thus this increase in single-arm designs should be criticised.[28] In a rare disease registry almost all patients with a particular disease are included. A rare disease registry creates therefore the opportunity to use data as historical controls from patients fulfilling the inclusion criteria of the study, when placebo or active comparators are e.g. not ethically acceptable. Moreover, they provide the opportunity to use information on the primary outcome data in the registry population to calculate the sample size for a new study or even to select patients for a randomized controlled study. Thus, disease registries can increase efficiency of drug development by providing a data collection tool for clinical trials.[29]

At the time of marketing authorisation often additional data are requested that is not routinely collected in daily practice. This can be illustrated on the basis of the need for long-term effectiveness and post-approval safety data for two oncological medicinal products, larotrectinib and entrectinib.[30-31] The results from the single-arm trials in small study populations released so far suggested that both medicinal products reduce the size of patients' tumours. Post-approval, studies are still awaited to confirm the efficacy in a larger sample size and the long-term safety in children. Regulators are currently still unsure what additional value registries or registries-based studies will have for collection of these relevant post-approval data. It is challenging to identify patients in these registries with matching tumour type, histology and line of treatment in a control population, because the tests to identify the tumour type are not standard clinical practice. The same applies for the collection documentation of diagnosis, documentation of treatment history, reasons for treatment choices and for discontinuation and measurement of the progress of disease. This makes the findings of single arm trials notoriously difficult to contextualise. If comparisons with historical controls, especially who received or are receiving "current state-of-the-art care" and with matching tumour types are missing, this can easily lead to claims on increased effectiveness of the novel therapy without proper data supporting such comparison. Oncology registries, however, can deliver data on the natural progression of the disease that may be used as non-concurrent controls to contextualise single arm trial data, or can provide long-term effectiveness and safety data. This may require linkage with e.g., pathology datasets and/or medical chart review to capture relevant patient characteristics, such frailty based on age or Eastern Cooperative Oncology Group performance status, a physician assessment of a patient's level of functioning in terms of self-care, daily activity, and physical ability.[32] Moreover,

prospective collection of the 'real world' characteristics of the target population are key to understanding the generalisability and relevance of the single arm trial study population and findings for the "typical" or "average" patient with this type of cancer.

Disease registries and the General Data Protection Regulation

When patients are asked to participate in a registry or a registry-based study, they should, in accordance with General Data Protection Regulation (GDPR), give informed consent.[33] The GDPR, a European law, covers the data protection and privacy of citizens in the European Union. There are some misunderstandings about the use of registry data in the context of the GDPR. A number of aspects of the GDPR with regard to clinical data sharing were discussed during a workshop at the EMA in 2017.[34] It was concluded that the regulation makes data sharing more complex, differs from legal requirements in the US and across European member states, e.g., there are differences between national consent and assent requirements for paediatric clinical trials in Europe due to national laws and regulations.[35-36] An opportunity to overcome this problem is the anonymisation of data, i.e., the removal of the association between the dataset and the subject. Anonymisation provides a mechanism to balance protection of personal privacy and a maximum use of data. Registry holders that coordinate the collection of individual patient data can play an important role in the aggregation of data and prevent double reporting. Individual patient data need to be protected by the individual treatment centre of the patients. To share data for the public interest, possible technical solutions for data anonymisation include the use of homomorphic encryption, secure multiparty computation and artificial intelligence.[34] For the protection of data, registry holders should be encouraged to use such techniques that intend to ensure maximal use of data, without violating privacy rules.

In the context of GDPR, however, the most important issue is that the patient should, independent of age, illness or vulnerability, be able to give informed consent for the use and re-use of data for scientific purpose. Therefore, the informed consent form should contain clear, understandable, readable information about the purpose of collecting and sharing data and how the data will be protected and how abuse or misuse of personal data is prevented.[34] So far, in the field of oncology and bone marrow transplantations academic groups are able to share and analyse these data, with the assurance that the risk of re-identification of the patients, i.e. the process by which anonymized personal data is matched with its true owner, is acceptably low.[37] This potential benefit of sharing of data is extremely important for the development of innovative medicinal products and should be clearly explained in the informed consent form to protect the confidentiality of the patient. To accomplish this, more transparency and guidance is needed for stakeholders, in particular for patients.

Proposals to increase the use of disease registries in regulatory decision making

Ideally a disease registry is an independent platform that enables fast collaboration at an international level.[38] To date, the knowledge coming from product registries

set-up by industry may not be freely exchangeable or accessible for analysis by third parties[10], which is a missed opportunity. Rare disease registries could be used more often as a basis for recruitment for studies for regulatory purposes. An example is the International Niemann-Pick Disease Registry (INPDR), that is a collaboration between clinicians, scientists, researchers and patient associations across the world to collect clinical, genetic, diagnostic and outcome data in patients with Niemann-Pick Diseases. They share data to support research that improves care for patients affected by all types of Niemann-Pick disease and their families. Patient reported data can be included in the registry through an online self-enrolment process by a patient or caregiver. In September 2020, 300 patients were registered in the database. Participating sites are encouraged to evaluate all their patients with a confirmed diagnosis of Niemann-Pick, regardless of their treatment status. During the coming years the goal is to collect data from 1200 additional patients.[39] The data collected in rare disease registries should be easily accessible to relevant stakeholders, including healthcare professionals, patients and regulators, to enable the development of medicinal products, but obviously, only in case privacy regulations are met.

Registries provide an important data source to compare baseline characteristics of patients enrolled in registration trials with "typical" or "average" patients included in the registry.[40] This provides crucial information at the time of marketing authorisation of a medicinal product (also for more common diseases) on the generalizability of trial findings, that are often limited to highly selected homogenous patient groups.[41] The value of such registries is increasingly recognized in the US, where the use of registries for marketing authorisation of a medicinal product is growing fast. In 2019 for 49% of all medicinal products real world data was included in the dossier submitted to the FDA, and increased to 75% in 2020, mostly in the field of oncology and neuroscience.[42] For regulators RCTs remain the golden standard for assessing effects of therapies. However, after marketing authorisation the results of a trial with a relatively small number of highly selected trial subjects may turn out not to be representative of the effects observed in daily practice among large numbers of "real patients". The unpredictability of the effects of new products in real life and the limited knowledge about safety is still not generally acknowledged in the current regulatory decision framework.[43] The generalizability of the data for the use in daily practice deserves a higher priority. As a starting point, orphan medicinal products could be used as a pilot to explore the use of rare disease registries for registration purposes.

I believe that disease registries should be utilised more often to support important regulatory decisions. An ideal framework for use of registry data starts with the understanding that the regulatory question defines the data requirements (see Figure 1). Throughout the life cycle of a medicinal product, from the pre-submission to post-approval phase, data are needed to guide regulators, industry and registry holders (investigators) on the natural progression of the disease. Registry data may also be used to validate future (surrogate) endpoints / biomarkers to measure clinical outcomes in patients that participate in a disease registry. Over time – in the drug's

life cycle, other questions become relevant, such as whether the effects observed in a trial population also apply to a "typical" or "average" (real world) patient captured in a disease registry. Further, questions on long-term safety may only be answered when patients can be followed for many years, not just months. During each of these phases the registry holders, regulators and industry have a role regarding common data elements, data quality and governance. Aspects of data collection, data quality and governance are not static and may require different definitions depending on the regulatory question to be answered. Regulators, industry and registry holders need to interact early and align expectations, and come to a common understanding of what important questions can be answered with registry-based studies.

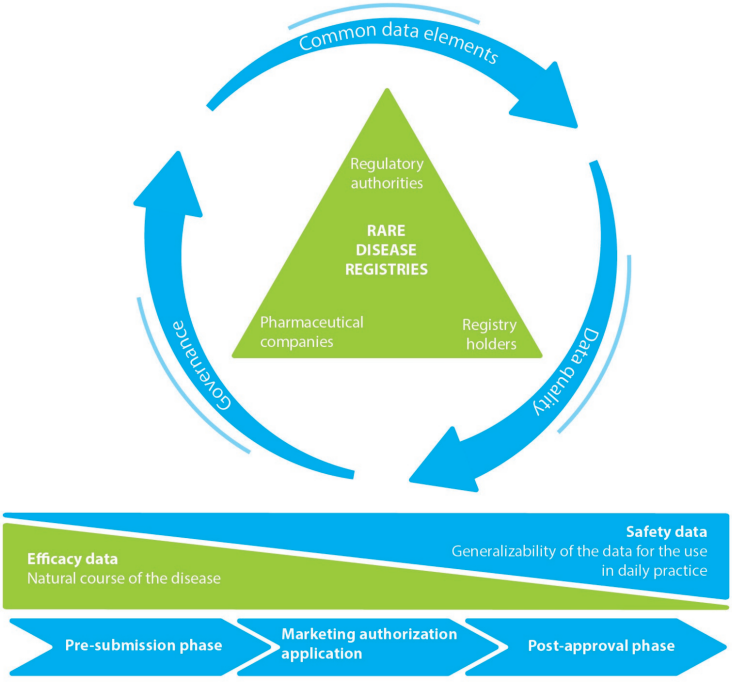


Figure 1

My recommendation would be to clarify the following steps in the application of registries in the regulatory process. The first step is to ensure that the collection of common data elements, for example safety outcomes, and the data quality of the registry is acceptable by the regulators. Secondly, the possibilities for sharing data between registry holders and regulators, independent from industry, or the requirements for accessibility of data to relevant stakeholders should be documented. Thirdly, compliance of data collection in the registry with GDPR should be secured. In general, registry holders should have a more defined role when it comes to their responsibilities for the design, the conduct and quality control of

data collection in registries. For registry-based studies, the recently published draft EMA/CHMP guideline on registry-based studies[44], provides a legal basis and further handles regulatory requirements. In addition, a 'best-practice guideline' might be helpful to conduct registry-based studies relevant for regulatory purposes.

Final message

Rare diseases registries will have an increasingly important role in the regulatory decision process. With the development of targeted therapies, e.g. in oncology, more applications will be based on small patient numbers in, often small and single-arm, clinical studies. Registries can serve as a better alternative or as additional tool to provide data on effectiveness and safety. Registries should also serve as a sampling frame for historical and external control patients and as a source for patient recruitment to support a marketing authorization application. In addition, they are instrumental to assess the generalizability of the data provided by single arm trials. The gap between registry holders, industry and regulators about the value of disease registries can only be closed if all stakeholders are involved. Regulators should be more open to explore how real world data such as registry data can be used to solve uncertainties about a medicinal product. Industry should involve registry holders in an early phase of the development of a new medicinal product. Registry holders should realize that for regulatory purposes quality, completeness and timing of data reporting are essential, for which financial and capacity incentives are essential. Recommendations are needed to specify the contracts between registry holders and the other stakeholders, including patients enrolled in the registry, to clarify how and when data can be used for regulatory purposes and how data can be shared with industry and/or regulators. A pilot could be the use of rare disease registries in the development of orphan medicinal products and gene therapy. Hence, the title of my thesis: Rare disease registries: a must for regulatory decision making.

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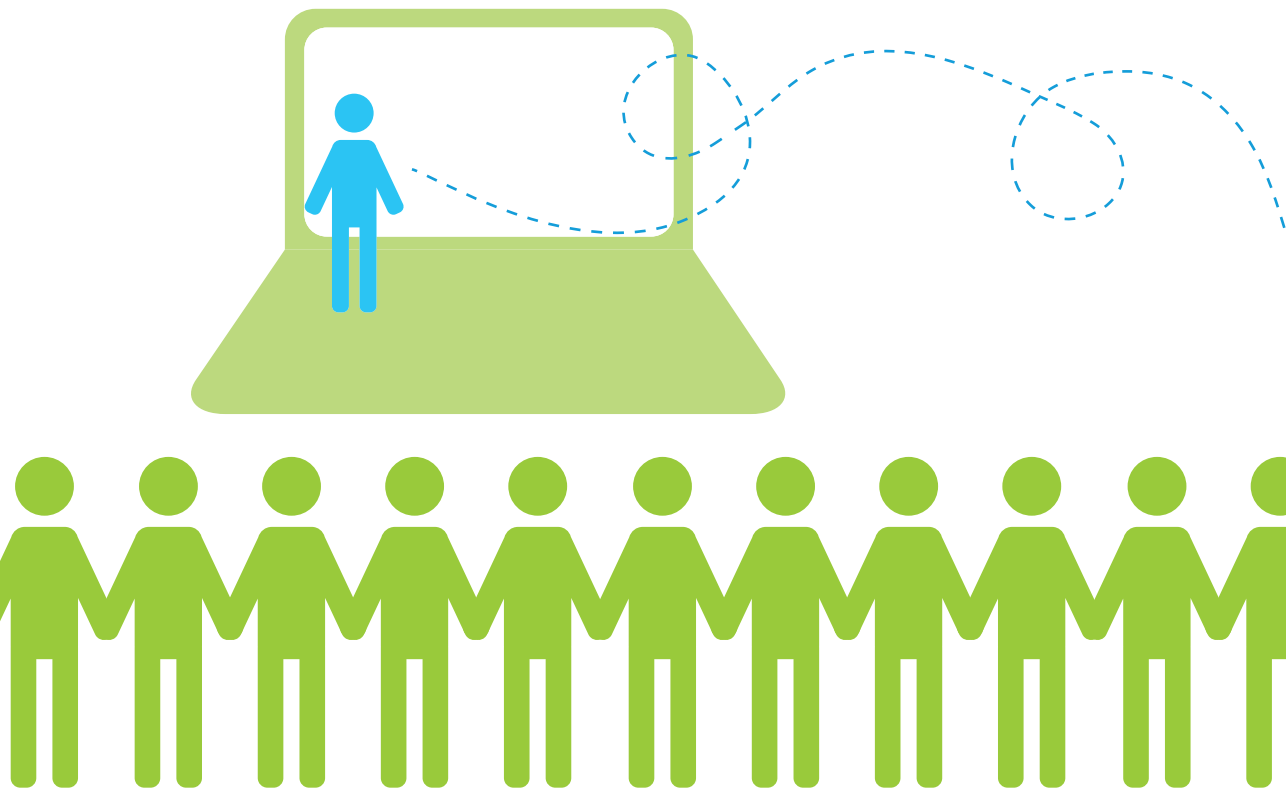

Chapter 8
Summary & Samenvatting

Summary

The aim for this thesis is to investigate the value of registries for regulatory decision-making. The field of haemophilia has been used as a case study, due to the experiences with long-term follow-up of patients included in haemophilia registries.

Chapter 2
In the first study we present the results of a review of all new medicinal products, which were approved in the European Union between 2007 and 2010. Registries offer the possibility for additional, post-approval, collection of data which was not available at time of the marketing authorisation. We investigated per medical product if post-approval a registry was requested, what the reason was, how often and the type of the registry. In this period 116 medicinal products were approved. For 43 (37%) medicinal products, one to six registry studies were identified, with a total of 73 registries. Of these 46 were disease registries and 27 (single) drug registries. The goal to request for a registry was primarily to collect further safety data (39 registries, 53%) or the impact of the use of a medicinal product during pregnancy (27 registries, 37%). We concluded that the majority of registries required by regulators are existing disease registries. The study showed that registries are an important and frequently used tool for post-approval data collection for orphan and innovative drugs.

Chapter 3
The aim of the second study, a follow-up of the first study, was to review whether registry studies for new medicinal products indeed were performed as agreed at time of approval. We reviewed the protocols and the follow-up reports for the 73 registry studies that were proposed for 43 medicinal products approved in the period 2007 to 2010. The data lock point was to taken to allow a 5-year follow-up period for each drug, to investigate the status of the different registry studies. At time of the data lock point, two studies (3%) in registries had been finalized, 19 registries (26%) had not enrolled any patients, and 52 studies (71%) were ongoing. For 41 out of 73 registries a predefined sample size was known. In this registry studies the median enrolment was 31% (interquartile range [IQR], 6–104) of the required number of patients. Data from 11 registry studies (15%) were published in peer-reviewed journals. Results of six registries were mentioned in European Public Assessment Report updates only, and for two medicinal products (eculizumab and influenza A [H1N1] pandemic vaccine) the results were added to the label. We concluded that enrolment of patients into post-approval registries is poor. The study also showed that for a few medicinal products only, the data generated from registries were published on the EMA-website or in peer-reviewed journals. This illustrates that so far registries only have a limited impact on resolving gaps in the knowledge of a drug's benefits and risks at time of marketing authorisation.

Chapter 4
In the third study we investigated the outcome data of clinical single-arm trials with the data of a registry in the field of haemophilia A. Haemophilia is an X-linked bleeding disorder that leads to a reduced synthesis of factor VIII (FVIII). It is rare disease detected in 1:5000 male new-borns. For the market authorisation of factor VIIII products the "Guideline clinical investigation on the of recombinant and human plasma-derived factor VIII products" is applicable. In the last revision the obligation to perform clinical trials in previously untreated patients (PUPs) for marketing authorisation purposes has been deleted. Instead post-authorisation studies based on a set of core data elements to be collected in haemophilia registries are requested. In our study we investigated the extent to which clinical trials and the PedNet registry did collect the set of core data as described in the guideline, as well as the incidence of inhibitor development in patients from both sources. For the study anonymized data of eight clinical trials in 369 PUPs performed from 1987 to 2009 were compared with each other and with 632 PUPs (born 2000-2009) from the PedNet registry. The presented analysis demonstrated that the clinical trials in PUPs were highly diverse, especially in number of patients, severity definition, follow-up period and inhibitor test modalities. This analysis exemplarily demonstrated that the PedNet registry collected data according to the parameters and conditions required by the guideline. The results of inhibitor development were comparable, regardless of the differences in data collection of both sources, especially when focusing on patients with severe haemophilia.

Chapter 5
In the next study we investigated whether a disease registry could serve as a suitable alternative to clinical studies to investigate safety of orphan drugs in children. For this study individual patient data from previously untreated patients (PUPs) with severe haemophilia A from the factor VIII (rAHF-PFM)-clinical study and the PedNet registry were used. The primary outcome was the patient characteristics at entry and the difference in inhibitor development between the clinical study and the registry-based study at 50 exposure days. It was shown that patient characteristics were slightly different between the clinical study and the registry-based study. In the clinical study, the prevalence of family history of inhibitors was higher and more patients had a high-risk gene mutation. In the clinical study, a higher percentage of patients developed an inhibitor. The number of withdrawals was higher in the clinical study; the completeness of the follow-up was better in the registry. This study indicates that registries like PedNet are potentially useful in assessing the inhibitor developments in treatments for haemophilia and may serve as an alternative to uncontrolled clinical studies for evaluation of high-titre inhibitors.

Chapter 6
So far we described that for one third of all new medical products a registry was requested, but that the recruitment within these registries was poor. We showed that in the field of haemophilia the PedNet registry collected data according to the parameters and conditions required by the guideline and that the number of patients

followed-up is this registry is higher than in single-arm studies. This illustrates that registries are potentially useful to collect data to collect long-term follow-data.
In chapter 6 the results are presented of a survey among industry and other stakeholders. In cooperation with the patient registry initiative we investigated the view of stakeholders about key aspects of rare disease registries that are used to support regulatory decision-making in the field of rare diseases and to compare the responses of employees from industry and other stakeholders. The web-based survey was sent to people working with registry data in the pharmaceutical industry, at regulatory authorities, at health technology assessment agencies, registry owners, and patient representatives. The survey covered the key aspects in terms of common data elements, data quality and governance for rare disease registries that were important (rated important of very important by >80% respondents) to stakeholders. For common data elements a set of demographics, clinical and medication-related data was identified that focused primarily on the disease of interest with much less emphasis on co-morbidities or adverse events. Respondents considered that 30% of source data verification and 20% missing data would provide acceptable levels of data quality. The opinion of both industry and other stakeholders towards data and governance is well aligned across parties, and issues of data and governance on their own should not pose a barrier to collaboration. If registries are used as data source for post authorisation safety studies, they should provide accurate, timely and follow-up data on adverse events in order to enable causality assessment. There were few differences between the industry and the other stakeholders with regard to governance aspects. The other stakeholders found it less relevant to share data with industry and found it less acceptable when a registry is financed by industry.

Lessons learnt

- Registries are often used to collect data for the regulatory-decision process.
- Within these registries the recruitment of patients was poor.
- In the field of haemophilia registries have demonstrated to be useful for safety data collecting for the regulatory-decision process.
- The opinion towards data collection and governance is well aligned across relevant parties (including regulators, industry, registry holders, academia and patients) and these issues should therefore not pose a barrier to collaboration.

Nederlandse samenvatting

Het doel van dit proefschrift is om de waarde van registers voor de regulatoire besluitvorming van geneesmiddelen te onderzoeken. Hemofilie is gebruikt als een case studie, omdat erin dit vakgebied ervaring is met langdurige follow-up van patiënten via registers.

Hoofdstuk 2
In de eerste studie presenteren we de resultaten van een review van alle nieuwe geneesmiddelen die tussen 2007 en 2010 in de Europese Unie zijn goedgekeurd. Registers bieden de mogelijkheid om na goedkeuring van een geneesmiddel aanvullende gegevens te verzamelen, die niet beschikbaar zijn op het moment dat de handelsvergunning verleend wordt. Voor elk geneesmiddel is onderzocht of er na goedkeuring een register is aangevraagd, wat de reden hiervoor was, hoe vaak en het type register. In de periode 2007 – 2010 waren er 116 geneesmiddelen goedgekeurd. Voor 43 (37%) geneesmiddelen waren één tot zes registerstudies geïdentificeerd, met in totaal 73 registers. Hiervan waren er 46 ziekteregisters en 27 (enkelvoudige) productregisters. Het doel van het aanvragen van een register was vooral gericht op het verzamelen van aanvullende veiligheidsgegevens (39 registers, 53%) of de impact van het gebruik van een geneesmiddel tijdens de zwangerschap (27 registers, 37%). We concludeerden dat de regulators voor de meeste geneesmiddelen studies uit bestaande ziekteregisters vragen. Uit het onderzoek bleek dat, voor het verzamelen van gegevens na goedkeuring van weesgeneesmiddelen en innovatieve geneesmiddelen, registers een belangrijk en veelgebruikt hulpmiddel zijn.

Hoofdstuk 3
Het doel van de tweede studie, een vervolg op de eerste studie, was na te gaan of de registratiestudies voor nieuwe geneesmiddelen waren uitgevoerd zoals voorgesteld op het moment dat het geneesmiddel goedgekeurd werd. We hebben de protocollen en de follow-uprapporten van 73 registerstudies beoordeeld. Deze registers waren gekoppeld aan de 43 geneesmiddelen die goedgekeurd waren in de periode 2007 tot 2010. Om de status van de verschillende registerstudies te onderzoeken is voor elk geneesmiddel als data lock point een follow-upperiode van 5 jaar genomen. Op het moment van het data lock point waren twee registerstudies (3%) afgerond, 19 registers (26%) hadden geen patiënten geïncludeerd en 52 studies (71%) liepen nog. Voor 41 van de 73 registraties was vooraf de omvang van de steekproef gedefinieerd. In de registerstudies was de mediane inclusie 31% (interkwartielsafstand [IQR], 6-104) van het vereiste aantal patiënten. Gegevens van 11 registerstudies (15%) waren gepubliceerd in peer-reviewed tijdschriften. De resultaten van zes registers waren vermeld in de updates van het European Public Assessment Report en voor twee geneesmiddelen (eculizumab en influenza A [H1N1] pandemisch vaccin) waren de resultaten opgenomen in de productinformatie. We concludeerden dat de inclusie van patiënten in registers slecht is. Uit het onderzoek bleek dat slechts voor enkele

geneesmiddelen de resultaten uit de registerstudies gepubliceerd waren op de EMA-website of in peer-reviewed tijdschriften. Dit illustreert dat registers tot op heden een beperkte toegevoegde waarde hebben betreffende het oplossen van hiaten in de kennis, die ontbreekt op het moment dat een geneesmiddel goedgekeurd wordt, over de voor- en nadelen van geneesmiddelen.

Hoofdstuk 4
In de derde studie onderzochten we de resultaten van een single-arm klinische studie met de gegevens van een hemofilie-register. Hemofilie is een X-gebonden bloedziekte die leidt tot een verminderde synthese van factor VIII (FVIII). Het is een zeldzame ziekte die wordt gedetecteerd bij 1:5000 mannelijke pasgeborenen. Voor de markttoelating van factor VIIII-producten is de "Guideline clinical investigation on the of recombinant and human plasma-derived factor VIII products" van toepassing. Bij de laatste herziening van deze richtlijn is de verplichting, om na markttoelating klinische onderzoeken uit te voeren bij previously untreated patients (PUP's), geschrapt. In plaats daarvan wordt gevraagd om een aantal core data elementen in hemofilieregisters te verzamelen. In deze studie hebben we onderzocht in hoeverre klinische studies en het PedNet-register de core data elementen en de incidentie van de remmer-ontwikkeling verzamelden. Voor het onderzoek werden geanonimiseerde gegevens van acht klinische studies in 369 PUP's (uitgevoerd in de periode 1987 - 2009) met elkaar en met gegevens van 632 PUP's (geboren 2000-2009) uit het PedNet-register vergeleken. De analyse toonde aan dat de klinische onderzoeken bij PUP's zeer divers waren, vooral wat betreft het aantal patiënten, de definitie van de ernst van de hemofilie, de follow-upperiode en de testen om remmers te meten. Ook toonde deze analyse aan dat het PedNet-register gegevens verzamelde conform de parameters en voorwaarden van de richtlijn. De resultaten van de remmer-ontwikkeling, en met name bij patiënten met ernstige hemofilie, waren vergelijkbaar, ongeacht dat de gegevens in beide bronnen verschillend verzameld waren.

Hoofdstuk 5
In de volgende studie onderzochten we of een ziekteregister een geschikt alternatief zou kunnen zijn voor klinische studies om de veiligheid van weesgeneesmiddelen bij kinderen te onderzoeken. Voor deze studie werden individuele patiëntgegevens gebruikt van previously untreated patients (PUP's) met ernstige hemofilie A uit de VIII (rAHF-PFM)-klinische studie en het PedNet-register. De primaire uitkomstmaten waren de patiëntkenmerken bij inclusie en het verschil in de remmer-ontwikkeling na 50 behandelingsdagen (Exposure Days) tussen de klinische - en de registerstudie. Tussen de klinische - en de registerstudie was er een verschil in patiëntkenmerken. In de klinische studie was de prevalentie van familiegeschiedenis met een remmer hoger en hadden meer patiënten een hoog-risico gen mutatie. In de klinische studie ontwikkelde meer patiënten een remmer. Het aantal uitgevallen patiënten was hoger in de klinische studie; in de het register was de follow-up completer. Deze studie geeft aan dat registers zoals PedNet een mogelijke bron zijn voor het beoordelen van remmer-ontwikkeling in de behandeling van hemofilie. Registers kunnen een goed alternatief zijn voor ongecontroleerde klinische studies om hoge-titer remmers te evalueren.

Hoofdstuk 6

Uit de eerdere studies bleek dat voor een derde van alle nieuwe geneesmiddelen een register werd aangevraagd, maar dat de inclusie in deze registers slecht was. We toonden aan dat op het gebied van hemofilie het PedNet-register gegevens verzamelde conform de parameters en voorwaarden van de richtlijn. Verder was het aantal patiënten in dit register hoger dan in single-arm studies. Dit illustreert dat registers potentie hebben om lange termijn gegevens te verzamelen.

In hoofdstuk 6 worden de resultaten gepresenteerd van een enquête die gehouden is onder de industrie en andere belanghebbenden. In samenwerking met het patient registry initiative onderzochten we de mening van belanghebbenden over belangrijke aspecten van registers van zeldzame ziekten voor de regulatoire besluitvorming van weesgeneesmiddelen. Naast de evaluatie van de antwoorden zijn ook de antwoorden van werknemers uit de industrie en andere belanghebbenden met elkaar vergeleken. De web-gebaseerde enquête is naar personen gestuurd die in de farmaceutische industrie werken, bij regelgevende instanties, beoordelingsbureaus voor gezondheidstechnologie, eigenaren van registers en patiëntvertegenwoordigers. In het onderzoek werden vragen gesteld over de belangrijkste aspecten van registers van zeldzame ziekten in termen van common data elementen, data kwaliteit en governance. Een aspect was belangrijk als >80% respondenten het aspect als belangrijk of zeer belangrijk had beoordeeld. Voor common data elementen werd een reeks demografische, klinische en medicatie gerelateerde gegevens geïdentificeerd die primair gericht waren op de ziekte van belang, en veel minder op co-morbiditeit of bijwerkingen. De respondenten waren van mening dat 30% source data verificatie en 20% van de ontbrekende gegevens een acceptabel niveau van data kwaliteit zouden opleveren. De mening van zowel de industrie als andere belanghebbenden ten aanzien van data en governance komt goed overeen. Kwesties op het gebeid van data en governance op zich mogen geen belemmering vormen voor samenwerking. Als registers worden gebruikt als bron voor post-authorisation veiligheidsstudies, dan moet er voor een causaliteitsbeoordeling van bijwerkingen nauwkeurige, tijdige en follow-upgegevens beschikbaar zijn. Op het gebied van governance waren er weinig verschillen tussen de industrie en de overige stakeholders. De overige stakeholders vonden het minder relevant om data met het bedrijfsleven te delen en vonden het minder acceptabel wanneer een register door het bedrijfsleven wordt gefinancierd.

Lessons learnt

- Registers worden vaak gebruikt om gegevens te verzamelen voor regulatoire besluitvorming van geneesmiddelen.
- De inclusie van patiënten in deze registers was slecht.
- Op het gebied van hemofilie zijn registers een goed alternatief voor het verzamelen van veiligheidsgegevens voor regulatoire besluitvorming van geneesmiddelen.
- De mening over de data verzameling en governance is goed afgestemd tussen de relevante partijen (waaronder regelgevers, de industrie, registerhouders, de academische wereld en patiënten). Deze kwesties mogen daarom geen belemmering vormen voor samenwerking.

Publications related to this thesis

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https://pubmed.ncbi.nlm.nih.gov/34091881/

Curriculum Vitae

Carla Jonker was born in 1968 in Terneuzen. She completed successfully her VWO diploma at the RSG Petrus Hondius in Terneuzen and started with the study Biomedical Sciences at the University of Leiden. She obtained her Master's degree in 1992. Following graduation she had a position as Rayon Manager, Clinical Research Associate, Clinical Research Coordinator and Medical Advisor at the pharmaceutical industry, when she worked for respectively Glaxo, Quintiles Benelux, Parke-Davis and Pfizer.

In 2004 she started as Regulatory Project Leader at the Dutch Medicine Evaluation Board. From 2013 she combined this position with a PhD project at the Julius Center for Health Sciences and Primary Care at the University Medical Center Utrecht, University of Utrecht. During her PhD she was an actor in the European Medicine Agency's Cross Committee Task Force on Registries.

Currently Carla combines her position as Senior Regulatory Project Leader at the Medicine Evaluation Board with her work as National Expert in the Data Analytics and Methodology Task Force at the European Medicine Agency.

Dankwoord

Hier ligt mijn proefschrift. Het geeft een goed gevoel dat ik na vele jaren mijn promotie kan afronden. Ik heb dit niet alleen gedaan, daarom wil ik allereerst mijn promotoren en copromotor bedanken voor de begeleiding tijdens deze promotie.

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