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Lessons learned on the design and the conduct of European Post Authorisation Safety Studies (PASS): Review of 3 years of PRAC oversight

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Aos meus pais

Summary

Introduction

The new European Union (EU) Pharmacovigilance, implemented in 2012, aimed to establish a more proactive and efficient system for the early detection and prevention of issues related to the safety of medicinal products. This goal is reflected by the legal enforcement of Risk Management activities. As a consequence, it is necessary to submit a Risk Management Plan (RMP) with each application for a new marketing authorisation. This document includes a critical assessment of the known and unknown safety profile of the medicinal product and discusses the need to implement Pharmacovigilance and risk minimisation activities that go beyond the routine ones.

A Post-Authorisation Safety Study (PASS) is an additional Pharmacovigilance activity conducted with the goal of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk minimisation measures (RMMs). They bridge Pharmacovigilance, which defines the mission, with Pharmacoepidemiology which provides the study methods. PASS can be imposed as condition or special obligation to the marketing authorisation and may also be requested upon conclusion of a safety related referral.

The Pharmacovigilance Risk Assessment Committee (PRAC) is a committee of the European Medicines Agency (EMA) created by the new Pharmacovigilance legislation. It is responsible for the assessment of safety issues at EU level, as well as the monitoring of the Pharmacovigilance activities foreseen in the legislation. In addition, as a consequence of the efforts to increase transparency of the regulatory processes and decisions, the EMA publishes the PRAC monthly minutes on its website. These documents list all the assessed Pharmacovigilance procedures with a brief summary of the plenary decisions. The availability of these and other documents provided an opportunity to identify the PASS protocols submitted to the PRAC.

The objective of the current dissertation was to describe the PASS landscape during the first three complete years of the new Pharmacovigilance legislation by characterising the purpose and methodology of the studies. It also aimed to give a critical perspective on the level of public available information on the PASS review process and PRAC feedback.

Methods

The minutes of the PRAC meeting minutes held from July 2012 to July 2015 were chronologically reviewed to identify and track all PASS protocols and respective rounds of review. The information from the minutes was complemented with a review of the European Public Assessment Reports (EPARs) for the medicinal products covered in the PASS, which provided information about the regulatory background. Moreover, the European Union electronic Register of Post-Authorisation Studies (EU PAS) Register available in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website was also searched to find information about PASS methodology and protocol documents.

Upon protocol availability, it was possible to retrieve more granular information. Metrics regarding the PRAC assessment process were determined among protocols that were considered approved based on the following rules: there was information in the PRAC comments text, the PASS was found in the EU PAS Register, or more than one year had elapsed since the last assessment of that PASS protocol.

Descriptive analyses were performed on actual data, with no imputations for missing data. Comparisons using chi-square test (with a significance level of 5%) were conducted.

Results

In total, 189 different PASS protocols were identified by reviewing the minutes of the PRAC meetings from July 2012 to July 2015, corresponding to 353 PASS protocol submissions to the PRAC. The outcome of PRAC assessment was only available in the minutes for approximately one third (30%) of the 353 assessments. Only half of the 189 PASS were available in the EU PAS Register at the data lock, July 2015.

The majority of PASS (58%) concerned new marketing authorisations. About one third (31%) of the 189 PASS were imposed by the regulators.

The vast majority of PASS (74%) had at least one objective related with investigation of safety concerns, while approximately one third (34%) included at least one objective of assessing drug utilisation and one fourth (25%) incorporated at least one objective related with assessment of effectiveness of RMMs. Almost one third of the PASS (31%) combined objectives of at least two of those categories.

PASS were mainly designed as longitudinal studies (81%). However, the majority of PASS (56%) with at least one objective concerning the assessment of effectiveness of RMM had a cross-sectional design. Overall, slightly more PASS involved a primary data collection approach (58%). Among PASS with at least one objective related with assessment of drug utilisation, 58% leveraged data collection schemes already established for other purposes. More than two thirds of PASS (70%) focused on a single medicinal product as eligibility criteria (either patient exposure or prescribers of the medicinal product of interest), while broader exclusion criteria were less frequent.

Among the 57 available protocol documents, only one third (33%) mentioned a comparator, such as another medicinal product, a non-exposed group or external data sources. All 57 PASS included at least one European country.

The majority of the 18 available protocols in which at least one objective was to assess effectiveness of RMM did not specify how success of those measures would be ascertained. One third (33%) of these PASS aimed exclusively to assess effectiveness of RMM and were designed as cross-sectional studies using a questionnaire to assess knowledge and auto-reported behaviour.

The most common areas of the protocol referred as responsible for the rejection of the protocols by the PRAC were related to inadequate study design (37%) and concerns with study feasibility (30%) requiring evidence that bias and limitations were adequately considered. The comments corroborate the general insight that the there was a limited level of detail in the PASS protocols.

PRAC protocol assessment metrics were estimated among 37 imposed PASS considered approved. The results suggested a decrease in the median number of rounds of review from 3 to 2 and an average decrease of 6 months in overall review time between the first and the third year of the review.

Discussion

This was the first comprehensive characterisation of the PASS protocols submitted to the PRAC during the first three years under the new Pharmacovigilance legislation.

Overall, the results showed that despite the unprecedented level of transparency achieved, which made this study possible, there is still room for improvement in the level of information provided by regulators and MAHs. An increased publication of the outcomes of PRAC assessment and more adherence to the EU PAS Register, would increase the pool of knowledge available to further improve PASS.

It was also evident that there is and some lack of communication between different stakeholders, which may be worsened by the lack of uniform terminology. The limited level of detail in the protocols is not in line with good pharmacoepidemiology and good pharmacovigilance practices (GPP and GVP), both emphasising the need to include details on the reasoning behind the methodological decisions and feasibility considerations.

The recognition of the singularity of PASS, as pharmacoepidemiological studies that have a specific mission within the medicinal products' RMPs, calls for alignment of different parties and cross-pollination of different skills, including qualitative and quantitative approaches and combined study designs, to tailor the best approach for each safety question.

Conclusion

Cross-functional collaboration and communication across stakeholders, higher levels of transparency and the use of a harmonised terminology would be key to develop innovative methods, customised for the singular and multifaceted needs of PASS, an example of which being the assessment of effectiveness of RMM. The anticipated result would be the implementation of best practices that will certainly contribute to a safer use of medicinal products.

Keywords: Post Authorisation Safety Study (PASS); Pharmacovigilance; Risk Management; Pharmacoepidemiology; Pharmacovigilance Risk Assessment Committee (PRAC)

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Resumo

Introdução

A nova legislação europeia de Farmacovigilância, implementada em 2012, visou o estabelecimento de um sistema mais proativo e eficiente para a deteção atempada e prevenção de problemas de segurança dos medicamentos. A obrigação de submeter Planos de Gestão do Risco com todos os pedidos de Autorização de Introdução no Mercado (AIM) de novos medicamentos reflete esta direção. Nestes documentos o titular de AIM deve apreciar o perfil de segurança conhecido e desconhecido do medicamento e ponderar a necessidade de implementar atividades de Farmacovigilância ativa e medidas de minimização do risco para proteção da saúde pública.

Os estudos de segurança pós-autorização (*Post Authorisation Safety Studies, PASS*) são uma atividade de Farmacovigilância ativa cujo objetivo é identificar, caracterizar ou quantificar o perfil de segurança de um medicamento ou medir a eficácia das medidas de gestão dos riscos. Resultam da convergência entre a Farmacovigilância que define a missão e a Farmacoepidemiologia que fornece os métodos para o estudo. De acordo com a nova legislação, as autoridades competentes podem impor a realização de PASS como condições da AIM ou em sede de AIM concedida em circunstâncias especiais.

Outra novidade da nova legislação de Farmacovigilância foi a criação de um novo comité da Agência Europeia do Medicamento, o *Pharmacovigilance Risk Assessment Committee* (PRAC), que tem como objetivo avaliar todos os problemas de segurança de medicamentos ao nível da União Europeia e supervisionar todos os processos de Farmacovigilância que a legislação prevê. Como consequência dos esforços para aumentar a transparência das decisões e processos regulamentares, as minutas das reuniões mensais do PRAC são publicadas no website da Agência e listam todos os processos avaliados pelo PRAC, juntamente com um pequeno sumário das decisões tomadas em plenário. A disponibilidade destes documentos tornou possível a identificação dos protocolos dos PASS submetidos para avaliação do PRAC desde a implementação da nova legislação em Julho de 2012.

A presente dissertação teve como objectivo a caracterização exaustiva dos protocolos dos estudos PASS submetidos ao PRAC durante os primeiros três anos da nova legislação de Farmacovigilância, descrevendo o âmbito e a metodologia dos estudos em várias vertentes. Pretendeu-se também reflectir sobre o nível de informação que se encontra publicamente disponível.

Métodos

Foram revistas todas as minutas das reuniões mensais do PRAC entre os períodos de Julho 2012 e Julho 2015 de modo a identificar cronologicamente todos os protocolos de PASS submetidos para avaliação do PRAC durante os três primeiros anos da nova legislação de Farmacovigilância.

Para complementar a informação disponível nas minutas, foram consultados os Relatórios Públicos Europeus de Avaliação dos medicamentos em estudo, disponíveis no website da Agência, de forma a identificar o contexto regulamentar na origem do PASS. Por outro lado, foi também efetuada uma pesquisa no registo eletrónico de estudos de pós-autorização mantido pelo *European Network of Centres for Pharmacoepidemiology and Pharmacovigilance* (ENCePP) para obter informações mais detalhadas sobre a metodologia do estudo incluindo os próprios documentos dos protocolos que, estando disponíveis, providenciaram uma fonte de informação mais detalhada e exata.

O número de rondas de revisão a que os protocolos foram submetidos, assim como a duração do processo desde a primeira submissão do protocolo até à aprovação do mesmo, foram calculados para os protocolos considerados autorizados no fim do período em análise. Na ausência de informação sobre o resultado da última avaliação de um determinado protocolo, foi assumido que o protocolo fora aprovado quando se encontrava inserido no registo eletrónico do ENCePP ou quando o protocolo não fora novamente mencionado nas minutas do PRAC durante mais de um ano até Julho de 2015.

Foram utilizadas estatísticas descritivas e análises bivariadas recorrendo ao teste de qui quadrado com nível de significância de 5%.

Resultados

Da revisão das minutas das reuniões mensais do PRAC entre Julho de 2012 e Julho de 2015 foram identificados 189 protocolos de PASS, de um total de 353 submissões para avaliação pelo comité. O resultado da avaliação pelo PRAC estava disponível em apenas cerca de um terço (30%) das 353 avaliações. Somente metade dos 189 PASS (49%) tinha sido inserida no registo eletrónico do ENCePP até Julho de 2015.

A maioria dos 189 PASS (58%) dizia respeito a novas AIMs. Cerca de um terço (31%) dos 189 PASS foram impostos pelas Autoridades Regulamentares.

A maior parte dos PASS incluía pelo menos um objetivo relacionados com a investigação de riscos ou ausência dos mesmos (74%), enquanto cerca de um terço (34%) continha pelo menos um objetivo relacionado com a avaliação de padrões de utilização do medicamento, e um quarto (25%) inseria pelo menos um objetivo relativo a avaliar a efetividade de atividades de minimização de risco. Cerca de um terço dos PASS (31%) combinava objetivos de pelo menos duas destas categorias.

A grande maioria dos estudos PASS apresentava um desenho longitudinal (81%). No entanto, a maioria dos estudos com pelo menos um objetivo relacionado com avaliação da efetividade das medidas de minimização de risco (56%) tinha um desenho transversal. Constatou-se que um número ligeiramente superior de PASS (58%) tinha por base a recolha de dados primários (i.e. informação recolhida *de novo* para o estudo). Observou-se um padrão inverso entre os estudos com pelo menos um objetivo relativo à avaliação de padrões de utilização do medicamento dado que a recolha de dados em 58% destes estudos era baseada em fontes secundárias. No total, mais de dois terços (70%) dos estudos visavam a inclusão de uma população exposta exclusivamente ou prescritora do medicamento em avaliação. Verificou-se que os estudos com critérios de inclusão mais abrangentes, tais como outros medicamentos ou todos os doentes com determinada patologia, eram mais raros.

A análise mais detalhada dos 57 protocolos disponíveis revelou que apenas um terço (33%) dos estudos referia um comparador (quer outro medicamento ou ausência do medicamento em estudo quer fontes externas) e que todos os PASS planeavam a inclusão de pelo menos um país europeu.

Entre os 18 protocolos disponíveis de PASS com pelo menos um objetivo relativo à avaliação da efetividade das medidas de minimização do risco, a maioria não referia concretamente a forma como o sucesso das mesmas seria avaliado. Um terço desses protocolos (33%) visava exclusivamente investigar a efetividade dessas medidas através da aplicação de um questionário para avaliar o conhecimento e o comportamento auto-reportados.

As áreas dos estudos referidas mais frequentemente como responsáveis pela rejeição dos protocolos pelo PRAC estavam relacionadas com aspetos do desenho do estudo (37%) e de exequibilidade (30%), sendo necessárias considerações adicionais para demonstrar que eventuais viés e limitações tinham sido adequadamente ponderados. Estes comentários corroboram a observação geral de que o nível de detalhe incluído na maioria dos protocolos era escasso.

A análise das métricas relativas ao número de revisões de cada protocolo e duração total do processo de revisão dos 37 protocolos com evidência de terem sido aprovados, sugeriu uma evolução positiva entre os PASS submetidos pela primeira vez no primeiro ano em análise e aqueles submetidos pela primeira vez no terceiro ano (redução de uma mediana de 3 para 2 revisões por protocolo e uma redução média de 6 meses na duração total de revisão).

Discussão

Este trabalho permitiu descrever pela primeira vez os protocolos de PASS submetidos ao PRAC durante os três primeiros anos da nova legislação de Farmacovigilância.

Embora o facto deste trabalho ter sido possível reflita um nível de transparência sem precedentes, o nível de informação disponível é ainda limitado. Uma maior partilha das recomendações do PRAC resultantes da avaliação dos protocolos, uma maior adesão ao registo de PASS no portal eletrónico do ENCePP e o desenvolvimento de uma terminologia mais consistente, será importante para a partilha de boas práticas de modo a fomentar o desenvolvimento de PASS mais robustos.

Por outro lado, o limitado nível de detalhe presente nos protocolos sugere alguma inconformidade com as boas práticas de Farmacoepidemiologia e Farmacovigilância, as quais enfatizam a fundamentação e descrição crítica dos métodos selecionados. Adicionalmente a articulação entre os objetivos dos PASS enquanto medidas adicionais de Farmacovigilância e os métodos empregues poderá beneficiar de uma maior colaboração entre os peritos de diferentes áreas.

Conclusão

Uma maior colaboração e partilha de informação e conhecimento entre diferentes áreas levará ao desenvolvimento de novos métodos customizados para as necessidades singulares dos PASS, tais como metodologias multidisciplinares direccionadas para avaliar a efetividade das medidas de minimização do risco. O resultado, contribuirá certamente para o estabelecimento de processos mais robustos e levará ao uso mais seguro dos medicamentos

Palavras-chave: Estudo de Segurança Pós Autorização; Legislação de Farmacovigilância; Gestão do Risco; Farmacoepidemiologia; Pharmacovigilance Risk Assessment Committee (PRAC)

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List of Abbreviations

ADR	Adverse drug reaction
ATC	Anatomical Therapeutic Chemical
CAP	Centralised Authorisation Procedure
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
CPRD	Clinical Practice Research Datalink
DUS	Drug Utilisation Study
EC	European Commission
EMA	European Medicines Agency
EMR	Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPAR	European Public Assessment Report
EU	European Union
EU-ADR	Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge Project
EU PAS	European Union electronic Register of Post-Authorisation Studies
EU-PATI	European Patients' Academy
FDA	Food and Drug Administration
GePaRD	German Pharmacoepidemiological Research Database
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professionals
HSD	Italian Health Search Database
ICH	International Conference on Harmonisation
IMI	Innovative Medicines Initiative
IPCI	Interdisciplinary Processing of Clinical Information
IQR	Interquartile Range
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
OECD	Organisation for Economic Co-operation and Development
PASS	Post-Authorisation Safety Studies
PCORI	Patient-Centered Outcomes Research Institute
PIL	Patient Information Leaflet

PMDA	Pharmaceuticals and Medical Devices Agency
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RMM	Risk Minimisation Measure
SD	Standard Deviation
SmPC	Summary of Product Characteristics
THIN	The Health Improvement Network
US	United States
WHO	World Health Organisation

Preamble

The historical background in which the current project is inserted is one of alliances. On the one hand, Post-Authorisation Safety Studies (PASS) sits in the intersection between Pharmacoepidemiology and Pharmacovigilance. On the other hand, the understanding of PASS as a public health enabler stands under the umbrella of Regulatory Science which bridges science and society, as PASS are also a product of a socioeconomic context at a given period of time.

The connection between Pharmacovigilance and Pharmacoepidemiology has its roots on drug safety tragedies. The infamous thalidomide crisis fostered the development of Pharmacovigilance systems and transformed the drug development framework, as new methodologies, such as the ones from the epidemiology field were applied to study the benefits and risks of medicinal products used in real-world practice.

However, both areas followed distinct paths. Within the pharmaceutical industry, the focus had traditionally been on clinical trials to provide evidence to support licensing while having Pharmacovigilance as a post marketing lighthouse to detect spontaneous case reports. Conversely, Pharmacoepidemiology developed mainly in the academic and institutional research contexts as a response to the recognised need to understand the effects of medicinal products in the broader population complementing the information from the clinical trials.

The convergence between the two fields was facilitated by the incorporation of Risk Management principles in regulations over the past decade. In the framework of a pharmaceutical Risk Management system, the Marketing Authorisation Holders (MAHs) need to proactively consider all the evidence about the medicinal product (what is known and unknown about the targeted disease, the product efficacy and safety and the expected target population) from pre-marketing research and literature sources. By critically assessing all this information, the MAH establishes the safety concerns for which Pharmacovigilance activities (collection of data to identify and characterise risks) and Risk Minimisation Measures (RMM) (actions to mitigate the harms) may need to be implemented to optimise the benefit-risk of their medicinal products. In order to close the loop, it is then critical that the MAHs also assess the effectiveness of the Risk Management system in place.

It is in the process of planning which activities will best address the established safety concerns that the pharmacoepidemiological methods emerge as pertinent tools to answer the questions formulated in the Risk Management process. Within this context, PASS are a perfect reflection of the bridge between Pharmacovigilance and Pharmacoepidemiology and its incorporation in the regulatory pharmaceutical practice.

PASS also represent a clear shift from the traditional passive collection of safety data, by providing the means to proactively investigate the most important safety concerns, assessing pattern of drug use deemed critical to monitor the safe utilisation of the product and also, assessing the effectiveness of RMM.

The European Union (EU) 2010 Pharmacovigilance legislation, implemented in 2012, further endorsed these activities by establishing legal mechanisms to enforce the conduct of Risk Management activities. As a consequence, it is necessary to submit a Risk Management Plans (RMP) with each application for a new marketing authorisation.

Four years have passed since the new legislation was implemented. It is now a good time to assess what was achieved so far. An initiative from the European Medicines Agency (EMA) is underway to measure the impact of Pharmacovigilance activities at EU and Member States level. This is a complex task that would need a collaborative approach among all the stakeholders involved.

This work aims to make a contribution to this important goal by providing a deep dive into PASS submitted during the first three years of the new legislation. The review would not have been possible without the availability of public data sources, the existence of which reflects another cornerstone of the new Pharmacovigilance legislation, an increase in transparency and communication from the EMA.

Introduction

1 A Note on Regulatory Science

As this work can be viewed under the umbrella of Regulatory Science, it is opportune to start with an introduction to this concept.

According to Irwin *et al*, "the study of regulatory science can provide an insight into the changing conditions of scientific practice-and especially the operation of science within an area of industry-governmental-academic relations which is also pressured by the need to make potentially far-reaching decisions (in terms of both public health and economic costs) on a regular basis."(1)

In the healthcare field, the need for this new branch of science has evolved and the last decade witnessed the integration of Regulatory Science in the core activities of key regulators such as the EMA, the United States (US) Food and Drug Administration (FDA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).(2-4)

The EMA defines Regulatory Science as the "range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine. It encompasses basic and applied medicinal science and social sciences, and contributes to the development of regulatory standards and tools".(3)

Among the numerous fields of application of this science to the pharmaceutical arena, Pharmacovigilance is one prominent field given the major changes introduced by the 2010 legislation.

A deep dive into the history of Pharmacovigilance and of drug development regulations will reveal how the new legal framework has implications that go much beyond the Pharmacovigilance activities, appealing for a change in the development, assessment and use of pharmaceutical products.

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2 The History of Pharmacovigilance

2.1 Early Beginnings

Early publications of the New England Journal of Medicine at the beginning of the 19th century described case reports of today's well known toxic effects of arsenic and mercury; they revealed the uncertainty of whether the effects were caused by the chemicals, as a manifestation of the underlying disease, or even, a prognostic sign of the substance's efficacy. It was not until the beginning of the 20th century that the safety of the medicinal products was fully appreciated.(5)

The history of pharmaceutical regulation and Pharmacovigilance has been always shaped by crisis: impactful adverse drug reactions (ADRs) to medicinal products demanding a reaction from the system.

In the early days of the 20th century, the manufacturers were not required to demonstrate efficacy or safety of the medicinal products launched into the market. The first regulatory reaction to drug safety incidents may have been implementation of the Pure Food and Drug Act by the FDA in 1906, in response to excessive misbranding of food and medicinal products. These rules required manufacturers to accurately label the contents of their medicinal products. (5, 6)

A couple of decades later, in 1937, one of the first episodes with high media impact in the tragic history of drug safety took place in the US, when more than 100 people died after being exposed to

a new antibiotic, sulphanilamide which was dissolved in diethylene glycol, a lethal solvent. The manufacturer of that product was only charged for misbranding as there was no requirement to test or even provide evidence that literature had been dully searched before the product was launched. (5) As a consequence, stricter regulation was implemented through the 1938 Food, Drug, and Cosmetic Act. It imposed the requirement for manufacturers to submit evidence of preclinical toxicity testing and drug safety data to the FDA before the launch of a medicinal product.(6)

It was almost 30 years later, in 1962, that the world's most infamous tragedy in the history of human medicines occurred, the thalidomide disaster. Thalidomide was launched as a sedative and antiemetic medicinal product to relieve the discomfort of pregnant women. More than 10,000 children worldwide were born with phocomelia, a congenital disorder involving malformation of the limbs found to be an ADR to thalidomide. This tragedy was the main driver for legislative reforms in many health systems and triggered the first systematic international efforts to address drug safety issues.(7)

The Sixteenth World Health Assembly (1963) adopted a resolution that reaffirmed the need for rapid dissemination of information on ADRs. This led to the creation of the World Health Organisation's (WHO) Pilot Research Project for International Drug Monitoring in 1968. The purpose of this project was to develop an international system to detect previously unknown or poorly understood ADRs. As a consequence, WHO advocated the establishment of guidelines and national centres for drug monitoring that would contribute to the international system.(7) It was the official birth of Pharmacovigilance.

Pharmacovigilance is defined by the WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".(7) The goals of Pharmacovigilance are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the benefit-risk profile of medicines. (7)

From these beginnings, systems were developed in the different countries for the collection of individual case histories of ADRs and their evaluation. In the early 1980s, the Council for International Organizations of Medical Sciences (CIOMS), in close collaboration with the WHO, launched its programme on drug development and use. CIOMS provided a forum for policy makers, pharmaceutical manufacturers, government officials and academics to make recommendations on the communication of safety information between regulators and the pharmaceutical industry. (7)

Despite the more stringent process for drug regulation, a series of major ADRs leading to the withdrawal of medicinal products kept occurring. Several examples of medicinal products and ADRs responsible for their removal from the market can be cited, such as: proctalol and oculomucocutaneous syndrome cases (1976); phenacetin and nephropathy (1980); benoxaprofen and jaundice (1982); tolcapone and trovafloxacin and hepatotoxicity (1998, 1999); cisapride and cardiac arrhythmias (2000); cerivastatin and rhabdomyolysis (2001); rofecoxib and valdecoxib and thhrombotic events and cardiovascular and cutaneous disorders, respectively (2004, 2005); sibutiramine and cardiovascular disorders (2010), among others.(8, 9)

2.2 Towards the Need for Real-world Evidence: a Parallel with Clinical Research Developments

It is interesting to note that the most infamous tragedy in the history of drug safety has also significantly shaped the history of drug research.

The US Kefauver–Harris Amendments (1962) changed the medicinal products' legislation as a consequence of the thalidomide disaster regardless of the fact that this medicinal product had never been approved for use there. The changes strengthened the requirements to submit preliminary evidence of drug safety, requiring extensive preclinical pharmacologic and toxicological testing even before a medicinal product could be tested in humans. In addition, clinical testing had to demonstrate "substantial evidence that the drug would have the effect it claims to have". "Substantial

evidence" was defined as "adequate and well controlled investigations, including clinical investigations".(6)

In Europe, as reaction to the thalidomide disaster, the First European Directive, known as 65/65/EEC, was enacted by the Council of the European Economic Community in 1965 stating that no medicinal product could be placed into a Member State's market unless authorisation had been issued by the competent authority in that Member State. This included the need to submit results of physico-chemical, biological or microbiological tests, pharmacological and toxicological tests and clinical trials.(10)

In the following years, the demonstration of a positive benefit-risk profile through randomised clinical trials has been the state of the art method to gather the proof required to submit to the regulators when applying for a new marketing authorisation.(8) The attention was turned to patients' rights and protection rather than the scientific methodologies.

The Helsinki Declaration was published in 1964, adding to the ethical principles embedded in the code of Nuremberg from 1949. Later, in 1978 another statement of ethical principles was published, the Belmont Report. They established principles regarding moral, ethical, and legal requirements of research involving human subjects including the right to give informed consent, the precedence of the well-being of individual research subjects over the interests of the research and the following principles: (1) respect for persons and their autonomy; (2) beneficence (maximize possible benefits and minimize possible harms); and (3) justice (fairness in the selection of subjects for clinical research).(11)

The following historical episodes of interest in the context of this work are the first manifestations of patients' voice in the context of clinical research. Events in the 1980s sharpened the rights of research subjects as movements from society started to make pressure on the focus and priorities of research. As examples, acquired immune deficiency syndrome activists claimed for earlier access to innovative drugs and advocates for women's health began to call for more focused research on health problems that directly concerned their lives, such as breast cancer and hormonal replacement therapy.(12)

The active movements from society, requesting to be an active participant on clinical research decisions, coincided with the economic changes of the 1990s, frequently known as "globalisation", and the need for a different mindset from the research community, to promote collaboration and common grounds for research.(8)

The industry, at that time, was becoming more international. However the different technical requirements from country to country were such that, many time-consuming and expensive test procedures needed to be replicated in order to meet the requirements of individual markets. The urgent need to rationalise and harmonise regulation was impelled by concerns over rising costs of research and development and the need to meet the public demand for early access to innovative treatments. This led to the creation of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 1990 to harmonise regulatory requirements between Europe, US and Japan. ICH's mission has been to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.(13)

In the context of clinical research, ICH developed the Good Clinical Practices (GCPs) to provide an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials.(14) In the context of Pharmacovigilance, the ICH has published a great number of documents setting standards for safety (clinical and non-clinical).(13)

By this time there was an increased harmonisation of procedures to develop and register new medicinal products and an increased access to medicinal products and knowledge. However, the healthcare professionals (HCPs), which are the clinical decision makers, and the patients, which are the users of the medicinal products started demanding more evidence of the most appropriate treatments. A campaign launched in the 1990s, by a group known as the Evidence-Based Medicine Movement, advocated the need to enhance the evidence on which medicine was practiced to improve

the outcomes of diagnosis and treatment. This highlighted that there could be a gap between the evidence of the adequate benefit-risk profile of medicinal products required by the regulators and the clinical decisions made by the HCPs based on their opinion and clinical judgement.(15)

The concept of evidence-based medicine considered a hierarchy of reliability of evidence for clinical decision-making with randomised clinical trials at the top.(15) Therefore, in order to implement evidence-based medicine in clinical practice, results of the clinical trials needed to be available to the healthcare community. This propelled several initiatives and guidelines to put pressure on the industry and regulators to publish the results of research, by incentivising the registration of studies in public registries, peer reviewed scientific journals or scientific congresses.(16)

Despite the major contributions of evidence-based medicine to the publication of evidence and to the development of clinical guidelines, it is also acknowledged today that, the strong focus on objective data from clinical trials and guidelines has some boundaries. (8, 15)

Clinical trials are subject to limitations such as:

- Lack of representativeness of patient populations: the populations studied in clinical trials are limited in number and quite homogeneous as these studies have clearly defined eligibility criteria, typically excluding more vulnerable patients such as those severely ill, those with comorbidities and concomitant treatments, paediatric patients, elderly patients and pregnant women.
- Long-term therapy: The clinical trials have a limited duration which restricts the knowledge about benefits and risks to short-term treatment. Some ADRs may manifest after long periods of use or under certain disease characteristics which may change over time.

Therefore, despite the unquestionable strengths and needs for clinical trials, an over-reliance on these studies has proved to be insufficient.(15)

Scurti *et al* suggested that the following statement is conceptually widely acknowledged but easily disregarded: “drugs (and their use) cannot be considered primarily *objects* to be studied *per se*, but rather as *tracers* of health needs and policies, prescribing attitudes, and market exigencies i.e. of the way medicine and public health are perceived and pursued in society”.(8) Therefore, the author suggested that an evaluation technique or strategy centered on medicinal products outside their context of use may not adequately reflect the “registered” benefit-risk profile of a medicinal product to the real-world patients and populations.

By citing Archie Cochrane (1972), Scurti *et al*, synthesised the need for a renewed culture and practice of Pharmacovigilance: “he [Archie Cochrane] anticipated a renewed culture and practice of Pharmacovigilance with the present awareness of trials and epidemiology, efficacy and effectiveness, risk management and rights of patients and populations as a continuum of complementary tools, strategies, and actors to make institutions and health care systems accountable to and in dialogue with society”.(8)

As will be seen further below, these observations are intimately related with the changes implemented in the 2010 European Pharmacovigilance legislation and with the need for real-world evidence in general.

2.3 Towards a Proactive System

The limitations of the clinical trials in predicting the safety of medicinal products in the “real-world” highlight the need for collection of safety data throughout the life cycle of a medicinal product. This has been recognised since the creation of Pharmacovigilance in the 1960s but, at the beginning of the new millennium, the practice of Pharmacovigilance was still mainly based on the detection of spontaneous ADRs and reactive actions to signals or alerts flagged through this system.

However, in parallel in an academic or instructional research setting, the needs to develop systematic approaches to study the effects of drug use in large number of patients motivated the use of Epidemiology methods and the creation of a new discipline, Pharmacoepidemiology. The term

Pharmacoepidemiology derived from “pharmaco” and “epidemiology” bridging clinical pharmacology and epidemiology by applying the methods of epidemiology to the content area of clinical pharmacology.(6)

In fact, during the WHO Consultation Meeting in 1971, an important landmark from the early days of Pharmacovigilance, it was recognised that for a Pharmacovigilance system to be effective, it would require the systematic monitoring of populations, review of health statistics and of drug utilization data, and that effective analysis of input data anticipate the need for systematic data collection.(7)

Therefore, remarkably, the need to act upon the incidence of ADRs was a main contributor to both the birth of Pharmacovigilance (studying ADRs at case level) and Pharmacoepidemiology (studying ADRs at population level).

The following decades saw the publication of the first pharmacoepidemiologal studies and the creation of the first dedicated Pharmacoepidemiology research units.(6) A recent publication even considers that from a “historical perspective, observational studies have shaped second-generation Pharmacovigilance”, citing examples of studies from the 1970s that unveiled safety concerns by linking voluntary reporting data to consumption data, followed by case population methods, case-control methods and, in the late 1970s-1980s, the first studies linking prescription records with individual patient files.(17) However, until recently, observational research mainly evolved outside the context of industry and regulators, which, as explained above, for decades continued to privilege the conduct of interventional clinical trials.(6)

The creation of the International Society of Pharmacoepidemiology (ISPE) in 1984 and of the European Society of Pharmacovigilance in 1992 marked the formal introduction of Pharmacovigilance into the research and academic world, as well as its increasing integration into clinical practice. Specialist medical journals have appeared, and a number of countries have implemented active surveillance systems to complement conventional methods of drug monitoring.(6, 7) Therefore, outside the Pharmaceutical Industry, Pharmacoepidemiology was generating new evidence in the interests of drug safety.

It was not until the new millennium that regulatory changes reflected the need for industry and regulators of medicinal products to supplement the existent methods with more proactive strategies. It was recognised that stricter assessment before drug approval and more intensive post-marketing surveillance through additional post marketing activities such as randomised clinical trials, observational studies and use of registries could have prevented or limited previous incidents.(18)

A more proactive approach towards the identification and quantification of safety concerns was targeted by the ICH guideline on Pharmacovigilance planning (ICH E2E, 2004) which introduced the notion of Risk Management programs.(19) A new community legislation was implemented in 2005, introducing additional tools to complement existing legislative requirements. These included the submission of RMPs in the context of new/significant change in a marketing authorisation on request from a competent authority or by MAH/applicant initiative.(20)

RMPs (covered in more detail in *Introduction Section 4*) reflect what is known and unknown about a medicinal product and proactively plan activities to increase knowledge of the safety specification and to minimise risks. PASS are among those activities aiming to investigate uncertainties. PASS (covered in more detail in *Introduction Section* 5) employ pharmacoepidemiological methods at Pharmacovigilance’s service and represent the realisation of the needs to bridge Pharmacovigilance and Pharmacoepidemiology and integrate them in the regulatory decision-making armamentarium.

This chapter described the birth of Pharmacovigilance and its intertwined relations with regulatory changes in clinical research. From the thalidomide disaster, regulations for clinical research and Pharmacovigilance followed separate pathways but demand from the society, HCPs, regulators and industry created the need for a proactive collection of real-world evidence, for instance, through the inclusion of Risk Management and Pharmacoepidemiology in the toolkit for Pharmacovigilance. The following chapter will further detail the most recent changes in the regulatory framework.

3 New Pharmacovigilance Legislation

3.1 The Need for a Regulatory Change

The growing awareness that the scope of Pharmacovigilance should be extended, led to the initiation in 2004, of an assessment on the EU Pharmacovigilance system. On December 2008 the European Commission (EC) proposed legislative changes to amend the European legislation on Pharmacovigilance.(21) The report published in 2008 is a good starting point to understand the rational for the major change in Pharmacovigilance regulation to be witnessed.(22)

This report cited the following estimates of public health burden of ADRs from the medical and scientific literature:

- 0.12%-0.22% of hospital admissions resulted in death due to an ADR corresponding to100,800-197,000 deaths annually in the EU (the fifth most common hospital cause of death);
- 3%-10% of hospital admissions were caused by ADRs corresponding to 2.5-8.4 million annually in the EU;
- 2.1%–6.5% of hospitalised patients suffer an ADR, corresponding to 1.8-5.5 million annually in the EU;
- ADR-related costs other than those caused by hospitalisation were estimated at €63.2 billion annually in the EU;
- €79 billion represented a reasonable estimate of the total societal cost of ADRs occurring in the EU.

In addition, it was suggested that a weak Pharmacovigilance system adversely impacted innovation based on the assumption that, if regulators are confident in the Pharmacovigilance system they will more likely allow a product into market and this is of crucial benefit to patients with unmet medical needs.

It was found that, despite the previous introduction of proactive toolkits such as RMPs, they were not being effectively used. Several activities proposed in the RMPs were not considered adequate for handling the risks of the medicinal products and did not prevent the occurrence of the safety concerns which, for instance, in the case of rimonabant led to its withdrawal couple of years after the RMP was in place.(18) In addition, although EMA was recommending the conduct of PASS, several companies were not implementing those activities.(18, 23) It was considered that under the regulatory framework at that time, compliance by the company with the measures in a Risk Management system would remain problematic as the legal requirement was to describe the measures and not to conduct them, i.e. there was no legal basis to enforce those measures.(23)

On a different perspective, the Member States were not consistently implementing the recommendations made by the EMA's Pharmacovigilance Working Party.(21) In addition, the conclusions of some safety issues being discussed at this Working Party were never made public which exacerbated the discrepancy in decision-making and regulatory action. As a consequence to

the lack of harmonisation regarding Pharmacovigilance requirements, there was an increased the regulatory burden on the industry.(22)

Moreover, the EU committees responsible for Pharmacovigilance did not systematically interact with HCPs and patients which did not have a voice in decision-making on safety issues. Thus, decisions could be taken without all the relevant experience and information being made available. This lack of inclusiveness of stakeholders in the processes of Pharmacovigilance, coupled with the lack of transparency was considered a contributor to a lack of trust by patients in the regulation of medicinal products and, more generally, in the pharmaceutical industry.(21, 22)

These findings reflect the socioeconomic, cultural and scientific challenges and changes observed in the history of medicinal products described in *Introduction Section* 2 and culminated in a major regulatory change to enforce a more proactive, transparent and inclusive Pharmacovigilance system.(22)

3.2 The New EU Pharmacovigilance Legislation

The preparation of the new EU Pharmacovigilance legislation took approximately nine years. Implemented in July 2012, the 2010 EU Pharmacovigilance legislation was the biggest change to the regulation of human medicines in the EU since 1995.(24) A new Directive and Regulation were adopted by the European Parliament and the Council of Ministers in December 2010: Directive 2010/84/EU and Regulation (EU) No 1235/2010 amending Directive 2001/83/EC and Regulation (EC) No 726/2004, respectively.(25-28) The legislation was accompanied by the Commission Implementing Regulation (EU) No 520/2012 providing details on the operational implementation of the legislation.(29) In October 2012, the Pharmacovigilance legislation was further amended by Directive 2012/26/EU and Regulation (EU) No 1027/2012 which provided strengthened measures for monitoring medicines safety and carrying out reviews at a European level.(30, 31)

The EMA and Member States have also produced, in consultation with relevant stakeholders, good Pharmacovigilance practice guidelines (GVP) for the conduct of the different Pharmacovigilance activities and replaced the Volume 9A.(32),(20)

The implementation of the legislation has been a complex process with significant changes in the EMA's responsibilities and significant implications for applicants and MAHs. The EMA worked with the EC, the national competent authorities and a wide range of stakeholders including patients, HCPs and industry, to ensure effective implementation and operation of the new Pharmacovigilance rules. Priorities were set so that public health activities were implemented first, followed by transparency and communication activities and lastly by simplification of activities.(33, 34)

The new EU Pharmacovigilance legislation aimed to offer better promotion and protection of public health through the following objectives(24):

- The collection of better data on medicines and their safety;
- Rapid and robust assessment of issues related to the safety of medicines;
- Effective regulatory action to deliver safe and effective use of medicines;
- Empowerment of patients through reporting and participation;
- Increased levels of transparency and better communication.

3.3 European Regulatory Stakeholders

3.3.1 The Role of the European Medicines Agency (EMA)

The EMA has a central role in the EU system, co-ordinating the activities and providing technical, regulatory and scientific support to the Member States and industry. It also provides the essential infrastructure required by the system and has specific tasks laid down in the legislation in the conduct of Pharmacovigilance including signal detection for medicinal products authorised through a centralised authorisation procedure (CAP).(35)

The new EU Pharmacovigilance legislation established an additional scientific committee, the Pharmacovigilance Risk Assessment Committee (PRAC), whose members include experts in Pharmacovigilance and regulation working within the national competent authorities of the Member States (plus Iceland and Norway), representatives of patients and HCPs, and scientific experts in areas such as epidemiology, signal detection, biological medicines and risk communication. The PRAC meets monthly and is responsible for the assessment of safety issues at EU level and for the monitoring of many of the Pharmacovigilance activities foreseen in the legislation. It works closely with other scientific committees, especially the Committee for Medicinal Products for Human Use (CHMP) which leads on CAPs, and also with the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), a body representing the national regulators of the European Economic Area, which leads on many issues relating to nationally authorised medicines.(35)

3.3.2 Key Interactions between PRAC, CHMP and CMDh

The different PRAC outputs depend on the existence or not of a formal decision-making phase as defined in the Pharmacovigilance legislation. For the processes with a formal decision-making phase, the PRAC output is a recommendation and applies to safety referrals, single assessment of Periodic Safety Update Reports (PSURs) and PASS assessments. These recommendations are transmitted to the CHMP when a procedure concerns at least one CAP. The PRAC recommendations lead to CHMP Opinions which are then assessed by the EC which is responsible for issuing a decision. When there is no CAP involved, the recommendations are transmitted to the CMDh leading to a CMDh consensus that the Member States shall follow, or a CMDh majority that leads to an EC Decision.

Where the position/opinion of the CHMP/CMDh differs from the recommendation of the PRAC, the CHMP/CMDh shall attach a detailed explanation of the scientific grounds for the differences along with the recommendation. Figure 1 below depicts these interactions.

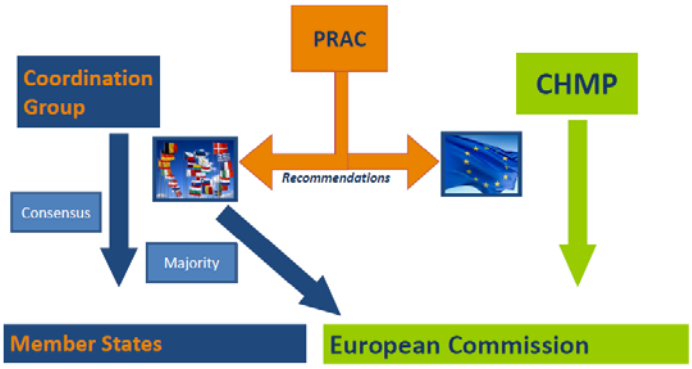

Figure 1 – Interaction between the different European Medicines Agency (EMA) committees and the European Commission (EC). Source: Arriegas M). Safety, Risk Management and Pharmacovigilance. [Presentation] Training Programme in Pharmaceutical Medicine. Universidade de Aveiro. Lisboa. March 2013.

3.3.3 The Role of the Member States

The national competent authorities supervise the collection of information on suspected ADRs of medicinal products, particularly spontaneous reports from patients and HCPs. Equally, they provide much of the resource base and knowledge needed to assess signals of possible emerging safety issues. Member State experts also take the lead (as the so-called rapporteur and co-rapporteur teams) in evaluating and analysing data when a safety issue is assessed at the European level (a referral). They play a critical role in tailoring and communicating safety messages to HCPs, patients and the public at a national level.

Member States also maintain the inspectorates that carry out the work of ensuring that the medicinal products marketed in the EU are manufactured appropriately and are of suitable quality, the Pharmacovigilance systems of the industry are working as they should, and checking that the clinical studies that provide the evidence of the safety and effectiveness of medicines are performed in line with appropriate standards.(36)

3.3.4 The Role of the Commission

The EC is the competent authority for CAPs and supplies the legal authority that underpins the EU Pharmacovigilance system. It provides the legislative framework needed to carry out its functions in the most efficient way.

This chapter described the objective and governance model of the current EU Pharmacovigilance legislation. The following chapters will now cover in more detail the object of interest of this study by starting with a description of pharmaceutical Risk Management to explain the overarching structure in which PASS play a very important role. The understanding of Risk Management is essential to understand that PASS, which use Pharmacoepidemiological methodologies, have features that make them different from other Pharmacoepidemiology studies as they have a mission to accomplish within the strategy planned for a given medicinal product. This mission can be either to act as additional Pharmacovigilance activities and/or as tools to assess effectiveness of RMM.

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4 Risk Management

According to the Pharmacovigilance legislation a "Risk related to the use of a medicinal product" is "any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment".(27)

Typically, a medicinal product has multiple risks, varying in terms of severity, effects on individual patients and public health impact. The successful identification of the most impactful ones (significant safety concerns) before the medicinal product is on the market allows for the planning and implementation of preventive or minimising strategies to mitigate them, thus optimising the benefit-risk profile of the medicinal product.(37)

However, not all actual or potential risks would have been identified at the time when an initial authorisation is sought and many of those associated with the use of a medicinal product will only be discovered and characterised after the medicinal product is on the market. For that reason, in addition to activities to prevent and minimise known and suspected risks, it is also important to consider activities to detect or further characterise risks for which there are still important uncertainties.(37)

Risk Management has three stages which are inter-related and iterative. The initial two comprise risk identification and characterisation and the third, minimisation or mitigation(37):

1. Characterisation of the safety profile of the medicinal product including what is known and not known;
2. Planning of Pharmacovigilance activities to characterise and identify new risks and increase the knowledge in general about the safety profile of the medicinal product;
3. Planning and implementation of risk minimisation and mitigation and assessment of the effectiveness of these activities.

Figure 2 below presents the steps of a Risk Management cycle representing the phased steps.

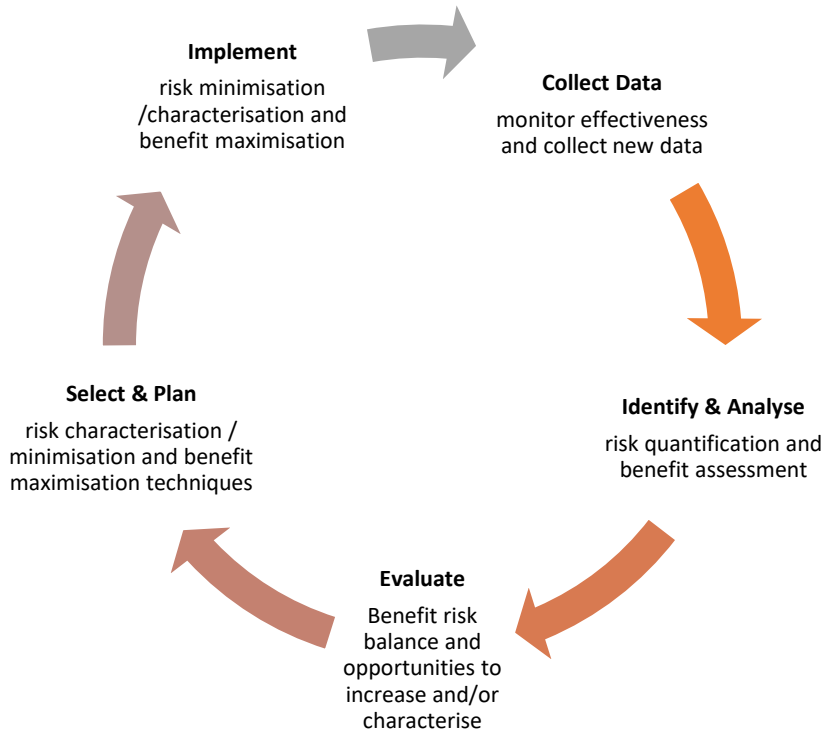

Figure 2 – The Risk Management Cycle. Source: European Medicines Agency. Guideline on good Pharmacovigilance practices (GVP): Module V – Risk Management systems (Rev 1). EMA/838713/2011 Rev 1.(37)

4.1 Risk Management Plan

As previously described, RMPs were introduced in the Pharmacovigilance guidelines in 2005 but there was no legal basis for implementing them. The new Pharmacovigilance legislation enforced the obligation to submit a RMP with all the applications for a new marketing authorisation, with a significant extension of indication, or if there is a public health concern.(37)

The RMP is the product of executing the three steps described above. In addition, the RMP is expected to be a live document, periodically updated as new knowledge about the risks and the benefits of the medicinal product arises from the post-marketing experience.(37)

Characterisation of the medicinal product safety profile(37)

When developing a RMP, the MAH need to reflect on what is known and unknown about the medicinal product taking into consideration the results of pre-marketing research (non-clinical and clinical studies) and also conducting extensive literature research on safety findings with medicinal products or patients with similar characteristics to those targeted by the medicinal product of concern. Therefore, the first sections of an RMP are dedicated to the identification and assessment of safety concerns (important identified risks, important potential risks and missing information).

According to GVP, each of those safety terms is defined as follows(38):

- An “identified risk” is “an untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest”;
- A “potential risk” us “an untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but this association has not been confirmed”;
- “Missing information” is a “gap in knowledge about a medicinal product, related to safety or use in particular populations which could be clinically significant”.

Risk Management activities should not contemplate all the identified and potential risks. Instead, they should focus the important safety concerns, which according to GVP are defined those that "could have an impact on the risk-benefit balance of the product or have implications for public health". What constitutes an important risk depends upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health.(38)

Failure to prioritise the safety concerns and target too many of them, could incorrectly flag a medicinal product for additional scrutiny, potentially lead to regulatory delays and limiting medicinal product uptake. Therefore it could affect the prescription patterns of the physicians, potentially leading them to not treat patients in great need of a certain medicinal product by choosing instead, alternatives with a poorer benefit-risk profile.(39-41)

Risk Identification and Characterisation(37)

Upon establishing the important identified/potential risks and missing information (safety concerns), the Applicant/MAH needs to reflect on whether there is need for additional Pharmacovigilance activities to further detect and characterise safety concerns.

Pharmacovigilance activities are post-marketing activities designed to detect, identify and characterise risks relating to the medicinal product. They can be grouped as routine and additional activities:(38)

- Routine Pharmacovigilance activities include the spontaneous collection, assessment and reporting of ADRs, signal detection, literature monitoring and submission of PSURs summarising the benefit-risk profile of the medicinal product throughout the product lifecycle including a summary of all Pharmacovigilance activities in place. The use of specific ADR follow-up questionnaires to obtain structured information on reported ADRs of special interest and collection of additional information of interest (e.g. recording of tests) would still be considered routine Pharmacovigilance activities, provided the tests were performed as routine practice and only the recording of the information is an additional requirement;
- Additional Pharmacovigilance activities are typically non-clinical studies, clinical trials or non-interventional studies. Situations when additional Pharmacovigilance activities are needed, can include for instance, a medicinal product intended for chronic, for which there is only evidence of short term follow-up data at the time of authorisation. Long-term follow-up of patients (e.g. in a cohort study) may provide additional reassurance on the long term effects of the medicinal product. PASS are additional Pharmacovigilance activities.

An efficient planning of the necessary Pharmacovigilance activities to characterise the safety profile of the medicinal product should be based on specific issues identified from pre- or post-authorisation data and from pharmacological principles. Therefore, an accurate *a priori* identification of significant safety concerns of a medicinal product minimises unanticipated ADRs and provides a focus for RMM in preventing the occurrence of the significant safety issues.

Risk Minimisation

The ultimate objective of risk identification and characterisation is the prevention or mitigation of safety concerns.

Risk minimisation is defined as "an intervention intended to prevent or reduce the probability of the occurrence of an ADR associated with the exposure to a medicine or to reduce its severity should it occur".(38)

The MAH should assess if RMM are required to address each safety concern. In practice, the RMM are public health interventions intended to optimise the benefit-risk balance of a medicinal product by guiding the use of medicinal product that support the provision of the right drug, at the right dose, at the right time, to the right patient and with the right information and adequate monitoring.(42)

RMM activities are classified as follows(37):

- Routine RMMs which include labelling such as, including information about the risks (appropriate dosing, contraindications, special precautions, known ADRs) in the Summary of Product Characteristics (SmPC) for HCPs and in the Patient Information Leaflet (PIL) for patients, respectively. Decisions on the distribution channels and ease of access to the product (prescription only or over the counter medicinal product), number of units per package are also typical routine RMM and for the majority of the medicinal products they are sufficient;
- Additional RMMs may be necessary to optimise the benefit-risk balance of a medicinal product when it is considered that routine measures are not sufficient. They may consist in extra communication and education for patients and HCPs (e.g. patient card, Direct Healthcare Professional Communication and educational materials), controlled distribution systems or pregnancy prevention programs (e.g. in order for the medicinal product to be prescribed the patient needs to show the negative results of pregnancy tests).

Key goals of RMM can be the appropriate patient selection to exclude high-risk patients from treatment, minimisation of the occurrence of ADRs or optimisation of outcomes by maximising benefits.(43)

It is well recognised that the successful implementation of additional RMMs requires contributions and compliance from all stakeholders, including MAHs, patients and HCPs. The performance of RMM in the healthcare systems requires an ongoing assessment to ensure that their objectives are fulfilled and that the measures in place are proportionate taking into account the benefit-risk balance of the medicinal product and the burden of those measures to the HCPs and the patients.(44)

4.2 Assessing Effectiveness of Risk Minimisation Measures (RMM)

Monitoring the effectiveness of RMM is an explicit requirement from Directive 2001/83/EC which states that the MAH shall "monitor the outcome of RMMs which are contained in the RMP or which are laid down as conditions of the marketing authorisation".(27)

The publication from Pietro *et al,* which laid the foundation for GVP Module XVI dedicated to the assessment of the effectiveness of RMM, justifies the need for that assessment: "in the same way that public health interventions aim to minimise risks associated with a pharmaceutical product, it is imperative to systematically evaluate the effectiveness of the intervention in order to determine whether the intended effect/outcome has been achieved or an alternative activity needs to be identified and implemented".(39, 42)

Since the introduction of pharmaceutical Risk Management, several programs to minimise risks and to assess those measures have been developed.(43, 45) In 2010, the proportion of CAPs with additional RMMs in the EU had increased from the reported 5% among products authorised before the RMP became mandatory in 2005 to 29% among products approved afterwards.(44)

Figure 3 below illustrates the dual-evidence-based approach to evaluate effectiveness of additional RMM, endorsed by GVP Module XVI and consistent with ICH E2E principles. It builds on two distinct levels of evidence: the actual implementation of the RMM (measured by process indicators) and the attainment of the final objective of the RMM (measured by outcome indicators)(39):

- Process indicators: Provide evidence that the implementation steps of the additional RMMs have been successful. They provide insight into what extent the programme has been executed as planned and whether the intended impacts on behaviour have been observed;
- Outcome indicators: Provide an overall measure of the level of risk control that has been achieved with the RMM. For instance, where the objective of an intervention was to reduce the frequency and/or severity of an ADR, the ultimate measure of success shall be linked with this objective. The assessment requires traditional epidemiologic methodology addressing if the desired outcome was attained.

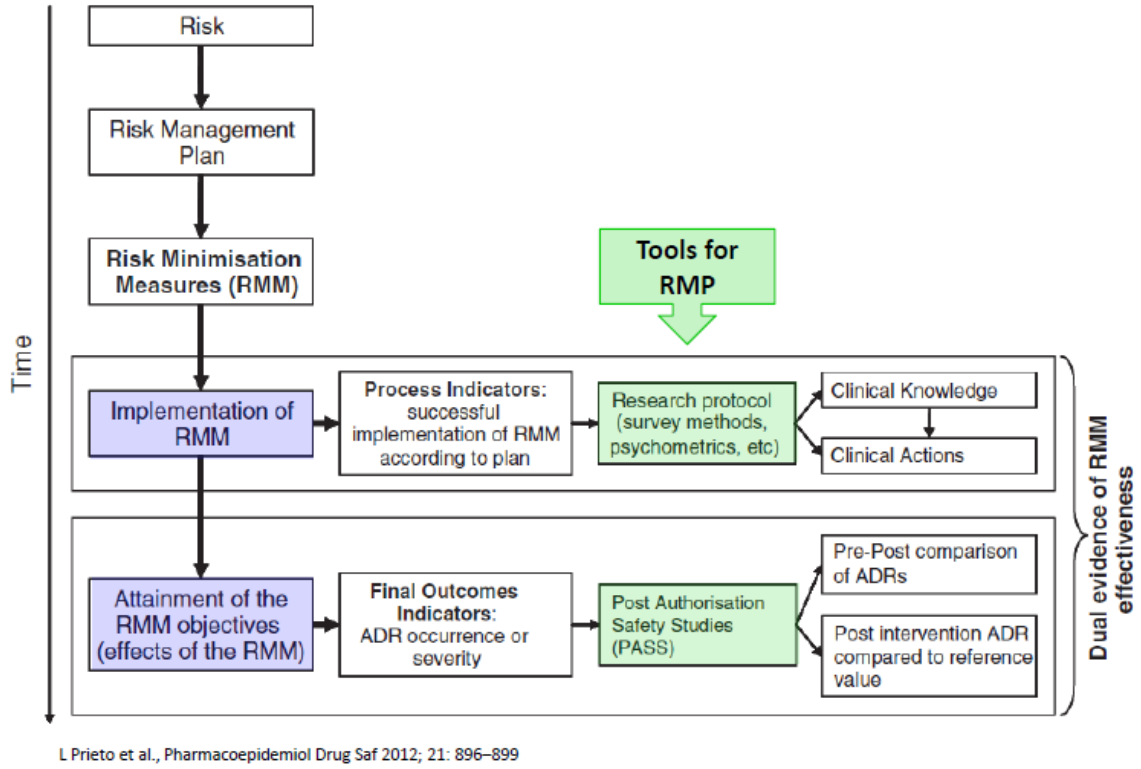

Figure 3 – Dual-evidence-based approach to evaluate effectiveness of additional risk minimisation measures (RMMs). Source: European Medicines Agency. Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators (Rev 1). EMA/204715/2012 Rev 1.(39)

Process and outcome indicators are viewed as complementary and not alternative. Even if the ultimate goal of assessing effectiveness of a RMM is to determine if there was a beneficial outcome of the intervention, in order to understand an eventual lack of success or proactively anticipate a lack of success, it is important to collect data on implementation of the program (process indicators), such as the successful delivery to the target population, the use of those measures by the population and if they were correctly understood, so that they ultimately become part of the routine clinical practice.(39)

The guidelines emphasise that sound scientific methods should guide the assessment of both indicators. For example, 'if surveys and/or measurement scales are involved in the assessment of RMM appropriate methods and psychometric properties of the instruments involved should be considered. When RMM involve the provision of information to HCPs, resulting clinical actions should be measured and not only clinical knowledge". It is also necessary to take into consideration, the differences in healthcare systems and all the stakeholders involved in the RMM.(39, 42)

Specific recommendations for assessment of outcome indicators include the comparison of epidemiological measures of outcome of interest (e.g. incidence of hepatotoxicity or surrogate endpoint that anticipates a safety concern) before and after the implementation of the RMM (i.e. pre-post design), which can be addressed by a PASS. When a pre-post design is not feasible (e.g. the RMM is put in place before the product is launched) then an outcome reference value (e.g. from literature, historical data, expected value in the population) can be used for comparison, provided it is duly justified.(39)

As a result of the assessment of the effectiveness of the RMM, it may be concluded that the measures should remain unchanged or, that modifications need to be made to the existing activities.(39)

Expanding the considerations from Pietro *et al*, and the GVP Module XVI, Banerjee *et al*, proposed a 5-level model with different evaluation levels representing increasing utility of information to

determine RMM effectiveness (Figure 4). The evaluation levels range from risk-minimisation tool coverage (level 1), evaluating the distribution of the RMM awareness and usage (level 2), assessing knowledge acquired (level 3), analysing the impact of knowledge on behavioural change (level 4) and ultimately, the effects on safety outcomes which the RMM aims to minimise (level 5). The authors suggest methodologies for each of these levels.(43)

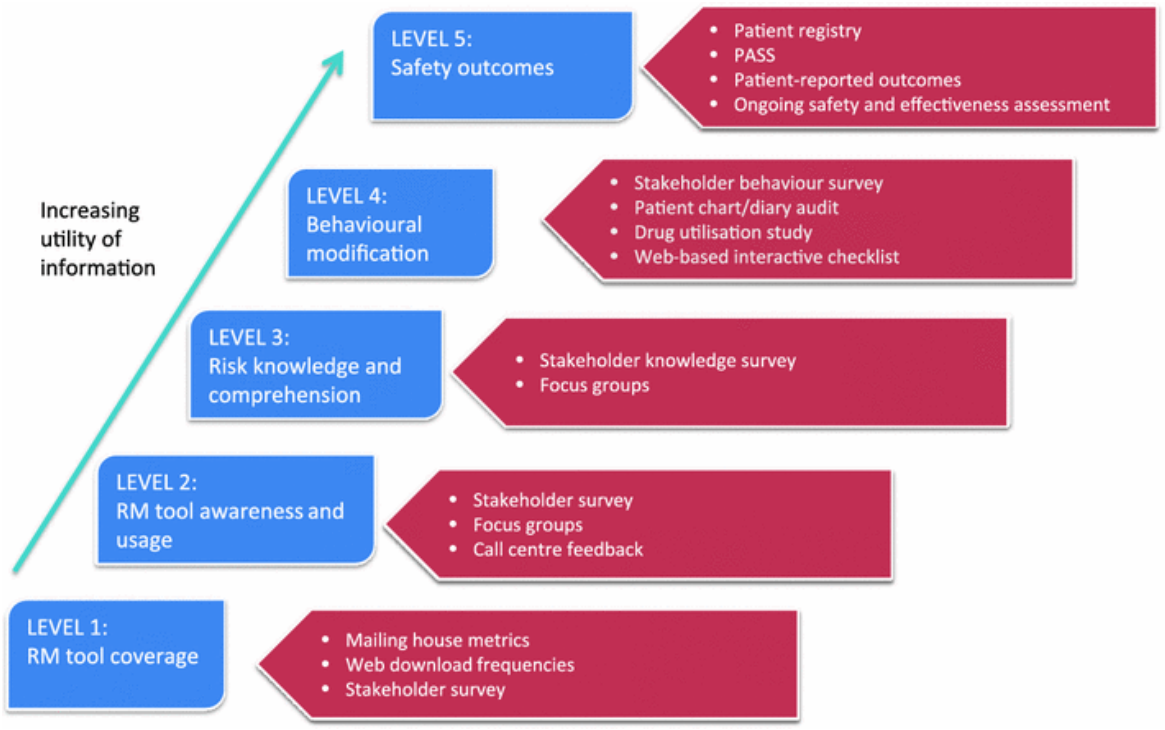

Figure 4 – A 5-level framework covers both individual risk-minimisation tools and programme evaluation. Source: Banerjee AK *et al* (2014).(43)

Figure 5 presents an additional model, suggested by Zomerdijk *et al*, in which, taking a chronological approach, it is provided complementary information relevant for the assessment of the RMM's impact on the benefit-risk balance of the drug.(46) It can be observed that the indicators of success are similar to those presented in the other previous described models.

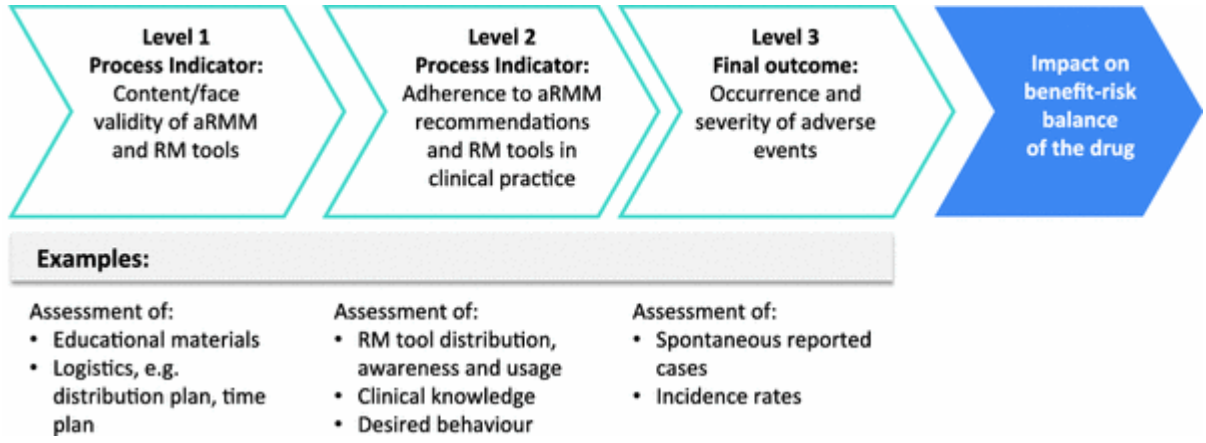

Figure 5 – Evaluation steps increase in utility of information with time after implementation. Source: Zomerdijk *et al* (2013).(46)

The three models discussed above constitute examples of frameworks that have been developed. It has been acknowledged that there are still hurdles in this area to overcome. Thus an optimal method to assess effectiveness of RMM is yet to be found.(42, 43, 46)

It is important to note, as will be seen in the following chapter, that according to the legislation, a study measuring the effectiveness of a RMM is considered a PASS.(25) Given the anticipated increase in number of additional RMMs after the 2010 Pharmacovigilance legislation, an increased demand for studies assessing the effectiveness of RMMs is also anticipated, making it an interesting sub-population of PASS to study as they may reflect the performance of the overarching Risk Management systems.

The previous chapter introduced the Risk Management framework describing the activities that can be implemented by the MAHs to identify new risks and further characterise known risks and mitigate the occurrence of risks through the application of RMMs which effectiveness need to be continuously assessed. PASS play a major role in the success of these plans by providing the methods to proactively investigate important safety concerns and/or assess if the implemented RMM are effective. They are the perfect reflection of the needs of the industry and regulators to use pharmacoepidemiological measures to foster understanding of the safety profile of the medicinal products, thus ensuring the right actions can be put in place at the right time to protect public health.

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5 Post-Authorisation Safety Studies (PASS)

5.1 Background

The impact assessment of the previous Pharmacovigilance legislation revealed that, PASS, an essential part of Risk Management activities, were frequently not conducted or completed. In addition, based on a 2006 industry survey, it was concluded that these studies already involved substantial industry resources (€356.9 million, with a lower and upper range of €202.0 and €511.8 million, respectively). However, the studies were often of poor quality and frequently conducted for promotional rather than safety reasons. It was considered that under the regulatory framework at that time, there were no guiding principles and no adequate oversight for non-interventional safety studies.(22)

According to a published review of PASS before the new Pharmacovigilance legislation, 52 of 60 requested PASS had progressed through planning to potentially starting data collection.(47) Another review, also from authors from regulatory authorities and prior the new legislation, reported the majority of PASS protocols were not submitted or were incomplete.(23) This corroborated similar findings regarding the RMPs in general and their planned activities.(18) The compliance seemed to be very good when the studies were requested by CHMP rather than just recommended.(47)

Blake *et al* recommended earlier discussions between the sponsor and the CHMP on PASS adequacy to avoid delays and the implementation of unfeasible studies. It was highlighted the need for "careful consideration of the requirements for studies and their feasibility into Risk Management planning before the granting of a marketing authorisation or a new indication".(47)

The new Pharmacovigilance legislation introduced aspects which address the abovementioned findings as non-interventional PASS could be imposed as legally binding conditions. In addition, the EMA would take the role of overseeing a PASS if conducted in more than one Member State. These changes intended to decrease the number of poor quality studies, as well as, of studies with a promotional nature. Furthermore, while it was initially suggested that the authorities' objection to a PASS protocol would be limited to refusing those with a promotional nature, it was decided in the

end, that the authorities could also object protocols based on scientific/ public health concerns, strengthening the role of the authorities in the scientific oversight.(22)

5.2 A Legal Framework for the Conduct of Post-Authorisation Safety Studies (PASS)

The new legislation set forth a firm legal background for PASS and established clear rules, from protocol development to final study reporting. A PASS is defined in Directive 2001/83/EC Article 1(15) as "any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of Risk Management measures".(27)

A PASS may be initiated, managed or financed by a EU MAH voluntarily (non-imposed PASS) or pursuant to an obligation imposed by a competent authority (Directive 2001/83/EC Articles 21a and 22a), in which case it is considered a condition to the marketing authorisation and are mandatory and subject to penalties of not implemented (imposed PASS).(27) GVP Module VIII provides detailed guidance on PASS.(48)

In the Pharmacovigilance Plan section of the RMP, PASS are categorised as(48):

- Category 1: imposed as condition to the marketing authorisation by the regulatory authorities based on being considered key to the benefit-risk profile of the product;
- Category 2: imposed on a marketing authorisation for being a specific obligation in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances[1];
- Category 3: considered voluntary in the Directive but also considered required as they are part of the Pharmacovigilance plan agreed with the authorities;
- Other studies not required by a regulatory authority do not need to be reported in the RMP (category 4).

Category 1 and 2 PASS are imposed PASS (mandatory and subject to penalties) and are supervised according to Art 107 (n)-(q) of Directive 2001/83/EC. In summary, the MAH shall submit a draft protocol to the PRAC or to the national competent authority, depending on if the study is to be conducted in more than one Member State or a single Member State, respectively. In the 60 days following the submission of the draft protocol, the national competent authority or the PRAC shall issue(27):

(a) A letter endorsing the draft protocol;

(b) A letter of objection, which shall set out in detail the grounds for the objection, in any of the following cases:

(i) It considers that the conduct of the study promotes the use of a medicinal product;

(ii) It considers that the design of the study does not fulfil the study objectives; or

(c) a letter notifying the MAH that the study is a clinical trial falling under the scope of EU Clinical Trials Directive (Directive 2001/20/EC).

Additional guidance is provided in the document "Post-authorisation safety studies: questions and answers", as follows: "in the instances when PRAC adopts a letter of objection, submission of an amended protocol may be required within X month(s) or within 14 days. In the former case, submission of the amended protocol is requested within X months depending on the extent of the revisions; the revised protocol will then follow a 30- or 60-day PRAC review procedure. In the case

[1] According to the EMA website, "exceptional circumstances" apply when the applicant can show that they are unable to provide comprehensive data on the efficacy and safety of the medicine for which authorisation is being sought, due to the rarity of the condition it is intended for, limited scientific knowledge in the area concerned, or ethical considerations involved in the collection of such data.

of a re-submission within 14 days, the PRAC will review the amended protocol within 15 days. This 30-day timeframe for the PRAC decision is applied when the PRAC considers that the protocol needs to be resubmitted quickly to allow endorsement at the following PRAC meeting".(49)

The study may only start when the written endorsement has been issued. Then, the MAH shall forward the protocol to the competent authorities of the Member States in which the study is to be conducted, follow any specific requirements and after, the study can be initiated according to the endorsed protocol.(48)

In addition, in order to support transparency on non-interventional imposed or non-imposed PASS and to facilitate exchange of Pharmacovigilance information between all parties, the MAHs is highly expected to, make study information (including for studies conducted outside the EU) available in a dedicated EU electronic Register of Post-Authorisation Studies (EU PAS), maintained by the European Network of Pharmacovigilance and Pharmacoepidemiology (ENCePP) and coordinated by the EMA. Any Pharmacoepidemiological and Pharmacovigilance studies can be registered. The application is voluntary, free of charge and can be submitted by researchers or any individual on their behalf. (50)

Despite there is no legal mechanism to enforce study registration, in a non-interventional PASS pursuant to an obligation imposed by an EU competent authority, the date of study registration in the EU PAS register shall be included as a milestone in the final study report.(29) In addition, according to the GVP module VIII, and to incentivise transparency, it is strongly recommended that all PASS (imposed and non-imposed) are entered in the register, and optimally, before the start of data collection. The study protocol should be uploaded as soon as possible after its finalisation and prior to the start of data collection. Updated study protocols in case of substantial amendments, progress reports and the final study report should also be entered in the register (as soon as possible and preferably within two weeks after their finalisation).(48)

The ENCePP aims to uphold high standards throughout the research process based on the principles of robust methodologies, transparency and scientific independence.(47) PASS that follow those principles can further qualify for obtaining an ENCePP seal.(51)

The MAH shall submit a final study report to the national competent authority or the PRAC as applicable within 12 months of the end of data collection unless a written waiver has been granted (Directive 2001/83/EC Art 107).(27)

5.3 PASS Principles and Guidance

PASS should be designed according to strong scientific and methodological pharmacoepidemiological principles.

From the previous chapters it is also clear that PASS have a distinctive purpose, interlinked with the overall Risk Management strategy. An immediate evidence of this particular nature stands out from the definition of PASS, which combines Risk Management and pharmacoepidemiological terms(48):

"A post-authorisation study should be classified as a PASS when the main aim for initiating the study includes any of the following objectives:

- To quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another medicinal product or class of medicinal products as appropriate, and investigate risk factors, including effect modifiers;
- To evaluate the risks of a medicinal product used in a patient population for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);
- To evaluate the risks of a medicinal product after long-term use;
- To provide evidence about the absence of risks;

- To assess patterns of drug utilisation that add knowledge regarding the safety of the medicinal product or the effectiveness of a Risk Management measure (e.g. collection of information on indication, off-label use, dosage, co-medication or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern);
- To measure the effectiveness of a Risk Management measures".

The fact that, the definition of a PASS is strictly related to the purpose of the study is further strengthened as follows: 'Whereas the PASS design should be appropriate to address the study objective(s), the classification of a post-authorisation study as a PASS is not constrained by the type of design chosen if it fulfils the criteria as set in DIR Art 1(15). For example, a systematic literature review or a meta-analysis may be considered as PASS depending on its aim".(48)

This GVP Module also states that the development of PASS protocols should be developed by individuals with appropriate scientific background and experience. The different sections that need to be present in a PASS protocol are detailed in this guideline and leverage those also present in the ISPE Good Pharmacoepidemiology Practices (GPP).(48, 52) There are specific templates for PASS protocols and reports which establish the mandatory sections and which information each section should contain. In addition, there are also templates for the assessment of PASS protocols and reports by regulators, including guidance on how to assess the content provided in each section.(53)

In addition, protocols need to append the ENCePP Checklist for Study protocols (available at http://www.encepp.eu/standards_and_guidances/index.html), which was developed to promote the quality of studies aligned with scientific and regulatory developments relevant to Pharmacovigilance and Pharmacoepidemiology, such as(54):

- Stimulate researchers to consider important epidemiological principles when designing a pharmacoepidemiological study and writing a study protocol;
- Promote transparency regarding methodologies used in pharmacoepidemiological studies;
- Increase awareness about developments in science and methodology in the field of Pharmacoepidemiology.

GVP Module VIII further reference as scientific guidelines, the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, a document covering state of the art methodological considerations including hyperlinks to internationally agreed recommendations and highlighting key points from important guidelines, published articles and textbooks.(55)

6 Assessing the Effectiveness of Regulatory Actions

According to the Organisation for Economic Co-operation and Development (OECD) (August 2012), "in recent years, governments around the world have established procedures to try to analyse the impacts of new regulatory proposals before they are adopted. By contrast, they have paid remarkably little attention to analysing regulations after adoption or to evaluating the impacts of the procedures and practices that govern the regulatory process itself".(56)

Regulations are supposed to effectuate some improvement in the conditions of the world by changing individual or organisational behaviour in ways that generate positive impacts in terms of solving societal and economic problems. According to the OECD source: "at its most basic level, regulation is designed to work according to three main steps: (1) Regulation is implemented, which leads to changes in (2) The behaviour of individuals or entities targeted or affected by regulation, which ultimately leads to changes in (3) Outcomes, such as amelioration in an underlying problem or other (hopefully positive) changes in conditions in the world".(56)

The parallel with the considerations described in *Introduction Section 4.2* on the assessment of the effectiveness of RMM are remarkable. As with the assessment of RMM, evaluating regulation

entails an inquiry, that takes place after regulation has been put in place, into how it has changed behaviour and ultimately if it has led to positive or negative outcomes.

If assessing an individual RMM is already challenging, as previously described, it is not surprising that the process of evaluating a regulation change is extremely complex and outside the limits of any individual research group. In most cases, the evaluation of a regulatory framework would encompass the assessment of the individual rules that compose the legislative body.

In January 2016 the PRAC adopted a strategy for measuring the impact of Pharmacovigilance activities including health outcomes at EU and Member States level which relies on a collaborative approach of all stakeholders. Measuring the impact of key Pharmacovigilance activities will allow regulators and stakeholders to determine which activities are most successful and to identify enablers and barriers for generating positive health impacts, which will contribute to the further development of proactive Pharmacovigilance systems and to promote best practice across the EU. It is expected that the strategy will support the collection of more data relevant to the health impact of the EU Pharmacovigilance system.(57)

Meanwhile, there are already some published results on metrics on the new Pharmacovigilance processes. In May 2014, the EC published a report by the EMA on the tasks undertaken during the first year of application of the new legislation together with national competent authorities in Member States and the EC.(34) More recently, in August 2016, a new report was published to cover the first three years of EU legislation, based on data collected from July 2012 to December 2014 and discussing relevant tasks and processes over the whole 3-year period up to July 2015. Reported metrics supported conclusions that spontaneous reporting increased since 2012 (including an increased awareness of medication errors), the analysis of safety signals contributed to early updates of product information or other regulatory measures, hundreds of RMPs, PASS protocols and PSURs were centrally reviewed by the PRAC and the number of inspections increased.(36)

In addition, the EMA considered that the new system delivers faster advice and warnings to use of medicines and quicker detection of safety issues. The Agency considered that patients and HCPs are being engaged by reporting ADRs and contributing to safety-referral procedures and that there is a better co-ordination and collaboration between regulators and other stakeholders, including academia and industry. In addition to those points, the EMA also highlights an unprecedented level of transparency with prompt communication on safety concerns, public access to agendas and minutes of the PRAC, outcomes of signals and PSURs and aggregated data on suspected ADRs.(36)

An in-depth analysis of this metrics and the outcomes on public health will be essential to confirm the effectiveness of the new legislation. Smaller and/or specific evaluations of individual rules, or new processes from different perspectives and different stakeholders will not be enough to accomplish such a challenging endeavour but can, nevertheless, make small contributions and hopefully be of interest to complement all the other evidence.

7 Study Rational

The current dissertation aims to contribute to the overarching goal of understanding the impact of the new Pharmacovigilance legislation by focusing on the review of available data of PASS submitted to the EMA since the implementation of the new legislation.

As a consequence of the effort to improve transparency, one of the main pillars of the new legal framework, a broad spectrum of data on the different Pharmacovigilance activities performed by the EMA became available, including on PASS. The availability of the large variety of information has provided a unique opportunity to describe the PASS landscape under the new EU Pharmacovigilance legislation.

Figure 6 presents the conceptual map of the study, showing how the different concepts introduced in the previous chapters interact, the role of each individual component to be explored in the results and the dynamics between each component, which will be addressed in the discussion.

The grey glowing arrows symbolise the expected increased level of transparency that makes it possible to investigate PASS: on the top of the diagram, the MAH submits PASS protocols to the EMA (with a certain legal basis and at a certain point in the lifecycle of the marketing authorisation). There are exchanges between the stakeholders and after the final protocol is agreed, it is possible to estimate the duration of the overall assessment process (number of rounds of exchange, duration and type of feedback) represented at the bottom of the diagram.

In the middle of the diagram, PASS are depicted as a product of Pharmacovigilance and Pharmacoepidemiology. By having to submit RMPs, the MAHs need to consider what is known and unknown about the medicinal product to establish the critical safety concerns that may affect the safety of the medicinal product (safety specification). For each safety concern, the MAHs need to establish a plan of action by considering whether routine activities are sufficient or, if additional activities are necessary. Some activities are designed to acquire more knowledge on the safety profile of the medicinal product (Pharmacovigilance activities) while others aim to mitigate the occurrence and/or severity of the safety concerns (RMMs).

The consideration of the safety specification of the medicinal product by either the MAH or the regulators may raise questions, either related to the need to better characterise the known risks or detect unknown risks (investigate safety concerns, represented in orange), or concerns that the drug utilisation in real-world practice might differ from the expected or studied use, being important to monitor it actively (drug utilisation, represented in green). In addition, it is also established as part of the Risk Management cycle the need to investigate if the RMMs in place are being effective (assess effectiveness of RMM, depicted in purple). All these research questions are appropriate to address using Pharmacoepidemiology methods. Therefore PASS are studies with objectives derived from the safety specification which use pharmacoepidemiological methods to fill those gaps.

In order to describe PASS in this dissertation, information on the type of research questions and the study methods were investigated. Research questions were described in line with the three abovementioned categories (depicted in orange, green and purple in the diagram). Methods were described in terms of study design, population targeted for study (inclusion based criteria), data collection approach (new data or leverage existing data), sample size and analysis (use of comparator, subgroups of interest, types of statistical methods). These characteristics were analysed in the light of guidelines and scientific knowledge that have been generated and disseminated to implement Pharmacoepidemiology in the activities of the industry and regulators. In particular, an in-depth analysis of the PASS aiming to assess effectiveness RMM was considered of interest given their position in closing the loop of a Risk Management cycle.

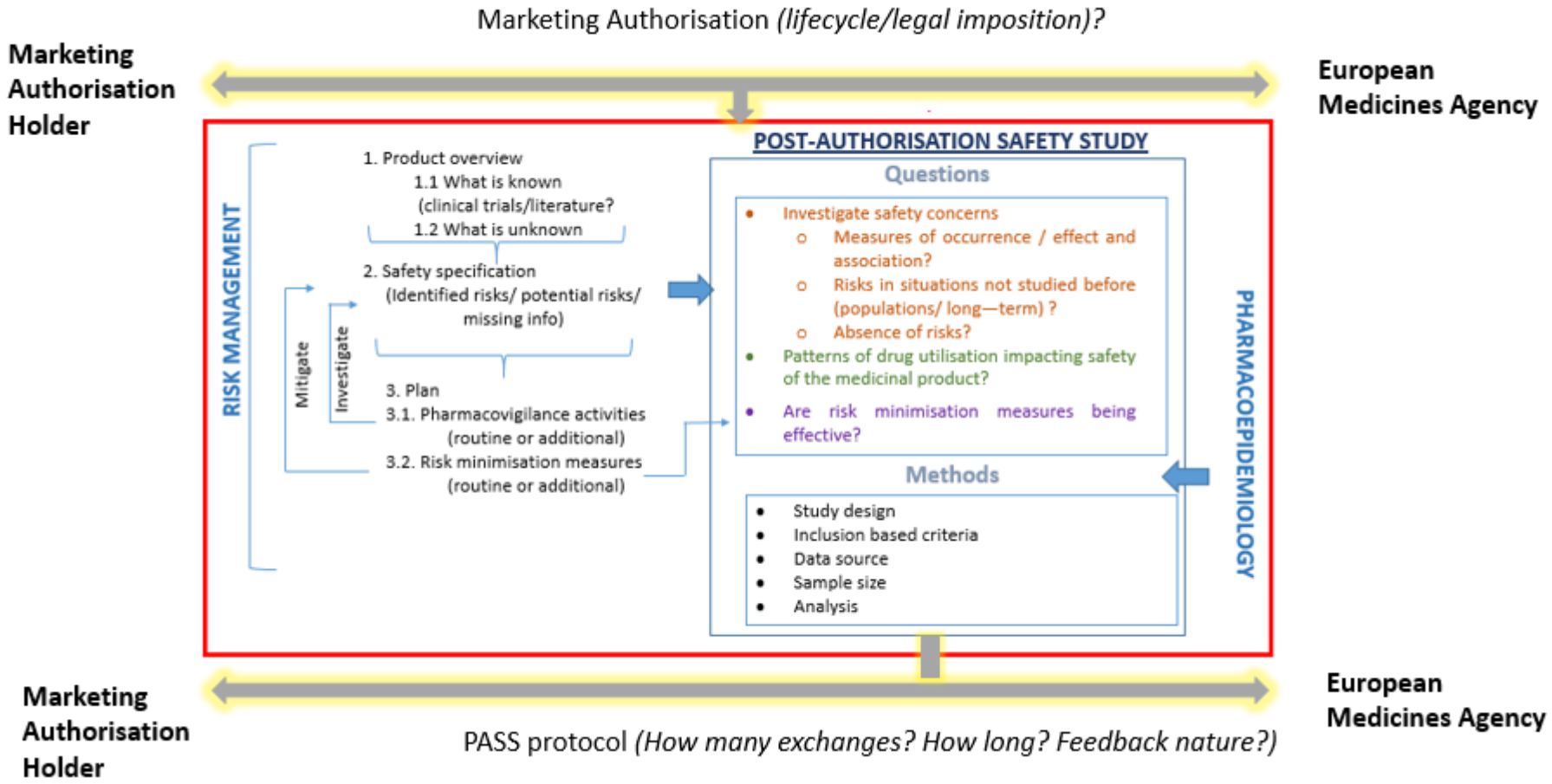


Figure 6 – Conceptual map

Study Objectives

The current dissertation aimed to draw, for the first time, the PASS landscape during the first three years under the new Pharmacovigilance legislation, by describing the first cohort of PASS protocols submitted to the EMA since the first inaugural PRAC meeting in July 2012 to July 2015.

To the best of the author's knowledge, this is the first time that PASS submitted since the new Pharmacovigilance legislation are described and characterised. There are no *a priori* hypotheses.

Specific objectives are:

- To characterise PASS protocols in terms of regulatory context, study objectives, therapeutic area, study design, source of data collection, and other methodological considerations;
- To estimate PASS protocol assessment metrics, such as, the number of rounds of review and duration of PASS protocol assessment by the PRAC, and to identify the most common reasons for protocol rejection;
- To determine the amount of PASS assessment comments publicly available and how many studies were entered in the EU PAS Register;
- To understand to what extent PASS are designed as methodologically and feasibly sound studies, by reviewing protocol content, PRAC feedback and running a more in depth analysis of PASS assessing effectiveness of RMMs.

Methods

In natural and social sciences quantitative and qualitative research methods are often seen as two irreconcilable approaches by advocates of each style. While the methods used in quantitative research attempt to maximize objectivity, replicability, and generalisability of findings, and are typically interested in prediction, qualitative approaches focus mainly on exploring meaning, purpose, or reality. The question of quantitative versus qualitative measures is currently more assumed to be a false one, as more researchers see them as complementary approaches.(58-61)

Quantitative approaches are often associated with the use of deductive reasoning, characterised by top-down logic in which, the structure of the analysis is based on previous knowledge and/or experience (i.e. *a priori* definitions and decisions about the variables) moving from the general to the specific. Conversely, qualitative approaches are associated with the use of inductive reasoning, characterised by bottom-up logic as it moves from the specific to the general, in the sense that particular instances are observed and combined into larger whole or general statements. Therefore, themes and categories emerge from the data.(62)

The nature of this dissertation's objectives and the available sources to address them invited the use of qualitative methodologies. First, the need to understand PASS in the context of the new regulatory framework and its background. Second, the public availability of different textual sources documenting PASS and their assessment by the Regulators which made them attractive data sources to address the objective via the scientific study of its content.

1 Study Design

The public availability of different textual sources documenting PASS made them a pertinent data source in which to conduct a documentary analysis.

1.1 Data Sources

The minutes of the PRAC monthly minutes provided the means to identify the different PASS protocols and respective rounds of revision by the PRAC. After identifying each PASS protocol, two other data sources were searched to find more granular information regarding the regulatory background and the protocol methods: the European Public Assessment Reports (EPARs) of the medicinal products covered in the PASS (also available in the EMA website), and the EU PAS Register (available in the ENCePP website). When no information was available in the abovementioned sources, the website ClinicalTrials.gov was searched to check if PASS were eventually registered there. In addition, a pool of protocols available within the author's organisation was also checked in case it contained additional protocols.

The following sections further describe each of these data sources and the type of information retrieved.

1.1.1 Minutes of the PRAC Monthly Meetings(63)

As a consequence of the efforts of the EMA to increase transparency of the regulatory processes, the full minutes of the PRAC monthly meetings are published, in English, every month, listing all the processes assessed by the PRAC in the previous month. In addition, a short description of the background and PRAC comments may be provided for those procedures discussed during the plenary meeting. These official and authentic EMA documents available online, at the EMA website, provided an unique opportunity to identify and track, in a chronological order, all PASS protocols submitted to the EMA during the first three years under the new legislation by reviewing all the minutes covering the period since the PRAC inaugural meeting in July 2012 until the PRAC meeting in July 2015.

As in any documentary analysis, the first step was to assess the level of information provided in these documents and their potential to characterise PASS.(64) Annex 1 described the structure of these documents and the information available regarding PASS.

The following information was retrieved from the PRAC meeting minutes when available: name of active substance, MAH, whether it was an imposed or non-imposed PASS, PRAC assessment outcome (endorsement/ objection or need for revision/ administrative procedural information/ unknown). PRAC reasons for objection/ revision were further categorised by area of concern (study objectives and endpoints/ study design/ data source and population/ data collection and management/ study variables/ sample size/ data analysis/ milestones and timelines/ feasibility and bias considerations/ other/ missing).

1.1.2 European Public Assessment Report (EPAR)(65)

For each of the medicinal products studied in the PASS protocols identified from the minutes, a search was conducted on the EMA website to retrieve information from the EPARs using the search engine "Find medicine" and looking for that particular medicinal product. Annex 2 describes the types of information available through this search for a medical product.

While the EPARs are only available for CAPs, medicinal products authorised through national authorisation procedures and subject to a referral could also be found by searching for the name of the active substance which would list any existent referrals under Article 20, Article 30 or Article-107i procedures. Therefore, information about the PASS resultant from referrals could also be found by reviewing the outcome of these processes.

The information from the EMA website mainly provided details on CAP medicinal products: marketing authorisation date, MAH, orphan drug status, the regulatory background of PASS such as imposed or non-imposed PASS category and life cycle stage of the medicinal product in which PASS was implemented.

1.1.3 The ENCePP Website: EU PAS Register(50)

Since July 2012 the EU PAS Register serves as the official EU register for post authorisation studies regardless of whether initiated, managed or financed by MAHs voluntarily or pursuant to an obligation, or whether conducted by research centres of the ENCePP network or any other research centre, including from outside the EU. Annex 3 describes the structure and data elements contained in the EU PAS Register (at July 2015).

The EU PAS register was searched to identify if the PASS were registered and in those cases, if the protocols were made available. Since the objective of the work was to describe the PASS protocols, whenever available, these documents were the privileged data sources to collect the information about the PASS objectives and methodology.

Main methodological characteristics retrieved from this data sources were study design, inclusion based criteria, data collection approach, sample size and analysis.

1.1.4 Other Sources

When information regarding PASS methodology was not available from the abovementioned data sources, an internal pool of protocols accessible to the author's organisation was searched. No confidential or sensitive information was disclosed as part of this work. The data was matched with the data retrieved from the other public data sources.

In addition, the ClinicalTrials.gov, a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world, was also searched. Most of the

records in ClinicalTrials.gov describe interventional clinical trials but it may also include records describing observational studies. International sponsors less familiarised with the European data sources might use this data source to publish information on PASS. Therefore, this data source was also screened for the medicinal products and the PASS identified in the PRAC Meeting minutes.(66)

1.2 Data Source Hierarchy

The described data sources were mostly complementary as different PASS characteristics were typically retrieved from each one. However, in the cases in which the same type of information was available in more than one of the data sources, a hierarchy was established to decide which data source to privilege, as presented in Figure 7.

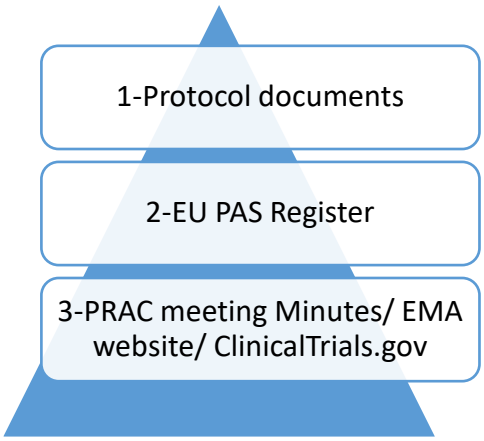


Figure 7 – Hierarchy of data sources

The protocol documents were the most reliable source of information on PASS objectives and methodology as they are the written documents describing the PASS plan. When this document was not available for a certain PASS, preference was given preference to the information recorded in the EU PAS Register as it contains some data structured elements from the protocol as described above.

If the PASS protocol was not available nor registered in the EU PAS Register, then information about study objectives and methodology was retrieved from the minutes (a brief description was sometimes available, e.g. “PASS protocol for a drug utilisation study (DUS) in selected European countries: multinational, retrospective, observational study to assess effectiveness of risk-minimisation measures”) or in the EPARs, as the objectives of the PASS and any requirement on the design were sometimes established even before the protocol is developed (e.g. “observational database study [cat 3]: to assess the risk of thyroid and pancreatic cancers in observational databases of sufficient size that provides long term longitudinal follow up of patients”). In these cases, those sources were considered the best estimates of the actual content that would be described in the protocol documents. In addition, the website ClinicalTrials.gov was also reviewed in case the studies were registered there. However, the data elements presented in this website, which is tailored for interventional studies, were less relevant to characterise PASS than those in the EU PAS Register.

1.3 Identification of PASS Protocols

All the PRAC monthly minutes (from July 2012 to July 2015) were included in the analysis. From the review of these documents in a chronological order, all the entries related to PASS protocol were recorded in an excel spreadsheet.

Each PASS protocol could appear more than once in the consecutive meeting minutes corresponding to the reassessment of a revised version of the protocol resubmitted after previous PRAC recommendations.

Each distinct PASS protocol assessment was sequentially recorded in different rows of the excel matrix. Further assessments of the same protocols were registered using the same PASS protocol designation, and a sequential number was assigned for each assessment/reassessment of a certain PASS protocol (column "round of review").

The process of discriminating between different PASS protocols and different rounds of assessment of the PASS protocols was iterative and the following rules were established to ensure consistency (Annex 4 contains examples in illustrate these rules):

- Every new PASS protocol "entry" identified through the chronological review of the minutes was considered to be the "first round" of assessment for that PASS protocol;
- If in the same, or subsequent minutes, another entry of a PASS protocol of the same medicinal product was identified, then the text was carefully revised to decide if it was the same PASS protocol already presented before (see Annex 4: examples 1 and 2), or if it was a different PASS protocol for that medicinal product (see Annex 4: examples 3 and 4 and the glycopyrronium bromide PASS protocol mentioned in example 5). Then:
    - In case it was determined that it was the same PASS protocol already presented before for the same medicinal product, this PASS protocol assessment was considered a new round of evaluation of the same PASS protocol: recorded as a new PASS protocol assessment round in a new row of the excel matrix using the same PASS identification designation, with an indication that it was a subsequent round of assessment in the respective column (i.e. "round 2" and so forth);
    - Conversely, if determined that the new PASS protocol entry refers to a different PASS for the same medicinal product, this PASS protocol was recorded in the excel matrix with a new designation and as the first round of assessment of this new PASS protocol (i.e. a new row assigned "round 1");
    - It should be noted that from the minutes of the meeting held on February 2014 onwards, the task was facilitated since each PASS protocol entry started presenting additional fields, namely, the procedure number, the procedure scope and MAH, which make it easier to identify new submissions *versus* resubmissions of PASS protocols (see Annex 4 examples 5).
- When the text from a certain PASS protocol entry in the minutes indicated that two different PASS protocols for a certain medicinal product were concomitantly assessed, even though they were recorded in the minutes under the same subheading, they were split when recorded in the excel matrix, in order to account for each individual PASS protocol (see Annex 4 example 6).

As a PASS protocol could be referred in more than one row of the spreadsheet, it was decided that all the PASS characteristics would be collected in the first row for that PASS protocol (i.e. "round 1"). Therefore, even if resubmissions of the same PASS protocol present information about the PASS protocol that was unavailable before, all the information pertaining to that same PASS protocol was recorded in the first row for that PASS protocol ("round 1"). The investigator was aware of the possibility that the information provided in a subsequent round of assessment could contradict information provided in a previous round of the same PASS protocol. However, that situation did not occur as the level of information provided in different rounds was often very limited.

1.4 Data Collection

For each different PASS protocol identified as described in *Methods Section 1.3*, the data sources (introduced in *Methods Section 1.1*) were searched and used according to the established hierarchy (see *Methods Section 1.2*) to collect information about PASS characteristics.

An excel spreadsheet was used as data collection instrument. Each PASS protocol assessment, identified from the chronological review of the PRAC meeting minutes, was sequentially recorded in excel matrix rows. The columns were the characteristics of interest, some of which were transcribed information from data sources, while others were derived information or coded information that resulted from the application of the final defined rules. Please refer to Annex 5 for a list of variables, definitions and operational rules. The final database is provided as an electronic supplementary material.

2 Data Analysis

2.1 Iterative Development of the Coding Scheme

The analysis of the information contained in the different documents followed the main principles of a content analysis technique which is defined by Krippendorf K (1980) as "a research technique for making replicable and valid inferences from texts (or other meaningful matter) to the contexts of their use".(59) It is well accepted in this area, that, while variables and categories can be defined *a priori* and applied following a top-down rational, iterative loops of feedback from a qualitative review of the data may reshape the pre-defined "classes" of data. Specially, when a researcher is analysing a subject for the first time, even if there are *a priori* expectations, new or different patterns may be revealed while he/she is getting familiar with the data.(62, 67)

In light of the above considerations, it seemed pertinent to allow for flexibility when considering the method in the current project. Despite an initial choice on the set of variables to start PASS characterisation, the novel nature of the content being analysed made it necessary to further revise the initial coding scheme as new data emerged from the analysis. The previous variables and categories were not satisfactory to capture the distinctive features of the PASS and were progressively refined through several iterative cycles of coding and recoding until the final coding scheme was established (see Annex 5) containing variables capturing different PASS traits with exhaustive and mutually exclusive categories. The final set of rules was systematically implemented to all units in the excel matrix (even if they had been previously classified with previous versions coding rules), thus, creating the final study database.

In addition to the general variables collected for all protocols, some more granular analyses required additional considerations as follows.

2.2 Units of Analysis and Specific Considerations

To address the different objectives of the study, it was necessary to use different sets of units, which could be retrieved from the excel spreadsheet using the rules described below. The analyses performed to address the study objectives are also described.

2.2.1 Characterisation of PASS Entities

To analyse the different PASS protocols (irrespective of having documents available), the excel spreadsheet was filtered by column G ("Rounds of PRAC evaluation =1"). As explained in *Methods Section 1.3*, the cumulative characterisation of each PASS protocol was made on its first database record even if some information was only available on a subsequent minutes' entry.

2.2.2 Sub-analysis of PASS Protocols with Documents Available

Some of the PASS characteristics of interest were only retrievable from the protocol documents, hence, a detailed characterisation was performed among the subset of PASS with protocols available. By filtering the spreadsheet by column AI ("Protocol available (yes/no) = yes") it was possible to select the subset of PASS with the most complete information available.

2.2.3 Sub-analysis of PASS Protocols Assessing Effectiveness of RMM

The sub-analysis of methods used in PASS assessing effectiveness of RMM was conducted by filtering the excel matrix by the same columns indicated in the previous bullet point and also by column AT ("PASS focus: eRMM = yes").
The protocols of those PASS were analysed in detail and structured as shown in Annex 6 according to the following criteria:

- ID: The number of the row from the excel matrix corresponding to the PASS assessing effectiveness of RMM;
- PASS safety objectives: Information from column AQ of the excel matrix, capturing whether the PASS objectives were exclusively dedicated to assessing effectiveness of RMM or if those PASS protocols contained PASS objectives of the other categories;
- Study design/ data source: Whether the design was longitudinal/ cross-sectional, used primary or secondary data collection approaches and the detail of the data source;
- Sampling frame: Details of the population targeted and included in the PASS specifying if there was sample randomisation;
- Indicators: The types of indicators of effectiveness of RMM that seemed to be covered in the PASS (use of RMM/ knowledge/ behaviour/ outcome);
- Interesting aspects: any observation of interest.

2.2.4 Analysis of PASS Protocol Review Process

Each row in the matrix corresponded to a different PASS protocol assessment. In order to determine the number of rounds of PRAC assessment and overall duration of PRAC assessment process (from the first PASS protocol submission to the PRAC until the protocol was considered approved), it was necessary to ascertain whether the PASS protocols contained in the analyses were approved at the data lock point of July 2015.
Since the information available in the minutes' PRAC comments was often very limited, there were several cases were there was no explicit information on whether the PASS protocol had been finally endorsed. In these cases, the following assumptions were made to ascertain whether or not a certain PASS protocol assessment process could be considered finalised at the data lock point (July 2015):

- The PASS was found in the EU PAS Register, which usually occurs after the protocol is approved, or
- More than one year had elapsed since the last assessment of that PASS protocol per the minutes (i.e. the last PASS protocol submission was recorded in the minutes of the July 2014 meeting or earlier). This was regarded as a reasonable amount of time to consider that another PASS protocol submission was unlikely;
- In addition, PASS for which there was not enough evidence that their assessment was initiated only after the implementation of the new Pharmacovigilance legislation, were excluded, since for this particular analysis on the PRAC assessment process, the focus was only on PASS protocols fully assessed within the new Pharmacovigilance legislation.

PRAC review metrics were estimated among the subset of PASS protocols that met the conditions enumerated above: the number of rounds of assessment for a certain PASS protocol corresponded to the number of entries for that PASS protocol in the excel database (number of rounds of review),

and the duration of protocol review was the number of months elapsed since the first and the last entry for a certain PASS protocol.

2.2.5 Analysis of PASS Comments' Text

The PRAC comments' text recorded in the minutes was specifically analysed with the support of the qualitative data analysis software MAXQDA™ (2007 version) in order to characterise PRAC assessment outcomes. All the "PRAC comment" fields from the excel database were imported to the software and analysed through iterative cycles of open codification. Open Coding includes labelling particular sections of the text and defining and developing categories based on recurrent patterns in all comments. Through repeated cycles of reading and code review, different themes were identified as follows:

- PRAC outcome decision (column P in the excel spreadsheet, see definition in Annex 5): to capture whether the outcome of a certain round of a PASS protocol assessment was the need for resubmission;
- Areas of the protocol requiring revision (column Q in the excel spreadsheet, see definition in Annex 5): for the PASS protocol rounds in of review in which the PRAC objected or required revision, the underlying protocol areas of concern were identified. The result of the codification is presented in Annex 7.
- The submission and assessment timetable established by the PRAC for the protocol revision (columns R and S in the excel spreadsheet see definition in Annex 5).

2.3 Statistical Methods

Analyses were performed with the statistical software SPSS, Version 21.0.

Descriptive analyses were performed among i) all the PASS protocols submitted ii) the subsample of PASS with protocol documents available, iii) the PASS protocols assessing effectiveness of RMM; iv) the PASS protocols for which the assessment process was considered concluded, v) the full consecutive PRAC comments published in the minutes.

Categorical variables were summarised by the number and percentage (%) of PASS in each category, excluding missing data. Continuous variables were summarised using descriptive statistics (mean, standard deviation [SD], median, quartiles, minimum and maximum values).

Proportions were calculated excluding missing data from the denominator. Comparisons using chi square (considering a significance level of 5%) were performed for categorical variables.

All analyses were performed on actual data, with no imputations for missing data.

Results

1 PASS Disposition

1.1 Study Population

In total, 353 PASS protocol assessments were identified by reviewing the minutes of the PRAC meetings from July 2012 to July 2015.

Eight others were excluded due to missing data for all variables, and consequent impossibility to assess whether they corresponded to a submission or resubmission.

Figure 8 below presents the disposition of the study population considering the different analysis datasets that address study objectives.

Each of the 353 PASS protocol assessments was considered in terms of available information on PASS protocol and PRAC comments.

The 353 PASS protocol assessments identified in the minutes corresponded to 189 different PASS protocols (with at least one round of assessment), with the remaining 164 PASS protocol assessments being related to additional rounds of assessment of those protocols (considered as resubmissions of PASS protocols).

Protocols were available for approximately one third of PASS (n=57/189, 30%) allowing the most detailed study characterisation. The second highest hierarchical source of evidence (*see Methods Section 1.2*), the EU PAS Register, was used to classify 22% (n=42/189) of PASS, while for the remaining 48% (n=90/189) information was retrieved from the minutes, ClinicalTrials.gov and the EMA website, in the absence of more detailed sources.

For approximately half of 189 different PASS (n=103/189, 54%) there was reasonable evidence to assume that the assessment process had been concluded at the data lock, July 2015 (see rules established in *Methods Section 2.2.4*): 15 had enough evidence in the minutes' text to conclude the assessment was finalised, 66 others were entered in the EU PAS Register and for 22, despite the inexistence of registration in the EU PAS, more than one year had elapsed since the last presentation of the PASS protocol in the minutes up to July 2015.

Regarding the PRAC comments, these were only available for 106 of the 353 different PASS assessments (n=106/353, 30%). Upon review of the 106 PRAC comments' text, it was determined that PRAC outcomes were the following: 16 protocol approval (n=16/106, 15%), 71 protocol objection or need for revision (n=71/106, 67%) and 19 concerning other matters (n=19/106, 18%) such as administrative or procedural information.

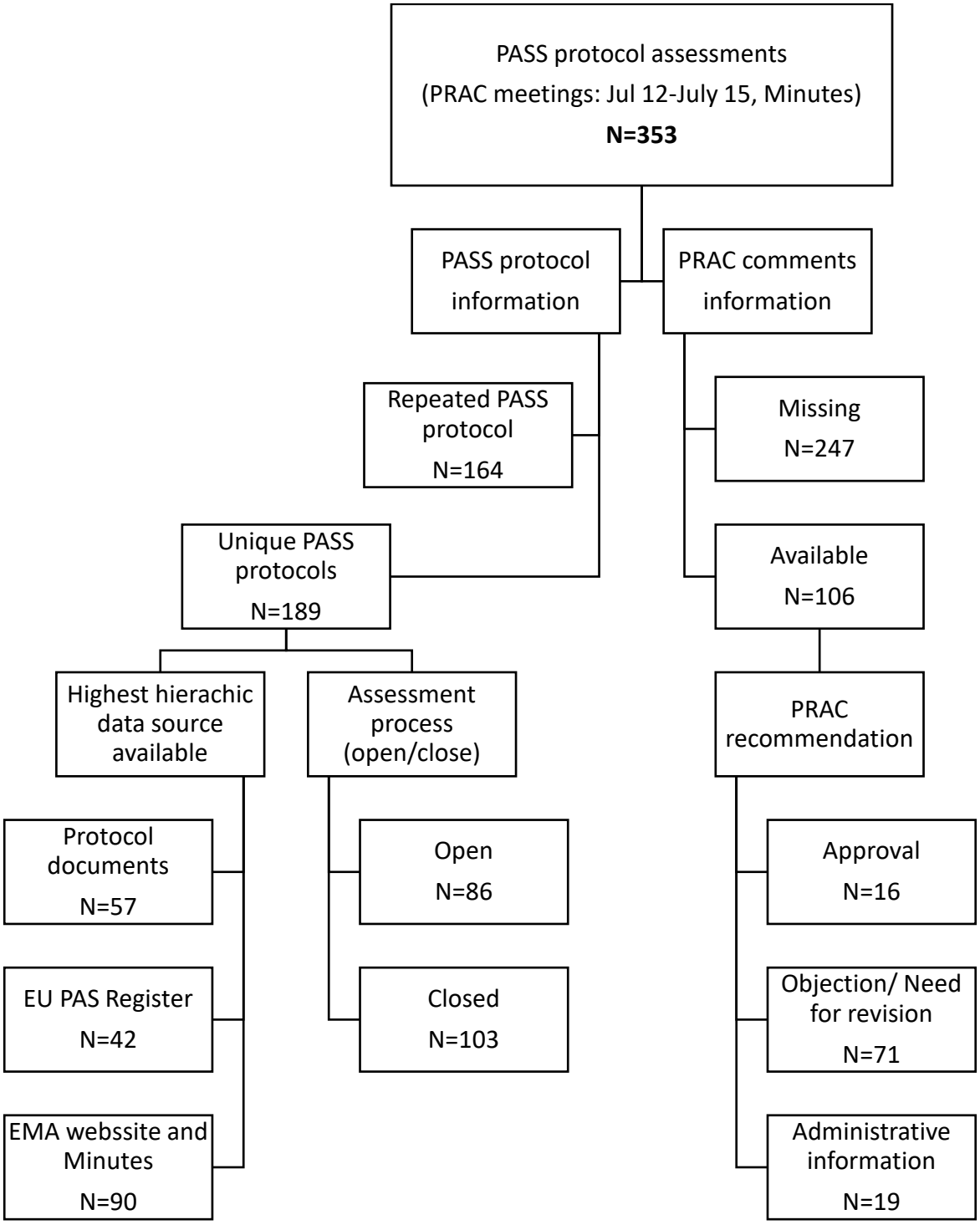


Figure 8 – Study population

1.1.1 Representativeness of the Subset of PASS with Protocol Available (n=57)

The protocol documents were available for 57 PASS. Table 1 below summarises the distribution of both the 189 different PASS and the subset of 57 PASS with protocol documents available by the main PASS characteristics.

The proportion of PASS within each category of the variables was very similar in the two datasets. The highest differences were observed in terms of data collection (42% of the 189 PASS used secondary data collection *versus* 33% among the subset of 57 PASS with protocol available) and inclusion based criteria (70% of the 189 PASS based on single product and 21% based on multiple products *versus* 81% and 12%, respectively, among the subset of 57 PASS with protocol available).

However, the magnitude of the differences was still small. In fact, a comparison between the PASS with protocol available and those without revealed no statistically significant differences (chi-square test, $p<0.05$).

For the abovementioned reasons, the subset of 57 PASS protocols was considered representative of the overall 189 PASS population. Since the availability of these documents allowed a more in-depth characterisation of the PASS protocols, some results were based on the information contained in these documents and extrapolated to the overall PASS population.

Table 1 – Distribution of PASS characteristics (comparison of all PASS and the subset with protocol available)

PASS Status	Overall (n=189)*	Protocol available (N=57)
Regulatory Aspects	n (%)	n (%)
Imposed	**58 (30.7)**	**17 (29.8)**
Condition to MA (Cat. 1)	28 (14.8)	10 (17.5)
Specific obligation (Cat. 2)	7 (3.7)	2 (3.5)
Referral	23 (12.2)	5 (8.8)
Non-imposed	**131 (69.3%)**	**40 (70.2)**
RMP (Cat. 3)	116 (61.4)	36 (63.2)
Other‡	15 (7.9)	4 (7.0)
Orphan Drug Status	25 (13.2)	6 (10.5)
Joint PASS§	16 (12.1)	7 (12.3)
Study specifics	n (%)	n (%)
PASS focus**		
To investigate safety concerns	140 (74.1)	43 (75.4)
Drug utilisation study	65 (34.4)	23 (40.4)
Assess effectiveness of RMM	48 (25.4)	18 (31.6))
Data collection††		
Primary	81 (57.9)	38 (66.7)
Secondary	59 (42.1)	19 (33.3)
Study Design‡‡		
Longitudinal follow-up	110 (80.9)	47 (82.5)
Transversal/ cross-sectional	26 (19.1)	10 (17.5)
Study population inclusion based criteria§§		
Type of exposure		
Disease	13 (8.4)	4 (7.0)
Multiple medicinal products	33 (21.3)	7 (12.3)
Single medicinal product	109 (70.3)	46 (80.7))
Special populations focus		
Pregnant women	9 (11.5)	3 (5.3)
Paediatric population	14 (17.9)	8 (14.0)
Healthcare providers	17 (21.8)	9 (15.8)

Abbreviations: MA = Marketing Authorisation; PASS = Post-Authorisation Safety Study; RMM = RMM = Risk Minimisation Measure; RMP = Risk Management Plan.
Categories are mutually exclusive unless otherwise specified.
* Percentages calculated excluding missing values.
‡ Considered to be category 4, by exclusion.
§ More than one Marketing Authorisation Holder sponsored the study. Missing data (applicable to overall column only): imposed = 17 (29.3%), non-imposed= 40 (30.5%); total = 57 (30.2%)
**Categories not mutually exclusive.
†† Primary: collection of data specifically for the study; Secondary: use of existent data collection schemes. Missing data (applicable to overall column only) = 49 (25.9%).
‡‡ Longitudinal: involves collection of variables at least two points in time; Transversal: involved collection of variables at a certain point in time. Missing data (applicable to overall column only) = 53 (28.0%).
§§ Common inclusion criteria: in terms of exposure (patients with a certain disease irrespective of medicinal products, restricted to single medicinal product exposure/ prescription or exposure/ prescription of more than one predefined medicinal product/ treatment modalities. Missing data (applicable to overall column only) = 34 (18.0%).
Special population focus: Inclusion restricted to special groups of interest (children, pregnant women). Missing data (applicable to overall column only) = 111 (58.7%).

1.2 Volume of PASS Protocol Assessments

Figure 9 presents the number of PASS protocols assessed each month during the study period, according to the minutes of the PRAC meetings from July 2012 to July 2015. "Number of new PASS protocols evaluated" refer to protocols that appeared for the first time in the concerned monthly minutes and "number of PASS protocols evaluated (including resubmissions)" correspond to total number of PASS protocols presented in the concerned monthly minutes irrespective of whether it was a first occurrence or a subsequent round of assessment for a PASS protocol already presented before.

Overall, the number of PASS protocols assessed increased prominently after June 2013, with the majority of new PASS protocols (n=146/189, 77%) and the majority of overall submissions (n=299/353, 85%) occurring in the last two years covered in this study period.

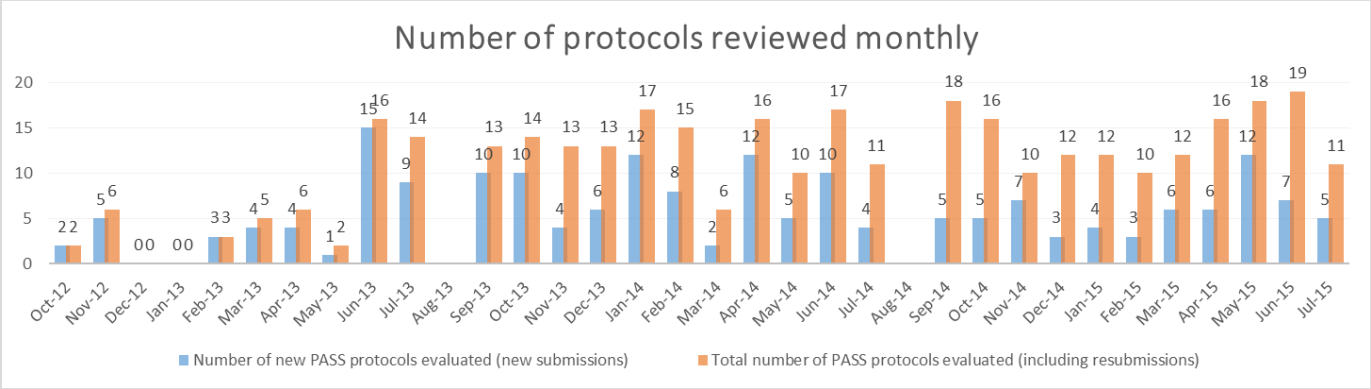
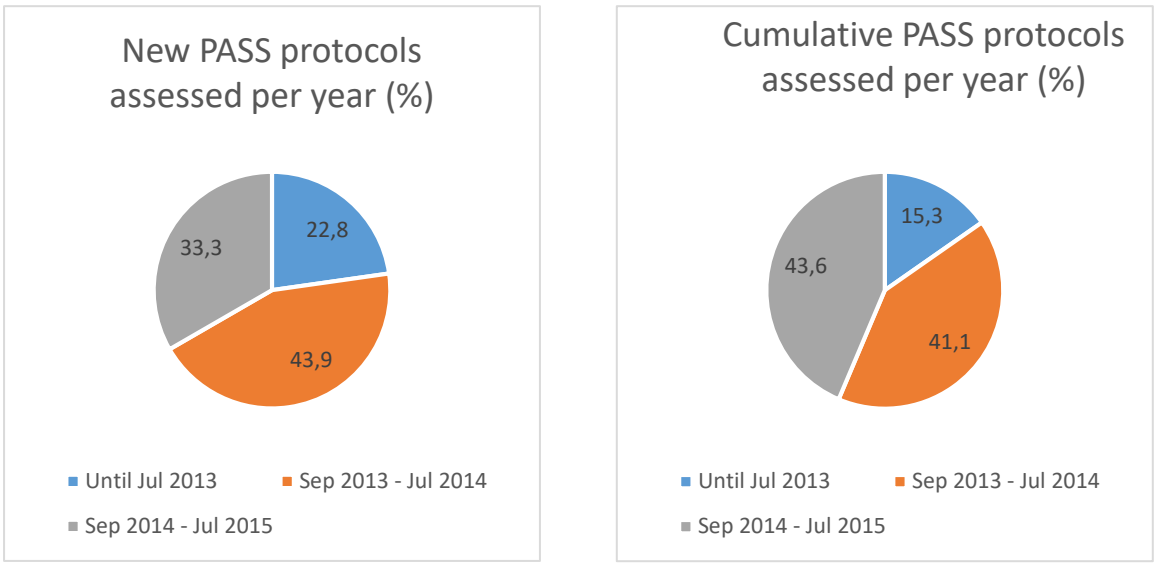


Figure 9 – Number of PASS protocols reviewed monthly (new submissions and resubmissions)

More detailed information is presented in Figure 10 below. While approximately as many PASS overall were assessed in the second and third year (July 2013-July 2014 and July 2014-July 2015), the majority of new PASS protocols was assessed in the second year of the study period (n=83/189,



44%).

Figure 10 – Distribution of PASS protocols submissions (new and cumulative) *per* year in review

1.3 ENCePP Registration

As of July 2015, half of the 189 PASS (n=93/189, 49%) were entered in the EU PAS Register, with a higher proportion among the 58 imposed PASS (n=34/58, 59%) as compared to non-imposed (n=59/131, 45%); chi-square test, $p<0.05$. Almost half of the EU PAS entries had the protocol documents available (n=40/93, 43%).

Table 2 below summarises the proportion of PASS registered in July 2013, 2014 and 2015. There was an increased registration in the third year of the analysis as reflected by an increase in over 20% registration of both imposed and non-imposed PASS from July 2014 to July 2015, which had previously shown a negative trend from July 2012 to July 2013.

Table 2 – Registration of PASS in EU PAS Register over the study period

	% Imposed PASS registered	% Non-imposed PASS registered
July 2012-July 2013	40%	28%
July 2012-July 2014	35%	23%
July 2012-July 2015	59%	45%

Very few of the PASS registered (n=4/93, 4%) had requested and were granted an ENCePP seal, which recognises studies following the ENCePP principles of standards, transparency and independence.

2 Description of the PASS Protocols Submitted to the PRAC during the Initial Three Years under the New Pharmacovigilance Legislation

2.1 Reasons for Initiating a PASS, Regulatory Status and Sponsorship

Figure 11 presents the regulatory basis of the 189 PASS and the lifecycle phase of the concerned medicinal products when PASS were planned.

Overall, approximately one third (n=58/189, 31%) of the 189 different PASS were imposed on the marketing authorisation. Nearly half of them (n=28/58, 48%) were imposed as a condition to the marketing authorisation (category 1) and approximately one tenth (n=7/58, 12%) were imposed as specific obligations in the framework of a marketing authorisation under exceptional circumstance (category 2). In addition, despite not being part of the categorisation of imposed PASS *per* the Pharmacovigilance legislation, 40% of PASS (n=23/58, 40%) were mandated following EMA conclusions under the framework of an Article 107i or 20 referral procedures (benefit-risk reassessment procedures conducted triggered by safety concerns).

Among the 131 non-imposed PASS, the vast majority (n=116/131, 89%) were included in the RMP (category 3). No information about the reason for conducting the PASS was found for the remaining 15 non-imposed PASS (11%). Since they were not included as an annex neither to the marketing authorisation nor in the summary of the RMP, they were considered possibly category 4 PASS (voluntary PASS).

For those PASS that were conditions to the marketing authorisation or requirements of the RMP (category 1 and 3), the "regulatory lifecycle event" leading to the PASS imposition or requirement was analysed (e.g. planned/imposed with the initial marketing authorisation; after a variation to extend indication to a new disease or to the use in a new approved population such as paediatric patients; after a renewal of the marketing authorisation; as a consequence to a variation due to a change in manufacturing or a new dose or route of administration; after the assessment of the PSURs, etc.). Approximately two thirds of either the PASS imposed as condition to the Marketing

Authorisation (n=18/28, 64%) or those required in the RMP (n=85/116, 73%) were planned with the initial marketing authorisation for the medicinal product. All category 2 PASS (n=7) were imposed with the initial marketing authorisation. Therefore, the majority of PASS concerned initial marketing authorisation (n=110/189, 58%).

Other common triggers for requesting a PASS were variations to the marketing authorisation, mainly after an extension of the indication of the medicinal product to a new condition (n=5/28, 18% of category 1 PASS and n=13/116, 11% of category 3 PASS). An extension of the marketing authorisation to approve the use of the medicinal product for paediatric patients was associated with 7% (n=2/28) of the category 1 PASS and 6% (n=7/116) of category 3 PASS.

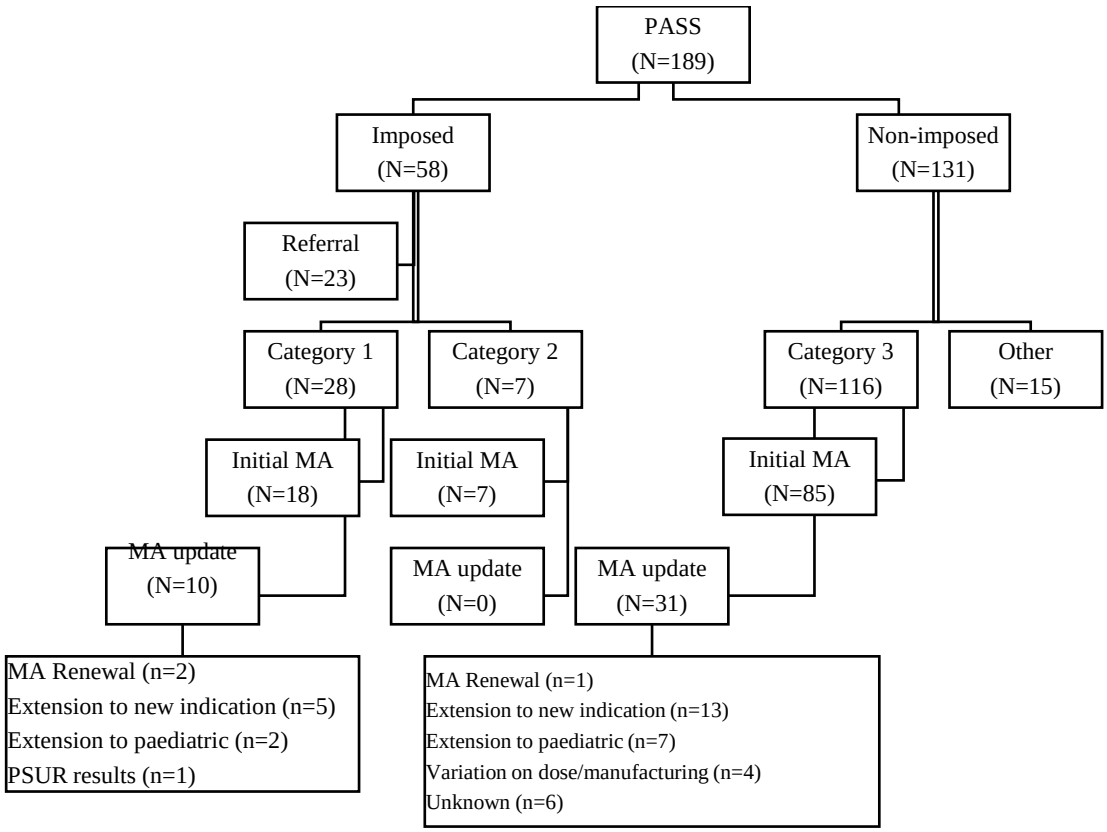


Figure 11 – PASS categorisation in the lifecycle of the marketing authorisation

Figure 12 below presents the distribution of PASS protocols assessed each year in terms of imposed/non-imposed status.

The majority of the PASS protocols assessed each year were non-imposed. The proportion of imposed PASS assessed by year was higher in the latter two years of the analysis (approximately one third of the overall PASS protocols assessed in the second and third year of the study *versus* approximately one fifth of those analysed in the first year).

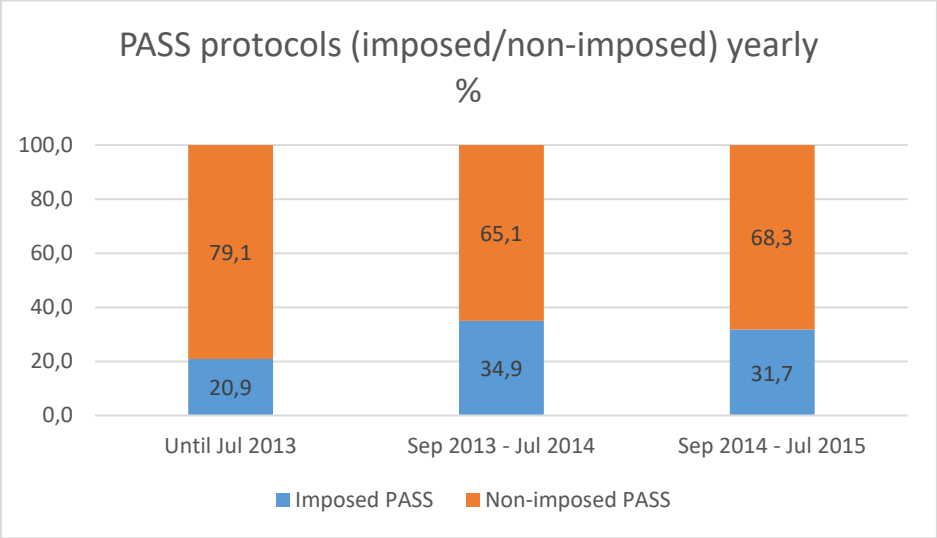


Figure 12 – Distribution of PASS assessed over the three years in the study period by legal status

Most PASS had a unique sponsor with only 12% PASS, among 132 for which there was available information, identified as jointly sponsored (n=16/132, 12%). The majority of the joint studies concerned PASS mandated as a consequence of a referral, which is generally applicable to all medicinal products of a certain active substance and therefore also included national authorised medicinal products (n=10/16, 63%).

2.2 Characteristics of the Studied Medicinal Products

2.2.1 Therapeutic Class

The medicinal products covered in the PASS were diverse in terms of Anatomical Therapeutic Chemical (ATC) code of the active substances as summarised in Table 3 below.

The four main ATC classes were by descending order: antineoplastic and immunomodulation agents (n=32/189, 17%), products acting on the alimentary tract and metabolism (n=30/189, 16%), antiinfectives for systemic use (n=27/189, 14%) and products acting on blood and blood forming organs (n=21/189, 11%).

Similar patterns were observed among the imposed and non-imposed PASS. Substances acting on the cardiovascular system and on the genito-urinary system and sex hormones were slightly more common among imposed PASS compared with the non-imposed. In contrast, antiinfectives for systemic use, active substances acting on the nervous system and of the class “various” were slightly more common among the non-imposed PASS.

Table 3 – Therapeutic class of the active substance covered in the PASS

ATC class (1st level)	Imposed PASS (n=58)	Non-imposed PASS (n=131)	Overall PAS (n=189)
	n (%)	n (%)	n (%)
Antineoplastic and immunomodulating agents (L)	9 (15.5)	23 (17.6)	32 (16.9)
Alimentary tract and metabolism (A)	7 (12.1)	23 (17.6)	30 (15.9)
Antiinfectives for systemic use (J)	5 (8.6)	22 (16.8)	27 (14.3)
Blood and blood forming organs (B)	8 (13.8)	13 (9.9)	21 (11.1)
Nervous system (N)	4 (6.9)	14 (10.7)	18 (9.5)
Cardiovascular system (C)	8 (13.8)	6 (4.6)	14 (7.4)
Genito-urinary system and sex hormones (G)	7 (12.1)	7 (5.3)	14 (7.4)
Various (V)	1 (1.7)	11 (8.4)	12 (6.3)
Respiratory system (R)	5 (8.6)	4 (3.1)	9 (4.8)
Musculo-skeletal system (M)	2 (3.4)	2 (1.5)	4 (2.1)
Sensory organs (S)	0 (0.0)	4 (3.1)	4 (2.1)
Dermatologicals (D)	2 (3.4)	1 (0.8)	3 (1.6)
Systemic hormonal preparations, excluding sex hormones and insulins (H)	0 (0.0)	1 (0.8)	1 (0.5)

2.2.2 Orphan Status

When applying for a new marketing authorisation, a MAH may apply for obtaining an orphan designation for the medicinal product. Orphan designation is based on the criteria laid down in Regulation (EC) No 141/2000 (see definition in Annex 5: description of column AB).

Overall, 13% (n=25/189) of the PASS concerned a medicinal product with an orphan designation. The proportion of PASS addressing a medicinal product with an orphan designation was higher among the imposed PASS as compared to the non-imposed PASS (22% *versus* 9%, chi-square test, $p<0.05$). To note, four of the seven PASS imposed as a specific obligation to the marketing authorisation (category 2) concerned orphan medicinal products.

2.2.3 Authorisation Procedure

The vast majority of the 189 PASS presented in the PRAC minutes covered medicinal products authorised by a CAP (n=166/189, 88%). All but two of the 23 nationally authorised medicinal products' PASS followed a decision implemented after a referral procedure. The remaining two PASS were imposed as a condition of the marketing authorisation and involved more than one Member State.

2.3 PASS Objectives

PASS objectives were categorised as "to investigate safety concerns", "to study drug utilisation" and/or "to assess effectiveness of RMMs" consistent with the types of objectives that make a post-authorisation study be considered a PASS (see Annex 5: description of column AQ).

Figure 13 below present the results in a Venn diagram.

Overall, the vast majority of PASS (n=140/189, 74%) had at least as one of the primary objectives, "to investigate safety concerns" which could be either to quantify risks, to evaluate the risks of use of the medicinal product in patient populations for which the information is limited or missing, to evaluate the risks of a medicinal product after long-term use or to provide evidence about the absence of risks.

Approximately one third of the PASS (n=65/189, 34%) had, at least as one of the primary objectives, "to study drug utilisation", and approximately one fourth of the PASS (n=48/189, 25%) had, at least as one of the primary objectives, "to assess effectiveness of RMMs".

Almost one third of the 189 PASS (n=58/189, 31%) combined at least two of the three PASS focus categories under the same protocol. In particular, half of the PASS that, had at least as one of the primary objectives "to study drug utilisation", also aimed "to investigate safety concerns" (n=31/65, 48%), or to "assess effectiveness of RMMs (n=12/65, 18%) or both (n=6/65, 9%). Therefore only one fourth (n=16/65, 25%) of the PASS that had at least one primary objective of "study drug utilisation" did not combine objectives of the other two PASS focus categories.

In addition, the majority of the PASS that had, at least as one of the primary objectives, "to assess effectiveness of RMMs" (n=27/48, 56%), also combined objectives of the other PASS focus categories, mainly "to study drug utilisation" (n=18/48, 38%).

Conversely, the majority of PASS which had at least one of the main focus "to investigate safety concerns" did not combine PASS objectives of the other categories (n=94/140, 67%).

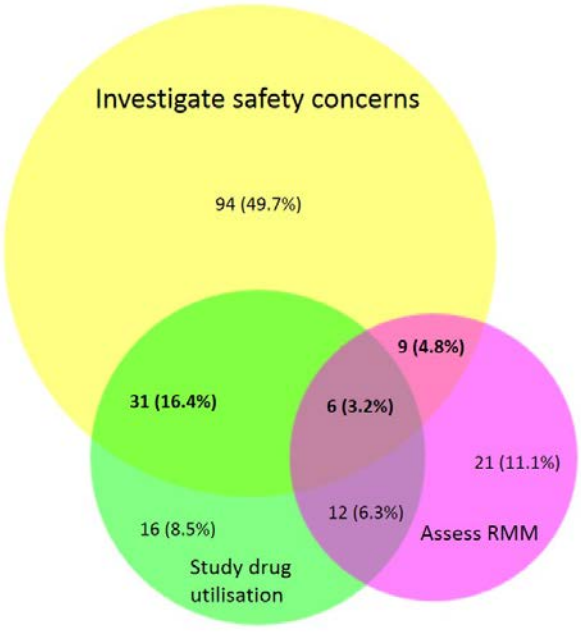


Figure 13 – PASS focus

Note: Overall number of PASS with each safety concern: to investigate safety concerns (N=140); to study drug utilisation (N=65); to assess effectiveness of risk minimisation measures (RMMs) (N=48).

Figure produced with the support of http://www.cmbi.ru.nl/cdd/biovenn/index.php

The review of the summary tables of the RMPs from the EPARs, provided showed the safety concerns considered in the RMPs and the planned PASS to address each of those concerns.

Safety concerns were diverse and a comparison between those mentioned in the EPAR and those addressed in the protocols would have required a more complex investigation. However, it was noted when analysing the EPARs of the PASS that combined objectives of "investigating safety concerns" with at least one objective of the other categories, that there were some recurrent types of safety concerns. Safety concerns often analysed in PASS with those objectives were related with exposure in populations for which there was missing information, off-label use and the effects of long-term use of the medicinal product.

The higher harmonisation observed in this subgroup of PASS made it feasible to perform an exploratory analysis to verify if the safety concerns deemed to be investigated in the concerned PASS according to the plan (EPAR) were actually reflected in the protocols objectives.

The analysis is presented in Figure 14.

The proportion of each of the three types of safety concerns in the PASS protocols was lower than it would have been expected from the EPARs.

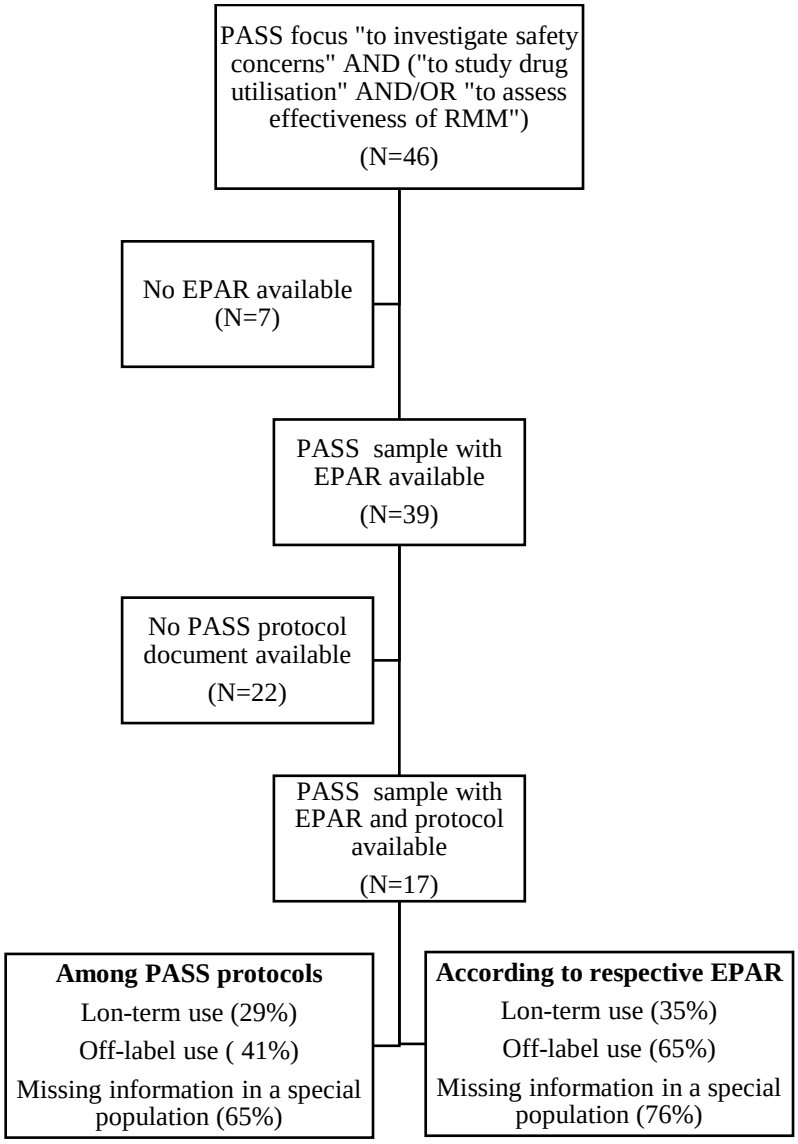


Figure 14 – Analysis of safety concerns described in PASS protocols and those targeted to be addressed in a PASS according to the EPARs

In addition to the safety objectives, the review of the 57 PASS with protocol documents available, revealed that approximately one third of those (n=20/57, 35%) also included objectives related with the assessment of effectiveness/benefit endpoints in addition to safety ones. Those endpoints were generally related with disease progression, long-term clinical response to the medicinal product, results from physician assessment scales, premature discontinuation and/or need to use alternative medicinal products.

The proportion of PASS protocols assessing effectiveness endpoints among each therapeutic class was particularly high among PASS of "antineoplastic and immunomodulating agents", as six of the eight PASS protocols of these active substances, assessed effectiveness as part of the study objectives, namely, overall survival/best overall response, progression free survival and event-free survival.

2.4 PASS Methodology

Table 4 below summarises the main PASS methodological characteristics that will be explored in the following subchapters.

Table 4 – Summary of PASS methodological characteristics

PASS Status	Imposed (n=58)	Non-imposed (n=131)	Overall (n=189)	Chi-square test (p-value)
	n(%)	n(%)	n(%)	-
Data collection††				
Primary	25 (56.8)	56 (58.3)	81 (57.9)	0.866
Secondary	19 (43.2)	40 (41.7)	59 (42.1)	
Study Design‡‡				
Longitudinal follow-up	42 (89.4)	68 (76.4)	110 (80.9)	0.068
Transversal/ cross-sectional	5 (10.6)	21 (23.6)	26 (19.1)	
Study population inclusion based criteria§§				
Type of exposure:				
Disease	6 (11.8)	7 (6.7)	13 (8.4)	0.319
Multiple medicinal products	13 (25.5)	20 (19.2)	33 (21.3)	
Single medicinal product	32 (62.7)	77 (74.0)	109 (70.3)	
Special populations focus:				
Pregnant women	1 (4.5)	8 (14.3)	9 (11.5)	0.226
Paediatric population	5 (22.7)	9 (16.1)	14 (17.9)	0.491
Healthcare providers	3 (13.6)	14 (25.0)	17 (21.8)	0.274

Abbreviations: MA = Marketing Authorisation; PASS = Post-Authorisation Safety Study; RMP = Risk Management Plan.
For each variable, the percentages were calculated excluding missing values. Categories are mutually exclusive unless otherwise specified
†† Primary: collection of data specifically for the study; Secondary: use of existent data collection schemes. Missing data: imposed = 14 (24.1%), non-imposed= 35 (26.7%); total = 49 (25.9%)
‡‡ Longitudinal: involves collection of variables at least two points in time; Transversal: involved collection of variables at a certain point in time. Missing data: imposed = 11 (19.0%), non-imposed= 42 (32.1%); total = 53 (28.0%)
§§ Common inclusion criteria: in terms of exposure (patients with a certain disease irrespective of medicinal products, restricted to single medicinal product exposure/ prescription or exposure/ prescription of more than one predefined medicinal product/ treatment modalities. Missing data: imposed = 7 (12.1%), non-imposed= 27 (20.6%); total = 34 (18.0%)
Special population focus: Inclusion restricted to special groups of interest (children, pregnant women). Missing data: imposed = 36 (62.1 %%), non-imposed= 75 (57.3%), total = 111 (58.7%)

2.4.1 Study Design

The vast majority of the PASS (n=110/136, 81%) were designed to collect data from patients from at least two time points (longitudinal design) with a slightly higher proportion among the imposed PASS *versus* the non-imposed (89% *versus* 76%) while cross-sectional designs were more common among the non-imposed PASS than among the non-imposed (24% *versus* 11%), chi-square test, $p<0.05$. Specifically, the majority of the PASS with cross-sectional design (n=16/26, 62%) were category 3 PASS (required in the RMP).

The study design seemed to be associated with the PASS focus as 94% (n=97/103) of PASS with at least one objective of "investigating safety concerns" and design available information, had a longitudinal design, while 61% (n=20/33) of the PASS without objectives related to "investigate safety concerns" and design available information had a cross-sectional design; chi-square test, $p<0.05$.

On the other hand, 56% (n=20/36) of the PASS with at least one objective of "assessing effectiveness of RMMs" and design available information had cross-sectional design, while 94% (n=94/100) of PASS without this objective, had a longitudinal design; chi-square test, $p<.005$. More specifically, among PASS in which the only objective was to "assess effectiveness of RMMs" (n=15), all but one (n=14/15, 93%) had a cross-sectional design.

Differently from the other two categories of PASS objectives, no significant statistical differences were observed between the PASS with at least one objective of "assessing drug utilisation" and those without such objective.

Among the 47 PASS with protocol available that had a longitudinal study design and information available on patient follow-up (n=39/47, 83%), the median patients' follow-up was 3 years (interquartile range [IQR]: 4.0 years). It ranged from 24 hours (n=3, in PASS of medicinal products used in emergency care units) to 15 years (n=1, a disease registry).

Among the imposed PASS, the median patient follow-up was 4.5 (IQR 6.0, n=13) years and among the non-imposed was 2.0 (IQR 3.6, n=26).

The majority of the 34 longitudinal PASS having at least one objective of "investigating safety concerns" and patient follow-up duration available, had patient follow-up periods equal to or longer than three years (n=21/34, 62%).

2.4.2 Selection Criteria

The population were targeted for enrolment in the PASS based on a single medicinal product (exposure or prescription), multiple medicinal products (exposure or prescription) or disease (prevalence or incidence).

More than two thirds of PASS with available information (n=109/155, 70%) focused on single medicinal product as eligibility criteria:

- 83% (n=90/109) targeted patients exposed to the single medicinal product;
- 8% (n=9/109) targeted HCPs that prescribed or administered the single medicinal product;
- 6% (n=7/109) targeted both patients exposed and HCPs that prescribed or administered the single medicinal product;
- 3% (n=3/109) did not contained more detailed information.

Among the 16 PASS that enrolled HCPs, 12 aimed to "assess effectiveness of RMMs", two aimed to "assess drug utilisation" and the remaining two combined both those objectives in the same protocol. All but one of these 16 PASS had a cross-sectional study design.

Approximately one fifth of the PASS (n=33/155, 21%) selected the study population based on more than one medicinal product, all being patients with predefined exposures of interest. Among those 33 PASS, 26 had enough information to assess whether the inclusion of the multiple medicinal products was for comparative purposes. In all but one, the medicinal products were used as comparators of the main medicinal product of interest in the PASS. In the remaining one, the inclusion of multiple exposures aimed to assess the safety of a combination of different medicinal products.

Finally, a minority of the PASS (n=13/155, 8%) selected the study population based on disease (12 enrolling patients with the disease of interest and the remaining targeting both patients and HCPs). Approximately half of these 13 PASS (n=6/13, 46%) studied medicinal products with orphan status, which may suggest those were rare diseases.

However, not all orphan medicinal products were investigated in PASS with such a broad inclusion criteria, since among all PASS studying orphan medicinal products (n=22), the most frequent inclusion based criteria was single medicinal product.

It is also of note that all the PASS selecting patients based on disease or multiple products had at least one study objective belonging to PASS focus "to investigate safety concerns". In addition, approximately one fourth of those also included as primary objectives to "assess drug utilisation" (n=11/46, 24%).

Some PASS targeted populations who are typically excluded from the clinical trials such as pregnant women and paediatric patients. Among 78 PASS with enough information to assess if the inclusion was based on one of these special populations, 12% (n=9/78) were found to be pregnancy registries and 18% (n=14/78) included only paediatric patients, the majority of the later, paediatric patients exposed to a single medicinal product (n=8), and the remaining either to multiple medicinal products or paediatric patients with a certain disease.

In terms of geographic coverage, the review of the 57 PASS protocols showed that all PASS involved at least one European country, and that the majority of them (n=44/57, 77%) were conducted in European countries only, with half of those in five or fewer countries. Approximately one fifth (n=13/57, 23%) of PASS were to be conducted not only in Europe, but also in other continents, mainly in North America (US [n=9] and Canada [n=7]).

2.4.3 Data Collection

Among 140 PASS with information available on data collection, slightly more PASS involved the collection of original primary data (n=81/140, 58%), i.e. data collection scheme to address the study objectives was built for the purpose of the study. Conversely, the remaining PASS (n=59/140, 42%) leveraged data collection schemes already established for other purposes (either administrative or other research projects).

There were no statistically significant differences between imposed and non-imposed PASS. However, data collection approach seemed to be associated with PASS focus as 58% (n=28/48) of PASS with at least one objective of "assessing drug utilisation" and data collection available information, used a secondary data collection approach, while 66% (n=61/92) of the PASS without objectives related to "assessing drug utilisation" and data collection available information used a primary data collection approach, chi-square test, $p<0.005$.

Overall, among the 81 PASS with a primary data collection approach, 38 had PASS protocols available (n=38/81, 47%), with approximately one fifth of those (n=8/38, 21%) including Patient Reported Outcome (PRO) measurements such as assessments of symptoms, burden of disease and quality of life.

The review of the 57 PASS with available protocols and information on informed consent requirements showed that informed consent was required in all PASS targeting patients for primary data collection (n=31) and in half of those targeting HCPs (n=6). Overall the proportion of PASS

requiring informed consent was higher in studies with a primary data collection approach than in those leveraging secondary data. (n=33/37, 89% *versus* n=7/19, 37%).

Among the 59 PASS using a secondary data collection approach, 37 (n=37/59, 63%) had information available regarding the used data sources. They were specifically of the following types:

- 11 (n=11/37, 30%) abstracted data from the review of local patients' medical charts;
- 20 (n=20/37, 54%) retrieved data from existent databases (automated electronic medical records [EMRs] and/or claims databases);
- 5 (n=5/ 37, 14%) leveraged data available from other research programs such as existing registries;
- The remaining was a Pharmacogenomic study which used data from a clinical trial database.

The majority of the 20 PASS using existing databases were conducted in the United Kingdom (n=14/20, 70%) followed by Spain (n=12/20, 60%), Italy and Netherlands (n=9/20, 45% each) and Denmark (n=8/20, 40%).

The most commonly used automated databases were the following:

- Claims database: German Pharmacoepidemiological Research Database (GePaRD) from Germany;
- EMRs: Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN) from the United Kingdom; SIDIAP from Spain, the Italian Health Search Database (HSD), and the Dutch Interdisciplinary Processing of Clinical Information (IPCI);
- Pharmacy-based medical record linkage systems: Pharmo from the Netherlands and the Danish National Health Service Prescription Database.

The majority of PASS conducted in databases, involved multiple databases (n=16/20, 80%), five of which were part of the Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge Project (EU-ADR) collaboration. However, it should be noted that four of these five PASS were sponsored by the same MAH and involved the same active substance (two protocols for the single active substance and two for a fixed combination of the active substance).

The number of countries involved in these 16 multidatabase PASS ranged from two to nine, with a median of four. The most common medicinal product's ATC class was respiratory system (n=5/20, 25%), followed by cardiovascular and nervous system (n=3/20, 15% each).

Protocols were available for one fourth of the 16 multidatabase PASS (n=4/16, 25%). Only one of the four protocols mentioned a method to consolidate the results from the different databases (a meta-analysis). In addition, while three of the four PASS had a common protocol, the remaining PASS presented four separate protocols, one for each of the four databases included in the PASS.

2.4.4 Sample Size (assessed among the subset of 57 available protocols)

The median sample size was 1000 patients (IQR 1700, n=49) and 289 HCPs (IQR 500, n=9). Ten of the 11 PASS protocols (n=10/11, 91%) with broader patient exposure inclusion based criteria (disease or multiple medicinal product) had samples equal or larger than the overall median, while the majority of the PASS protocols selecting patients based on single exposure (n=23/40, 58%) had sample sizes lower than the overall median.

Figure 15 describes the rationale behind sample size calculation/ estimates according to the analysed PASS protocols.

Approximately half of the PASS protocols based the sample size calculation on estimation of the parameter of interest with a certain degree of precision (n=29/57, 51%), while in approximately one fifth (n=11/57, 19%) of the PASS protocols sample size was chosen to give adequate power to detect an effect of a given magnitude. An additional fifth PASS protocols (n=12/57, 21%) provided practical considerations to justify sample size, such as availability of patients in the selected data

source and market uptake. For the remaining five PASS protocols (n=5/57, 9%) there was no rationale for the target sample size.

Among the 29 PASS protocols that based the sample size calculation on a precision around an estimate, slightly less than half of them (n=14/29, 48%) provided support to the given estimated value, either based on previous studies conducted by the MAH or on literature references. The remaining PASS protocols did not provide a rationale for the expected value, which was set at 50% (most conservative estimate) or a range of options were simulated. In addition, six PASS (n=6/29, 21%) consisting of surveys assessing effectiveness of RMMs, established the target proportion of correct answers to consider the RMMs successful but did not provide a justification for the chosen threshold.

Amongst the 11 PASS protocols which chose a sample size that would give adequate power to detect an effect of a given magnitude, five (n=5/11, 45%) provided support to the assumptions used for the calculation, either from literature or previous studies. The majority of the remaining PASS based the sample size calculation on a simulation of ranges of values for the parameters needed to compute the size. In addition, for one of the PASS protocols, the sample size was fixed for pragmatic reasons but it was demonstrated that the size would give an adequate power to address the study objectives.

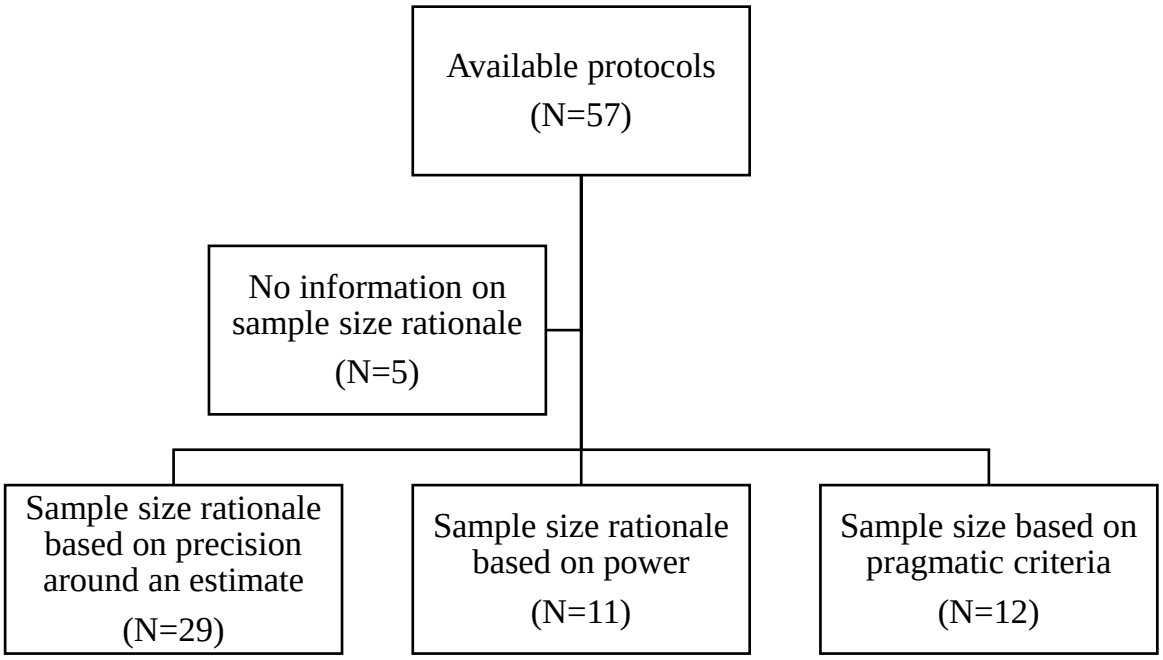


Figure 15 – Sample size rational (among the 57 available PASS protocols)

2.4.5 Analysis (assessed among the subset of 57 available protocols)

Analysis of subgroups of patients of interest such as those for which there was missing information from the clinical trials and vulnerable populations, was mentioned in approximately one third of PASS protocols (n=20/57, 35%), the most common being elderly patients (n=11/57, 19%), hepatic impaired patients (n=10/57, 18%), renal impaired (n=9/57, 16%) and patients with cardiovascular disease (n=9/57, 16%).

The majority of the available PASS protocols did not mention a comparator (n=38/57, 67%). Among the 19 PASS protocols with comparators, the majority of those were other products or standard of care (n=8/19, 42%), participants unexposed to the product being studied (n=5/19, 26%), comparison with data from external data sources (n=5/19, 26%) or comparison before and after the occurrence of an event of interest (n=3/19, 16%), for instance, before and after introduction of RMM and before

and after the approval of a paediatric indication. Two of the PASS included both comparisons with an external data source and also with an exposed group.

As described in *Results Section 2.4.2*, the majority of PASS using other medicinal products as comparators, included those multiple medicinal products as inclusion criteria. However, comparators were not necessarily established as inclusion criteria. Among 46 PASS enrolling participants based on a single medicinal product and for which the protocols were available, eight (n=8/46, 17%) included a comparator in the analysis, namely, an external data source (n=3), comparison pre-post an event of interest (implementation of RMM or approval of a paediatric indication) (n=3), an external data source and an exposed group (n=1) and one with both unexposed group and historical cohort (n=1).

The majority of the 57 PASS protocols only mentioned descriptive analysis, i.e. description to show or summarise data in a meaningful way (n=34/57, 60%).

Figure 16 below presents a sub-analysis of PASS protocols to explore the statistical methods used. Table 5 summarises the different statistical methods mentioned among the available protocols with a longitudinal design.

An *a priori* hypothesis was only present in three (n=3/57, 5%) PASS. The remaining PASS with a longitudinal design but no *a priori* hypothesis testing and for which the analysis section was available (N=42), had, in general, a little detailed analytic plan. Four of them (n=4/42, 10%) presented only vague statements of methods that could be use after descriptive analysis, such as, using a "general linear model", "performing multivariate analysis" conducting "statistical modelling" but not providing any granular consideration or rationale.

Overall, statistical testing for comparison of groups was considered among approximately one fifth of the analysed protocols (n=8/45, 18%). Survival analysis was present in 44% of the protocols (n=20/45, 44%): 13 referring to Kaplan Meier and seven to Cox regression. Other models were mentioned among 14 (n=14/45, 31%) of the protocols, mainly Logistic regression (n=4/45, 9%), Poisson regression (n=4/45, 9%), and propensity scores (n=3/45, 7%).

Sensitivity analysis were planned for one fourth of the PASS protocols for which there was enough information to make that assessment (n=13/52, 25%). Sensitivity analyses were significantly more common among the PASS protocols using secondary data collection approaches than among the PASS using a primary data collection approach (4% *versus* 14%, $p<0.05$).

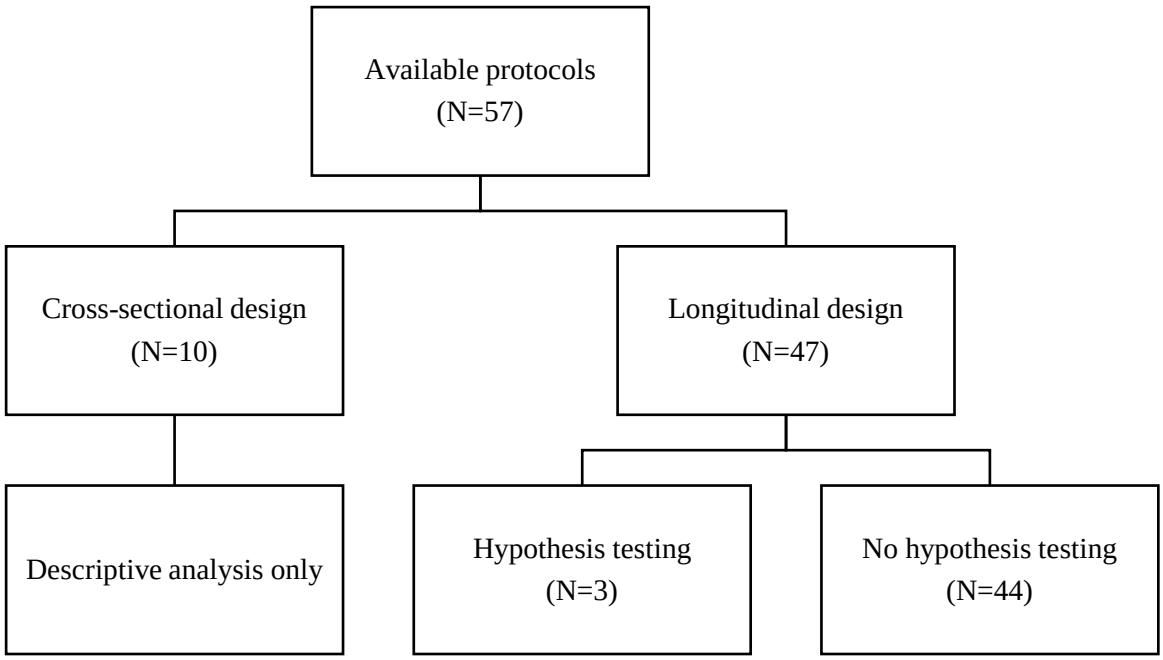


Figure 16 – Sub-analysis of PASS protocols' statistical methods

Table 5 – Statistical methods among available longitudinal PASS available protocols

Available PASS protocols with longitudinal design			
Statistical Methods	**Hypothesis testing (N=3)**	**No hypothesis testing (N=42)***	**Total (N=45)***
	n (%)	n (%)	n (%)
Data summarisation only	**0 (0.0)**	**22 (52.4)**	**22 (48.9)**
Data summarisation + Exploratory analysis to be defined later	**0 (0.0)**	**4 (9.5)**	**4 (8.9)**
Group comparison (tests)	**3 (100.0)**	**5 (11.9)**	**8 (17.8)**
Survival analysis	**2 (66.0)**	**18 (42.9)**	**20 (44.4)**
Kaplan Meier	1 (50.0)	12 (66.7)	12 (66.7)
Cox regression	1 (50.0)	6 (33.3)	7 (35.0)
Models	**2 (66.0)**	**12 (28.6)**	**14 (31.1)**
Logistic regression	0 (0.0)	4 (33.3)	4 (28.6)
Poisson regression	1 (50.0)	3 (25.0)	4 (28.6)
Propensity scores	0 (0.0)	3 (25.0)	3 (21.4)
Other†	1 (50.0)	2 (16.7)	3 (21.4)

*Two documents with missing information on the statistical methods were excluded.
† Other included: analysis of covariance and meta-analysis (in two protocols not testing a hypothesis) and scan statistics in a protocol testing hypothesis.

2.4.6 Sub-analysis of PASS Assessing Effectiveness of RMM

The protocols were available for 38% (n=18/48, 38%) of the PASS assessing effectiveness of RMM. Detailed characteristics of these PASS are presented in Annex 6.

Figure 17 presents a summary of the design, data collection and types of indicators assessed in the available 18 PASS protocols.

In one third of the available protocols of PASS assessing effectiveness of RMMs (n=6/18, 33%), this was the only PASS objective. These six PASS had a cross-sectional design and used questionnaires as primary data collection instruments: two PASS targeted both patients and HCPs (separate questionnaires), and the remaining four only targeted HCPs.

The indicators of effectiveness of RMMs present in all these six PASS were based on the assessment of self-reported awareness of the RMMs and understanding of the conveyed messages (knowledge). In addition, half also assessed self-reported behaviour to scenarios described in the surveys which goal was to estimate the compliance with the RMM.

In order to determine if there were additional PASS to complement the assessment of effectiveness of RMM for the six abovementioned protocols, the PASS database was searched for additional PASS for the six active substances covered in these PASS. There were additional PASS for half of the substances (n=3) but two did not have a protocol available. For the remaining active substance, two additional PASS were found in the database with sufficient information that suggested they would also contribute to assessing effectiveness of RMMs for that active substance (one was a cross-sectional survey assessing prescribing patterns and the other intended to use secondary data sources to assess drug utilisation before and after RMMs).

Two thirds of the 18 PASS protocols assessing effectiveness of RMMs (n=12/18, 67%) also included objectives from the other "PASS focus" categories ("investigate safety concerns" [n=4], "study drug utilisation" [n=3] or both [n=5]). It was noted that, in these PASS, the goals related with the

assessment of effectiveness of RMM objectives were just vaguely described, generally stating that the PASS would monitor compliance with RMMs, either broadly or detailing particular messages of the RMMs such as assessing compliance with medical monitoring procedures highlighted by the RMMs, but not providing granular information.

The majority of these 12 PASS assessing effectiveness of RMMs among other safety objectives, had a longitudinal design (n=8/12, 67%). Three PASS combined in the same protocol, a longitudinal patient follow-up with cross-sectional surveys. In these studies with a combined design, the assessment of effectiveness of RMMs was to be performed through the cross-sectional component only, based on the administration of questionnaires to patients or HCPs to assess awareness and understanding of the RMMs or satisfaction with the RMMs. Whether the longitudinal component of these three PASS would also contribute to the assessment of effectiveness of RMM in an integrated approach was not clear from the protocol text.

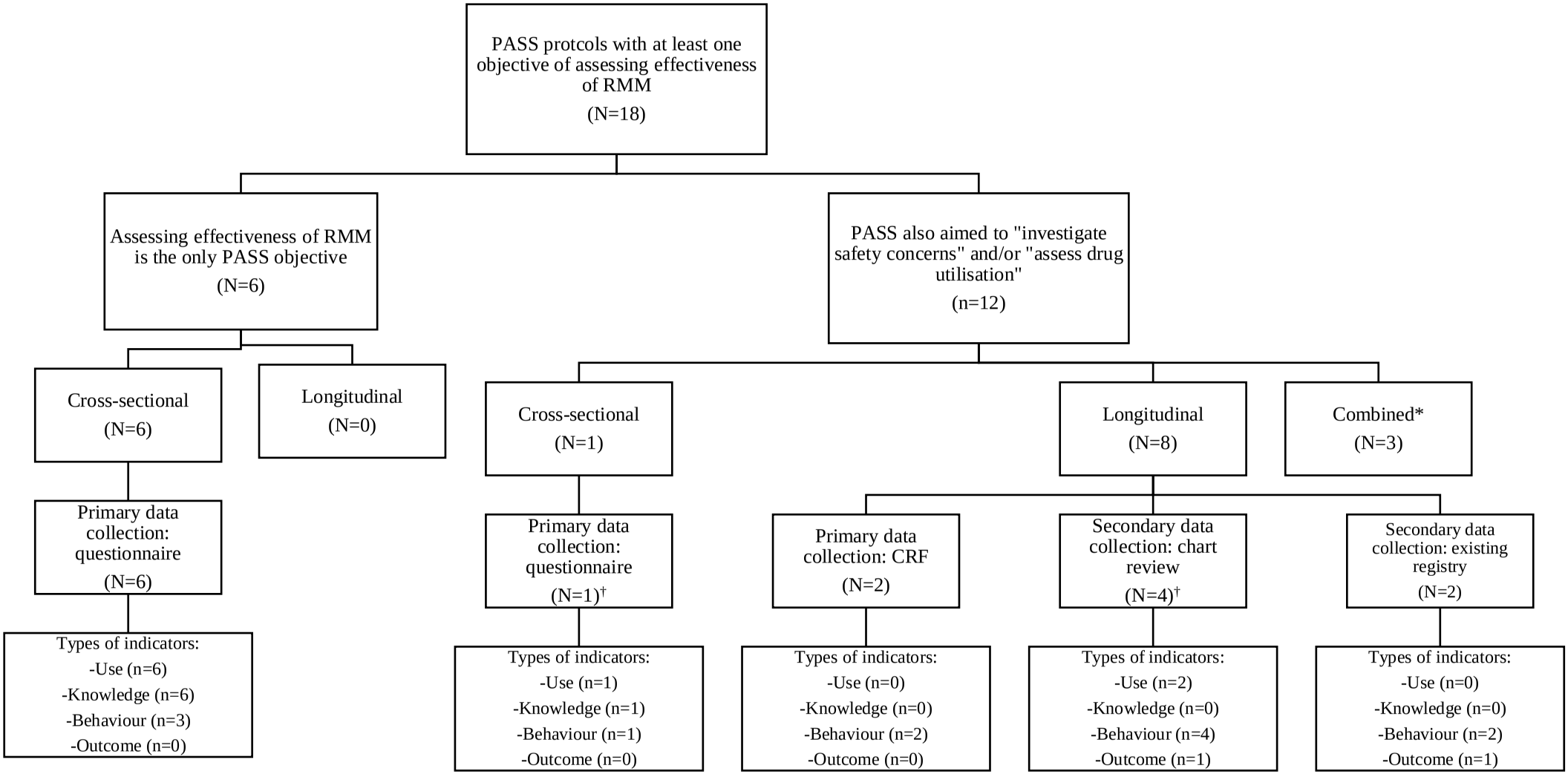
Among the eight PASS with a longitudinal design, two consisted in the establishment of a new patient registry (primary data collection). The registry itself was part of the RMMs as in one of the cases the medical product was only distributed to sites which commit to enrol the patients in a registry and, in the other, a medicinal product with restricted prescription, there was emphasis in the educational materials of the importance to enrol patients in the registry.

Conversely, the remaining six PASS with longitudinal designs used secondary data collection approaches: two retrieving drug utilisation information from existing registries and four from patients' medical records/chart. Data abstraction from the medical records/chart was made at aggregate level in one of the PASS and at individual patient level in the other three, one reviewing data retrospectively and, the other two following-up the patients through prospective review of the charts. To note, one of these PASS protocols described a method similar to a prescription event monitoring approach where the patients were selected by follow-up of orders placed for the medicinal product with an invitation to the clinician to provide data for the PASS.

In summary, the most common observed PASS study designs among those with at least one objective of assessing effectiveness of RMMs were cross-sectional primary data collection through questionnaire use (n=7/18, 39%), followed by longitudinal patient follow-up leveraging patient medical records/charts (n=4/18, 22%), PASS with longitudinal design and nested cross-sectional surveys (n=3/18, 17%), and finally longitudinal patient follow-up with primary data collection (ad hoc registries) and longitudinal patient follow-up leveraging data from existent registries (n=2/18, 11% each).

The most common indicators for assessing effectiveness of RMMs were related with behaviour (prescription patterns and treatment use) (n=15/18, 83%), followed by indicators of awareness/utility of the RMMs (n=11/18, 61%) and knowledge/understanding of the messages on how to correctly prescribe/use the medicinal product (n=9/18, 50%). Outcome indicators were rarely used (n=2/18, 11%). The two PASS protocols describing outcome indicators were also the only PASS using a pre-post RMM design (comparison between frequency of the off-label use before and after implementation of RMMs).

It was noted that, in the PASS protocols with objectives to "investigate safety concerns" and also to "assess effectiveness of RMM", some of the safety concerns' being investigated were also those that the RMMs aimed to minimise. However, the PASS protocols did not clearly interlink both objectives and therefore there was no indication in the protocol text that the safety concerns being assessed as primary endpoints would be also used as outcome indicators of the success of the RMMs. In fact, none of the PASS assessing effectiveness of RMMs and also investigating safety concerns and/or assessing drug utilisation, described the criteria that would be used to determine if the RMM was successful.



Notes: *Three of the PASS had a main longitudinal design with a cross-sectional component for the assessment of effectiveness of RMM; Indicators: Use (n=2), Knowledge (n=2), Behaviour (n=3), Outcome (n=0); †Two PASS contained aggregate data rather than individual-level data (one cross-sectional questionnaire and one longitudinal PASS leveraging data from patients' charts).

Figure 17 – Results of the sub-analysis of PASS assessing effectiveness of RMM

In total, 10 of the 18 PASS assessing effectiveness of RMMs used questionnaires to patients and/or HCPs as data collection tools. The following observations summarise the methodology described in these protocols:

- Countries were selected based on the justification of being sufficiently heterogeneous and also large enough to ensure recruitment;
- The sampling frame was based on a simple or stratified random sample from available panels of prescribers mentioning the possibility of *a posteriori* adjustments. There was no evidence from the protocol text that the sampling had occurred before the protocol was written;
- Half of these protocols mentioned that the questionnaires would be tested before their administration. However, the level of details about the methods used for questionnaire validation was limited, referring only to qualitative validation, such as, language and cultural adequacy and cognitive pre-test interviews;
- Threshold for success was established as 80% or 85%, although no rational was provided for the choice;
- The questionnaires were deemed not to take more than 20 minutes to complete and were mostly accessible on-line;
- Only two of the protocols have the questionnaire available.

For three of these 10 PASS using questionnaires, the protocol also described that compliance with SmPC would be assessed by collecting drug utilisation data, which would provide a complementary way to assess actual behaviour. However the details on how this assessment would be operationalised and considered successful were missing.

3 PRAC Assessment Process

3.1 PRAC Comments

Overall, PRAC comments were available in the minutes, for approximately one third of the 353 PASS protocol submissions (n=106/353, 30%). Among the 130 submissions of imposed PASS protocols, 55% had PRAC comments available (n=71/130, 55%), while among the 223 assessments of non-imposed PASS protocols, 16% had PRAC comments available (n=35/223, 16%), chi-square test, $p<0.05$.

Figure 18 below presents the proportion of PASS protocol submissions, recorded in the PRAC meeting minutes, for which there were PRAC comments available, by year in the analysis.

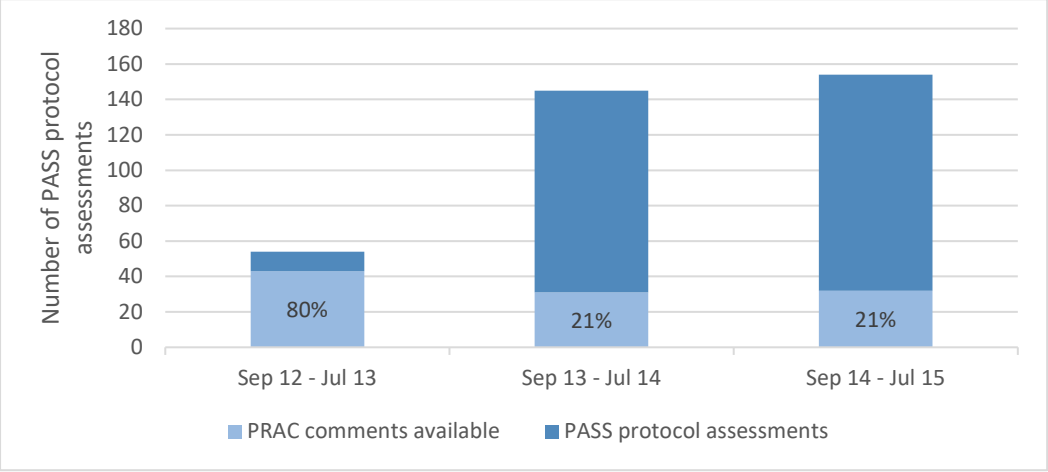


Figure 18 – Yearly proportion of PRAC comments available among PASS protocols presented in the PRAC meeting minutes

Overall, the proportion of PASS submissions for which there were PRAC comments available in the meeting minutes, decreased significantly over time from 80% of the 45 PASS protocol submissions during the first year to 21% of the 154 PASS protocols submitted during the last year of the analysis (chi-square test, $p<0.05$).

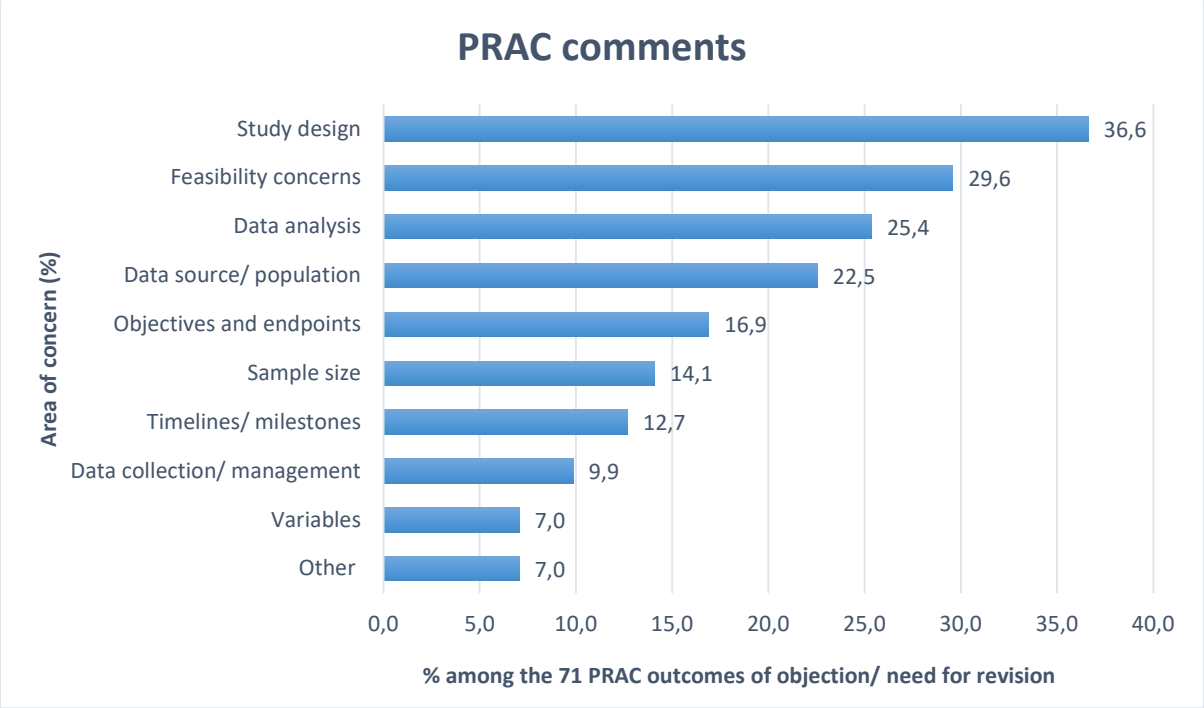
The review of the 106 PRAC comments allowed the categorisation of the outcome of PRAC assessment as:

- Protocol approved/endorsed (n=16);
- Protocol needed to be revised either through a formal objection based on the grounds of Article 107n, for protocols pursuant to an obligation as established in Article 21a, or, without this formal process but with PRAC recommendations to further amend the protocol (n=71);
- Other information (n=19): included comments related with the establishment of timetables to assess subsequent protocol submissions and nomination of the PRAC Rapporteur (n=14), recommendation to conduct joint PASS for PASS protocols that followed a referral procedure (n=4) and one PASS protocol where the PRAC determined that the study was not required anymore. The following rational was provided for this latter case:
  "The PRAC noted that based on the evolution of the product lifecycle to gather information on off-label use was no longer considered a public health concern. Moreover the original recommendation to perform a Drug Utilisation Study was not driven by specific safety concerns or due to RMMs. Therefore the need for the Drug Utilisation Study was reappraised and the PRAC concluded that a Drug Utilisation Study should no longer be a request within the RMP and thus no further detailed comments on the protocol were pursued."

Among the 71 PRAC comments indicating that the PASS protocol version being assessed, needed revision, 27 (n=27/71, 38%) had clear textual indication of a formal objection process (referring to the objection letter and/or Article 107n of Directive 2001/83/EC), typically with the following sentence: "the design of the study did not fulfil the study objectives". In only one case there was another reason mentioned for objection, namely "it was considered that the conduct of the study promotes the use of a medicinal product". All the PASS with a formal objection statement were imposed PASS. For the remaining 44 PRAC assessments (14 related to imposed PASS and 30 to non-imposed PASS), there was no direct mention to a formal objection, but the text indicated the PASS protocols needed to be further revised (e.g. "the protocol could be acceptable provided an updated protocol addressing (…) is submitted to the EMA".

The 71 PRAC comments related with objection/need for further revision of the protocols were further categorised by areas of concern. Annex 7 presents the results of the PRAC comments' text analysis.

Figure 15 presents the distribution of the areas of the protocol identified among the PRAC comments as responsible for the objection/need for revision of the protocol, irrespective of imposed or non-imposed status.



Note: Among the 71 PASS protocol submissions for which the PRAC outcome was protocol objection or need of further protocol revision. Other *ad hoc* comments were related to data protection, change of obligation status (to imposed PASS), safety reporting and rational/background section.

Figure 19 – Methodological issues raised by the PRAC and documented in public PRAC meeting minutes (July 2012 – July 2015)

The following paragraphs summarise the types of comments under each protocol area, from the most to the least frequent.

Study design (n=26/71, 37%): "Inadequate study design" was the standard text for objection of an imposed PASS and the majority of the PRAC comments did not provide more granular details.

Among the minority which had further detail, the following reasons were listed:

- Absence of a comparator;
- Inappropriateness of design to address different safety objectives under the same methodology;
- Inadequate design to address the safety concerns of the RMP;
- Design not safeguarding a non-promotional and non-interventional study nature;
- Preference for an inclusion based on disease rather than single exposure.

Feasibility (n=21/71, 30%): This term grouped concerns with operational viability and scientific validity of the study to address its objectives. They were mainly related with the lack of evidence in the protocols to assure some important considerations were accounted for when designing the study. Those comments included:

- Concerns with bias and confounding;
- The need to develop strategies to ensure operational feasibility;
- Requirement to demonstrate preliminary evidence or rationale to support adequacy of study methods;
- Methodological considerations to safeguard scientific validity.

Data analysis (n=18/71, 25%): Included requests to further detail or clarify the proposed plan. Almost half of the PRAC comments related to this area of concern did not provide more granular information.

Data sources and/or population (n=16/71, 22%): Comprised concerns with recruitment, sampling strategy, and justification for the selection of certain data sources. The majority of these comments did not provide specific details.

Objectives/Endpoints (n=12/71, 17%): Included the need to add/amend objectives, to have more measurable objectives, include better defined endpoints, or to have objectives consistent with the study purpose according to the RMP.

Sample size (n=10/71, 14%): Comments were related with concerns with statistical precision or power, or the need to further clarify or amend the proposed sample size.

Timelines/Milestones (n=9/71, 13%): Included recommendations to avoid study delay or considerations on appropriateness of timelines.

Data collection/management (n=7/71, 10%): Included advice on specific instruments (e.g. inclusion of a patient's diary), the need to collect or validate certain data or the need for further clarification on the data collection methods.

Variables (n=5/71, 7%): Only one comment had details (the need to include concomitant medication among study variables).

Other (n=5/71, 7%): There was a comment regarding rational and background, one regarding data protection, two comments regarding the need to impose a PASS that was initially non-imposed to stimulate the study initiation, and one comment related to the safety reporting section.

Figure 20 presents the distribution of areas of concern by obligation status. The proportion of imposed PASS protocols in need for revision due to "study design" was approximately the double of those among the non-imposed PASS protocols. Conversely, a higher proportion of non-imposed PASS protocols' assessments, had comments related with the feasibility of the study and the data analysis.

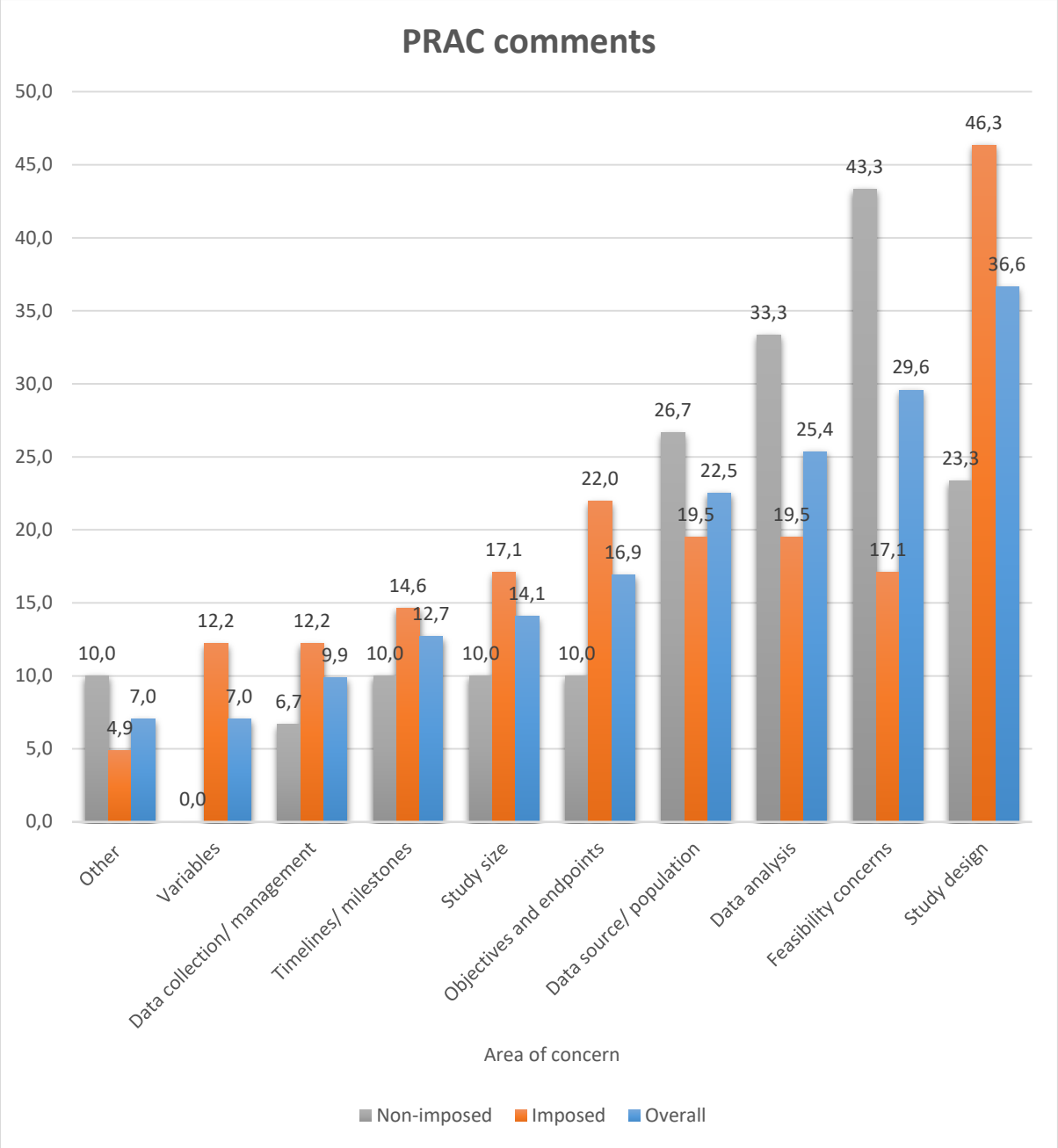


Figure 20 – Methodological issues raised by the PRAC and documented in public PRAC meeting minutes (July 2012 – July 2015) by PASS obligation status

An insight from reading all the PRAC comments and also the available PASS protocols was that, independently of the specific section of the protocol, the level of granular detail provided in the protocols was limited, most of the times lacking the critical reasoning behind the methodological decisions. In addition, the acknowledgement of study limitations, a reflection on their impact and on how they would be minimised, and/or arguments to support the practical feasibility of the methods and their robustness to obtain valid study conclusions, were often minimal.

3.2 Resubmission and Reassessment Timetables

The PRAC comments in the minutes also contained information on the timetables that would follow a resubmission and reassessment of a PASS protocol after being rejected. Table 6 summarises the timetables referred to in the PRAC comments' text among those associated with the need for a further round of revision of a PASS protocol.

The majority of the 41 imposed PASS protocol assessments with PRAC comments available needed to be resubmitted within 30 days (n=16/41, 39%), or 60 days (n=14/41, 34%). Less than 10% were urgent resubmissions (14 days). Among the 30 non-imposed PASS protocols, the majority did not have a timetable assigned (n=11/30, 37%) or the text only mentioned the protocol needed to be revised before the study started (n=8/30, 27%).

The majority of the reassessment timetables established for the imposed PASS protocol assessments were of 30 days (n=16/41, 39%) while 27% (n=11/41) had a 60-day assessment timetable. Despite the vast majority of the non-imposed PASS protocols did not have an established assessment timeline, three non-imposed PASS protocol assessments were given a 30 or 60 days assessment timeline.

Table 6 – PASS protocols' submission and assessment timetables according to the PRAC comments on meeting minutes related to the need for protocol resubmission (N=71)

	Protocol submission timetable			**Protocol assessment timetable**		
	Imposed (n=41)	**Non-imposed (n=30)**	**Total (n=71)**	**Imposed (n=41)**	**Non-imposed (n=30)**	**Total (n=71)**
Time	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
14 days	1 (2.4)	0 (0.0)	1 (1.4)	NA	NA	NA
15 days	2 (4.9)	0 (0.0)	2 (2.8)	2 (4.9)	0 (0.0)	2 (2.8)
30 days	16 (39.0)	6 (20.0)	22 (31.0)	16 (39.0)	1 (3.3)	17 (23.9)
60 days	14 (34.1)	2 (6.7)	16 (22.5)	11 (26.8)	2 (6.7)	13 (18.3)
90 days	2 (4.9)	1 (3.3)	3 (4.2)	NA	NA	NA
"Before procedure finalisation"	0 (0.0)	2 (6.7)	2 (2.8)	NA	NA	NA
"Before study start"	2 (4.9)	8 (26.7)	10 (14.1)	NA	NA	NA
Missing	4 (9.8)	11 (36.7)	15 (21.1)	12 (29.3)	27 (90.0)	39 (54.9)

3.3 Estimate of PASS Protocol Review Duration

PRAC process metrics were estimated among the PASS protocols for which the PRAC review was assumed complete (n=103/189, 54%), see Figure 8.

Approximately one third of the endorsed PASS protocols (n=31/103, 31%) appeared only once in the minutes, and the PRAC comments were not conclusive on whether they were approved on that round. The vast majority of those (n=25/31, 81%) were non-imposed PASS, which are not required to follow the same formal submission process as the imposed PASS. Therefore, it was decided not to compute metrics on the PRAC review process for the non-imposed PASS.

For the imposed PASS protocols appearing more than once (n=32/38, 84% of the imposed PASS considered approved), the data suggested a decrease in the median number of rounds of review from 3 (N=9) to 2 (N=6) and a mean (SD) decrease in time of review from 10.2 months (SD=4.7) to 3.8 months (SD=1.6), when comparing PASS protocols submitted for the first time, between July 2012-

July 2013 and those submitted for the first time between July 2014-July 2015, as shown in the Figure 21.

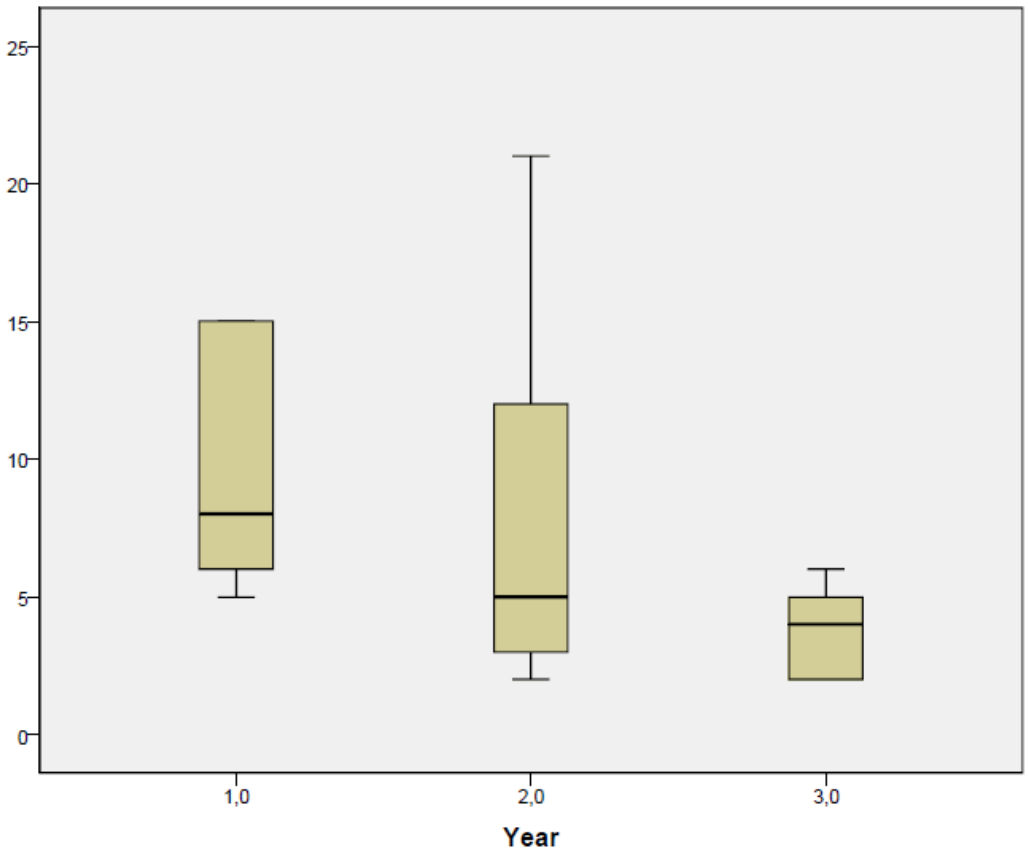


Figure 21 – Estimate of PASS protocol assessment duration since first submission until approval for which the PRAC review was assumed complete (N=32; year 1 = 9, year 2 = 17; year 3 = 6)

Discussion

Over the last decades, numerous public health crises have shaped regulatory changes and led to the creation of Pharmacovigilance, along with, innovative surveillance systems and safety epidemiologic methods. Although those initiatives have contributed to the safer use of medicinal products, enforcement of additional measures was deemed necessary at the beginning of the new millennium. Among the new activities, PASS gained prominence as pharmacoepidemiological methodology offered tools to investigate uncertainties related with safety concerns.

This review aimed to draw, for the first time, the PASS landscape during the first three years under the most recent Pharmacovigilance legislation. This was accomplished by describing the first cohort of PASS protocols submitted to the EMA since the first inaugural PRAC meeting in July 2012 to July 2015, charactering PASS and reflecting on the achieved levels of transparency and on the extent to which, PASS incorporate Pharmacovigilance and Pharmacoepidemiology principles.

Overall, the results showed that despite the unprecedented level of transparency achieved, which made this study possible, there is still room for improvement in the level of information provided by regulators and MAHs. It was also evident that there is and some lack of communication between different stakeholders, which may be worsened by lack of uniform terminology.

In addition, the results suggested some discrepancy between PASS as conceived in the RMP and the PASS protocols developed, highlighting the need to reinforce the bridge between Pharmacoepidemiology and Pharmacovigilance. To exemplify this point, a more in-depth analysis was conducted among the subset of PASS assessing effectiveness of RMMs. These types of PASS constitute a good example of the required convergence between Pharmacovigilance and Pharmacoepidemiology and are part of a key component of the Risk Management cycle by providing constructive feedback to allow the refinement of the Risk Management activities.

The recognition of the singularity of PASS, as pharmacoepidemiological studies that have a specific mission within the medicinal products' RMPs, calls for alignment of the different parties to tailor the best approach for each safety question. Cross-functional collaboration and communication across stakeholders, higher levels of transparency and a common terminology would be key to foster best practices that will surely contribute to a safer use of medicinal products.

1 The First Comprehensive Drawing of PASS Landscape

PASS were introduced in European guidelines in 2005. Two reviews published in 2009 and 2011, respectively, described PASS for the first time from the perspective of the regulators making recommendations to streamline the regulatory review, engage earlier with the MAH to discuss the objectives, design and study feasibility and build more expertise and capacity in preparation for the upcoming Pharmacovigilance legislation.(23, 47) More than three years have now elapsed since the implementation of the new Pharmacovigilance legislation and no study had yet attempted to explore the landscape of PASS submitted under the new framework. The current dissertation aimed to suppress this gap by examining multiple facets of PASS. The following paragraphs outline the main findings describing PASS genesis, objectives and methods of PASS protocols and insights into the protocol review process.

1.1 PASS in Medicinal Products' Lifecycle: Towards a Proactive Approach

The new legislation aimed to shift from a reactive system to a more proactive one. The implementation of measures such as PASS, early in the lifecycle of the medicinal products could swiftly address uncertainties, thus, prompting early action to prevent or minimise the occurrence of safety concerns.(21) Therefore, it is not surprising that the majority of the submitted PASS were established with the initial marketing authorisation, either as an imposition or a commitment in the RMP agreed with the EMA.

However, the second most common lifecycle events originating PASS were safety referral procedures.[2] Measures implemented as a consequence of a referral imply that some safety concerns have already occurred. As more proactive measures are implemented early in the lifecycle of new medicinal products, a decrease in the need for safety referrals may be expected. However, it is still early to judge the effects of the new legislation in the medicinal products already approved under the new regulatory framework, as recent findings indicated a referral procedure occurs on average 18.7 years after the launch of new medicinal products.(68)

Hopefully, early implementation of PASS will provide a continuous influx of information to smoothly manage the benefit-risk profile of the medicinal products without the need for a major reassessment of the marketing authorisation consequent to safety occurrences. In fact, the new legislation brings the possibility of the regulators to legally enforce the PASS, by imposing them as condition to the marketing authorisation when the safety question is critical to ensure the positive benefit-risk of the medicinal product, or, as a special obligation to the marketing authorisation for the situations where it is not possible to obtain comprehensive data on the efficacy and safety under normal conditions of use (i.e. because the condition to be treated is rare or collection of full information is not possible or ethical). Therefore, it is not surprising that the proportion of PASS addressing a medicinal product with orphan medicinal product status was higher among the imposed PASS as compared to the non-imposed PASS (22% versus 9%, $p<0.05$). Orphan medicinal products are those for the treatment, prevention or diagnosis of a rare disease that is life-threatening or chronically debilitating for which there are no therapeutic alternatives.(69) Since medical and scientific knowledge about rare diseases is lacking upon marketing authorisation of orphan medicinal products, it is not surprising that to the regulators enforce the implementation of PASS as condition or special obligation to maintain the marketing authorisation based on the proactive collection of evidence of the safety of those orphan medicinal products.

[2] A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines

1.2 PASS Protocol Submission and Assessment: Towards Quicker PASS Implementation

Under the new legal framework, only imposed PASS must be submitted to the PRAC and having a specific procedure and timelines for assessment. However, our results suggested that, sponsors of non-imposed PASS were following the same procedures with more than two thirds of the total PASS mentioned in the PRAC minutes, being non-imposed.

Notwithstanding, the majority of the PRAC comments of non-imposed PASS assessments did not mention a specific timetable, which is consistent with the fact that there is no formal assessment established for these. This may also explain why, the proportion of imposed PASS protocols in need for revision due to "study design" was approximately double than that of the non-imposed PASS protocols since there is a standard text for objection of PASS protocol according to Directive 2001/83/EC (Article 107n), "the design of the study does not fulfil the study objectives", which is applicable to imposed PASS protocols. Therefore, it is possible that this statement was generally used in the PRAC comments' text to indicate rejection due to scientific reasons and not necessarily with the study design section of the protocol.

The PRAC comments in the minutes also provided insight on the submission and assessment timetable of PASS protocols. Although the minutes may not accurately represent the formal decision that would be available to the MAHs, it was still informative to analyse the information provided.

For the vast majority of the cases, the PRAC did not consider necessary to accelerate the review process as less than 10% of the PRAC comments on imposed PASS referred to the 30-day time frame (15 days for PASS resubmission followed by 15 days for PRAC assessment) which can be enforced when "the PRAC considers that the protocol needs to be resubmitted quickly to allow endorsement at the following PRAC meeting".(49)

The results suggested a trend towards quicker implementation of PASS protocols. When comparing the metrics of the PASS protocols submitted for the first time during the first year in the analysis, with those submitted for the first time during the third year, there was a decrease in the median number of rounds of assessment from 3 to 2 corresponding to an average decrease of the overall review process of 6 months. Even if the results are based on a small number of imposed PASS, they corroborated the positive trend reported during a presentation by the EMA at an Information Day on Post Authorisation Studies held on June 2005.(70)

The general improvement in the assessment timeframe may be due to the more stringent regulatory requirements or to early engagement on study objectives and study design as recommended in the two reviews of PASS conducted before the new legislation.(23, 47) Ideally, PASS planning and feasibility should start within Risk Management planning.(47) Although this was not possible to assess in this study, the EMA scientific advice pilot initiated late 2015, where companies can voluntarily submit non-imposed PASS for early scientific advice, demonstrates the EMA's commitment towards a proactive Pharmacovigilance planning.(49)

In addition to the establishment of a defined assessment process and timelines, PRAC oversight was regarded with much expectation to reduce the insufficient adoption and lack of synchronisation in the implementation of the recommendations from the previous Pharmacovigilance Working Party, which had a more limited scope of influence.(21) Despite the achievement of a higher level of harmonisation with the creation of PRAC, which oversees PASS conducted in more than one Member State, PRAC recommendations still need to be endorsed by the other EMA committees and, afterwards, to be implemented at country level. At that stage, they may be subject to different requirements, which in turn, may challenge the setup and execution of multi-country and multi-centre PASS. Two recent studies highlighted the variety of regulatory requirements by geography and that early determination of those are key to ensure a successful implementation of the PASS.(71, 72)

The upcoming 2016 new clinical trial regulation (Regulation EU No 536/2014) will hopefully contribute to more harmonised decisions among European Ethics Committees with regards to the

classification of PASS as interventional or non-interventional. However, the introduction of "low interventional clinical trials" definition could result in many PASS assessments no longer being led by the PRAC.(73)

1.3 PASS are Not Taken as a Collective Endeavour Yet

The PASS were typically sponsored by a single MAH. Joint sponsorship was more commonly observed in PASS resulting from referral procedures since those apply to multiple medicinal products with the same active substance or to a class of products.(68) These results seem to indicate that MAHs tend to collaborate more when prompted to do so as a consequence of the occurrence of safety concerns.

Joint sponsorship is recommended by the new legislation.(25) Some EU initiatives represent good opportunities to expand joint efforts, leveraging new governance models and increasing visibility of existing data sources to support their use in a cross-border setting for both public health and research needs. The EMA patient registry initiative aims to identify and evaluate existing data sources and develop a methodological toolkit for establishing new registries if needed.(74) The Innovative Medicines Initiative (IMI) ADVANCE project is also a good example of an ongoing initiative to bring together multiple stakeholders in order to develop a common framework capable of rapidly delivering reliable data on the benefits and risks of vaccines.(75)

1.4 Expected and Unexpected PASS Objectives

A post-authorisation study is classified as a PASS when the main aim for initiating the study includes the quantification and assessment of risks or their absence, either known or for which there are uncertainties (e.g. in patient populations for which safety information is limited, or after long-term use), to assess patterns of drug utilisation that add knowledge on the safety profile of the medicinal product, or to measure the effectiveness of a RMM.(48)

Therefore, a PASS is defined by its objectives and not by its design. PASS objectives were divided into three categories based on the above definition: to investigate safety concerns, to study drug utilisation and/or to assess effectiveness of RMM. Approximately one third of the PASS combined in the same protocol at least two of the three defined categories. In particular, the majority of studies assessing drug utilisation or the effectiveness of RMM also combined objectives of the other categories.

In addition to safety objectives, one third of the PASS also assessed benefit endpoints. This may suggest that the setup of PASS represent good opportunities for MAHs to also capture routine effectiveness and real-world information for other stakeholders such as Health Technology Assessors. However, adding extra objectives is usually discouraged if they jeopardize the addressing of safety objectives, are too burdensome for the study conduct and possibly lead to Ethics Committees' protocol rejection.(76)

1.5 PASS Typically Enrolled European Patients Exposed to the Medicinal Product of Interest

All PASS involved at least one European country and more than three quarters were conducted in European countries only, which represents an improvement from the situation reported in 2009 where one third of the PASS did not include EU populations, which was considered a limitation to the generalisability of the results.(47) However, half of the PASS were conducted in five or less European countries which may raise concerns about the generalisability of the results to all European populations. The importance of internal *versus* external validity in Pharmacoepidemiology has been a recent topic of debate, reflected by the agenda of the recent International Conference on Pharmacoepidemiology & Therapeutic Risk Management.(77) From the regulatory point of view,

decisions are normally based on different types of evidence, representativeness being particularly important for assessing effectiveness of RMM, which is highly dependent on the local context where the RMM are applied.(78)

More than two thirds of the PASS (70%) were restrictive in the exposure criteria used to define the study population, by focusing only on the exposure to the medicinal product.

In addition, almost one third of PASS, for which the protocol documents were available, enrolled only patients typically excluded from clinical trials, where safety information is considered missing or limited, such as, paediatric patients (mainly when PASS followed an extension of the marketing authorisation to the paediatric population) and pregnancy registries. Another third of those PASS planned a sub-analysis of vulnerable populations typically excluded from clinical trials such as, elderly patients and patients with hepatic, renal or cardiovascular comorbidities.

1.6 A Snapshot of PASS Methods

The comparison between imposed and non-imposed PASS protocol across the different characteristics analysed in this review did not suggest any significant difference in terms of the assessed PASS characteristics. Overall, the vast majority of PASS (81%) were designed to collect data from study participants from at least two time points (longitudinal design) with an estimated follow-up median of 3 (IQR: 4) years. While cross-sectional designs represented the minority of designs for both imposed and non-imposed PASS, they were more common among the non-imposed ones.

The results suggested an association between study design and PASS focus, as the vast majority of PASS with at least one objective related to investigate safety concerns had a longitudinal design (94%), while the majority of PASS not containing any objective of this category had a cross-sectional design (61%). On the other hand, 56% of PASS with at least one objective of assessing effectiveness of RMM had a cross-sectional design, while 94% (n=94/100) of PASS without this objective, had a longitudinal design.

In terms of data collection approaches, slightly more PASS (58%) involved the development of *de novo* data collection tools specific for the study (primary data collection) rather than leveraging data collection schemes already established for other purposes such as administrative or other research projects (secondary data collection). Data collection approach seemed to be associated with PASS focus as 58% of PASS with at least one objective related to studying drug utilisation were using secondary data collection approaches, while 66% of PASS not containing such objective were mainly using a primary data collection approach.

According to the *AHRQ Handbook on Registries for Evaluating Patient Outcomes*, "primary data collection is typically used when the data of interest are not available elsewhere or, if available, are unlikely to be of sufficient accuracy and reliability for the planned analyses and uses. Primary data collection increases the probability of completeness, validity, and reliability because the particular study drives the methods of measurement and data collection".(79) Those advantages may reflect the preference for the use of primary data collection approaches among PASS in particular if safety information was not routinely available in existing data sources or not collected in a homogenous way. In addition, among the available protocols of PASS with a primary data collection approach, approximately one fifth included PRO assessments. PRO provide a unique perspective that is not available through any other means, for instance, treatments not necessarily prescribed by clinicians and quality of life.(79)

Among secondary data collection approaches, while data abstraction of information from local medical records still represents a common approach (30%), the use of wider systems, such as, automated EMRs, claims databases and data from existent patient registries, already represents the majority of the secondary data collection approaches. The use of electronic databases in Pharmacoepidemiology has increased in the past decade since they confer several advantages, namely, increased speed, minimise recall and reporting bias and lower costs.(80) In addition, they

usually contain very large patient populations including children, elderly and other groups often under-represented or totally excluded from clinical trials. Therefore, their large size allows the study of rare events and, overall, they seem to be considered representative of routine clinical care.(6, 78)

While the use of databases is increasingly popular, particular PRAC comments related to concerns with selection bias highlighted the need for an appropriate consideration of the available data sources and justification for the selection of certain ones.

The ENCePP Inventory of Databases provides a catalogue of data sources available in EU research organisations, to serve as a hub, in which researchers can identify a potential resource for their investigation.(81) An ongoing EMA initiative will aim to increase visibility of existing data sources and support their use in a cross-border setting for both public health and research needs.(74)

In addition, there is a need to carefully consider the quality of the databases. Validation studies have been encouraged to ensure validity of study results, estimate the extent of misclassification and impact on the study results.(82) In addition, since PASS are often multi country studies, additional considerations on how to combine different databases are important and have been subject to intense research over the past years.(83-85)

Regarding the analytic methods, the majority of PASS protocols had limited or vague information. This is also reflected by the PRAC comments on the data analysis section, the majority of which requiring a revision of this section to include more details or clarification of the planned analysis. *A priori* hypothesis were present in only 5% of the protocols. The majority of the remaining contained only descriptive analysis, rarely accounting for confounders or effect modifiers.

The fact that the vast majority of PASS focused on enrolling patients or prescribers of single exposure of interest (70%) implied the absence of an active comparator group. However, among the available protocols, approximately one fifth of the single-drug exposure PASS protocols available contained implicit or explicit comparators such as absence of the exposure, comparison with external data source/ historical data or pre-post event of interest. Overall, two thirds of PASS protocols did not including a comparator. The particular nature of the research questions addressed by PASS may justify this approach as it will be further discussed in the following section. Only a case by case analysis of the protocol would allow an appraisal of the appropriateness of this choice. However, given that 2 of the 26 PRAC comments related with study design, requested a broader inclusion criteria than single drug exposure for comparison reasons, may suggest that the selection of single exposure design might not have been the most adequate approach in some PASS.

Sensitivity analysis were documented in slightly less than one third of PASS overall and were significantly more common in PASS using a secondary data collection approach, which is consistent with recommendations to use these methods when conducting database studies.(83)

Approximately half of the PASS protocols available based the sample size calculation on an estimation of the measure in question with a certain degree of precision. Among the remaining, an equal number of PASS based sample size on the adequate power to detect an effect of similar magnitude and on practical considerations such as, estimated market uptake and available patients in a data source. One tenth did not provide any rationale. Moreover, even among those who presented sample size calculations based on precision or power, only a minority provided the background for the given expected values and assumptions used in the calculations.

2 Increased Transparency but Still Some Clouds in the Way

Lack of transparency had been identified as a major limitation to assess pharmaceutical Risk Management activities including PASS before the new Pharmacovigilance legislation. The lack of publicly available data on study protocols and their timelines were referred as limitations for researchers outside the EMA(18) and even within the EMA it was challenging to track the different processes and decisions.(47)

The establishment of PRAC oversight, specific procedures and timelines for PASS submission, the publication of the monthly meeting minutes and the endorsement of the EU PAS register as the official database for PASS registration represent major achievements of the new legal framework.(86) In particular, the EU PAS register was regarded with much expectation.(18, 47)

The fact that it was possible to track PASS protocols being discussed at the EMA from available meeting minutes already reflects an unprecedented level of publicly available information from the regulators.

Notwithstanding, the results of this work, allowed the identification of three areas that are still impairing knowledge access and sharing: partial availability of information, scattered data and inconsistent terminology.

2.1 Insufficiently Published Data

2.1.1 At the Regulators' Level

PRAC feedback on the submitted protocols was very limited, restricting the possibility to learn from the assessment of the submitted protocols.

Firstly, PRAC assessment comments were available in the publicly available meeting minutes for only one third of the submissions, and the results do not anticipate an improvement, as the availability of PRAC comments in the minutes was higher in the first year of the new legislation but decreased during the following two years.

Secondly, within the available PRAC comments, the outcome of PRAC assessment (i.e. whether or not protocols were considered approved, rejected, or in need of revision) was rare and unclear, requiring several assumptions to be made. Granular details regarding the specific weakness and recommendations were very limited. Despite these limitations, the analysis of the available PRAC comments revealed that irrespective of the status of PASS (imposed or non-imposed), comments and requested revisions of protocols were consistent with previous results.(23, 87)

2.1.2 At the Industry Level

The results showed that only half of the PASS covered in the study period were entered in the EU PAS Registry by July 2015, suggesting a lack of adherence to the Registry from the pharmaceutical industry. This result has to be balanced with the fact that registration is legally binding and subject to financial penalties only for imposed PASS at the time of final study report. Nevertheless, registration of PASS in the EU PAS Register is strongly recommended by the guidelines.(48) A positive trend in the registration is observed though, with an increase of over 20% of both imposed and non-imposed PASS registration from July 2014 to July 2015. However few documents, such as, protocols were available. The regulators should keep emphasising the importance of this registration. A recent update to the EU PAS Register includes incentives for MAHs to provide dates to track the study milestones from "date when funding contract was signed" to "date of final study report" as reminders are sent after the planned date for the start of data collection, and after the planned date of the final study report.(88) This and upcoming updates on the guidelines or functionalities of the EU PAS Register will be important to strengthen the use of the Register.(50)

In addition, to the insufficient registration, a few general observations from the review of the available PASS protocols can be made regarding the level of information provided in the protocols. There was a limited level of detail provided, many times lacking the critical reasoning behind each methodological decision, the acknowledgement of study limitations and of their impact and ways to minimise them was often not explicit. Furthermore, there was a general lack of arguments to support the practical feasibility of the methods and their robustness to obtain valid study conclusions. These findings were corroborated by the high number of PRAC comments related with feasibility concerns, such as, the absence of enough evidence to support that the planned strategy was feasible, lack of discussion on limitations (e.g. bias) and strategies to minimise those, absence of adequate pilot study, lack of preliminary feasibility data and of evidence that collected data would be valid to address study objectives. Several comments on other protocol sections also reflected the insufficient level of detail provided in the analysis, the rationale for the choice of data source and the need to provide more specific objectives.

In addition, PASS utilising questionnaires rarely appended the questionnaire to the protocols. Given that questionnaire design can affect results interpretation, there have been several claims for questionnaires to be available to the research community.(89)

The lack of granular detail in the study protocols was also a finding in the review of PASS before the new legislation.(23) The limited level of detail in the protocols is not in line with the major guidelines in the area (GPP and GVP), both emphasising the need to include details on the reasoning behind the methodological decisions and feasibility considerations.(48, 52)

There is clear evidence that the EMA implemented mechanisms to promote the development of well-though and robust protocols. The specific EMA template for PASS protocols embeds text and guidance consistent with the guidelines. In addition, it specifies the need to complete and append the "ENCePP checklist for study protocols". One of the goals of the ENCePP checklist for study protocols is to "promote transparency regarding methodologies used in pharmacoepidemiological studies". The checklist includes a list of topics that should be taken into consideration to develop and demonstrate that PASS are planned with scientific quality.

Without granular information on protocols, it is not possible for a reader to assess whether or not the appropriate operational and methodological considerations were taken into account. This constitutes a major obstacle to the assessment and communication over a certain PASS protocol and impairs sharing best practices and lessons learned. Increased transparency in methods has been a common pledge among other reviews.(83, 85, 90, 91)

Furthermore, lack of details on the study methodology fails one of the core principles of the epistemological nature of the scientific method, as only by specifying *a priori*, the details of an experiment, it is possible to attempt at refusal later on. Popper stated that "the criterion of the scientific status of a theory is its falsifiability, or refutability, or testability".(92)

Therefore, despite the visible efforts implemented by the regulators to promote sufficiently detailed and well though studies, it is important to keep emphasising the need to provide more robust protocols that would allow a fruitful discussion between regulators and sponsors to increase the probability of the study to be able to achieve its goal.

2.2 Broken Chain of Information

The methods section of this dissertation reflects the complexity of tracking the different PASS protocols submitted through the meeting minutes and complementing the information with data from the EPARs and the EU PAS Register. Therefore, the same challenge identified by the EMA authors of a previous review that the "fragmented nature of the available data did not facilitate further analysis" was also felt in this review.(47) However, while these challenges were previously only felt by the regulators, which were the only stakeholders with access to information, they are now also experienced by researchers outside that context, which already represents a step forward in transparency, and a different reality from what was possible before.

From the minutes of the February 2014 meeting on, the inclusion of the EMA procedure number and scope facilitated the tracking of consecutive versions of the same protocol and helped to more quickly identify the relevant EPARs. However, it is unfortunate that there is no single document tracking all the different regulatory submissions by medicinal product. The document "changes since initial authorisation of medicine" available for each product in the EMA website records some of the changes to the marketing authorisation such as variations. It would be useful to integrate among the chronological entries, reference to other regulatory processes such as RMP and protocol assessments and approvals.

2.3 Lack of a Common Language

From an early stage of the project, it became apparent that different terms are used inconsistently to define study designs, and that a given term may be interpreted in different ways. This made the developing of a coding scheme very challenging and the need to create a unique coding dictionary to overcome the lack of consistent standards.

The lack of consensus in terminology may lead to different interpretations of protocol content among different stakeholders. Therefore, rather than a mere preference on semantics, the consequences of lack of harmonisation severely impact the ability to collaborate and communicate among different parties and individuals.

This problem seems well acknowledged in the field of Pharmacoepidemiology as illustrated by the following quote from one of the main textbooks in the field: "The same term is sometimes used by different authors to describe different concepts. Unfortunately, when reading a scientific paper, there is no way of determining which usage the author intended".(6)

Inconsistent use of language is even observed within and between guidelines and the EU PAS Register.

2.3.1 Inconsistencies within Guidelines

The fact that guidelines themselves are ambiguous or contradictory in the choice of terminology makes it challenging to promote a consistent language in the field. Some highlights are discussed below.

Prospective versus Retrospective design:

These terms are sometimes used from the perspective of how study participants are selected and followed-up (prospective would be the patients selected based on exposure and then followed-up until the outcome) or from the perspective of how data are collected for the study (if the patients are selected based on exposure but all data was already collected in the past, the design is considered retrospective in line with this viewpoint).

Primary versus Secondary data collection:

GVP Module VIII presents ambiguous information. On the one hand, the module's introduction implies that secondary use of data consists on "database research or review of records where all the events of interest have already happened" and connotes primary data collection with "prospective observational studies and registries in which the data collected derive from routine clinical care". On the other hand, the definitions given in appendix section "data sources" do not refer to "primary" and "secondary" data collection. Instead a distinction is made between "field studies" (collection of data from subject interviews or from consulting paper-based medical records) and "automated databases" (containing medical records and administrative ones).

The definitions used in the introduction of the abovementioned module indicate that secondary data collection is synonymous to a retrospective design and primary data collection is the same as having a prospective design. This seems to be a common fallacy. Since in secondary data collection

schemes, the data collection tool is already built, retrieval of data already collected is generalised to retrospective data collection. Conversely, data collection tools in primary data collection studies are developed for the planned study and there is no data collected before the study beginning, thus being associated with prospective data collection.

However, the use of the terms interchangeably results in an oversimplification of the different shades of study designs that can only be captured by using both pairs of terms to describe different characteristics. An example of a situation in which a study can use primary data collection and have a retrospective design, could be the collection of past exposures by interviewing patients with certain outcomes of interest given that there is no database or records with the available information of interest. Conversely, an example of a situation in which a study can use secondary data collection and have a prospective design, could be the collection of data from the exposure to a new medicinal product by real-time follow-up of patients through the monitoring of a routine EMR which already contains all the necessary data fields of interest.

As seen in these examples the use of both terms provided additional information to understand the study design.

In this dissertation, the lack of granular information hindered the correct ascertainment of whether a longitudinal design had a prospective or retrospective perspective. Therefore, study design was classified as "longitudinal" or "cross-sectional" and types of data collection as "primary" if data collection scheme was implemented *de novo* for the study and "secondary" if data was retrieved from an existing data collection scheme.

Registry vs. cohort

GVP Module VIII differentiates PASS study designs as "Active surveillance (Intensive monitoring schemes/ Prescription event monitoring/ Registries)" and "Observational studies (Cross-sectional study / Cohort Study/ Case-control study/ Case-only designs/ Clinical trials/ Large simple trials and Drug utilisation studies)".

The limited availability of information for most PASS prevented such a granular design classification. However, the use of such classification could be challenge from a practical perspective. For example, 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.(48, 79) Therefore, the definition of a registry can also fit in the definition of an observational cohort.

In addition, GVP also mentions that a registry can be used as a data source for other studies, which was the case in some of the described PASS in this review. Therefore the term registry can be both connoted with a study design or with data source. This may lead to an ambiguous message if there is no further information. In the current study, the term was used as a secondary data source to identify the cases in which PASS were embedded in, or collected information from, pre-existing registries.

Drug utilisation study as PASS focus rather than design

On the other hand, the term "drug utilisation study" is defined in GVP Module VIII Appendix 1 as a type of study design. However, none of the more common definitions of drug utilisation study[3,4] suggest that the term is bound to a particular study design and/or data collection schemes used in Pharmacoepidemiology. For example, given that drug utilisation information can be obtained

[3] "The marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (WHO 1977)

[4] ""An eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes."(vander Stichele and Wettermark, 2008)

through an organised data collection scheme, the use of the terms “registry” or “cohort” as incompatible deigns with “drug utilisation study” does not seem to be logical.

In the context of PASS, the implications of the term “drug utilisation” are particularly relevant as the definition of PASS is based on the nature of the objectives rather than on the nature of the design. Among the types of objectives that define PASS there is “To assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors)”. If “drug utilisation” is interpreted as a type of design/ methodology (and not as an objective), it may lead to the replication of a certain methodology without attention to the particular needs for assessing drug utilisation in different situations.

2.3.2 Inconsistencies within the EU PAS Register

In addition to the ambiguous terminology from the guidelines, the structure of the EU PAS register does not promote a greater harmonisation. Some terms are used in multiple data fields of the formulary, and/or are not consistent with guidelines, even with the ones from the ENCePP.

To start with, “case-control surveillance” is an option both for “source of data” and for “study design”, “drug utilisation study” is both used as “scope of the study” and as “study design” which reflects the previous discussion concerning this term, and “prescription event monitoring” is used both as “source of data” and “study design”.

In addition, “prospective patient-based data collection” is provided as an option for “source of data” thus, contributing to the misuse of the term as synonym to primary data collection, as already highlighted in the previous section.

Moreover, the “scope of study” field in the formulary does not include one of the objectives that is part of PASS scope, namely, the assessment of effectiveness of RMM.

Unfortunately, there is no glossary or description of the terms used by the EU PAS Register so the interpretation is left open to the registrants. For the EU PAS Register to hold promise of a greater transparency, by serving as a common repository to share pharmacoepidemiological research, it would be key to promote the use of a common language, or, at least an unequivocal interpretation of the data fields that an applicant need to fill.

Such an effort for harmonisation would prove to be a difficult one as different taxonomies and terminologies can be found in different sources, but certainly would facilitate collaboration and the accuracy of communication.

The challenges with terminology acquire a bigger proportion in the specific context of PASS as there seems to be some challenges in perceiving PASS as a study which is defined by its objectives rather than by its design. These challenges will be further discussed in the following section.

3 Bridging Pharmacovigilance and Pharmacoepidemiology

In any Pharmacoepidemiology study, the choice of the methodological approach should be tailored to the research question to be addressed.(6) The fact that there is no "one size fits all" formula acquires particular relevance in the context of PASS.

What distinguishes a PASS from other pharmacoepidemiological studies, is its specific mission within Pharmacovigilance. Each PASS is conceived as part of the Risk Management strategy for a certain medicinal product.

It then is expected that PASS contribute to increase the knowledge on the medicinal product's safety profile and fill in the most critical uncertainties, which should be determined in advance.

In a review conducted prior to the new legislation, the RMP safety concerns of medicinal products approved between 2006 and 2009 were followed for 5 years. The authors concluded that approximately only one fifth of those uncertainties were resolved, which was considered insufficient. They recommended the implementation of more robust activities such as methodological stronger studies.(93) A different publication goes even further in their recommendation by considering that post marketing studies should be systematically conducted to assess long-term safety and detect rare ADRs as the anticipation of safety concerns is a complex exercise and not all safety concerns might have been foreseen.(41) However, the new Pharmacovigilance legislation endorsed proactivity but also proportionality of the measures put in place, to avoid unnecessary burden to the healthcare system. Therefore, GVP Module V considers that "Planning of the necessary Pharmacovigilance activities to characterise the safety profile of the medicinal product will be improved if it is more closely based on specific issues identified from pre- or post-authorisation data and from pharmacological principles".(37) Therefore, not all medicinal products would necessarily require a PASS, as in most cases, routine Pharmacovigilance activities would be adequate to manage the uncertainties with the safety profile. (37) The most critical step to ensure a proportional and adequate plan is in place to manage the benefit-risk profile of the medicinal product (by selecting the best strategies to address each concern) is an initial adequate planning.

Therefore, rather than conducting PASS for all new marketing authorisations it is more important to start developing the RMP as early as possible, engaging with the necessary stakeholders. When all the evidence gathered suggests that routine activities (e.g. spontaneous reporting, signal detection, routine monitoring of drug utilisation through database screening, etc) are not sufficient to address certain safety concerns, additional measures should be considered. These considerations requires a balance between the impact of the risk and the burden of the additional activities.(37)

Hence, PASS are called into action to effectively provide on the spot answers to the knowledge gaps that the routine Pharmacovigilance activities are not able to fill, either because answers are needed quicker to prevent adverse occurrences, or the specific nature of the questions to be addressed are not routinely available. This sense of urgency and need to efficiently address the critical questions, could explain why some regulators are reluctant in accepting additional research questions in PASS protocols (e.g. effectiveness information) if they would detract the study from proficiently providing the necessary answers in a timely manner. In fact, some of the PRAC comments suggested PASS protocols containing additional information not relevant to address important safety concerns were considered to be unduly delaying the finalisation of the PASS protocol.

From the above, it is clear why, according to the legislation, a post-authorisation study is classified as a PASS when the main aim for initiating the study includes objectives directly linked to uncertainties derived from the RMP. This is why their definition considers PASS aims to investigate safety concerns, to assess patterns of drug utilisation that add knowledge on the safety profile of the medicinal product or to measure the effectiveness of RMM. Thus, a PASS is defined by its objectives and not by its design.

In order to assess if PASS were designed according to these principles it would have been necessary to have access to both protocols and RMPs and allow for an extended follow-up time to examine if the results of PASS effectively contributed to answer the initial uncertainties. Nevertheless, the

following preliminary findings suggested that there may be some disconnection between the PASS as conceived in the RMP and the PASS protocols developed.

Firstly, the comparison of safety concerns planned to be addressed by the PASS (as *per* the RMP summary in the EPAR) *versus* the safety concerns actually addressed in PASS protocols, performed among the subgroup of PASS combining objectives of "investigate safety concerns" and at least one other safety objective (see *results Section 2.3*), revealed some discrepancies.

Secondly, some PRAC comments referred as reason for protocol rejection the lack of alignment of the objectives in the protocol with those in the RMP.

Lastly, approximately half of the analysed PASS protocols did not mention the RMP. This may suggest that the teams responsible for developing the PASS may have not leveraged all the information contained in the RMPs which could enrich the study design as those documents contain, for instance, considerations about the epidemiology of the disease, suspect or known risk factors and effect modifiers to the safety concerns, resultant from literature research and pre-marketing findings. This information can be used to account for confounders and effect modifiers thus contributing for more robust results.

To achieve a harmonious articulation between the PASS mission and its methods, it would be important to involve pharmacoepidemiologists in the RMP development, to contribute to the selection of the best safety activities to put in place to address each safety concern, as they may provide early input into whether or not it is feasible to address certain questions with a PASS. The involvement of these experts only after the safety concerns and Pharmacovigilance activities are agreed with the regulators may result in less appropriate activities or an inconsistent Risk Management strategy. A recent publication has extensively reflected on the role of the pharmacoepidemiologist in the integrated benefit-risk assessment and its communication and evaluation concluding that these professionals are able to bring the methodology expertise, research and public health perspectives that can be instrumental in the optimisation of the benefit-risk profile of the medicinal products.(94)

The following chapters reflect on some of the challenges that may need to be addressed before a functional bridge is considered definitely established between Pharmacovigilance and Pharmacoepidemiology. Further training from teams on both sides, increased collaboration and cross-pollination will allow for the recognition of the singularities of PASS and foster development of new methods and frameworks. This will help the definite establishment of PASS as fully functional multi-level, multi-stakeholder activities that effectively and impactful contribute to safer medicinal products.

3.1 More Collaboration and Cross-pollination

Experience and literature research has shown that people who develop RMP (who are aware of, and manage the benefit-risk profile of the medicinal product) will typically not be the same people developing the PASS. Each activity is normally executed by people with a different set of skills and background experience within different departments within an organisation.(94)

Within pharmaceutical companies, safety teams developing the RMP may not be involved with the clinical teams conducting the pre-marketing clinical studies nor with the people in possession of the data on patient and provider needs (typically housed within medical affairs and the commercial organization). Consequently, experts in Pharmacoepidemiology may not be in close contact with all work streams which may have insight into the real-world use of the medicinal product (94, 95)

If the teams who develop the PASS methodology are not aware of the safety specification and the overall Risk Management strategy for the medicinal product, they may lack clear understanding of the specific mission the PASS is supposed to accomplish. The resultant PASS may not capture the "missing pieces of the puzzle", which the other Pharmacovigilance activities are not able to complete. As a consequence, PASS may fail to identify critical findings that would prevent the occurrence of ADRs with public impact.

It has been recognised that more awareness and engagement in Risk Management strategies could have important benefits. Morrato and Smith highlighted the advantage of "incorporating risk minimisation thinking through the development and commercialisation process" as "companies can be more proactive and nimble in their response should serious events requiring management emerge." In addition they suggested that "pharmaceutical companies have been slow to recognise and embrace the significant potential these programs offer in terms of enhancing trust with HCPs and patients and for providing a mechanism for bringing products to the market that would not otherwise have been approved".(95)

Since leveraging data, knowledge and skills from different stakeholders may take time, earlier engagement, ideally before the marketing authorisation, is recommended. Early engagement with regulators has also been advocated by EMA.(47)

In addition to bringing different departments and activities together, there is also a particular need for cross-pollination of skills such as Pharmacovigilance and Risk Management, Pharmacoepidemiology and also other new skills that may still be not common in the Pharmaceutical setting like experts in qualitative methods.

Perhaps the most critical example is illustrated by the sub-analysis of PASS assessing effectiveness of RMM.

3.1.1 Assessing Effectiveness of RMM: a Multi-level Multifaceted Endeavour

Assessment of effectiveness of RMM "is an evolving area of medical sciences with no universally agreed standards and approaches".(39) It is a multifarious and complex endeavour for companies and regulators. Firstly, because it requires a thorough understanding of the RMM put in place in a certain Risk Management program, their rationale, objectives and interlink with the other post marketing activities. Secondly, because the success of RMM depends on multiple factors such as their robustness, the healthcare setting where they are implemented, the success of the logistics to deliver them, the knowledge and motivations of HCPs and patients, among others.

As noted in *Introduction Section 4.2*, different indicators have been proposed to assess effectiveness of the RMM, taking into consideration the various steps that may condition the success of these activities: from the operational implementation to the desired outcome. Some frameworks and models have been developed, to offer some guidance for the assessment of effectiveness of RMMs.(39, 43, 46) However, the analysis of protocols of PASS with at least one objective concerned with assessing effectiveness of RMM, suggested the published models and orientations have not been leveraged systematically, which is in line with other authors' findings.(96, 97)

Assessing Knowledge and its Impact on Behaviour: the Need for Qualitative Methodologies

The implementations of the proposed models to assess effectiveness of RMM require the assessment and articulation of different indicators of success. The diversity of these indicators may require coupling different skills that are normally attributed to different areas of expertise such as Pharmacoepidemiology (typically more associated with quantitative methodologies) and social sciences (typically more associated with qualitative methodologies).

On the one hand, to assess knowledge of the RMM messages and its effects on patients' and HCPs' behaviours, it is necessary to consider qualitative techniques. On the other hand, to observe patterns of behaviour and its effect in the desirable RMM outcome could be appropriately addressed with epidemiological techniques (e.g. if upon implementation of an educational program highlighting the need to periodically monitor patients' liver enzymes, the number of hepatotoxicity cases attributed to the medicinal product decreased).

A PASS could be a good instrument to articulate these components. However, our results did not suggest those factors were being taken into consideration.

Firstly, all PASS uniquely designed to assess effectiveness of RMM had the same design, cross-sectional survey using questionnaires as tools to assess patient and/or HCP awareness/use/satisfaction/knowledge/understanding of the RMM and/or self-reported behaviour via answering hypothetical scenarios. While surveys may be the most appropriate tool to assess awareness and knowledge of the RMM by patients and HCPs, there are general limitations regarding self-reported behaviour information as a proxy of actual behaviour.

In addition, while it may seem easy to design a questionnaire, the design of an appropriate questionnaire is not a straightforward task. (98) When looking at the 5 step model from Banerjee *et al* which, as most evaluation frameworks, follow the basic principles from Kirkpatrick's model to assess training programs, it can be noted that the questionnaires used in PASS mainly covered tool awareness and usage and risk knowledge and comprehension, but failed to assess behavioural modification.(99)

Publications on implementation science have suggested that a number of constructs originating from social cognitive theories are the most promising for assessing behaviour change in health professionals.(100) Instruments to assess the impact of educational activities on physicians' performance have been developed based on a solid conceptual model for the study of HCPs' behaviours and intentions. This illustrates that determining if a RMM positively impacted patients and HCPs behaviour is a complex task and requires a solid understanding of these conceptual models.

The adoption of best practices from Implementation Science (the study of strategies to adopt and integrate evidence-based health interventions and change healthcare practice patterns within specific settings) such as the ones described in the previous paragraph have recently been encourage in the field of assessing effectiveness of RMM.(45)

Differently from these recommendations, the available protocols of PASS employing questionnaires did not describe a conceptual model able to assess latent constructs such as attitude and motivation. Less than half described critical methodological considerations such as questionnaire validation. Even among those that did refer to validation aspects, the level of information was very limited, generally only briefly referring to cognitive pre-test interviews for wording, culture adequacy and clarity of the message. None considered the psychometric properties of the questionnaires such as reliability, validity and responsiveness. Questionnaires should be developed in light of sound methodological qualitative and quantitative techniques and several textbooks may provide such guidance but may not be part of the library often used by pharmacoepidemiologists yet.(101)

In addition, the sampling frame is of particular importance in surveys. Given that RMMs are locally implemented, their effectiveness is highly dependent on the healthcare context they are inserted in. Therefore, targeting a representative sample of subjects for which the RMM are designed to is critical in this context.(78) Most of the available PASS protocols using questionnaires planned for simple or stratified randomised samples from panels of prescribers which is consistent with GVP’s recommendation. However, this guideline highlights the importance of considering the representativeness of sponsor lists or panels of HCPs to ensure that the results would be generalisable to the target population.(39) Among the analysed protocols, none provided evidence that this was considered by the sponsors as the level of details was limited. In terms of country selection, the PASS protocols often did not describe considerations concerning the different healthcare systems and the countries involved. In addition, they generally briefly justified the selection of some of the biggest EU countries on the basis of anticipated larger market uptake, heterogeneity of healthcare systems and favourable environment to conduct research, but did not provide more granular details.

Assessing Behaviour and Outcomes

A) The need for Objective-driven Pharmacoepidemiology methods

Even when questionnaires are designed according to best practices, there are limitations to the application of those instruments. Firstly, the results may be influenced by participation in the survey (such as the Hawthorne effect). Secondly, people who respond may not be representative of the target population given that participation is more likely amongst engaged HCPs and/or more motivated or educated individuals (non-responder bias). Lastly, it is subject to recall bias.(39) A review of effectiveness of RMM methodologies by the FDA has even recommended that methods should not rely solely on survey data.(97)

Therefore, while questionnaires may be the most adequate instrument to assess the impact of a RMM initiative on HCPs' or patients' knowledge, attitudes and motivation, it would be important to complement those results with the observation of actual behaviour in real-world practice and ultimately, the effects on minimising the safety outcome targeted by the RMM. This is the rationale for the endorsement of a dual evidence-approach by the GVP.(39)

When considering the three types of objectives of a PASS: to investigate safety concerns, to assess drug utilisation and to assess effectiveness of RMM, it can be seen that they can address the different facets of a safety concern and emphasises the importance of clearly understanding the rationale behind the PASS and the specific answers required. An example is provided below:

Hepatotoxicity is an identified risk for a certain medicinal product but previous evidence shows that this ADR can be avoided by not prescribing the medicinal product to a specific subset of patients. The medicinal product is launched with the contraindication stated in the SmPC. However, the occurrence of hepatotoxity is higher than would be expected. The company decides to further emphasise these precautions in an educational brochure and to actively monitor the safety concern with a PASS. The PASS would address this safety question as follows: it will investigate the safety concern (hepatotoxicity) by assessing its incidence and characteristics of the cases; it will assess patterns of drug utilisation to evaluate compliance with the SmPC and the educational program and will compare the incidence of hepatotoxicity before and after the implementation of the RMM (educational program).

This example intended to illustrate that a PASS can simultaneously investigate the safety concern(s) and also provide evidence whether or not the RMM is being effective, and if not, the information on how the medicinal product is being used may help redefine the RMM strategy. In different cases, drug utilisation can also anticipate the occurrence of ADRs.

The analysis of 12 available PASS protocols, in which the goal was to assess effectiveness of RMM and to investigate safety concerns and/or assess drug utilisation, showed that, in those protocols, the latter two objectives seemed to drive the study methodology with little attention dedicated to effectiveness of RMM. This objective was generally only vaguely stated, for instance, referring that compliance with RMM would be assessed but lacking details on how that would be achieved, such as what variables and analysis will answer that particular safety question.

These situations may again suggest some discrepancy between the purpose of PASS conceived within the risk management strategy, and that reflected in the PASS protocol. This can result in missed opportunities for a PASS to address the various facets of an overarching plan to address safety concerns and/or fail to provide the expected results to meet its purpose.

B) The need for innovative designs

Besides the correct formulation of PASS objectives aligned with the other Risk Management activities, there are limitations in the methodological design of studies to address these multidisciplinary questions.

Only one tenth of the available protocols of PASS assessing effectiveness of RMM were following GVPs' recommendations to assess outcome indicators by comparing the frequency of the outcome of interest before and after the implementation of the RMM or using reference values. One of the available PRAC comments specifically addressed this issue by requiring "amendment of the research question and objectives to reflect comparisons before and after" the implementation of the RMM. The lack of comparator/reference group and of a pre-post RMM analysis were also highlighted in one literature review and one presentation from the EMA about strategies to assess effectiveness of RMM.(96,102)

These are recognised hurdles to successfully assess effectiveness of RMM. The lack of comparators is more challenging for RMMs implemented with the initial marketing authorisation. In addition, there are no standard outcome measures since each RMM is applicable to particular medicinal products with particular safety concerns. In addition, it could be challenging to operationalise an indicator of success of the RMM as some of their objectives may be broad and ambiguous (e.g. "use the drug with caution", "carefully select patients").(46)

Moreover, the data to address this multifaceted mission is difficult to access. Ideally, it would require access to unbiased prescription and utilisation information to correlate with awareness and knowledge transmitted by the RMM. Then, as already mentioned, the assessment of whether the instructions/ recommendations from a RMM are being followed requires the interpretation and use of techniques more common in qualitative techniques.

The use of secondary data sources such as EMRs including information on prescription (which can be considered a reflection of the HCPs' behaviour) have been suggested as efficient ways to assess RMM without interfering with routine practice. The analysis of prescription records linked to other patients' records, containing demographic and clinical data, may enable the assessment of prescribing behaviour with regards to the indication, dosage and prescriber characteristics, assessment of off-label use, prescription of interacting medical products, compliance with laboratory monitoring recommendations, etc. In addition, the available clinical information, may allow for the investigation of occurrence of safety outcomes in the light of the drug utilisation, which would reflect the patients' and HCPs' behaviour.(43,46, 89)

However, not all data required to address the research questions may be available in these data sources. Despite the fact that, they can provide useful information to understand prescription behaviour, some variables may not be available, such as, whether or not particular procedures emphasised by an educational program were performed (e.g. regular monitoring of liver enzymes). In particular, indicators of knowledge resultant from the RMM would not be available in these databases.(39,43)

Alternatively, more detailed and accurate data can be obtained by collecting data directly from the prescribers or patients. However, while specific and detailed information on patients' or HCPs' knowledge, behaviour, and medicinal products' use can be collected in this way, it is limited by the issues concerning recruiting of participants, time delays and small or unrepresentative sample sizes.(39) In the specific case of questionnaires, as already discussed above, while these instruments can be particularly useful to assess knowledge, there are particular challenges such as, lack of objective standards to measure knowledge of risks, non-response bias and the reliance on subject's ability to recall events or expectations, rather than direct measurement of how risk education affects behaviour. This may fail to reflect the real tool use and utility among target population, and may also cause an increased burden on clinical practice leading to low response to these surveys.(39,43,44)

In summary, the results suggested that the PASS assessing the effectiveness of RMM were too simplistic. The main focus was on knowledge assessment but without taking into account important considerations for the development of questionnaires able to assess the impact of knowledge on behaviour. Behaviour was mainly assessed through self-reported answers to hypothetical scenarios, despite some longitudinal PASS including assessment of effectiveness of RMM as part of the study goals but not providing evidence that data collected this way would be used to address that objective. Most of those longitudinal PASS relied on a primary data collection approach which would have allowed the collection of tailored information to address behaviour, but was prone to the Hawthorne effect, selection and non-responder bias.

The development of combined approaches and innovative designs may provide more options to assess effectiveness of RMM in its multiple facets. RMM development and assessment is a multi-level, multi-stakeholder activity, in which, the engagement of different functions and different areas of expertise will be essential progress levers.

It is anticipated that, as the number of medicinal products with RMM growths, new techniques are applied and acceptable outcome measures established. Banerjee *et al* recommended "an overt regulatory policy on greater transparency on publication of the results of effectiveness evaluation" to foster development in the area. Therefore it is important to continue sharing lessons learned on how to assess effectiveness of RMM.(43)

3.1.2 Patient and HCP Engagement

Another pillar of the new Pharmacovigilance legislation was to involve patients and HCPs in the regulation of medicinal products, as a consequence of the perceived lack of trust by society, as described in some of the episodes presented in the historical background. None of the PASS protocols reviewed described patient or HCPs' involvement in their development. Once again PASS assessing effectiveness of RMM are a good example of the need to engage HCPs and patients as it is necessary to understand the impact of the RMM in their knowledge, attitudes and behaviours. The engagement of different stakeholders is another call for collaboration within different departments and the integration of different skills and techniques commonly used in qualitative methods such as focus groups and content analysis.

Initiatives such as the European Patients' Academy (EU-PATI) aim to enable patients to understand drug development and regulations and capacitate them to collaborate in academic and industry research, authorities and ethics committees.(103) In the area of clinical effectiveness research, the Patient-Centered Outcomes Research Institute (PCORI) has already showed the ability of these stakeholders to provide fruitful inputs.(104) Patients and their families are generally able and motivated to give feedback on how treatments affect their autonomy and their satisfaction within the contexts of healthcare and life in which the patients are inserted.(8)

There are also key advantages on engaging HCPs in the conduct of observational research, changing their self-perception as "security" agents who just comply with guidelines, to "safety" agents who take part in the research contributions.(8) By understanding how the collection of data would contribute to improve knowledge and their patients' health, the HCPs may become more motivated, for instance, to provide comprehensive and accurate information.(82)

3.1.3 Are PASS Methodological Simplistic Studies?

There are currently no specific tools to assess the quality of neither PASS nor pharmacoepidemiological safety studies in general.(105)

From all that was discussed above, the fact that PASS are pharmacoepidemiological studies with a particular mission in drug regulation makes them a multifaceted object. Therefore the adequacy of PASS methodology needs to be assessed on a case by case basis in the context of a particular medicinal product with a particular safety specification and a particular action plan.

The fact that two thirds of PASS did not include a comparator, should be considered in the light of particular objectives of PASS. Some PASS are established as active surveillance platforms where patients treated with a particular medicinal product are followed-up through a Risk Management system to collect long term data or detect rare ADRs as signal amplification collection platforms, rather than, with the objective of assessing a particular safety concerns. In addition, as with comparative effectiveness reviews, reasons for not including comparators may be justified, for instance, for hypothesis generation or due to lack of sufficient information to rationalise a comparative hypothesis when the medicinal product is new.(90) Therefore, to identify new risks, to reassure the absence of risks in the long-term, or to understand how the medicinal product is being used in the real-world context, it may not be necessary to include a comparator. Conversely, to estimate the rate ratio or rate difference of safety concerns, a comparator would be paramount, as would also be methods to address confounders and effect modifiers, to investigate if a certain outcome is due to a certain exposure.

In addition, the vast majority of the analysed PASS protocols described more straightforward methods, such as purely primary or secondary data collection approaches, and were mainly using descriptive statistics. While this may be appropriate to a program which simply aims to monitor long-term use, the application of appropriate statistical methods (e.g. time series analyses, survival analyses, logistic regression) to a cohort of medicinal products users, may allow the assessment of different aspects of prescription or use and provide insights beyond purely descriptive evidence.(89)

The previous chapter illustrated the complexity of the research purpose of a PASS and the need for dialogue among stakeholders involved in the safety specification definition and the Risk Management planning. Adequate and complete communication is also key to avoid terminology “traps” that may lead to misinterpretation.

For the teams working on Risk Management and thus identifying the research topics that needed to be addressed by a PASS, the terms may more often be perceived as “study objectives”. For the teams working in Pharmacoepidemiology and thus designing study methodology, some terms maybe perceived as “study design”. Therefore, if the communication between teams is restricted to a small amount of information including ambiguous terms, there are chances the end result may miss the target.

The fact that the purpose of PASS in the context of its use as a Risk Management may be perceived as “methodologies types” may lead to the application of “recipes” used in PASS with that perceived “methodology type” whereas in fact, the nature of the safety concerns and the particular needs of the PASS might have been significantly different. Thus, the interpretation of “study objectives” as types of PASS *per se* may threaten the ability of the study to address the questions of interest for which they were conceived.

The results suggested that PASS aiming to assess RMM tended to use a cross-sectional design and PASS aiming to study drug utilisation tented to use secondary data collection approaches. It is imprudent to draw conclusions on whether or not those were the most adequate approaches without knowing if alternative approaches were considered. The lack of details available in the protocols limit such analysis, but it is worth considering the previous enunciated points regarding the importance of tailoring the methods of the PASS to the needs of the safety questions to investigate, which may include combining different approaches. Therefore, even if a given data source or data collection approach was successful to study drug utilisation in one particular PASS, it may not be

adequate for a medicinal product with a different safety specification as the key variables would not be the same, and consequently may not be available in certain data sources.

In summary, given that one third of PASS were combining objectives from different PASS focus categories ("investigate safety concerns", "study drug utilisation" and "assess effectiveness of RMM") and, each of these PASS focus categories may encompass diverse research questions from diverse Risk Management systems of diverse medicinal products, it is easy to understand that rarely a PASS design could be replicated to another PASS without attention to the particular objectives that make PASS unique.

Therefore, rather than using "recipes" based on *a priori* conceptions of study types and replication of methods applied in studies with similar underlying assumptions, it is key to tailor the design to the particular nature of the research question the PASS aims to address. This will foster innovative designs tailored to the specificities of the research questions.

A more extensive critical appraisal of PASS methodology was limited by the insufficient granular information provided in each protocol. The general lack of details in PASS protocols restrains the ability to share knowledge and, more importantly, may reflect insufficient planning which may lead to the overlook of important considerations, which if taken earlier might have minimised the need for further PRAC revisions or remedial future actions.

Given the complexity of the PASS mission and the need to consider multiple stakeholders and new skills there is no doubt that PASS should be planned as early as possible in the drug development process.

The integration of Pharmacoepidemiology in the industry and regulatory activities is in its early days and has required adaptation of multiple stakeholders and new interactions between different teams and across regions. Continuous engagement between parties and efforts in the development of a common language and mutual understanding of the Risk Management strategy would help establish PASS as a solid bridge between Pharmacoepidemiology and Pharmacovigilance.

4 Strengths and Limitations

The major strength of this dissertation is the comprehensive review of multiple sources of information about PASS submitted after the new Pharmacovigilance legislation. In addition, almost as a reflection of the encouragement to merge Pharmacoepidemiology with methods traditionally used in social sciences, the review was oriented by the principles of content analysis framework giving a solid methodological backbone to derive the observed results. As explained in the methods section, the use of a mixed methods approach provided a starting point for the classification of PASS, but also allowed for reshaping the coding rules and dictionary as new insights emerged during the review. As previously discussed, the lack of harmonisation in PASS terminology challenged the use of *a priori* conceptions, but was also an opportunity to explore the similarities and differences between PASS, and define new discriminant variables and categories which hopefully contribute to a tailored approach to understand PASS. Therefore, this work may contribute to raising awareness towards the singularity of PASS, which may deserve a unique taxonomy given the similarities and dissimilarities between PASS and other pharmacoepidemiological studies.

One other main strength of the study was the high degree of comparability between the nested cohort of 57 full protocols and the overall 189 PASS protocol population that allowed the extrapolation of most of the methodological findings.

Although the possibility to track numerous data on all single PASS submitted since July 2012 is the major strength of the review, the amount of missing and incomplete information constitutes also its main limitation. In particular, tracking the different PASS in the successive meeting minutes was complex and impacted the ability to draw robust conclusions on PRAC assessment timelines, as well as methodological issues raised by the PRAC.

Another recognised limitation of the study is the fact that PASS with an interventional design and PASS to be implemented only in one country are not submitted to the PRAC and therefore were left out of the analysis. In addition, PASS discussed in PRAC plenary meetings could correspond to the most complex or priority ones and therefore it is possible that for those PASS there was more information available in the minutes. It is also possible that not all PASS protocols were captured by the review of the PRAC meeting minutes as some PASS protocols may be discussed within the RMP assessment.

5 Opportunities for Future Work

There are several opportunities to further expand this work.

The most immediate, is the follow-up of the PASS protocols contained in this review until their study results are available. As a result, firstly, it will be possible to compare the reports with the protocols to estimate if there were differences between what was initially planned and what was later executed. Secondly, it would be possible to ascertain if planned PASS milestones were met and therefore if PASS are being completed in the timeframe agreed with the regulators, since this was a concern expressed by a recent review of post marketing studies imposed as specific obligations to the licence of conditionally authorised medicinal products in the EU. In this study, it was suggested that critical ethical and logistical challenges faced by the study sponsors may be compromising study execution and completion within the timeframe expected by the regulators, which may be less aware of the operational barriers faced by the MAHs.(106)

In addition, it would be important to investigate what actions followed the publication of the results to understand how PASS contributed to the knowledge maturation for a certain medicinal product and if it would lead to preventive actions (e.g. RMM, motivating labelling changes etc.). However, it is anticipated that it would be difficult to assess the necessary documentation to achieve this later goal.

Moreover, the current database could be supplemented with additional data fields to assess more granular details about the PASS (e.g. study limitations and measures to minimise them, an in-depth assessment of study objectives and respective methods being used). This could bring important insights that might help the development of a tailored tool to assess PASS quality which currently is not available. An example would be to assess if, given the nature of a particular objective, the design should contain an assessment of an exposure-outcome dyad for which considerations on confounders and effect modifiers should not carefully considered.

It would also be interesting to check the Risk Management summaries of all the new marketing authorisations since the new Pharmacovigilance legislation was implemented and to identify plans for the conduct of PASS and the specific safety concerns to be addressed in order to estimate how many have been submitted for PRAC review (a proxy of those who reached the protocol stage). This approach would sustain an improvement from the situation reported before the new legislation where a considerable number of PASS planned according to the RMP were not being implemented and some did not even reach the protocol stage.(18,47)

It will also be relevant to follow-up the trend regarding the number of PASS initiated as a consequence of a safety referral, as well as, if the safety concerns to be assessed in those PASS were already captured in the RMPs to determine how effective these are in predicting the important safety concerns, so that adequate measures are proactively being implemented. Given that referral procedures usually consist of reactive actions to safety problems that have already manifested, the fact that PASS are initiated earlier could reflect an increased proactivity in gaining knowledge on safety concerns for newly approved medicinal products. Going forward, a decrease in the number of safety referrals could be a pertinent indicator of a change towards a more proactive system.

By assessing the impact of PASS on the other Pharmacovigilance activities and on the effective reduction of ADR burden, it would be possible to estimate the real contribution of PASS to public health.

Conclusion

The public availability of a large variety of information on PASS has provided critical insights in the design and the conduct of PASS under the new EU Pharmacovigilance legislation.

PASS are a complex by-product of the needs to bring together Pharmacovigilance and Pharmacoepidemiology and its multidisciplinary nature requires a broad variety of skills and techniques.

The recognition of the singularity of PASS as pharmacoepidemiological studies with a specific mission within the post marketing plan for the medicinal product, require the alignment of different parties to tailor the best approach for each safety question. A clear understanding of the safety specification and of the critical uncertainties that PASS should be able to address are key to design a successful PASS. Risk Management and PASS should be planned as early as possible in the drug development process to allow for the involvement of different stakeholders, careful methodological decisions and feasibility exercises that culminate in the development of the most robust study.

In order to foster collaboration between different stakeholders, it will be essential to further increase the level of information publically available, to improve visibility and tracking of regulatory processes, to promote the use of harmonised terminology, to develop protocols with an adequate level of detail, including the rationale behind the methodological decisions, and to encourage an effective cooperation between people working on Risk Management and those developing PASS.

In addition, cross-pollination of skills with other areas of expertise such as qualitative methodologies may be critical to tackle the multidisciplinary needs of the PASS mission, in particular, in the area of assessing effectiveness of RMM where it is necessary to assess the impact of measures on patients' and HCPs' behaviour.

Cross-functional collaboration and communication across stakeholders, higher levels of transparency and the use of a harmonised terminology would be key to develop innovative methods, customised to the singular and multifaceted needs of PASS, an example of which being the assessment of effectiveness of RMM. The anticipated result would be implementation of best practices that will certainly contribute to a safer use of medicinal products.

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Annex 1

The PRAC monthly meeting minutes contents follow the following structure:

- Item 1: Introduction
- Items 2 and 3: EU referral procedures for safety reasons
- Item 4: Signal assessment and prioritisation
- Item 5: RMPs
- Item 6: Assessment of PSURs
- Item 7: Post-Authorisation Safety Studies
- Item 8 (introduced from March 2013); the subsequent chapters were renumbered as consequence): Renewals of the marketing authorisation, conditional renewal and annual assessments
- Item 9: Product-related Pharmacovigilance inspections
- Item 10: Other safety issues for discussion requested by the CHMP or the EMA
- Item 11: Other safety issues for discussion requested by the Member States
- Item 12: Organizational, regulatory and methodological matters
- Item 13: Any other business
- Annexes:
    - RMP
    - PSURs
    - PASS
    - Renewals of the marketing authorisation , conditional renewals and annual reassessments
    - List of participants

Therefore, information about PASS can either be found in the minutes' section 7 (the one containing more extensive details PASS), the annex, or sporadically other sections. Those areas of the minutes with PASS content were typically divided in information about PASS protocol and about PASS reports assessed by the PRAC on the concerned month. Only PASS protocols were assessed since this study focused only on the PASS protocols as it aimed to describe PASS at their earlier stages within the new legal framework.

Although some changes were observed in the minutes structure over the three years, item 7 typically presented the following elements:

- A numbered sub header identifying a certain PASS protocol assessment by the following elements: the active substance name, the brand name and the type of marketing authorisation procedure (centralised or national authorisation procedures);
- Then, under each distinct PASS protocol assessment:
    - A sentence summarising the reason for the introduction of that particular item in the PRAC meeting (e.g. "evaluation of an imposed PASS protocol");
    - The PASS legal basis: imposed as subject to supervision set in Art 107 (m)-(q) of Directive 2001/83/EC or non-imposed
    - Regulatory details: identification of PRAC Rapporteur;
    - Administrative details (introduced in the minutes from February 2014 onwards): EMA procedure number, EMA procedure scope (which could contain brief information on study background, aim and design) and the MAH;
    - Background (when available) with a summary context of the PASS protocol submitted;
    - Endorsement or Refusal of the protocol / Summary of advice / PRAC comments (when available): could provide information on the PRAC assessment outcome and whether the PASS protocol would need to be resubmitted for new assessment after revision by the MAH, the timetable to be applied and feedback on the main reasons for rejecting a PASS protocol.

For the PASS protocols presented in the minutes' annex, the level of information was more limited and did not provide context or the conclusions of PRAC assessment. The following sentence was common to all the minutes' annex PASS sections: *"Since all comments received on the assessment of these studies were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below without further plenary discussion"*. Therefore PASS protocols assessed by the PRAC rapporteur that did not require discussion in PRAC plenary session were listed in this section but, there was no information on whether or not the PASS protocols were endorsed/ approved as the only information presented is that PRAC agreed with the rapporteurs' conclusions.

Examples of the data elements and structure of a PASS protocol assessment in the minutes (one for section 7 and other Annex) are presented below (both include in the minutes of the PRAC meeting held on September 2014 PRAC meeting):

Examples of PASS protocol assessments recorded in the minutes

7.1.3. Strontium ranelate – PROTELOS (CAP), **OSSEOR** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/00560/ANX 034, EMEA/H/C/00561/ANX 034
Procedure scope: Non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice
MAH(s): >>>>>>>censored>>>>>>>>

Background
The requirement for the conduct of a non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice, patterns of use and cardiovascular risk, was introduced as an obligation of the Annex II of the marketing authorisation for Protelos and Osseor following the conclusion of the review conducted under referral Article 20 of Regulation (EC) No 726/2004 (see EMA/112925/2014). A draft protocol for such study was submitted and assessed by the rapporteur for review by the PRAC

Endorsement/Refusal of the protocol
The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC objected to the draft protocol as the Committee considered that the design of the study does not fulfil the study objectives. In particular changes in the therapeutic indication should be taken into consideration in the analyses of utilisation patterns as well as relevant timing regarding implementation of the revised product information and distribution of the related DHPC.
The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 30 days-assessment timetable will be applied.

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16. ANNEX I Post-authorisation Safety Studies (PASS)
Since all comments received on the assessment of these studies were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below without further plenary discussion.
16.1.1. Glycopyrronium bromide, indacaterol – ULTIBRO BREEZHALER (CAP)**, ULUNAR BREEZHALER** (CAP), **XOTERNA BREEZHALER** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)
Administrative details:
Procedure number(s): EMEA/H/C/002679/ANX 002.1, EMEA/H/C/003875/ANX 003, EMEA/H/C/003755/ANX 002.1
Procedure scope: Evaluation of the updated PASS protocol for a multinational database cohort study to assess RMP specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe
MAH(s): >>>>>>>censored>>>>>>>>

Annex 2

The following elements were reviewed from the European Public Assessment Reports (EPAR) respective information tabs:

- *Authorisation details* tab:
    1. Anatomical therapeutic chemical (ATC) code;
    2. Date of issue of marketing authorisation valid throughout the EU;
    3. Identification of whether it had an orphan designation;
    4. Identification whether it concerned a product subject to additional monitoring.
- *Product information* tab: "EPAR – Product Information" Annex IIB sections "Other conditions and requirements of the marketing authorisation" and "Conditions or restrictions with regard to the safe and effective use of the medicinal product" to identify any PASS conducted as a condition or special obligation to the marketing authorisation (category 1 and 2, respectively);
- *Assessment history* tab: Chronological review of the EPAR(s) available in this section, starting with the "initial marketing authorisation documents" to subsequent EPAR(s), until the concerned PASS was identified (e.g. an EPAR on the assessment of a new indication, etc). In particular, the section "Risk Management Plan" of the EPARs was revised as it presented the table with the safety concerns and the Pharmacovigilance Plan of the medicinal product. Therefore, it would normally contain the description of the planned and/or ongoing PASS and which safety concerns they aim to address.

Annex 3

An EU PAS Register record contains the following structure and data elements (at data lock: July 2015):

- *Administrative details* tab:
    1. Study identification (official title, study title acronym, study type [i.e. active surveillance, observational study, clinical trial or other], brief description of study, if the study was requested by a regulator and if yes, which one);
    2. Research centres and investigator details (coordinating study entity, details of lead investigator, if the study is carried out within the collaboration of a research network, other centres where the study is conducted and countries in which the study is conducted);
    3. Study timelines: initial administrative steps, progress reports and final report;
    4. Sources of funding and estimates of the percentage of funding by source for the study;
    5. Contact details for public and scientific enquiries;
- *Targets of the study* tab:
    6 Study drug information (active substance/ brand name/ multi-constituent/ATC);
    7 Medical condition to be studied;
    8 Populations under study (by age categories, gender and special population, if applicable, among the following possibilities: renal impaired, hepatic impaired, pregnant women, immunocompromised);
    9 Number of patients (estimated total number);
    10 Source of data (if an established data source is used and if yes, which one among the following options: Prospective patient-based data collection/ Disease/case registry/ Prescription event monitoring/ Administrative database, e.g. claims database/ Routine primary care electronic patient registry/ Exposure registry/ Pharmacy dispensing records/ Case-control surveillance/ Spontaneous reporting/ Other);
- *Methodological aspects tab:*
    11 Scope of the study (necessary to choose one of the following as primary scope: Disease epidemiology/ Risk assessment/ Drug utilisation study/ Effectiveness evaluation/ Other);
    12 Main objective (and if there are primary and secondary outcomes and which);
    13 Study design (Sentinel sites/ Intensive monitoring schemes/ Prescription event monitoring/ Cross-sectional study/ Cohort study/ Case-control study/ Case-series/ Case-crossover/ Self-controlled case series/ Drug utilisation study/ Pharmacokinetic study/ Pharmacodynamic study/ Drug interaction study/ Randomised controlled trial/ Non-randomised controlled trial);
    14 Follow-up of patients (if applicable);
    15 Data analysis plan (brief summary of the analysis method);
- *Documents tab:*
    16 ENCePP Seal;
    17 Protocol (embedded document – full or redacted);
    18 Study results (allow embedding of study report);
    19 Other relevant documents (Conflicts of interest, Composition of steering groups and observers, Code of conduct, ENCePP protocol checklists and others).

Annex 4

Example 1 – A typical PASS protocol entry from the first PRAC meeting minutes

From Pharmacovigilance Risk Assessment Committee (PRAC): Minutes of the Meeting 1-3 October 2012; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2012/11/WC500134637.pdf

7. Post-authorisation Safety Studies (PASS)
7.1. Post-authorisation safety studies protocols
7.1.1. Ivacaftor – KALYDECO (CAP)
Evaluation of PASS protocol: observational study to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis (CF)
Regulatory details:
PRAC Rapporteur: Miguel Angel Macia (ES)
PRAC Co-Rapporteur: Julia Pallos (HU)
Background
Ivacaftor is a selective modulator of the cystic fibrosis transmembrane conductance regulator (CFTR) used in the treatment of cystic fibrosis.
A PASS protocol for Kalydeco, a centrally authorised medicine containing ivacaftor, was presented for review by the PRAC in the context of the evaluation of the long-term safety of ivacaftor in patients with cystic fibrosis (title 'An Observational Study to Evaluate the Long-Term Safety of ivacaftor in Patients with Cystic Fibrosis (CF)').
Endorsement/Refusal of the protocol
The PRAC, having considered the draft protocol version 1.2 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Kalydeco (ivacaftor) as the Committee considered that the design of the study did not fulfil the study objectives.
The PRAC therefore recommended that:
The MAH should submit a revised PASS protocol within 60 days. A standard 60 day-assessment timetable will be applied.
The MAH was encouraged to contact EMA within two weeks in order to receive clarification on any issues in advance and facilitate the resubmission of an adequate protocol.

Recorded in the PASS database as follows:

PASS database column name	Inserted text	Rationale
ID	1	This was the first PASS protocol related entry the PRAC meeting minutes.
PASS protocol identification	Glycopyrronium bromide - ENUREV BREEZHALER (CAP), SEEBRI BREEZHALER (CAP), TOVANOR BREEZHALER (CAP) - DUS	In the PRAC meeting minutes from the meeting held in April 2013, there were two separate entries in section 7 (7.1.4 and 7.1.5) clearly identifying two different PASS protocols for this medicinal product (one imposed PASS protocol

		and one Drug Utilisation Study included in the RMP). In the Set 2013 PRAC meeting minutes both PASS protocols are presented (corresponding to the second round). However they are presented in different sections (one dedicated to imposed PASS and other to non-imposed PASS). From the annex heading presented here it is clear it concerns the non-imposed PASS so the PASS protocol mentioned here must be the one previously referred as "Drug Utilisation Study"
PRAC Meeting date	01-03 Oct 2012	Date of the respective PRAC Meeting minute
Rounds of PRAC evaluation	1	The first entry for this PASS protocol
Subject	Evaluation of PASS protocol: observational study to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis (CF)	Verbatim text below the sub header of the section
Section	7.1. Post-authorisation safety studies protocols	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Miguel Angel Macia (ES)	---
Procedure number	Not available	This information was only introduced in PRAC meeting minutes from February 2014
Scope	Not available	Same as above
MAH	Not available	Same as above
Background	Ivacaftor is a selective modulator of the cystic fibrosis transmembrane conductance regulator (CFTR) used in the treatment of cystic fibrosis. A PASS protocol for Kalydeco, a centrally authorised medicine containing ivacaftor, was presented for review by the	---

	PRAC in the context of the evaluation of the long-term safety of ivacaftor in patients with cystic fibrosis (title 'An Observational Study to Evaluate the Long-Term Safety of ivacaftor in Patients with Cystic Fibrosis (CF)').	
PRAC Comment	The PRAC, having considered the draft protocol version 1.2 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Kalydeco (ivacaftor) as the Committee considered that the design of the study did not fulfil the study objectives. The PRAC therefore recommended that: •the MAH should submit a revised PASS protocol within 60 days. A standard 60 day-assessment timetable will be applied. The MAH was encouraged to contact EMA within two weeks in order to receive clarification on any issues in advance and facilitate the resubmission of an adequate protocol.	--

Example 2 – Identification of a related information to the same PASS protocol already presented in a previous PRAC meeting minute (i.e. same unit of analysis as example 1 but a different unit of observation)

From Pharmacovigilance Risk Assessment Committee (PRAC): Minutes of the meeting 26-29 Nov 2012; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/01/WC500137660.pdf

7. Post-authorisation Safety Studies (PASS)
7.1. Post-authorisation safety studies protocols
7.1.3. Ivacaftor – KALYDECO (CAP)
Letter from the EMA Paediatric Committee (PDCO) - collection of long-term data on disease progression in the 5-year post-authorisation study (PASS)
Regulatory details:
PRAC Rapporteur: Miguel Angel Macia (ES)
PRAC Co-Rapporteur: Julia Pallos (HU)

Background
The PDCO contacted the PRAC regarding a request for modification of the Paediatric Investigational Plan (PIP) for Kalydeco. The MAH requested the removal of a two-year placebo-controlled study (study D) in children with Forced Expiratory Volume in 1 second FEV1 > 90% from the PIP on the basis that the study was no longer feasible. The study was to evaluate the impact of ivacaftor on disease progression.
The PDCO adopted a positive opinion on the PIP modification request but at the same time emphasised the importance of gathering long-term data on disease progression to ensure safe and effective use of Kalydeco in paediatric patients and recommended that the 5-year post-authorisation safety study (PASS) included in the Risk Management Plan be used to gather these data.
The PRAC discussed the PDCO letter and recommendations.
Summary of advice
The PRAC considers the lack of long-term data on disease progression (including rate of decline of lung function, diabetes mellitus and distal intestinal obstruction syndrome) to be an important knowledge gap that is of particular cause of concern in children with cystic fibrosis.
The PRAC therefore agreed on the need to amend the PASS protocol - for which a letter of objection (with recommendation for the submission of a new protocol) was agreed during the 3-5 October 2012 meeting - to include the additional objective of obtaining long-term disease progression data and specific endpoints.
A revised letter to the MAH was agreed by the PRAC requesting the MAH to further amend the PASS protocol and giving the MAH a one month extension to the deadline for submission of the revised PASS protocol.

Recorded in the PASS database as follows:

PASS database column name	Inserted text	Rationale
ID	4	This was the fourth PASS protocol related entry the PRAC meeting minutes.
PASS protocol identification	Ivacaftor - KALYDECO (CAP)	--
PRAC Meeting date	26-29 Nov 2012	Date of the respective PRAC meeting minute

Rounds of PRAC evaluation	2	From the text (please see specific segments highlighted in bold below) it is possible to ascertain this entry is related to the PASS protocol for Kalydeco presented in previous Meetings (ID 1) and therefore this entry is the second PRAC consideration regarding that study.
Subject	Letter from the EMA Paediatric Committee (PDCO) - collection of long-term data on disease progression in the 5-year post-authorisation study (PASS)	Verbatim text below the subheader of the section
Section	7.1. Post-authorisation safety studies protocols	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Miguel Angel Macia (ES)	---
Procedure number	Not available	This information was only introduced in PRAC meeting minutes from February 2014
Scope	Not available	Same as above
MAH	Not available	Same as above
Background	The PDCO contacted the PRAC regarding a request for modification of the Paediatric Investigational Plan (PIP) for Kalydeco. The MAH requested the removal of a two-year placebo-controlled study (study D) in children with Forced Expiratory Volume in 1 second FEV1 > 90% from the PIP on the basis that the study was no longer feasible. The study was to evaluate the impact of ivacaftor on disease progression. The PDCO adopted a positive opinion on the PIP modification request but at the same time emphasised the importance of gathering long-term data on disease progression to ensure safe and effective use of Kalydeco in paediatric patients and recommended **that the 5-year post-authorisation safety study (PASS) included in the Risk Management Plan be used to gather these data.**	--

	The PRAC discussed the PDCO letter and recommendations.	
PRAC Comment	The PRAC considers the lack of long-term data on disease progression (including rate of decline of lung function, diabetes mellitus and distal intestinal obstruction syndrome) to be an important knowledge gap that is of particular cause of concern in children with cystic fibrosis. **The PRAC therefore agreed on the need to amend the PASS protocol - for which a letter of objection (with recommendation for the submission of a new protocol) was agreed during the 3-5 October 2012 meeting - to include the additional objective of obtaining long-term disease progression data and specific endpoints.** **A revised letter to the MAH was agreed by the PRAC requesting the MAH to further amend the PASS protocol** and giving the MAH a one month extension to the deadline for submission of the revised PASS protocol.	--

Example 3 – A typical PASS protocol entry from the last year's PRAC meeting minutes

From Pharmacovigilance Risk Assessment Committee (PRAC): Minutes of the meeting 06-09/Jan015; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/02/WC500183280.pdf

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)27

7.2.1. Agomelatine – THYMANAX (CAP), **VALDOXAN** (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Ingebjørg Buajordet (NO)

Administrative details:

Procedure number(s): EMEA/H/C/000916/MEA 023, EMEA/H/C/000915/MEA 023
Procedure scope: Evaluation of a PASS protocol for a study using databases in four European countries to assess the incidence of hospitalisation for liver injury in current medical practice in comparison with other antidepressant drugs
MAH(s): <<<<censored>>>

Background

Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist indicated in adults for the treatment of major depressive episodes.
As part of the RMP for Valdoxan/Thymanax, centrally authorised products containing agomelatine the MAH was required to conduct a PASS using databases in four European countries in order to assess the incidence of hospitalisation for liver injury in current medical practice in comparison with other antidepressant drugs. The MAH submitted a protocol for such study (PASS for agomelatine and the risk of hospitalisation for acute liver injury (ALI)) which was assessed by the Rapporteur.

Summary of advice

- The study protocol for the proposed PASS for Valdoxan/Thymanax (agomelatine) could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA within 30 days. In particular, since the expected number of exposed patients remains low as per the inclusion criteria, suggestions aiming at strengthening the study were made intended to control the potentially significant impact of exposure/outcome misclassification.
- A 30 days assessment timetable will apply.

Recorded in the PASS database as follows:

PASS database column name	Inserted text	Rationale
ID	263	This was the 263th PASS protocol related entry the PRAC meeting minutes.
PASS protocol identification	Agomelatine – THYMANAX (CAP), VALDOXAN (CAP) – PASS	An additional ID was necessary to add because as seen in the following example there was another PASS protocol for the

		same medicinal product
PRAC Meeting date	06-09/Jan015	Date of the respective PRAC meeting minute
Rounds of PRAC evaluation	1	This is the first time a PASS protocol related to this medicinal product was mentioned in the consecutive PRAC meeting minutes
Subject	Evaluation of a PASS protocol	Verbatim text below the subheader of the section
Section	7.2. Protocols of PASS non-imposed in the marketing authorisation(s)	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Ingebjørg Buajordet (NO)	---
Procedure number	EMEA/H/C/**000916/MEA 023**, EMEA/H/C/**000915/MEA 023**	---
Scope	Evaluation of a PASS protocol for a study using databases in four European countries to assess the incidence of hospitalisation for liver injury in current medical practice in comparison with other antidepressant drugs	---
MAH	<<<<censored>>>	---
Background	Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist indicated in adults for the treatment of major depressive episodes. As part of the RMP for Valdoxan/Thymanax, centrally authorised products containing agomelatine the MAH was required to conduct a PASS using databases in four European countries in order to assess the incidence of hospitalisation for liver injury in current medical practice in comparison with other antidepressant drugs. The MAH submitted a protocol for such study (PASS for agomelatine and the risk of hospitalisation for acute liver injury (ALI)) which was assessed by the Rapporteur.	--
PRAC Comment	The study protocol for the proposed PASS for Valdoxan/Thymanax	--

	(agomelatine) could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA within 30 days. In particular, since the expected number of exposed patients remains low as per the inclusion criteria, suggestions aiming at strengthening the study were made intended to control the potentially significant impact of exposure/outcome misclassification. • A 30 days assessment timetable will apply.	

Example 4 – The identification of a different PASS protocol for a medicinal protocol with another PASS protocol already presented

From Pharmacovigilance Risk Assessment Committee (PRAC): Minutes of the meeting 06-09/Jan015; Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/02/WC500183280.pdf

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)27
7.2.2. Agomelatine – THYMANAX (CAP), **VALDOXAN** (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Ingebjørg Buajordet (NO)
Administrative details:
Procedure number(s): EMEA/H/C/000916/MEA 024, EMEA/H/C/000915/MEA 024
Procedure scope: Evaluation of a PASS protocol for a non-interventional post-authorisation safety study/pharmacogenomic study to explore the potential liver injury and potential associated risk factors, risk of hepatotoxic reactions associated with agomelatine in reasonable timelines.
Pharmacogenomic study: further explore the potential liver injury and potential associated risk factors, specific investigations are implemented for patients who exhibit abnormal liver enzymes (ALAT, ASAT or ALP value > 3 x upper limit of normal (ULN) or total bilirubin > 2 ULN) in the ongoing and planned clinical trials with agomelatine, with close follow-up of abnormalities until resolution, and determination of key variables in liver function assessment and appropriate etiological investigations. DNA should be taken allowing for search of the influence of different genetic polymorphisms
MAH(s): <<<<censored>>>

Background
Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist indicated in adults for the treatment of major depressive episodes.
As part of the RMP for Valdoxan/Thymanax, centrally authorised products containing agomelatine, the MAH was required to conduct a pharmacogenomic study to explore the potential for liver injury and potential associated risk factors with DNA samples to be taken allowing for investigation of the influence of different genetic polymorphisms. The MAH submitted a protocol for such study (human leukocyte antigen (HLA) alleles as genetic risk factors for evaluation of aminotransferases in patients treated with agomelatine) which was assessed by the Rapporteur.

Summary of advice

- The proposed study protocol for the for Valdoxan/Thymanax (agomelatine) pharmacogenetic study could be acceptable provided an updated protocol with the changes regarding sampling, sequencing, handling of missing data, inclusion of serious cases is submitted to the EMA within 30 days.

Recorded in the PASS database as follows:

PASS database column name	Inserted text	Rationale
ID	264	This was the 264th PASS protocol related entry the PRAC Meeting minutes.
PASS protocol identification	Agomelatine – THYMANAX (CAP), VALDOXAN (CAP) - PASS/PhGen	An additional ID was necessary to add to

		distinguish from the previous PASS protocol entry which concerned the same medicinal product. The different procedure number and remaining text information clear indicated the PASS protocol concerned in this entry is different from the previous one
PRAC Meeting date	06-09/Jan015	Date of the respective PRAC Meeting minute
Rounds of PRAC evaluation	1	This was not the first time a PASS protocol related to this medicinal product, as seen in the example above. However, from the distinctive characteristics of this PASS protocol is clear it is the first entry for this particular study.
Subject	Evaluation of a PASS protocol	Verbatim text below the subheader of the section
Section	7.2. Protocols of PASS non-imposed in the marketing authorisation(s)	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Ingebjørg Buajordet (NO)	---
Procedure number	EMEA/H/C/**000916/MEA 024**, EMEA/H/C/**000915/MEA 024**	---
Scope	Evaluation of a PASS protocol for a non-interventional post-authorisation safety study/pharmacogenomic study to explore the potential liver injury and potential associated risk factors, risk of hepatotoxic reactions associated with agomelatine in reasonable timelines. Pharmacogenomic study: further explore the potential liver injury and potential associated risk factors, specific investigations are implemented for patients who exhibit abnormal liver	---

	enzymes (ALAT, ASAT or ALP value > 3 x upper limit of normal (ULN) or total bilirubin > 2 ULN) in the ongoing and planned clinical trials with agomelatine, with close follow-up of abnormalities until resolution, and determination of key variables in liver function assessment and appropriate etiological investigations. DNA should be taken allowing for search of the influence of different genetic polymorphisms	
MAH	<<<<censored>>>	---
Background	Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist indicated in adults for the treatment of major depressive episodes. As part of the RMP for Valdoxan/Thymanax, centrally authorised products containing agomelatine, the MAH was required to conduct a pharmacogenomic study to explore the potential for liver injury and potential associated risk factors with DNA samples to be taken allowing for investigation of the influence of different genetic polymorphisms. The MAH submitted a protocol for such study (human leukocyte antigen (HLA) alleles as genetic risk factors for evaluation of aminotransferases in patients treated with agomelatine) which was assessed by the Rapporteur.	--
PRAC Comment	The proposed study protocol for the for Valdoxan/Thymanax (agomelatine) pharmacogenetic study could be acceptable provided an updated protocol with the changes regarding sampling, sequencing, handling of missing data, inclusion of serious cases is submitted to the EMA within 30 days.	--

Example 5 – PASS protocol entries from the annex section of PRAC meeting minutes

From Pharmacovigilance Risk Assessment Committee (PRAC): Minutes of the meeting 02-05/Sep2013; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/10/WC500152672.pdf

16. ANNEX I Post-authorisation Safety Studies (PASS)
Since all comments received on the assessment of these measures were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below.
16.1. Protocols of PASS imposed in the marketing authorisation(s)39
See section 7.
16.2. Protocols of PASS non-imposed in the marketing authorisation(s)4

16.2.9. Glycopyrronium bromide – ENUREV BREEZHALER (CAP), **SEEBRI BREEZHALER** (CAP), **TOVANOR BREEZHALER** (CAP)
• Evaluation of a PASS protocol
Regulatory details:
PRAC Rapporteur: Line Michan (DK)

16.2.4. Bromelain enriched proteolytic enzyme preparation from ananas comosus – NEXOBRID (CAP)
• Evaluation of a PASS protocol
Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

The entries were recorded in the PASS database as follows:

PASS database column name	Inserted text	Rationale
ID	62	Sequential ID
PASS protocol identification	Glycopyrronium bromide - ENUREV BREEZHALER (CAP), SEEBRI BREEZHALER (CAP), TOVANOR BREEZHALER (CAP) - DUS	In the PRAC meeting minutes from the meeting held in April 2013, there were two separate entries in section 7 (7.1.4 and 7.1.5) clearly identifying two different PASS protocols for this medicinal product (one imposed PASS protocol and one Drug Utilisation Study included in the RMP). In the Set 2013 PRAC meeting minutes both PASS protocols are presented (corresponding to the second round). However they are

		presented in different sections (one dedicated to imposed PASS and other to non-imposed PASS). From the annex heading presented here it is clear it concerns the non-imposed PASS so the PASS protocol mentioned here must be the one previously referred as “Drug Utilisation Study”
PRAC Meeting date	02-05/Sep2013	Date of the respective PRAC Meeting minute
Rounds of PRAC evaluation	2	See explanation above
Subject	Evaluation of a PASS protocol	Verbatim text below the subheader of the section
Section	16.2. Protocols of PASS non-imposed in the marketing authorisation(s)	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Line Michan (DK)	---
Procedure number	Not available	This information was only introduced in PRAC meeting minutes from February 2014
Scope	Not available	Same as above
MAH	Not available	Same as above
Background	Missing	--
PRAC Comment	Missing	--

PASS database column name	Inserted text	Rationale
ID	59	Sequential ID
PASS protocol identification	Bromelain enriched proteolytic enzyme preparation from ananas comosus - NEXOBRID (CAP)	
PRAC Meeting date	02-05/Sep2013	Date of the respective PRAC meeting minute
Rounds of PRAC evaluation	1	This is the first time a PASS protocol is

		mentioned for this medicinal product
Subject	Evaluation of a PASS protocol	Verbatim text below the subheader of the section
Section	16.2. Protocols of PASS non-imposed in the marketing authorisation(s)	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Martin Huber (DE)	---
Procedure number	Not available	This information was only introduced in PRAC meeting minutes from February 2014
Scope	Not available	Same as above
MAH	Not available	Same as above
Background	Missing	--
PRAC Comment	Missing	--

From February 2014 PRAC meeting minutes contain more information in the Annex section as seen in the following two examples. From Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting 8-11/Jun015;

Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/07/WC500190189.pdf

16. ANNEX I Post-authorisation Safety Studies (PASS)
Since all comments received on the assessment of these measures were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below.

16.1. Protocols of PASS imposed in the marketing authorisation(s)43

16.1.1. Cholic acid– KOLBAM (CAP) - EMEA/H/C/PSP/0017
Applicant: ASK Pharmaceuticals GmbH
PRAC Rapporteur: Rafe Suvarna
Scope: Evaluation of a PASS protocol for a patient registry to monitor the long term safety and efficacy in patients treated with cholic acid FGK

16.1.2. Ivabradine – CORLENTOR (CAP), PROCOLORAN (CAP) - EMEA/H/C/PSP/0019.1
Applicant: Les Laboratoires Servier
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a revised DUS protocol for a multinational, retrospective, observational study to assess effectiveness of risk-minimisation measures

The entries were recorded in the PASS database as follows:

PASS database column name	Inserted text	Rationale
ID	330	Sequential ID
PASS protocol identification	Cholic acid– KOLBAM (CAP)	--
PRAC Meeting date	8-11/Jun015	Date of the respective PRAC meeting minute
Rounds of PRAC evaluation	1	This is the first time a PASS protocol is mentioned for this medicinal product
Subject	Not applicable	The structure of the minutes does not contain this information anymore, instead the scope, inexistent in the previous examples, is now more informative.
Section	16.1. Protocols of PASS imposed in the marketing authorisation(s)43	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Rafe Suvarna	---
Procedure number	EMEA/H/C/PSP/0017	--
Scope	Evaluation of a PASS protocol for a patient registry to monitor the long term safety and efficacy in patients treated with cholic acid FGK	---
MAH	ASK Pharmaceuticals GmbH	---
Background	Missing	--
PRAC Comment	Missing	--

--	Inserted text	Rationale
--	331	Sequential ID
--	Ivabradine – CORLENTOR (CAP), PROCOLORAN (CAP)	--
PRAC Meeting date	8-11/Jun015	Date of the respective PRAC meeting minute
Rounds of PRAC evaluation	2	In the PRAC meeting minutes from the meeting held in May 2015, there was reference to a PASS protocol for this medicinal product, for which the procedure number was given (EMEA/H/C/PSP/J/0019).

		Therefore it is clear that this is a subsequent presentation of the same PASS protocol (procedure number EMEA/H/C/PSP/0019.1)
Subject	Not applicable	The structure of the minutes does not contain this information anymore, instead the scope, inexistent in the previous examples, is now more informative.
Section	16.1. Protocols of PASS imposed in the marketing authorisation(s)43	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Menno van der Elst	---
Procedure number	EMEA/H/C/PSP/0019.1	--
Scope	Evaluation of a revised DUS protocol for a multinational, retrospective, observational study to assess effectiveness of risk-minimisation measures	---
MAH	<<<censored>>>	---
Background	Missing	--
PRAC Comment	Missing	--

Example 6 – The identification of a different PASS protocol within the same PASS protocol entry in the PRAC meeting minutes

From Pharmacovigilance Risk Assessment Committee (PRAC): Minutes of the meeting 4-7 March 2013; Available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/04/WC500142504.pdf

7. Post-authorisation Safety Studies (PASS)
7.1. Protocols of post-authorisation safety studies
7.1.4. Tenofovir disoproxil fumarate – VIREAD (CAP)
• PRAC consultation on a PASS protocol included in the Pharmacovigilance plan of the RMP in accordance with Article 107m of Directive 2001/83/EC
Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)
The PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment protocol synopses for a PASS of HIV-1 and HBV infected paediatric patients included in the version 14 of the RMP since all comments were addressed in the consultation phase.

Recorded in the PASS database as two different rows as follows:

PASS database column name	Inserted text	Rationale
ID	15	This was the 15th PASS protocol related entry the PRAC meeting minutes.
PASS protocol identification	Tenofovir disoproxil fumarate - VIREAD (CAP) - HIV	From the text available it is clear that this PASS protocol entry refers to two different studies (please see segments highlighted in bold below). Therefore this entry was spilt in two, one for each PASS protocol.
PRAC Meeting date	04-07/Mar2013	Date of the respective PRAC meeting minute
Rounds of PRAC evaluation	1	This was not the first time a PASS protocol related to this medicinal product, as seen in the example above. However, from the distinctive characteristics of this PASS protocol is clear it is the first entry for this particular study.

Subject	PRAC consultation on a PASS protocol included in the Pharmacovigilance plan of the RMP in accordance with Article 107m of Directive 2001/83/EC	Verbatim text below the subheader of the section
Section	7.1. Post-authorisation safety studies protocols	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Isabelle Robine (FR)	---
Procedure number	Not available	This information was only introduced in PRAC meeting minutes from February 2014
Scope	Not available	Same as above
MAH	Not available	Same as above
Background	Missing	--
PRAC Comment	The PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment protocol synopses for **a PASS of HIV-1 and HBV** infected paediatric patients included in the version 14 of the RMP since all comments were addressed in the consultation phase.	--

PASS database column name	Inserted text	Rationale
ID	16	This was the 16th PASS protocol related entry the PRAC meeting minutes.
PASS protocol identification	Tenofovir disoproxil fumarate - VIREAD (CAP) – Hep B	From the text available it is clear that this PASS protocol entry refers to two different studies (please see segments highlighted in bold below). Therefore this entry was spilt in two, one for each PASS protocol.
PRAC committee month	04-07/Mar2013	Date of the respective PRAC meeting minute

Rounds of PRAC evaluation	1	This was not the first time a PASS protocol related to this medicinal product, as seen in the example above. However, from the distinctive characteristics of this PASS protocol is clear it is the first entry for this particular study.
Subject	PRAC consultation on a PASS protocol included in the Pharmacovigilance plan of the RMP in accordance with Article 107m of Directive 2001/83/EC	Verbatim text below the subheader of the section
Section	7.1. Post-authorisation safety studies protocols	The header of the PRAC meeting minutes section where the PASS protocol is described
PRAC Rapporteur	Isabelle Robine (FR)	---
Procedure number	Not available	This information was only introduced in PRAC meeting minutes from February 2014
Scope	Not available	Same as above
MAH	Not available	Same as above
Background	Missing	--
PRAC Comment	The PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment protocol synopses for **a PASS of HIV-1 and HBV** infected paediatric patients included in the version 14 of the RMP since all comments were addressed in the consultation phase.	--

On the subsequent PRAC meeting minutes, the abovementioned PASS protocols were presented separately which corroborated the need to consider PASS protocols entities separately even if they are grouped together in a certain minutes' entry.

Differently from the example above, it was also possible, for some PASS protocol entries, that only in a subsequent PRAC meeting minute if became apparent how many PASS protocols existed since the beginning for a certain medicinal product. In those cases the PASS database entry related with the "first round" of assessment for that medicinal product was split to capture all different PASS protocols.

Annex 5

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
A	General Identifiers	**ID**	Unique number assigned to each new PASS protocol assessment identified in the Minutes. Note that it does not identify a unique PASS protocol as one protocol could have been assessed more than once over the study period.	Ordinal	NA	The number is assigned to each PASS entry from the PRAC Meeting Minutes in chronological order
B		**PRAC Meeting date**	The date of the PRAC Meeting correspondent to the Minutes in which the PASS protocol assessment is identified	Nominal	NA	The date as recorded in the Meeting Minutes (e.g. 26-29 Nov 2012)
C		**Year**	Derived from "PRAC Meeting date" (column B in the matrix): the year of the PRAC Meeting	Ordinal	1; 2; 3	Derived from "PRAC Meeting date" (column B in the matrix). PASS protocol assessments identified in Minutes from Meetings held from July 2012 to July 2013 inclusive are assigned "1", those from Meetings held from August 2013 to July 2014 are assigned "2" and those from Meetings held from August 2014 to July 2015 inclusive are assigned "3".

The database is provided as electronic supplementary material (CD-ROM)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
D	**General Identifiers**	**Month**	Derived from "PRAC Meeting date" (column B in the matrix): the month of the PRAC Meeting	Ordinal	1 to 32	Derived from "PRAC Meeting date" (column B in the matrix). The first Minutes corresponded the PRAC Meeting held in October 2012 (month =1). The following months are numbered consecutively. August is not considered as no PRAC Meetings are held that month. Therefore July 2013 counts as month 10 and September 2013 as month 11.
E		**PASS protocol identification**	Identification of a unique PASS protocol. It is the identifier of each PASS protocol throughout the different rounds of submission.	String	NA	The identification should be composed by the following elements: Name of active substance – brand name (type of regulatory procedure) which is the same structure used in the PRAC Meeting Minutes. In addition, when more than one protocol is available for the same product they are distinguished either by a numeral or a differentiating characteristic
F		**Marketing Authorisation type of procedure**	The type of Marketing Authorisation Procedure of the medicinal product studied in the PASS	Nominal	CAP/ NAP	Derived from "PASS protocol identification" (column E in the matrix) as the authorisation procedure is part of the PASS protocol identification in the Minutes and in the matrix

The database is provided as electronic supplementary material (CD-ROM)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
G	**General Identifiers**	**Rounds of PRAC evaluation**	Identification of the assessment number for a certain PASS protocol. Therefore, any PASS protocol identified for the first time during the chronological review of the Minutes is considered to be the first round of assessment of that PASS protocol during the study period. Records of the same PASS protocol in the consecutive meeting are considered subsequent rounds of assessment of that PASS protocol during the study period.	Ordinal	A consecutive integer number	Every new PASS protocol identified in the consecutive PRAC Meeting Minutes is assigned "Round =1". Subsequent records of the same PASS protocol in subsequent PRAC Meeting Minutes are assigned subsequent sequential numbers.
H	**Textual transcript from the Minutes**	**Subject**	Contextual sentence (summarising the reason for the inclusion of that particular topic in the meeting) presented after the identification of each PASS protocol submission throughout the PRAC Meeting Minutes until April 2015 included	String	NA	Verbatim extracted from the PRAC Meeting Minutes: bullet point below each PASS protocol assessment entry (e.g. evaluation of an imposed PASS protocol)
I		**Section**	The section of the Minutes in which the PASS protocol assessment is presented (available since September 2013)	String	NA	Section number and header identification from the PRAC Meeting Minutes
J		**PRAC Rapporteur**	The name and country of the PRAC Rapporteur as recorded in the Minutes	String	NA	Verbatim extracted from the PRAC Meeting Minutes
K		**Procedure number**	The EMA's procedure number attributed to the PASS protocol assessment (available since February 2014)	String	NA	Verbatim extracted from the PRAC Meeting Minutes dated February 2014 and after (previous Minutes did not contain this information)

The database is provided as electronic supplementary material (CD-ROM)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
L	**Textual transcript from the Minutes**	**Scope**	A brief description about the scope, which could contain brief information on study background, aim and design (available since February 2014)	String	NA	Verbatim extracted from the PRAC Meeting Minutes dated February 2014 and after (previous Minutes did not contain this information)
M		**Marketing Authorisation Holder (MAH)**	The Marketing Authorisation Holder of the medicinal product studied in the PASS (available since February 2014)	String	NA	Before the Minutes of the February 2014 Meeting, the information was retrieved from the EMA website (search for brand name). Afterwards, the verbatim was extracted from the Minutes as the information started being included in these documents
N		**Background**	Textual transcription from the PRAC Meeting Minutes or other sources (mainly EPAR) of text relevant to understand the rational and background for the conduction of the PASS	String	NA	Verbatim text copied from the Minutes whenever "background" information was available for a PASS protocol assessment entry. When not available, but information was found in other sources (mainly the EPRAs), it was copied to/ summarised in this field.

The database is provided as electronic supplementary material (CD-ROM)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
O		**PRAC comment**	Verbatim copied from the PRAC Meeting Minutes (for the PASS protocol assessments entries with this information available)	String	NA	Verbatim copied from the PRAC Meeting Minutes sections "PRAC comments/ Summary of advice / Endorsement or Refusal of the protocol" (the name of the field) varied throughout the different Minutes) whenever available. Whenever the only information from the Minutes was "since all comments received on the assessment of the study protocol were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteur" and the PRAC Rapporteur conclusion is not reported, the PRAC comment was considered missing.
P	**Type of PRAC comments**	**PRAC outcome**	Derived from "PRAC Comment" (column O in the matrix): the outcome of the protocol assessment	Nominal	Endorsed	When there was clear information from "PRAC Comment" (column O in the matrix) that the protocol was considered approved

The database is provided as electronic supplementary material (CD-ROM)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
	Type of PRAC comments				Objection	The information from "PRAC Comment" (column O in the matrix) suggests a formal PRAC assessment process where a formal letter of endorsement/objection is emitted by the PRAC following amended DIR 2001/83/EC Article 107n (applicable to imposed protocols). According to the legislation, the standard text to describe the reasons for objection are "the conduct of the study promotes the use of a medicinal product" or "the design of the study does not fulfil the study objectives"
					Revision	When the text from "PRAC Comment" (column O in the matrix) does not suggest a formal endorsement/ refusal process as described for the previous category but the text clear indicates that the PASS protocol needed further revisions.
P		**PRAC outcome**			Other	Any other text in "PRAC Comment" (column O in the matrix) that is neither an objection/ revision/ missing information. This is the case of administrative information and organisational considerations such as the communication of the procedure timetable and Rapporteur or recommendations to submit joint PASS

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
					NA - same as previous	Used for the cases in which different PASS protocols for a certain medicinal product are recorded under the same topic of the Minutes, which are split as two different rows (PASS protocol assessments) per the established rules. However in order not to artificially repeat the same PRAC comment and avoid duplication, only one the rows in the matrix has the PRAC comment text and the other row is assigned with this code "NA - same as previous".
					Missing	No information available regarding the outcome: "PRAC Comment" (column O in the matrix) with no information.

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
Q	**Type of PRAC comments**	**PRAC comments (details categorised)**	For those with "PRAC comment" (column O) as "Objection" / "Revision" / "Other", this field provides information about the PASS protocol area of concern.	String	NA	More than one category allowed. The PRAC comments related with "Objection" or "Revision" outcomes (according to information on columns O and P) were coded with one or more areas of concern categories. Those comprised: Study objectives and endpoints/ Study design/ Data source and population/ Data collection and management/ Study variables / Study size/ Data analysis/ Milestones and timelines/ Feasibility considerations/ Other (included comments on rational and background or safety sections, data protection and change in the obligation status of the PASS)/ Missing. For those PRAC comments for which "PRAC outcome" (column P) was classified as "Other", briefly present here the nature of the comment (e.g. "joint PASS"/ "timetable established")

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
R	**PASS protocol assessment metrics**	**Next submission timetable**	For those with "PRAC comment" (column O) as "Objection" / "Revision" this field contains information about the required deadline for submission of a revised protocol according to the minutes.	String	NA	Verbatim copied from the PRAC Meeting Minutes sections "PRAC comment" regarding information indicative of the deadline for protocol resubmission.

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
S	**PASS protocol assessment metrics**	Next assessment timetable	For those with "PRAC comment" (column O) as "Objection" / "Revision" this field contains information about the assessment timeline to be followed by the PRAC following the submission of a new protocol version (according to the minutes).	String	NA	Verbatim copied from the PRAC Meeting Minutes sections "PRAC comment" regarding information indicative of the deadline for assessment of the PRAC of a new required protocol resubmission.

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
T	**PASS protocol assessment metrics**	**Number of rounds of PASS assessment over the study period**	Derived from "Rounds of PRAC evaluation" (column G). The number of rounds of assessment for a certain PASS protocol during the study period (i.e. the number of times a certain PASS protocol was recorded in the PRAC Meeting Minutes from July 2012 to July 2015)	Ordinal	Integer number, "ND"	Derived from "Rounds of PRAC evaluation" (column G).For each unique PASS protocol, it is the higher number of rounds recorded (in "Rounds of PRAC evaluation", column G). This was considered to be the number of times that PASS protocol was assessed during the study period, according with the information from the consecutive Minutes. Whenever the PASS protocol assessment rounds were not clear (e.g. if a certain medicinal product had more than one PASS and it was not clear to which one a certain PASS protocol assessment entry in the Minutes was referring to) "ND" was entered in this field (meaning the number of rounds of review of a certain PASS protocol was "not determined").

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
U	**PASS protocol assessment metrics**	**Duration of assessment process over the study period**	Derived from "Rounds of PRAC evaluation" (column G). The number of months elapsed since the first round of a certain PASS protocol assessment and the latest until the data lock point (July 2015)	Ordinal	Integer number, "NA"	Derived from "Rounds of PRAC evaluation" (column G). For each PASS protocol, it is the number of months elapsed since the first and the latest protocol assessment during the study period (i.e. between "round=1" and the highest round number for a certain PASS protocol). If a certain PASS protocol was recorded through the Minutes only once or the number of rounds is not clear (i.e. "Number of rounds of PASS assessment over the study period", column =1 or ND) then "NA" is used as the computation of duration is Not applicable.
V		**Tracking of PASS assessment**	Tracks if the assessment process for a certain PASS protocol is considered finalised at the data lock point (July 2015)	Nominal	Closed	There is explicit information in the Minutes that the PASS protocol assessment was concluded (e.g. "PRAC comments [column O] with information that the PRAC considered the protocol approved and no additional assessment of that protocol was recorded in later Minutes)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
V	**PASS protocol assessment metrics**	**Tracking of PASS assessment**	Tracks if the assessment process for a certain PASS protocol is considered finalised at the data lock point (July 2015)	Nominal	Unknown but more than 1 year elapsed since last appearance	There is no explicit information regarding whether or not the PASS protocol assessment was concluded (i.e. the text from the last assessment of a certain PASS protocol is inconclusive) and more than 12 months elapsed since that latest PASS protocol assessment record in the Minutes and the data lock point (i.e. last protocol assessment for that PASS protocol was recorded in the Minutes of the July 2014 meeting or earlier)
					Unknown but more than 6 months elapsed since last appearance	There is no explicit information regarding whether or not the PASS protocol assessment was concluded (i.e. the text from the last assessment of a certain PASS protocol is inconclusive) and between 6 to 12 months elapsed since that latest PASS protocol assessment record in the Minutes and the data lock point (i.e. last PASS protocol submission was recorded in the Minutes of the Meetings held between September 2014 and February 2015 included). Note: A reminder that there are no Minutes for August since the PRAC does not meet in that month.

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
V	**PASS protocol assessment metrics**	**Tracking of PASS assessment**	Tracks if the assessment process for a certain PASS protocol is considered finalised at the data lock point (July 2015)	Nominal	Unknown but less than six months elapsed since last appearance	There is no explicit information regarding whether or not the PASS protocol assessment was concluded (i.e. the text from the last assessment of a certain PASS protocol is inconclusive) and less than 6 months elapsed since that latest PASS protocol assessment record in the Minutes and the data lock point (i.e. last PASS protocol submission was seen in the Minutes of the Meetings held between March 2015 and July 2015 included).
W		**PASS protocol submitted for the first time before July 2012**	To identify those PASS protocols for which there was some evidence that they were firstly submitted for the first time before the new Pharmacovigilance legislation and therefore before the PRAC remit	Nominal	Yes	Selected when there was enough evidence that the first PASS protocol assessment for that study was before July 2012: text from the Minutes clearly indicates it, or the EPAR or EU PAS Register clearly referring to that PASS have a protocol date earlier than July 2012
					No	Selected when there was enough evidence that the first PASS protocol assessment for that study was after July 2012: the marketing authorisation date of the medicinal product is after July 2012 or EPAR or EU PAS Register clearly referring to that PASS have a protocol date later than July 2012
					Unclear	When there is not enough evidence to decide for one of the other categories (e.g. there is conflicting evidence across data sources)

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
X	**PASS protocol assessment metrics**	**PASS assessment closed (estimated)**	Derived from information from "Tracking of PASS assessment " (column T), "PASS protocol submitted for the first time before July 2012" (column U) and "Registered in EU PAS" (column AH) to estimate if a certain PASS protocol assessment has been concluded during the observation period (i.e. until July 2015 included)	Nominal	Yes/No	Derived from the results of the variables in columns T, U and AH as follows: "PASS protocol submitted for the first time before July 2012 = No" AND (("Tracking of PASS assessment = Closed" OR "= Unknown but more than 1 year elapsed slice last appearance") OR "EU PAS Register = Yes")
Y	**Information about the medicinal product studies in the PASS**	**MA date**	The Marketing Authorisation Date of the medicinal product studied in the PASS	Date	NA	Retrieved from the EMA website: “Find medicine” / “Authorisation details” tab / “Date of issue of marketing authorisation valid throughout the European Union”
Z		**Anatomical Therapeutic Chemical (ATC) Classification**	The first level of the ATC code for the active substance studied in the PASS	Nominal	All the first level ATC code categories	Coded based on the name of active substance, using the website: www.whocc.no/atc_ddd_index/
AA		**Therapeutic Area**	The main indication of the medicinal product studied in the PASS according to the EMA website	String	NA	Retrieved from the EMA website: “Find medicine” / “Authorisation details” tab / "Therapeutic area"

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AB	**Information about the medicinal product studies in the PASS**	**Orphan**	The official classification of the medicinal product studied in the PASS regarding the "orphan" designation (EU/3/08/556). To qualify for orphan designation, a medicine must meet a number of criteria: • It must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; • The prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; • No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.	Nominal	Yes/ No	Retrieved from the EMA website: “Find medicine” / “Authorisation details” tab / “Treatment of rare diseases”
AC		**Additional Monitoring**	Identifies if the medicinal product studied in the PASS is included in the EMA list of “medicines under additional monitoring” (those medicinal products that are being monitored particularly closely by regulatory authorities)	Nominal	Yes/ No	Retrieved from the EMA website: “Find medicine” / “Authorisation details” tab / “Additional monitoring”

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AD	**Regulatory/administrative information**	**Joint study**	When more than one MAH sponsor the study.	Nominal	Yes	Selected when there was enough evidence that the PASS was jointly sponsored: either the text from the Minutes describes several MAHs or the information in the EU PAS Register and/ or protocol list several MAHs
					No	Selected when there was enough evidence that the PASS was not jointly sponsored: either the text from the Minutes describes only one MAH or the information on the EU PAS Register and/ or protocol list only one MAH
					Unclear	When there is not enough evidence to decide for one of the other categories (e.g. contradictory information)
					Missing	When there is no information regarding this variable.

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AE		**Obligation**	Distinguishes the PASS that are imposed as a condition to the Marketing Authorisation or as a special obligation within an authorisation under exceptional circumstances (according to articles 21a, 22 and 22a of Directive 2001/83/EC) from the remaining PASS (non-imposed)	Nominal	Imposed/ Non-imposed	Retrieved from the EMA website: “Find medicine” / “Product information” tab / pdf document with the EPAR annexes: annex IIB: Conditions to the marketing authorisation: If the PASS is described on Sections D "Conditions or restrictions with regard to the safe and effective use of the medicinal product" or Section E "Specific obligation to complete post-authorisation measures for the Marketing Authorisation under exceptional circumstances" then it was considered "imposed". When it was not present in those sections it was considered "non-imposed".
AF	**Information about the medicinal product studies in the PASS**	**Study category (Pharmacovigilance Plan) - grouped**	This variable provides more granularity to the variable "obligation" (column AC) by classifying the PASS in the categories that define them in a Risk Management Plan: category 1 if it is a PASS imposed as a condition to the Marketing Authorisation (articles 21a, and 22a of Directive 2001/83/EC); category 2 if it is a PASS imposed as a special obligation within an authorisation under	Nominal	Condition to MA	Information retrieved from the EMA website: “Find medicine” / “Product information” tab / pdf document with the EPAR annexes / annex IIB: Conditions to the marketing authorisation: If the PASS is described on Section D "Conditions or restrictions with regard to the safe and effective use of the medicinal product" it is a condition to the Marketing Authorisation (category 1)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
			exceptional circumstances (according to article 22 of Directive 2001/83/EC); and category 3 if it is a PASS required in the Risk Management plan. In addition, PASS may be imposed as a consequence of a referral (a benefit-risk reassessment procedure conducted by the EMA which is triggered by safety concerns). Other studies not triggered by any of the mechanisms above are considered voluntary (category 4 studies).		Specific obligation	Information retrieved from the EMA website: "Find medicine" / "Product information" tab / pdf document with the EPAR annexes / annex IIB: Conditions to the marketing authorisation: If the PASS is described on Section E "Specific obligation to complete post-authorisation measures for the Marketing Authorisation under exceptional circumstances" it is a special obligation (category 2)
					Referral	Information retrieved from the EMA website: "Find medicine": if the results list one or more referrals – the outcomes of these referrals were reviewed to understand if the PASS was imposed as one of the outcomes of the referral.
AF	**Information about the medicinal product studies in the PASS**	**Study category (Pharmacovigilance Plan) - grouped**	This variable provides more granularity to the variable "obligation" (column AC) by classifying the PASS in the categories that define them in a Risk Management Plan: category 1 if it is a PASS imposed as a condition to the Marketing Authorisation (articles 21a, and 22a of Directive 2001/83/EC); category 2 if it is a PASS imposed as a special obligation within an authorisation under exceptional circumstances (according to	Nominal	RMP	If the PASS is not found in any of the options above, then search on the EMA website: "Find medicine" / "Assessment history" tab: review the documents in a chronological order (focusing on the section entitled "Risk Management Plan") starting from the Assessment Report of the initial Marketing Authorisation until a until finding the PASS, which is then considered a requirement of Risk Management Plan (category 3)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
			article 22 of Directive 2001/83/EC); and category 3 if it is a PASS required in the Risk Management plan. In addition, PASS may be imposed as a consequence of a referral (a benefit-risk reassessment procedure conducted by the EMA which is triggered by safety concerns). Other studies not triggered by any of the mechanisms above are considered voluntary (category 4 studies).		Other	If the PASS is not listed in any of the options above the PASS is coded as "other" (those are considered category 4 PASS)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AG	**Information about the medicinal product studies in the PASS**	**Study category (Pharmacovigilance Plan) - detailed**	Additional information or all PASS that are conditions or requirements of the RMP such as what was the "regulatory lifecycle event" of the medicinal product that led to the PASS (e.g. planned/imposed already with the initial marketing authorisation; after a variation to extend indication to a new disease or to the use in a new approved population such as paediatric patients; after a renewal of the Marketing Authorisation; as a consequence to a variation due to a change in manufacturing or a new dose or route of administration; after the assessment of the PSURs, etc.)	Nominal	NA	Further categorisation of PASS imposed as "condition to the MA" or "RMP" (from column AD). The following codes are used: Initial MA / After MA renewal / After MA variation due to extension to new indication/ After MA variation due to extension to new population/ After MA variation due to a change in the manufacturing process/ After MA variation due to the introduction of a new dose or route of administration/ other reason. This was information was retrieved from the chronological review of the EPARs available on the EMA website.

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AH	**Level of evidence available / data sources**	**Level of information available**	Although the primary data source to create the excel spreadsheet was the Minutes, other data sources were searched to retrieve more detailed information, especially on the PASS methodology. The hierarchy of relevance attributed to the data sources used to populate the variables related with the PASS focus and methods is the following: 1- the protocol as available in the EU PAS Register, 2- the protocol as available in other sources; If the protocol was not available in any source then, the following data sources were searched to infer the information for the classification of the PASS variables, when possible: 3- the information available in the EU PAS register; 4- If there is no information about the PASS in none of the sources above: use information from the Minutes, EPARs and any other sources to retrieve as many information as possible.	**Nominal**	Protocol available - ENCePP	Selected when the PASS protocol document was available in the EU PAS Register
					Protocol available - Quintiles	Selected when the PAS protocol was not available in the EU PAS Register but it was available from other data sources
					Protocol not available - Info in ENCePP registry	Selected when the protocol document was not available but the PASS was registered in the EU PAS Register, so the information available in its structured fields were used as preferred source
					Protocol not available - Info in EMA website/ Minutes for the variables available	Selected when none of the data sources above contained information about the PASS, thus, the information was retrieved only from the PRAC Meeting Minutes, the EPARs in the EMA website or other sources

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AI	**Level of evidence available / data sources**	**Protocol available (yes/no)**	Derived from "Level of information available" (column AF). Used to identify if the PASS protocol document was available as a source	Nominal	Yes/ No	Derived from "Level of information available" (column AF) whenever it was coded with "Protocol available - ENCePP" or "Protocol available - Quintiles"
AJ		**Registered in EU PAS**	Used to identify if the PASS was registered in the EU PAS Register	Nominal	Yes/ No	Whenever the PASS was found to be registered in the ENCePP website's EU PAS Register (http://www.encepp.eu/encepp/studySearch.htm)

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AK	**Level of evidence available / data sources**	**ENCePP seal**	Used to identify if the PASS registered in the EU PAS also had an ENCePP seal or not (when registering a study in the ENCePP register the sponsors can apply for the ENCePP seal which is attributed if the studies are adherent to all requirements and methodological principles underpinning the ENCePP code of conduct)	Nominal	Yes/ No	A record of a PASS registered in the EU PAS Register contains information on whether or not the has the ENCePP study seal
AL		**Registered in EU PAS (link)**	The hyperlink to the PASS record in the EU PAS register embedded in the study title retrieved from the register	Hyperlink	NA	Study title from the EU PAS register pasted with an hyperlink to the ENCePP EU PAS webpage containing the recorded PASS information
AM		**EMA link**	The hyperlink to the EMA webpage where information regarding the PASS can be found	Hyperlink	NA	The webpage address to the EMA page where the most relevant information regarding the PASS can be found
AN		**ClinicalTrials.gov**	This website was created to record information on clinical trials. However, some of the PASS were found to be recorded here, as well. In those cases the hyperlink to the ClinicalTrials.gov webpage with the PASS record was pasted here	Hyperlink	NA	The webpage address to the ClinicalTrials.gov containing the information on the PASS (when registered there). When the PASS was not recorded in this database, "No" was selected.

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AO	**Level of evidence available / data sources**	**Primary objectives**	The primary objectives of the PASS copied from the highest hierarchical evidence data source (i.e. protocol document/ EU PAS Register/ other sources)	**String**	NA	Summary of the primary objectives from the protocol. If protocol not available and PASS is registered in the EU PAS, information copied from data field "12. Main objective(s)". If none of the above but information is found on the EMA website (e.g. summary of Risk Management plan in the EPAR), then information extracted from there.
AP		**RMP Safety concerns addressed (according to EPAR)**	The safety concerns from the summary of Risk Management plan from the EPAR of the medicinal product that are related with the PASS (e.g. listed in the summary of the Pharmacovigilance plan presented in the EPAR to be assessed in the PASS)	**String**	NA	If a PASS is listed in the EPAR (summary of the Pharmacovigilance plan) the safety concerns which it aims to address (according to that document) are transcribed to the spreadsheet with the identification of the type of safety concern (i.e. identified risks/ potential risks/ missing information).

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AQ	**Study objectives**	**Study objectives (PASS focus)**	The definition of this variable was based on GVP Module VIII VIII.B.3. which states that a “post-authorisation study should be classified as a PASS when the main aim for initiating the study includes any of the following objectives: -to quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers; - to evaluate risks of a product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment); - to evaluate the risks of a product after long-term use; - to provide evidence about the absence of risks; - to assess patterns of drug utilisation that add knowledge on the safety of the product (e.g. indication, dosage, co-medication, medication errors); - to measure the effectiveness of a risk	Nominal	To investigate safety concerns	Selected when the/all the primary objectives are/is to assess one of the safety concerns listed in the Risk Management plan of the medicinal product or there is a clear focus on assessing one or more safety endpoints

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AQ	**Study objectives**	**Study objectives (PASS focus)**	minimisation activity." The first four bullet points are related to the investigation of safety concerns (either quantification and/or assessment of risks). They are captured by category "To investigate safety concerns". The other two bullet points are captured by the categories "Drug Utilisation Study" and "Assess effectiveness of risk minimisation measures".	Nominal	Drug Utilisation	Selected when the/all the primary objectives is/are related to assessment of drug use (e.g. drug utilisation patterns)
					Assess effectiveness of risk minimisation measures	Selected when the/all primary objectives is/are related to the assessment of the effectiveness of risk minimisation measures (e.g. see if HCPs or patients understood an educational program)
					To investigate safety concerns + Drug utilisation	Selected when the primary objectives of the study are to investigate safety concern(s) but also assess drug utilisation (see above)
					To investigate safety concerns + Assess effectiveness of risk minimisation measures	Selected when the primary objectives of the study are to investigate safety concern(s) but also assess effectiveness of risk minimisation measures (see above)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AQ	**Study objectives**	**Study objectives (PASS focus)**		Nominal	Drug utilisation + Assess effectiveness of risk minimisation measures	Selected when the primary objectives of the study are assess drug utilisation but also assess effectiveness of risk minimisation measures (see above)
					To investigate safety concerns + Drug utilisation + Assess effectiveness of risk minimisation	Selected when the primary objectives of the study are to investigate safety concerns, assess drug utilisation and also assess effectiveness of risk minimisation measures (see above)
AR		**PASS focus: inv saf concer**	Variable derived from AO: to identify the PASS when at least one of the main objectives is to investigate safety concerns	Nominal	Yes/ No	Selected based on the classification of the PASS for AP: if the classification contains "To investigate safety concerns" select "Yes"
AS		**PASS focus: DUS**	Variable derived from AO: to identify the PASS when at least one of the main objectives is to assess drug utilisation	Nominal	Yes/ No	Selected based on the classification of the PASS for AP: if the classification contains "Drug utilisation" select "Yes"
AT		**PASS focus: eRMM**	Variable derived from AO: to identify the PASS when at least one of the main objectives is to assess effectiveness of risk minimisation measures	Nominal	Yes/ No	Selected based on the classification of the PASS for AP: if the classification contains "Assess effectiveness of risk minimisation" select "Yes"

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AU	**Study objectives**	**Effectiveness info**	When there are also objectives related to assessing effectiveness (e.g. survival, disease progression, effective response to treatment)	Nominal	Yes/ No	If one or more of the PASS objectives is related with effectiveness then "Yes" is selected. Into brackets a brief description of the effectiveness assessment is provided.
AV		**Effectiveness simplified**	Variable derived from above (yes/no without the description of the effectiveness assessment)	Nominal	Yes/ No	This will have the same value as above without (Yes/ No) without presenting any additional details
AW	**Geography**	**Region and countries**	The continents and respective countries where PASS was planned to be conducted	String	NA	Used Information retrieved from the EU PAS Register “Countries in which this study is being conducted” and when not available: information retrieved from protocol if available internally, or information retrieved from the EMA website/ PRAC Minutes if some information was presented there. if it was there to categorise as “Europe only” when all countries are European, “Europe and Americas only” when all countries are from Europe and North/ South America and “Europe and/or Americas and other regions” when there is at least one country from outside Europe or American continents

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AX	**Geography**	**Region categorised**	Derived from previous variable: continents presented	Nominal	Different continents (Europe, Asia, North America, South America, Africa, Oceania)	The continents of the countries which PASS was to be conducted (e.g. Europe + Asia + North America, Europe + Americas, All continents etc.)
AY	**Methodology**	**Data collection**	Studies were classified as primary or secondary according to the main method of collection.	Nominal	Primary	The data was collected directly for the purposes for the study (i.e. physician reports data in the case report form after each patient visit)
					Secondary	The data that was collected leveraging pre-existing data collection schemes (e.g. routine clinical records of healthcare units)
					Primary + Secondary	If there is no clear "dominance" of either the primary or the secondary data collection approaches

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
AZ	**Methodology**	**Type of secondary data**	The AHRQ book was used as a reference to consider three main categories which comprehensively include the different options of secondary data sources: -Ad hoc chart review: primarily contain information collected as a part of routine medical care. These data reflect the practice of medicine or health care in general and at a specific level (e.g. geographical, by specialty care provider). -Automated electronic medical records and claims databases: Considered standardized databases in place in certain countries which contain data from many practices. -Existing registries: When the PASS was embedded in an ongoing registry (e.g. disease-specific registries managed by non-profit organizations, professional societies or other entities).	Nominal	Claims, database, automated EMR	Electronic medical records and record linkage of administrative health records are the main types of databases. Examples of the first and second are the CPRD in the UK and the national or regional databases in the Nordic countries, Italy, Netherlands and other countries, respectively. Administrative databases (claims) such as the ones from private and medical insurers were also considered in this category.
					Ad hoc chart review	The term was used to identify the use of information collected as part of routine care in a certain practice/ physician but not part of a broader standardised data collection database. Therefore, we included under these category, paper medical charts, provider-level databases, institutional or organizational databases.

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
					Existing registries	Included PASS that used data or were embedded in primary data collection registries (e.g. data collection on a specific treatment among ongoing big registries for patients with certain conditions e.g. registry of patients with psoriasis)
BA	**Methodology**	**Detail of the secondary data source**	The name of the data source(s) mentioned above (if available)	String	NA	The detail of the data source (e.g. CPRD)
BB		**Study design**	Epidemiological design in terms of whether all data was collected at a certain point in time ("snapshot") i.e. transversal/ cross-sectional design (exposure and outcomes collected at the same time), or if at least data was collected in two different time points (notion of follow-up; exposure and outcomes sequential) i.e. longitudinal	Nominal	Cross-sectional	If all the data is collected related to one point in time
					Longitudinal	If there is a follow-up/ longitudinal data collection of at least two data points for the patients. This classification is independent of any prospective/ retrospective notions.
BC		**Unit (patient/ HCPs)**	To identify whether the targeted population were patients or healthcare professionals (e.g. healthcare professionals are common in surveys) or if both patients and healthcare professionals were targeted (e.g. sample of patients and/or healthcare professionals)	Nominal	Patient	Selected when the eligibility criteria is applicable to patients
					HCPs	Selected when the eligibility criteria is applicable to healthcare professionals
					Patients + HCPs	Selected when the PASS will include both patients and healthcare professionals

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Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
BD	**Methodology**	**Main inclusion based criteria: exposure**	Used to identify the main criteria that define the population being studied. It allowed for the identification of patient registries (defined as an organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure and that serves one or more predetermined scientific, clinical or policy purposes). Therefore, it comprises disease registry (composed of patients who have or have had a disease or condition of interest), drug registries (composed of patients exposed to a health care product (drug or device). It create an additional category for the studies which enrol not all people with a certain disease but also not using a specific drug, so we categorise those as "multiple drugs" as they were interested in including patients with different drugs/ classes of drugs. An important clarification is that not all PASS targeted the enrolment of patients, as seen above others also targeted healthcare professionals and could be interested in	Nominal	Single product	Selected when the study focus of only the medicinal product studied in the PASS (e.g. inclusion of patients only exposed to that medicinal product or a cross-sectional survey to assess the understanding of the healthcare professionals regarding the correct use of that single medicinal product)
					Multiple drugs	Selected when the study focus not only on the medicinal product studied in the PASS but also others which are of interest for the objectives of the study (e.g. enrols patients exposed to the medicinal product of interest X and medicinal product Y as there is a particular interest in comparing them or a class of medicinal products Z etc.).

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
BD		**Main inclusion based criteria: exposure**	other aspects of the medicinal product such as understanding of the correct use of a medicinal product etc. Therefore this variable measures the object(s) of focus of the study in terms of single product, multiple products of interest or disease (the broader and most inclusive criteria).	Nominal	Disease	Selected when, despite the PASS is concerned with a certain medicinal product, the interest is in studying all the patients with a certain disease (not targeting specific medicinal products). Therefore this is the most inclusive criteria.
BE	**Methodology**	**Interest in special population(s) (use format "inclusion/"subgroup" - "type of population of interest")**	A different way of capturing the focus on the study is in terms of special populations of interest. This could include PASS enrolling only patients of a special population (e.g. pregnant women or paediatric patients) or even healthcare professionals as seen above (on the variable unit). Others do not restrict the inclusion criteria to certain populations but they could be interested in studying specific subgroups of patients as primary or secondary objective and therefore they are analysed separately. This variable includes both situations (the inclusion of special populations or the analysis of special populations). The later was only possible	Nominal + string	Inclusion - X	When special population(s) is part of the eligibility criteria for the study. The full list of possibilities is: "Inclusion - Pregnant", "Inclusion - Paediatric", "Inclusion - healthcare professionals", "Inclusion - Patients + healthcare professionals" (when the study includes both a sample of healthcare professionals and other of patients that will address different objectives/ analysis (e.g. drug utilisation assessed in the sample of patients and survey to assess effectiveness of risk minimisation measures among healthcare professionals) or even "Inclusion - Paediatric + healthcare professionals" or "Inclusion - Pregnant + healthcare professionals"

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
BE	**Methodology**	**Interest in special population(s) (use format "inclusion/"subgroup" - "type of population of interest")**	for the PASS for which there was access to the full protocol. It was important to distinguish studies including a special population as inclusion criteria (e.g. a PASS including only pregnant women obviously has a special interest in studying pregnant women) to other PASS including all population could also be interested in analysing the pregnant women. The categories specify whether the special population is reflected in the inclusion criteria or in the analysis ("inclusion", "subgroups") find the type of special population Examples: Inclusion paediatric; Subgroup – elderly, paediatric, cardiac impaired	Nominal + string	Subgroups - X	Identified when reading the full protocol. When the study objectives and/or analysis sections some of these subgroups of interest and considered as individual categories those who appeared in 5 or more studies and other for the remaining less frequent subgroups
BF		**Comparator**	Only the PASS with protocol available are coded with this variable. When reading the protocol, if the PASS specifically mentions that a comparison between groups of subjects would be made. After analysing all the different comparators we identified the following main categories as detailed in the next columns.	Nominal	No	No comparison will be made

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
BF	**Methodology**	**Comparator**	**Comparator**	Nominal	Other treatments	Studies where patients with different exposures (drugs, devices, other treatment, standard of care) were compared
					Unexposed	To identify studies were patients with a certain treatment exposure were compared to patients in which the only criteria was not being exposed to that specific treatment/ exposure (exposed versus unexposed patients)
					external data sources	If the results for the population in the PASS were compared to results of a population in other data source independent of the study (e.g. other registry or epidemiology data source)
					Pre and post a certain outcome of interest	Comparison of a population before and after certain occurrence (e.g. introduction of a educational program)
BG		**Comparator simplified**	Variable derived from above (yes/no comparator independent of the type of comparator)	Nominal	Yes/ No	This will have the same value as above without (Yes/ No) without presenting any additional details
BH		**PRO instrument**	Only the PASS with protocol available are coded with this variable. It identified if Patient Reported Outcomes (PRO) are used in the PASS.	Nominal	Yes/ No	If one or more PRO is mentioned "Yes" is selected. Into brackets the name or type of PRO is presented (e.g. SF-36/ burden of disease / quality of life) etc.
BI		**PRO instrument simplified**	Variable derived from above (yes/no comparator independent of the type of PRO)	Nominal	Yes/ No	This will have the same value as above without (Yes/ No) without presenting any additional details

The database is provided as electronic supplementary material (CD-ROM)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
BJ	**Methodology**	**Sample size**	Number of patients or HCPs (depending on the unit of analysis) the study aims to recruit. If there is a sample size for both patients and HCPs (a study that target both units) then include both in the following format: sample size for HCPs + sample size for patients	Scale	number (or number + number)	Retrieved from the protocol or when not available but registered in the EU PAS Register, from this register (field "9. Number of patients"). When an interval is provided (e.g. inclusion of 300 to 600 patients), the average number is presented (e.g. 450 in this case). When the PASS includes both patients and healthcare providers (e.g. 1000 patients and 250 healthcare professionals) the numbers are presented in the following format (number of healthcare professionals + number of patients, i.e. 250 + 1000)
BK		**Sample size (HCPs)**	Derived from "sample size": presenting just the number of healthcare professionals	Scale	number	Derived from the variable above. If the PASS involve healthcare professionals (check variable "Unit (patients/HCPs"), copy the same number, if not, selected "NA"
BL		**Sample size (patients)**	Derived from "sample size": presenting just the number of patients	Scale	number	Derived from the variable above. If the PASS involve patients (i.e. non-healthcare professionals), check variable "Unit (patients/HCPs"). Copy the same number, if not, selected "NA"
BM		**Sample size (patients + HCPs)**	Derived from "sample size": presenting the numbers of both patients and healthcare professionals	Scale	number+ number	Derived from the variable above. If the PASS involve both patients and healthcare professionals (check variable "Unit (patients/HCPs"). Copy the same numbers, if not, selected "NA"

The database is provided as electronic supplementary material (CD-ROM)

Matrix column identification	Theme	Variable Name	Variable definition	Variable type	Category	Coding rules
BN	**Methodology**	**Patient follow-up (years)**	The patient/HCP follow-up in years. If more than one unit (HCP and patient) is targeted then the same denomination as above should be used (i.e. follow-up of healthcare professionals + follow-up of patients).	Scale	number	Retrieved from the protocol or when not available but registered in the EU PAS Register, from this register (field "14. Follow-up of patients"). When an interval is provided (e.g. 3 to 5 years), the average number is presented (e.g.4.5 years). When the PASS includes both patients and healthcare providers the follow-up for each group are presented in the following format (number of follow-up for healthcare professionals + number of follow-up patients, i.e. 1 + 5 or NA+ 5 if there is no follow-up for one of the groups)
BO		**ICF**	Only the PASS with protocol available are coded with this variable. If according to the PASS protocol, informed consent will be requested or not.	Nominal	Yes/ No	If an informed consent process is mentioned then “Yes" is selected.

Annex 6

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
5	DHPC and updated SmPC	Assess effectiveness of risk minimisation measures+Drug Utilisation Study	Cross-sectional/ Primary data collection: Questionnaire to prescribers	Stratified random sample from provider's prescribers list.	Use of RMM Knowledge Behaviour (aggregate patient data to be provided by the prescribers)	On-line questionnaires for physicians; Pre-test in 6-8 physicians (understanding and wording). Physicians' comments will be implemented in the final version. Back and forth translation method; Duration of questionnaire: 10-15 minutes; Outcome measure: Not provided; Other PASS in the database? Yes (to assess drug utilisation using secondary data sources before and after RMM).

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
15	SmPC and patients' educational brochure	Assess effectiveness of risk minimisation measures+To investigate RMP safety concerns+Drug Utilisation Study	Longitudinal/ Secondary data collection: Existing registry (Pooled analysis of individual patient data from cohorts participating in the EPPICC registry: **before and after approval of RMM**)	All patients in the existent cohorts meeting eligibility criteria	Behaviour	Measures to assess success of RMM not provided; Patients will be described based on on-off/label status; Outcome measure: Not explicit but rational suggests off-label will be assessed before and after RMM; Other PASS in the database? No.
16	SmPC and educational brochure	Assess effectiveness of risk minimisation measures+To investigate RMP safety concerns+Drug Utilisation Study	Longitudinal/ Secondary data collection: retrospective chart review (three questionnaires sent to physicians over three years to request aggregate data)	Target all HBV treating physicians caring for paediatric patients (no information on how they will be identified)	Behaviour	No details on how the effectiveness of RMM will be assessed. Outcome measure: Not provided; Other PASS in the database? No.

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
27	Educational program for physicians and patients	Effectiveness of risk minimisation measures	Cross-sectional/ Primary data collection: Questionnaires to prescribers and patients	-Up to 5 European countries -Random sample (simple or stratified) from physician panel or prescriber list (as available and taking into account geographic location and setting) and reassessed after product is launched -Patients will be recruited when returning to second visit in practices prescribing the product	Receipt of RMM Knowledge Self-reported behaviour	On-line questionnaires for physicians and interview with trained personal for patients; Questionnaires tested through cognitive interviews in physicians and patients in local countries (with experience with the product); Duration of questionnaire: Not provided; Threshold for success: 85% for physicians and 50% patients (for sample size calculation); Physicians of the practices that include patients will complete questionnaire (for exploratory analysis, not included in the analysis); Questionnaire not available; Outcome measure: Not provided; Other PASS in the database? Other PASS for this medicinal product is recorded in database but no details available to access whether it complements this one.

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
51	Patients' educational materials	Assess effectiveness of risk minimisation measures+Drug Utilisation Study	Combined: Longitudinal primary data collection (prospective cohort) + Cross-sectional primary data collection (Questionnaire to a subset of patients from the cohort)	Selection of study sites will be determined at the country level in order to obtain a representative sample of sites reflective of the treatment patterns within each country (no details provided)	Patients: Receipt Knowledge	Patients to be contacted after administration of product (e-mail or telephone preference); No details on questionnaire development and validation; No details on questionnaire development and validation; The prospective data collection seem independent from the patients' answers; Outcome measure: Not provided; Other PASS in the database? No; The drug utilisation study component is not discussed as a component to address effectiveness of RMM.
58	Educational program for physicians and patients	Assess effectiveness of risk minimisation measures	Cross-sectional/ Primary data collection: Questionnaires to prescribers, patients and caregivers	List of prescribers to be provided by MAH - quotas of target participants (e.g. by specialist) will be randomised within stratum	Receipt and usage Knowledge Self-reported behaviour	Three (physician/patient/ caregiver) sets of web-based surveys; Duration of questionnaire: 25 min for HCPs and 15-20 minutes for patients; Threshold for success: 85%;

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
						The program will cover levels 1-4 of the Pope Woodhead model; No details on questionnaire validation Questionnaire not available; Effectiveness of RMM framework developed by Pope Woodland is referred; Outcome measure: Not provided; Other PASS in the database? No.
61	SmPC and physicians' educational brochure	Assess effectiveness of risk minimisation measures+To investigate RMP safety concerns (including those targeted by the RMM)+Drug Utilisation Study	Longitudinal / Secondary data collection: existing registry	Cohort of HIV-1 positive adult subjects within the European AIDS Treatment Network (NEAT-ID) considered a "good cross-section of HIV-positive treated patients in Europe."	Behaviour	Criteria to assess success of measures not provided; Outcome measure: Not provided (compliance with RMM); Other PASS in the database? No; Missing opportunity to use as outcome the incidence of ADRs which are part of the main study objective.

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
80	Patient Reminder Card	Assess effectiveness of risk minimisation measures+Drug Utilisation Study	Combined: Longitudinal secondary data collection (Chart abstraction) and primary data collection (patient diary to be filled by carers)+ Cross-sectional primary data collection (questionnaire to assess satisfaction of carers with RMM)	Patient invited to enrol during routine visits at selected sites (those identified to prescribe product – stated a feasibility assessment identified sites but no details provided)	Use (satisfaction with materials) Behaviour	Criteria to assess success of measures not provided; Prior to use in the study, data collection forms, including the Medication Record Sheet, will have undergone cognitive pretesting with a small number of patients and patient assistants in one of the countries using "a standard "think-aloud". Protocol mentions it is the patients physician who will do the chart abstraction (possible Hawthorne effect acknowledged); Outcome measure: Not provided (compliance with RMM); Other PASS in the database? No

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
84	SmPC	Assess effectiveness of risk minimisation measures	Cross-sectional/ Primary data collection: Questionnaire Survey to assess understanding and utilisation of the prescribing instructions contained in the SmPC to take product with meal)	Stratified random sample from provider panels of therapeutic area prescribers	Utilisation Knowledge	On—line questionnaire; Initial mini survey to investigate prescribing practices and attitudes towards product information to identify target groups (physicians could indicate other healthcare); Qualitative pilot testing of questionnaire; Survey conducted in accordance with the European Pharmaceutical Marketing Research Association (EphMRA) and the European Society for Opinion and Marketing Research (ESOMAR) guidelines; Duration of questionnaire: 15 min; Threshold for success: 80% success in 2 key question; Questionnaire not available; Outcome measure: Not provided; Other PASS in the database? No.

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
92	SmPC, restricted prescription and prescriber educational materials	Assess effectiveness of risk minimisation measures (including those targeted by the RMM)+To investigate RMP safety concerns	Longitudinal/ Primary data collection (prospective cohort: registry)	All physicians prescribing product will be targeted for enrolment	Behaviour	Criteria to assess success of measures not provided; "To evaluate whether prescribers of lomitapide enrolled at registry sites are following the screening and monitoring recommendations as specified in the PI and the prescriber educational materials aimed at risk minimisation; Hawthorne effect acknowledged (protocol states it would be minimised through emphasis on naturalistic and observational nature); It is unclear what is the global strategy to assess effectiveness of RMM as the MAH will "be collecting information on prescriber's use of these strategies and will assess their effectiveness in minimizing the occurrence of safety events as well as their effectiveness in

						reducing serum cholesterol"[5](…) Includes evaluation prescriber and patient compliance with prescribing information according to approved labelling in each country. generalized linear models will be used to determine the effect of these strategies on safety events and effectiveness endpoints; Outcome measure: Not provided (compliance with RMM); Other PASS in the database? No.
123	changes to the SmPC, a Direct to Healthcare Professional Communication (DHPC), and educational program	Assess effectiveness of risk minimisation measures+To investigate RMP safety concerns (including those targeted by the RMM)	Longitudinal/ Secondary data collection (Retrospective chart review to determine **off-label before and after introduction of RMM**)	All patients prescribed medicinal product from all sites in the highest prescribing countries with medical records available	Behaviour Outcome: incidence of off-label before and after RMM	Outcome measure: Not provided; Other PASS in the database? No; Acknowledged may be difficult to ascertain whether an off-label decrease due to RMM is the cause of less superinfections.

[5] Efforts to minimise the Hawthorne Effect (Roethlisberger et al., 1939) will be warranted given that the main outcomes of interest are to describe the patterns of use in usual care
and evaluate the effectiveness of risk minimisation interventions. Properly implemented,
a naturalistic design can decrease the impact of the Hawthorne Effect, which is the
tendency of people to act atypically when they know they are being observed. The Study Coordinating Centre will emphasize in the site training activities that the study protocol should not interfere with usual care treatment of patients, and that a critical review of physician practice is not an objective of the project.

124	Educational program for physicians and patients	Assess effectiveness of risk minimisation measures	Cross-sectional/ Primary data collection: Questionnaire to prescribers	All HCPs that receive the RM tools invited to participate in evaluation survey: those self-reporting prescribing the product will be eligible	Awareness/ Utilisation Knowledge Self—reported behaviour	On—line questionnaire; Questions user tested in one of the countries (for clarity and comprehension); Duration of questionnaire: 20 min; Threshold for success: 80%; Questionnaire not available; GVP Module XVI is referred; Outcome measure: Not provided; Other PASS in the database? Yes (use of secondary sources to monitor adverse outcomes associated with long-term use). It is unclear if it is complementary this PASS.

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
162	Administration checklist and patient alert card	Assess effectiveness of risk minimisation measures+To investigate RMP safety concerns (including those targeted by the RMM)+Drug Utilisation Study	Longitudinal/ Secondary data collection (prospective cohort based on medical records/charts)	Clinical sites in each country reflecting both academic and community hospitals in which acute cardioversions are routinely performed (no further details provided)	Receipt/ Read of materials Behaviour	Criteria to assess success of measures not provided. (compliance with RMM); Other PASS in the database? No.
186	SmPC, Pregnancy checklist	Assess effectiveness of risk minimisation measures+To investigate RMP safety concerns (including those targeted by the RMM)	Longitudinal / Secondary data collection (retrospective chart review) A method similar to prescription event monitoring is described	The patients will be selected by follow-up of orders placed for telavancin with an invitation to the clinician to provide data for this PASS.	Use Behaviour	Outcome measure: Not provided (compliance with RMM); Other PASS in the database? No.

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
194	Educational Materials for physicians	Assess effectiveness of risk minimisation measures	Cross-sectional/ Primary data collection: Questionnaire	Simple random sample from physician panels maintained by a propriety organisation (in larger countries stratified sampling based on physician speciality may be adopted)	Use Knowledge	Questionnaire can be completed through internet or phone interview; Development and test of questionnaire based on best practices described in DiBenedetti et al, 2013) including cognitive pre-test interviews; Duration of questionnaire: 15-20 min Threshold for success: 80%; Questionnaire available; Outcome measure: Not provided; Other PASS in the database? There are two other PASS for this medicinal product: one cross—sectional survey assessing prescribing patterns and other using secondary data sources to assess drug utilisation before and after RMM.

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
219	SmPC and restricted distribution	Assess effectiveness of risk minimisation measures+To investigate RMP safety concerns+Drug Utilisation Study	Longitudinal/ Primary data collection (prospective ad hoc registry)	The medicinal product will be distributed only to centres that accept to enrol patients	Behaviour	The registry is part of the RMM (mandatory for prescribing the medicinal product). The prescribers will be recommended to prescribe according to label; Outcome measure: Not provided (compliance with RMM); Mentions estimate contribution of suspect risk factors (e.g. not receive monitoring recommended in the SmPC) with occurrence of adverse outcomes of interest (no details); Other PASS in the database? No.
348	Educational materials	Assess effectiveness of risk minimisation measures+To investigate RMP safety concerns (including those targeted by the RMM)	Combined Longitudinal primary data collection (patients prospective cohort) + Cross-sectional primary data collection (prescribers questionnaire)	Physicians completing the appropriate education in all European countries where the product was launched and commercially available by prescription (no details)	Awareness Knowledge Behaviour	No details on questionnaire development and validation; Threshold for success in the survey: 85%; Outcome measure: Not provided (compliance with RMM); Other PASS in the database? No.

ID	Risk Minimisation Measures to be assessed	PASS safety objectives	Study design/ data source	Sampling frame	Indicators	Interesting aspects
349	Educational Materials for physicians	Assess effectiveness of risk minimisation measures	Cross-sectional/ Primary data collection: Questionnaire	Physicians registered in the MAHs database of trained physicians	Use (perceived usefulness) Knowledge	Questionnaire (pdf version) sent by e-mail or in paper format if preferred; Questionnaire development and validation information not provided; Duration of questionnaire: Not provided; Threshold for success: 80% for each question (questions with lower success rates will trigger revision of specific educational material domain); Questionnaire available; Outcome measure: Not provided; Other PASS in the database? No.

Annex 7

This annex displays the areas of concern considered responsible for the rejection/objection of the PASS protocols by the PRAC. The verbatim text is presented grouped by subcategory containing similar comments (bullet points) and the high-level category label attributed to similar comments with the number of comments in each one.

Study design (n=26):

- Lack of comparator (“despite challenges posed by recruitment, a comparator arm was necessary since historical controls were used in the clinical development ”)
- Inappropriateness to address different safety objectives using the same methodology (“single protocol to address both the requirement to conduct a disease registry and to perform a retrospective chart review to assess off-label use. The PRAC agreed that the MAH should conduct two separate studies”)
- Design could compromise the validity of the results “the design and conduct of the study that could threaten the validity of the results”
- Not appropriate to address the safety concerns of the RMP “new design of study was not considered consistent with the RMP or to address the points outlined in the Pharmacovigilance plan.”
- Design did not safeguard a non-promotional and non-interventional nature of the study (“reduce the promotional nature of the study and reduce residual sources of bias”, “some aspects should be simplified with the aim of reinforcing the observational nature of the study”, “the MAH should confirm that the proposed protocol can be classified as a non-interventional“)
- Preference for a inclusion based on disease rather than single exposure “a disease Registry collecting data about real world use of Revlimid and other therapies in patients with myelodysplastic syndromes would be of greater value than a product specific Registry. The reasons include allowing continued data collection in patients who switch between treatments, assessment of comparative safety and evaluation of long-term safety in a more complete way.”
- No specific details provided (n=18/26, 69%)

Feasibility (n=21):

- Measures to ensure operational feasibility “measures to limit the length of the recruitment period so that results can be obtained within an appropriate timeframe were still lacking”, “include a discussion on proposed lost to follow-up rate and discuss measures to be implemented if the observed lost to follow-up rate is higher than expected”, “appropriateness of the extended timeline”
- Concerns with scientific validity “the lack of information on patients aged 65 years and older might affect the study results”, “impact of the limitations of the design and the representativeness of the sample on the ability of the study to address the proposed objectives”, “impact of the limitations of the proposed data sources and the statistical analysis plan on the ability of the study to address the proposed objectives”, “sample size and the duration of follow up that could impact on the meaningfulness of the results”, “expand the geographical scope of the study (e.g. include additional databases) and/or extend the observation time in order to gain statistical precision for the study results”, “requested measures to guarantee that there is no interference between the prospective PASS and the retrospective DUS”, “approach to minimise selection bias and providing a clarification that the approach being used would be able to select a representative sample of the eligible patient population”, “concerns were expressed on the feasibility of the proposed study considering that the data source selected would not deliver the expected research questions within the specified timeframe due to limited statistical power”, “challenges associated with the study design’s ability to address concerns about the safety of the higher loading dose”, “design and conduct of the study that could threaten the validity of the results”, “clarifications on measures to monitor and avoid selection bias”, “measures to minimise confounding by indication.”, “reduce residual sources of bias”, “ suggestions aiming at strengthening the study were made intended to control the potentially significant impact of exposure/outcome misclassification”, “PRAC expressed concern that this database will suffer from selection bias based on the figures provided. “
- Preliminary evidence to support feasibility “presentation of a first analysis of the reactions to be studied in order to define the basis of calculation”, “PRAC requested the MAH to consider a pilot to test data collection methods” (n=2)
- No specific details provided (n=1, 6%)

Data analysis (n=18):

- Most comments had insufficient detail to understand the nature of the required revision stating the need to provide further details (n=2), clarifications (n=3), the need to submit a statistical analysis plan (n=1) regarding the presented analysis. Only three presented more detailed information (“handling of missing data”, “ particular changes in the therapeutic indication should be taken into consideration in the analyses of utilisation patterns as well as relevant timing regarding implementation of the revised product information and distribution of the related DHPC” and “set the minimum acceptable percentage of Healthcare Professionals providing correct answers for each of the study objectives in order to consider the overall programme to be adequately successful for each of the risks”)
- No specific details provided (n=8/18, 44%)

Data source/ population (n=16)

- Recruitment/ sampling strategy “In addition to recruitment of study participants via gynaecologists, the study is also to recruit study participants via general practitioners”, “inclusion of serious cases”
- Adequacy of data source: “concern that this database will suffer from selection bias based on the figures provided. The MAH should provide justification on the proportion of gynaecologists included in the database in the different countries”, the PRAC therefore recommended the MAH to provide a new study protocol for the safety evaluation, which should include: A thorough overview of all EU data sources potentially able to detect eligible patients”, “justification for use of a selected population over the total population of the selected database”
- No specific details provided (n=11/16, 69%)

Objectives/ endpoints (n=12)

- Need to consider additional/amend objectives “the protocol should include only treatments on-label as main objectives, the study objectives should be revised”, , amendment of the research question and objectives to reflect comparisons before and after the referral”, “to include the additional objective of obtaining long-term disease progression data and specific endpoints”
- Need to consider more measurable objectives/ endpoints definition “MAH should translate the overall goals of the PASS and DUS into more specific measurable objectives”, “provide clarification on the primary and secondary end-points”
- Objectives not addressing the purpose of the study set in the RMP “the study was included in the RMP to address other non-cardiovascular safety concerns. Nevertheless, these safety concerns are not adequately addressed in the protocol, therefore the PRAC suggested that such additional endpoints should be monitored appropriately”
- No specific details provided (n=5/12, 42%)

Sample size (n=10):

- Statistical precision “expand the geographical scope of the study (and/or extend the observation time in order to gain statistical precision for the study results”
- Statistical power “concerns were expressed considering that the proposed data source due to limited statistical power.”, “study size and power”
- Clarification/ need to amend sample size “discussion on proposed lost to follow-up rate (5 %), updating accordingly the number of patients to be enrolled (if applicable)”, “further justification is needed on the proposed small sample size”, “The PRAC considers that 3,000 patients is the required sample size for this drug utilisation study and therefore does not agree with the MAH’s proposal to only include 1,000 patients.”

- No specific details provided (n=4/10, 40%)

Timelines/ Milestones (n=9)

- Concerns to avoid study delay “The PRAC considered that a study with results delivered in 2015 was essential for the further characterisation of the venous- and arterial thrombotic risk of the product. The PRAC therefore advised that the CHMP impose an obligation for post-authorisation safety study”, “the study focus of the PASS should be the primary endpoint venous thromboembolism, and thus there should not be further delay to start the study in relation to additional secondary endpoints”, “The MAH is requested by the PRAC to start the survey as soon as possible ”
- Considerations on appropriateness of timelines “the appropriateness of the extended timeline will be provided upon provision of these data”, “a revision of the timelines to take into account the dissemination of educational material”
- No specific details provided (n=4/9, 44%)

Data collection/ management (n=7):

- Recommendation of specific instruments “the MAH should support the keeping of a treatment diary for all patients who have been included in the study to ensure a sufficient documentation of any adverse event during home treatment”,
- Need to collect certain data/ data validation “ the MAH should be requested to submit a summary of the data likely to be available on other key aspects of the safety profile to assess whether they meet the requirements included in the RMP”, “clarify data on exposure that will be recorded, and to provide a data validation plan”
- Need for clarification “clarify that the data collection will be performed in a completely retrospective way based on chart reviews”
- Other “pharmacogenetic study could be acceptable provided an updated protocol with the changes regarding sampling, sequencing”

- No specific details provided (n=2/7, 29%)

Variables (n=5):

Only one comment regarding the need to describe concomitant medications “including a description of any concomitant combined hormonal contraceptive (CHC) use, which is contraindicated”

No details provided (n=4/5, 80%).

Other:

- Rational and background “to clarify the rationale and background,”
- Data protection “The PRAC requests include information on how the use of anonymised data will be ensured”
- PASS obligation “The PRAC considered that a study with results delivered in 2015 was essential for the further characterisation of the venous- and arterial thrombotic risk of the product. The PRAC therefore advised that the CHMP impose an obligation for post-authorisation safety study in accordance with Article 10a of the Regulation (EC) No 726/2004.”, “The PRAC confirmed that the conduct of the PASS should be included as an obligation on the concerned marketing authorisation holder in accordance with Article 10a of Regulation (EC) No 726/2004”
- Safety reporting “management and reporting of adverse events/adverse reactions”

References

1. Irwin A, Rothstein H, Yearley S, McCarthy E. Regulatory Science - Towards a Sociological Framework. Futures. 1997;29(1):17-31.
2. PMDA. PMDA International Vision: PMDA EPOCH Toward 2020 [Internet]. 2011 Nov [cited 2016 Nov 23]. Available from: http://www.pmda.go.jp/files/000152824.pdf. PMDA November 2011.
3. Patient Health Protection. European Medicines Agency process for engaging in external regulatory sciences and process improvement research activities for public and animal health [Internet]. London: European Medicines Agency; 2013 Jan [cited 2016 Nov 23]. 11 p. Doc Ref No.: EMA/14946/2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500139888.pdf.
4. FDA. Advancing Regulatory Science [Internet]. Silver Spring: U.S. Food and Drug Administration [updated 2010 May 24; cited 2016 Nov 23]. Available from: http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/default.htm: FDA; [
5. Avorn J. Two centuries of assessing drug risks. The New England journal of medicine. 2012;367(3):193-7.
6. Strom BL, Kimmel SE, Hennessy S, editors. Pharmacoepidemiology. 5th ed. West Sussex, United Kingdom: John Wiley & Sons, Ltd; 2012.
7. World Health Organization.The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products [Internet]. Unites Kingdom: World Health Organization; 2002 [cited 2016 Nov 23]. 52 p. Available from: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf
8. Scurti V, Romero M, Tognoni G. A plea for a more epidemiological and patient-oriented pharmacovigilance. European journal of clinical pharmacology. 2012;68(1):11-9.
9. Borg JJ, Tanti A, Kouvelas D, Lungu C, Pirozynski M, Serracino-Inglott A, et al. European Union pharmacovigilance capabilities: potential for the new legislation. Therapeutic advances in drug safety. 2015;6(4):120-40.
10. Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [Internet]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31965L0065:EN:HTML
11. Williams JR. The Declaration of Helsinki and public health [Internet]. World Health Organisation; 2008 August [cited 2016 Nov 23]. Available from: http://www.who.int/bulletin/volumes/86/8/08-050955/en/.
12. Mastroianni A, Faden R, Federman D, editors. Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies: Volume I. Washington: National Academies Press 1994.
13. ICH. About ICH: Mission [Internet]. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [cited 2016 Nov 23]. Available from: http://www.ich.org/about/vision.html
[Available from: http://www.ich.org/about/vision.html.
14. ICH. Guideline for Good Clinical Practice E6(R1) [Internet]. ICH; 1996 Jun [cited 2016 Nov 23]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf [
15. Sheridan DJ, Julian DG. Achievements and Limitations of Evidence-Based Medicine. Journal of the American College of Cardiology. 2016;68(2):204-13.
16. Pansieri C, Pandolfini C, Bonati M. The evolution in registration of clinical trials: a chronicle of the historical calls and current initiatives promoting transparency. European journal of clinical pharmacology. 2015;71(10):1159-64.
17. Laporte JR. Fifty years of pharmacovigilance - Medicines safety and public health. Pharmacoepidemiology and drug safety. 2016;25(6):725-32.
18. Frau S, Font Pous M, Luppino MR, Conforti A. Risk Management Plans: are they a tool for improving drug safety? European journal of clinical pharmacology. 2010;66(8):785-90.

19. Heads of Medicines Agencies. Action Plan to Further Progress the European Risk Management Strategy [Internet]. London: European Medicines Agency; 2005 May [cited 2016 Nov 23]. 9 p. Doc Ref No.: EMEA/115906/2005/Final. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500006306.pdf
20. Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. [Internet]. 2008 Sep [cited 2016 Nov 23]. Available from: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf
21. Borg JJ, Aislaitner G, Pirozynski M, Mifsud S. Strengthening and rationalizing pharmacovigilance in the EU: where is Europe heading to? A review of the new EU legislation on pharmacovigilance. Drug safety. 2011;34(3):187-97.
22. Comission of the European Communities. Commission Staff Working Document: Accompanying document to the Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and the Proposal for a Directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use [Internet]. Brussels: Comission of the European Communities; 2008 Dec [cited 2016 Nov 24]. 61 p. Doc Ref No.: SEC(2008) 2670. Available from: http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/pharmacovigilance-ia-vol1_en.pdf.
23. Giezen TJ, Mantel-Teeuwisse AK, Straus SM, Egberts TC, Blackburn S, Persson I, et al. Evaluation of post-authorization safety studies in the first cohort of EU Risk Management Plans at time of regulatory approval. Drug safety. 2009;32(12):1175-87.
24. EMA. Pharmacovigilance legislation [Internet] [cited 2016 Nov 24]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp&mid=WC0b01ac058058f32d
25. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use [Internet]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF
26. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products [Internet]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF.
27. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [Internet]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_consol_2012_en.pdf
28. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [Internet]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20120702:EN:PDF
29. Comission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council [Internet]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF.

30. Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance [Internet]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:299:0001:0004:EN:PDF.
31. Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance [Internet]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:316:0038:0040:EN:PDF
32. EMA. Good pharmacovigilance practices [Internet]. [cited 2016 Nov 23]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c
33. Office of the Executive Director. Plan for implementation of the pharmacovigilance legislation by the European Medicines Agency: Activities to protect and promote public health 2012 in partnership with European Member States [Internet]. London: European Medicines Agency; 2012 Feb [cited 2016 Nov 24]. 6 p. Doc Ref No.: EMA/64750/2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500121837.pdf.
34. Pharmacovigilance Department. One-year report on human medicines pharmacovigilance tasks of the European Medicines Agency - Reporing period: 2 July 2012 to 1 July 2013 [Internet]. London: European Medicines Agency; 2014 May [cited 2016 Nov 24]. 44 p. Doc Ref No.: EMA/171322/2014 Corr. Available from: http://ec.europa.eu/health/files/pharmacovigilance/2014_ema_oneyear_pharmacov_en.pdf.
35. EMA. Committees, working parties and other groups [Internet]. [cited 2016 Nov 24]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000217.jsp&mid=
36. European Comission. Report from the Comission: Pharmacovigilance related activities of Member States and the European Medicines Agency concerning medicinal products for human use (2012 – 2014) [Internet]. Brussels: European Comission; 2016 Aug [cited 2016 Nov 24]. 17 p. Doc Ref No.: COM(2016) 498 final. Available from: http://ec.europa.eu/health/files/pharmacovigilance/pharmacovigilance-report-2012-2014_en.pdf
37. EMA. Guideline on good pharmacovigilance practices (GVP) – Module V: Risk management systems (Rev 1) [Internet]. London: European Medicines Agency; 2014 Apr [cited 2016 Nov 24]. 60 p. Doc Ref No.: EMA/838713/2011 Rev 1. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf
38. EMA. Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (Rev 3) [Internet]. London: European Medicines Agency; 2014 Apr [cited 2016 Nov 24]. 24 p. Doc Ref No.: EMA/876333/2011 Rev 3 . Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf
39. EMA. Guideline on good pharmacovigilance practices (GVP) – Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators (Rev 1) [Internet]. London: European Medicines Agency; 2014 Apr [cited 2016 Nov 23]. 22 p. Doc Ref No.: EMA/204715/2012 Rev 1*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf.
40. Zeitoun JD, Lefevre JH, Downing NS, Bergeron H, Ross JS. Regulatory review time and post-market safety events for novel medicines approved by the EMA between 2001 and 2010: a cross-sectional study. British journal of clinical pharmacology. 2015;80(4):716-26.
41. Zeitoun JD, Lefevre JH, Downing NS, Bergeron H, Ross JS. Regulatory anticipation of postmarket safety problems for novel medicines approved by the EMA between 2001 and 2010: a cross-sectional study. Pharmacoepidemiology and drug safety. 2016;25(6):687-94.
42. Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimization measures. Pharmacoepidemiology and drug safety. 2012;21(8):896-9.

43. Banerjee AK, Zomerdijk IM, Wooder S, Ingate S, Mayall SJ. Post-approval evaluation of effectiveness of risk minimisation: methods, challenges and interpretation. Drug safety. 2014;37(1):33-42.
44. Zomerdijk IM, Sayed-Tabatabaei FA, Trifiro G, Blackburn SC, Sturkenboom MC, Straus SM. Risk minimization activities of centrally authorized products in the EU: a descriptive study. Drug safety. 2012;35(4):299-314.
45. Smith MY, Morrato E. Advancing the field of pharmaceutical risk minimization through application of implementation science best practices. Drug safety. 2014;37(8):569-80.
46. Zomerdijk IM, Trifiro G, Sayed-Tabatabaei FA, Sturkenboom MC, Straus SM. Additional risk minimisation measures in the EU - are they eligible for assessment? Pharmacoepidemiology and drug safety. 2013;22(10):1046-53.
47. Blake KV, Prilla S, Accadebled S, Guimier M, Biscaro M, Persson I, et al. European Medicines Agency review of post-authorisation studies with implications for the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Pharmacoepidemiology and drug safety. 2011;20(10):1021-9.
48. EMA. Guideline on good pharmacovigilance practices (GVP) – Module VIII: Post-authorisation safety studies (Rev 2) [Internet]. London: European Medicines Agency; 2016 Aug [cited 2016 Nov 24]. 27 p. Doc Ref No.: EMA/813938/2011 Rev 2*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf.
49. Human Medicines Research and Development Support. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure [Internet]. London: European Medicines Agency; 2016 Nov [cited 2016 Nov 24]. 257 p. Doc Ref No.: EMEA-H-19984/03 Rev. 66. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500003981.pdf.
50. ENCePP. The European Union electronic Register of Post-Authorisation Studies (EU PAS Register) [Internet]. 2016 Nov [cited 2016 Nov 23]. Available from: http://www.encepp.eu/encepp_studies/indexRegister.shtml.
51. EMA. How to apply for the ENCePP Study Seal. – Guide [Internet]. London: European Medicines Agency; 2016 Jul [cited 2016 Nov 24]. 5 p. Doc Ref No.: EMA/615023/2012. Available from: http://www.encepp.eu/publications/documents/ENCePPStudySealGuide.pdf.
52. ISPE. Guidelines for Good Pharmacoepidemiology Practices (GPP) [Internet]. 2015 Jun [cited 2016 Nov 24]. Available from: https://www.pharmacoepi.org/resources/guidelines_08027.cfm.
53. EMA. Post-authorisation safety studies (PASS) [Internet]. [cited 2016 Nov 24]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000377.jsp&mid=WC0b01ac058066e979#section2.
54. ENCePP. ENCePP Checklist for Study Protocols [Internet]. 2016 Nov [cited 2016 Nov 24]. Available from: http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml
55. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 4). EMA/95098/2010. Available at http://www.encepp.eu/standards_and_guidances.
56. Coglianese C. Measuring Regulatory Performance: Evaluating the Impact of Regulation and Regulatory Policy [Internet]. Organisation for Economic Co-operation and Development; 2012 Aug [cited 2016 Nov 24]. 59 p. Available from: https://www.oecd.org/gov/regulatory-policy/1_coglianese%20web.pdf.
57. Pharmacovigilance Risk Assessment Committee. PRAC strategy on measuring the impact of Pharmacovigilance activities [Internet]. London: European Medicines Agency; 2016 Jan [cited 2016 Nov 23]. 8 p. Doc Ref No.: EMA/790863/2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/01/WC500199756.pdf.
58. Flick U, Kardoff E, Steinke I, editors. A companion to qualitative research. London: Sage Publications; 2004.

59. Krippendorff K. Content Analysis: An introduction to its methodology. 2nd ed. Thousand Oaks: Sage Publications; 2004.
60. Neuendorf KA. The Content Analysis Guidebook. Thousand Oaks: Sage Publications; 2002.
61. Roessner D. Quantitative and qualitative methods and measures in the evaluation of research. Research Evaluation. 2000;9(2):125-32.
62. Elo S, Kyngas H. The qualitative content analysis process. Journal of advanced nursing. 2008;62(1):107-15.
63. EMA. PRAC: Agendas, minutes and highlights [Internet]. [cited 2016 Nov 26]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf.
64. Bogdan RC, Biklen SK. Qualitative research for education: An introduction to theory and methods. 5th ed. United States of America: Pearson Education.
65. EMA. European public assessment reports: background and context [Internet]. [cited 2016 Nov 26]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000433.jsp.
66. U.S. National Institutes of Health. ClinicalTrials.gov [Internet]. [cited 2016 Nov 23]. Available from: https://clinicaltrials.gov/.
67. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC medical research methodology. 2013;13:117.
68. Bouvy JC, Huinink L, De Bruin ML. Benefit-risk reassessment of medicines: a retrospective analysis of all safety-related referral procedures in Europe during 2001-2012. Pharmacoepidemiology and drug safety. 2016;25(9):1004-14.
69. EMA. Orphan designation [Internet]. [cited 2016 Nov 24]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce.
70. Raine M. Pharmacovigilance Risk Assessment Committee Experience with Post Authorisation Studies. DIA/EMA Information Day on PAS; 5 June 2015; London2015.
71. Pan I, Walton A, Dieck G. ost Authorization Safety Studies (PASS): Application of Prospective Observational Study Methodology [Internet]. Express Scripts Holding Company; 2014 [cited 2016 Nov 24]. Available from: http://www.ubc.com/sites/default/files/library/icpe_2014_abstract_-_pass_prospective_obs_studies_0.pdf
72. Stein D, Payne K. Retrospective Chart Review Studies: Key Considerations for Fulfilling Safety Reporting Requirements [Internet]. Express Scripts Holding Company; 2014 [cited 2016 Nov 24]. Available from: http://www.ubc.com/sites/default/files/library/retrospective_chart_review_studies_safety_reporting_req_abstract.pdf
73. Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [Internet]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.
74. Inspections and Human Medicines Pharmacovigilance Division. Initiative for patient registries [Internet]. London: European Medicines Agency; 2015 Sep [cited 2016 Nov 24]. 6 p. Doc Ref No.: EMA/176050/2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195576.pdf
75. Kurz X. Looking towards the future: Brainstorming on funding mechanisms for PAS. ENCePP Plenary Meeting; 24 November 20152015.
76. Ramirez I. Navigating the maze of requirements for obtaining approval of non-interventional studies (NIS) in the European Union. GMS German Medical Science. 2015;13:Doc21.

77. ISPE. 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management: Agenda [Internet]. 2016 Jul [cited 2016 Nov 24]. Available from: https://www.pharmacoepi.org/meetings/32ICPE/agenda/index.cfm [
78. Kurz X. Views from a regulator. 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management; 26 August 2016; Dubllin2016.
79. Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. Available from: http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm.
80. Hall GC, Sauer B, Bourke A, Brown JS, Reynolds MW, LoCasale R. Guidelines for good database selection and use in pharmacoepidemiology research. Pharmacoepidemiology and drug safety. 2012;21(1):1-10.
81. ENCePP. ENCePP Resources Database [Internet]. [cited 2016 Nov 24]. Available from: http://www.encepp.eu/encepp/resourcesDatabase.jsp.
82. Ehrenstein V, Petersen I, Smeeth L, Jick SS, Benchimol EI, Ludvigsson JF, et al. Helping everyone do better: a call for validation studies of routinely recorded health data. Clinical epidemiology. 2016;8:49-51.
83. Klungel OH, Kurz X, de Groot MC, Schlienger RG, Tcherny-Lessenot S, Grimaldi L, et al. Multi-centre, multi-database studies with common protocols: lessons learnt from the IMI PROTECT project. Pharmacoepidemiology and drug safety. 2016;25 Suppl 1:156-65.
84. Gini R, Schuemie M, Brown J, Ryan P, Vacchi E, Coppola M, et al. Data Extraction and Management in Networks of Observational Health Care Databases for Scientific Research: A Comparison of EU-ADR, OMOP, Mini-Sentinel and MATRICE Strategies. EGEMS (Washington, DC). 2016;4(1):1189.
85. Bazelier MT, Eriksson I, de Vries F, Schmidt MK, Raitanen J, Haukka J, et al. Data management and data analysis techniques in pharmacoepidemiological studies using a pre-planned multi-database approach: a systematic literature review. Pharmacoepidemiology and drug safety. 2015;24(9):897-905.
86. Arlett P, Portier G, de Lisa R, Blake K, Wathion N, Dogne JM, et al. Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee. Nature reviews Drug discovery. 2014;13(5):395-7.
87. Engel P, Bulliard M, Parmenter L, Starzyk K, Dreyer N. Lessons learned on the design of European Post Authorisation Safety Studies (PASS): Review of 18 months of PRAC oversight. Pharmacoepidemiol Drug Saf 2014; 23 Suppl 1:S621.
88. EMA. EU PAS Register upgrade July 2016 – What's new? [Internet]. 2016 Jul [cited 2016 Nov 23]. Available from: http://www.encepp.eu/encepp_studies/documents/EUPASRegisterUpgrade_WhatsNew.pdf.
89. Gama H, Correia S, Lunet N. Questionnaire design and the recall of pharmacological treatments: a systematic review. Pharmacoepidemiology and drug safety. 2009;18(3):175-87.
90. Ip S, Paulus JK, Balk EM, Dahabreh IJ, Avendano EE, Lau J. Role of Single Group Studies in Agency for Healthcare Research and Quality Comparative Effectiveness Reviews. Research White Paper [Internet]. Rockville: Agency for Healthcare Research and Quality; 2013 Jan [cited 2016 Nov 24]. 28 p. Doc Ref No.: 13-EHC007-EF. Available from: hhttp://www.effectivehealthcare.ahrq.gov/ehc/products/501/1389/White-Paper-Role-of-single-group-studies-1-23-13.pdf.
91. Ranopa M, Douglas I, van Staa T, Smeeth L, Klungel O, Reynolds R, et al. The identification of incident cancers in UK primary care databases: a systematic review. Pharmacoepidemiology and drug safety. 2015;24(1):11-8.
92. Karl Popper, Conjectures and Refutations, London: Routledge and Keagan Paul, 1963, pp. 33-39; from Theodore Schick, ed., Readings in the Philosophy of Science, Mountain View, CA: Mayfield Publishing Company, 2000, pp. 9-13 [Internet] [cited 2016 Nov 23]. Available from: http://www.stephenjaygould.org/ctrl/popper_falsification.html.

93. Vermeer NS, Duijnhoven RG, Straus SM, Mantel-Teeuwisse AK, Arlett PR, Egberts AC, et al. Risk management plans as a tool for proactive pharmacovigilance: a cohort study of newly approved drugs in Europe. Clinical pharmacology and therapeutics. 2014;96(6):723-31.
94. Radawski C, Morrato E, Hornbuckle K, Bahri P, Smith M, Juhaeri J, et al. Benefit-Risk Assessment, Communication, and Evaluation (BRACE) throughout the life cycle of therapeutic products: overall perspective and role of the pharmacoepidemiologist. Pharmacoepidemiology and drug safety. 2015;24(12):1233-40.
95. Morrato EH, Smith MY. Integrating risk minimization planning throughout the clinical development and commercialization lifecycle: an opinion on how drug development could be improved. Therapeutics and clinical risk management. 2015;11:339-48.
96. Gridchyna I, Cloutier AM, Nkeng L, Craig C, Frise S, Moride Y. Methodological gaps in the assessment of risk minimization interventions: a systematic review. Pharmacoepidemiology and drug safety. 2014;23(6):572-9.
98 adicionando
97. Levinson DR. FDA lacks comprehensive data to determine whether risk evaluation and strategies improve drug safety [Internet]. US: Food and Drug Administration. 2013 Feb [cited 2016 Nov 23]. 38 p. Doc Ref No.: OEI-04-11-00510. Available from: https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf.
98 Hill MM, Hill A. Investigação por questionário. 2nd ed Lisboa: Edições Sílabo; 2005
99. Kirkpatrick DL: Evaluating training programs: the four levels. 1994, San Francisco: Berrett-Koehler edn: Berrett-Koehler Publishers Inc., San Francisco, California
100. Godin G, Belanger-Gravel A, Eccles M, Grimshaw J: Healthcare professionals' intentions and behaviours: A systematic review of studies based on social cognitive theories. Implement Sci. 2008, 3: 36-10.1186/1748-5908-3-36
101. Fowler FJ. Survey Research Methods. 4th Edition. Sage Publications: Thousand Oaks, California, 2009; Streiner DL, Norman GR. Health Measurement Scales: A Practical Guide to their Development and Use. 4th Edition. Oxford: Oxford University Press; 2008
102. Mazzaglia G. Overview of methodologies and studies evaluating risk minimisation measures. European Medicines Agency [Internet]. 2015 Sep [cited 2016 Nov 23]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/12/WC500198800.pdf
103. EUPATI. European Patients' Academy [Internet]. [cited 2016 Nov 23]. Available from: https://www.eupati.eu/
104. PCORI. Patient-Centered Outcomes Research Institute [Internet]. 2011 Nov [cited 2016 Nov 23]. Available from: http://www.pcori.org/
105. Neyarapally GA, Hammad TA, Pinheiro SP, Iyasu S. Review of quality assessment tools for the evaluation of pharmacoepidemiological safety studies. BMJ Open. 2012 Sep 25;2(5). pii: e001362.
106. Hoekman J, Klamer TT, Mantel-Teeuwisse AK, Leufkens HG, De Bruin ML. Characteristics and follow-up of postmarketing studies of conditionally authorized medicines in the EU. British journal of clinical pharmacology. 2016;82(1):213-26.