

Introduction

In recent years there has been more emphasis on pharmacovigilance (PV) of medicines in order to reduce the risk to patients and increase the benefits of medicines. One aspect of PV is the Post-Authorisation Safety Study (PASS), defined by the European Directive (Directive 2001/83/EC (DIR) Art 1(15)) as “A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.”

Pharmacovigilance (PV)

Pharmacovigilance is defined by the World Health Organisation as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”. Medicinal products in the European Union (EU) are only approved after undergoing stringent evaluation of their quality, efficacy and safety. Once approved and available on the market, PV is the continued monitoring of the medicinal product to ensure detection of any characteristic that could affect its safety profile and allowing appropriate action to be taken.

Within the EU, the PV system functions with the collaboration of the European Commission (EC), European Medicines Agency (EMA) and regulatory authorities in the Member States (MS). EU legislation around PV has been in place since July 2012 and its underlying objectives are to contribute towards protecting patients’ and public health.

The EMA has developed the good pharmacovigilance practices (GVP) to assist marketing authorisation holders (MAH) with PV activities. GVP has been developed by experts from the EMA and MS and rolled out over a period of time in modules. It applies to both centrally authorised medicinal products and nationally authorised medicinal products sanctioned through the mutual recognition or the decentralised procedure. Each module is based on a major part of the PV process. Module VIII of the GVP relates to PASS and has been effective since April 2013.

What is a PASS?

A PASS is a study of a medicinal product which is performed to confirm

Timing of a PASS Request

A PASS may be imposed on a medicinal product any time after the initial marketing authorisation application. The competent authority, may impose a PASS:

- at the time of granting marketing authorisation, to investigate further a safety concern identified during the assessment of the marketing authorisation application - PASS¹ (Figure 1);
- during the assessment of an extension, alteration or renewal of the marketing authorisation, sometime after the marketing authorisation - PASS² (Figure 1); or
- at some point after the marketing authorisation, due to concerns posed by a risk presented by the medicinal product, such as the identification of a safety signal - PASS³ (Figure 1).

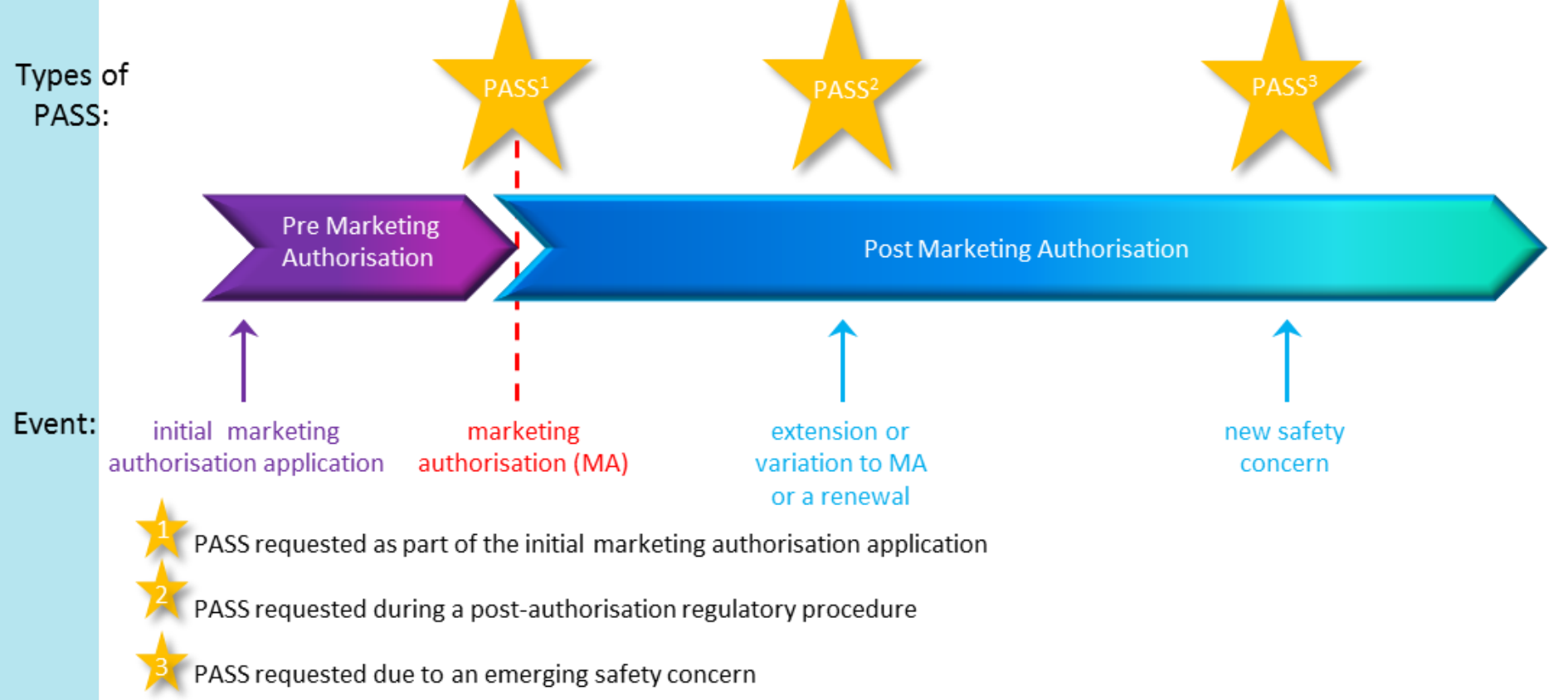


Figure 1: Timing of PASS in relation to marketing authorisation activities

Risk Management Plan (RMP)

The risk management plan (RMP) is a document within the EU, submitted with the marketing authorisation application that includes details of the medicinal product’s safety profile and how risks will be prevented or minimised in patients, alongside any planned studies to further investigate the medicinal product’s safety, PASS or efficacy, Post Authorisation Efficacy Study (PAES).

Post-Authorisation Efficacy Study (PAES)

A PAES is similar to a PASS in that it is imposed during or after marketing authorisation, to explore further some aspects of the efficacy of a medicinal product that can only be investigated after marketing of the product.

Clinical trials

Additional clinical trials are required post marketing authorisation if there are notable safety concerns, not addressed in the pre-authorisation clinical trials, that warrant further investigation. Sometimes there is concern about a specific population, who may metabolise the medicinal product differently who were poorly represented or not included at all in the pre-authorisation trials.

Observational Studies

Observational studies can be based on primary or secondary data collection, or a combination of both, however any primary data collection must be non-interventional, where data collected is from routine clinical care and the investigator does not intervene in the regular care of the patient for study purposes; simply records what happens. Observational study designs often include:

- cross-sectional studies
- case-control studies
- cohort studies

Drug Utilisation Studies (DUS)

Drug utilisation studies (DUS) analyse the use and prescription of medicinal products in regular medical practice within a large study population. DUS include patient populations who are often not included in clinical trials, such as the elderly, children and patients with renal or hepatic impairment.

Active Surveillance

Active surveillance is the process of identifying adverse events in an organised, proactive way as opposed to passive surveillance systems reliant on medical staff and/or patients coming forward to report adverse events. Active surveillance is more likely to yield thorough adverse event reporting. Types of active surveillance include:

- intensive monitoring schemes
- prescription event monitoring
- registries

Programmer Experiences of PASS

In the past few years, as a biostatistical programmer I have gained experience of working on PASS and have noted challenges they present. Two studies I was involved with, implemented to answer a specific obligation imposed by the EMA, used a combination of primary and secondary data. A secondary data database was used to identify specific subjects, (in this instance physicians), to be contacted based on certain characteristics in both studies (Figure 3). Once target physicians had been identified, they were approached and survey questionnaires taken (Study 1), and patients selected and their medical records (MR) reviewed (Study 2); primary and secondary data sources respectively.

PASS and the Programmer

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the safety profile or detect a potential safety concern not detected in the controlled clinical trial population. A PASS must have its main aim as one of the following objectives:

- to quantify potential or identified risks
- to assess risks of a medicinal product used in patient populations where 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 medicinal product after long-term use;
- to provide evidence about the absence of risks;
- to assess real world drug utilisation;
- to measure the effectiveness of a risk minimisation activity.

A PASS may be initiated voluntarily by the MAH or pursuant to an obligation by the competent authority (EMA or MS authority as applicable as to the marketing authorisation application) to support regulatory decision making under a category of obligation, as shown below in Table 1.

Category	Type	Definition
1	Imposed obligation	Main aim of the study is to meet a <u>requirement</u> of the marketing authorisation
2	Specific obligation	A study imposed in the framework of a marketing authorisation granted under exceptional circumstances
3	Required	A study which investigates a safety concern in the RMP or the effectiveness of risk management activities
4	Stated	A study providing safety information but its aim is not significant to support the safety profile

Table1: Categories of mandated activities stipulated by the competent authority

PASS Study Design

Both voluntary and imposed PASS may be either an interventional clinical trial or a non-interventional study. If significant safety risks are identified that require the need for the study design to be that of a clinical trial, it must follow Directive 2001/20/EC, Volume 10 of the Rules Governing Medicinal Products in the European Union and Good Clinical Practice, regardless of the aim of the study being in response to post-authorisation activities. A clinical trial may be called for, for example to further research the marketed drug in a specific population or to look into drug-drug interactions or food-drug interactions and may involve patients or healthy volunteers.

For a non-interventional PASS it must meet all the following criteria:

- patient assignment to a therapeutic strategy is not defined in advance by a trial protocol but is part of normal medical practice and the inclusion of the patient to the study is not related to the prescription of the marketed drug;
- treatment of a patient with the marketed drug is in the usual prescribed manner, in accordance with the terms of the marketing authorisation; and
- additional monitoring or diagnostic measures must not be undertaken on the patient outside of normal medical practice.

Pharmacovigilance Risk Assessment Committee (PRAC)

The remit of assessing an imposed non-interventional PASS protocol, study conduct and results is the responsibility of the Pharmacovigilance Risk Assessment Committee (PRAC), for centrally authorised medicinal products. The PRAC is a body within the EMA made up of scientific experts from the MS for the evaluation, supervision and pharmacovigilance of medicinal products and provides recommendations to the Committee for Medicinal Products for Human Use (CHMP). Each PASS will be supervised by a PRAC rapporteur, selected by the PRAC who liaises with the EMA and the MAH.

PASS Designs and Data Collection

Data collection for a PASS falls into two types, primary and secondary data collection. If data is specifically collected for the purpose of the PASS, it is called primary data collection. Secondary data collection is when data is collated from one or more sources already collected for another purpose. A study design may involve one or, more often, a combination of both types of data collection (Figure 2).

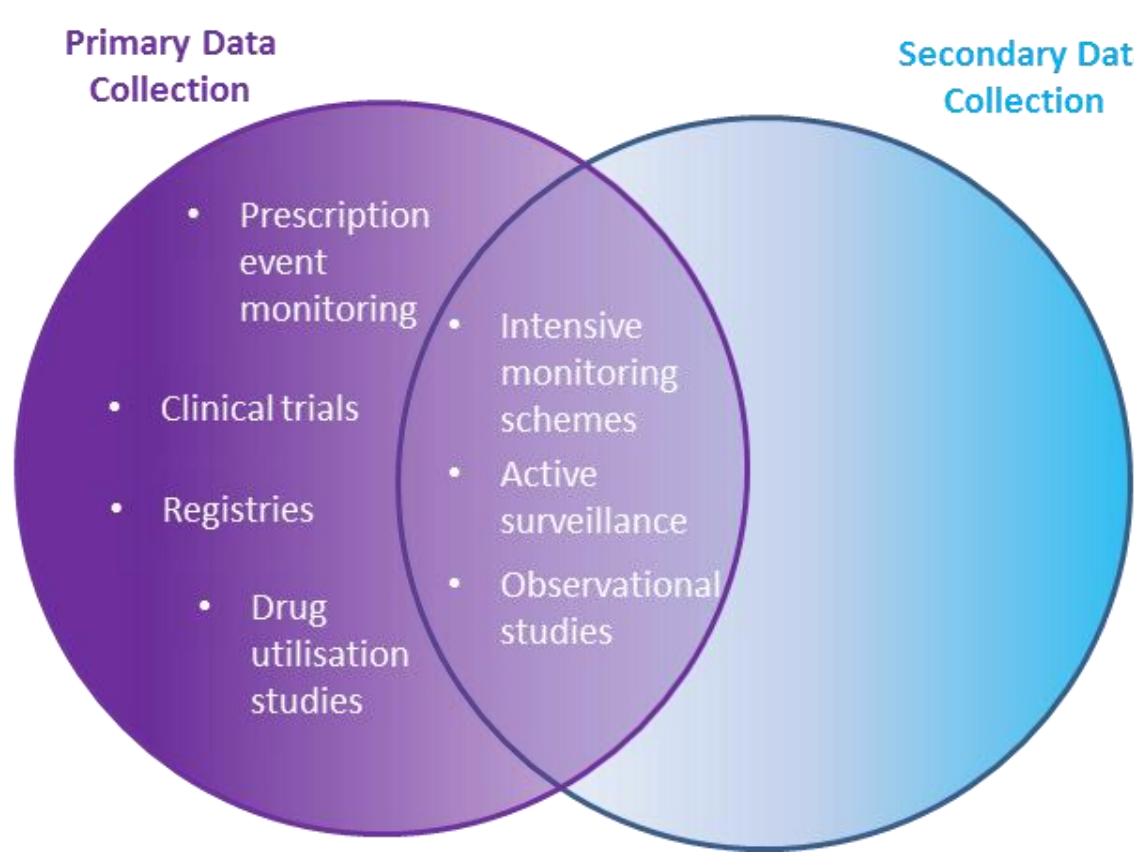


Figure 2: Primary and Secondary Data Methods for PASS

Primary data may be collected directly from sites (e.g. hospitals, nursing homes, physicians’ practices) through field studies, such as interviews with physicians, patients or others involved in the clinical process. Secondary data may also be collected from field studies from collating specific data from patient medical records. Large healthcare databases are becoming more commonplace and are an efficient source of secondary data for PASS. These may be essentially designed for medical insurance purposes or contain comprehensive medical information but their nature and contents can make them an excellent source for PASS data. Their large size, often containing millions of records is obviously beneficial but they can often lack detail or accuracy, which must be considered.

reviewed (Study 2); primary and secondary data sources respectively.

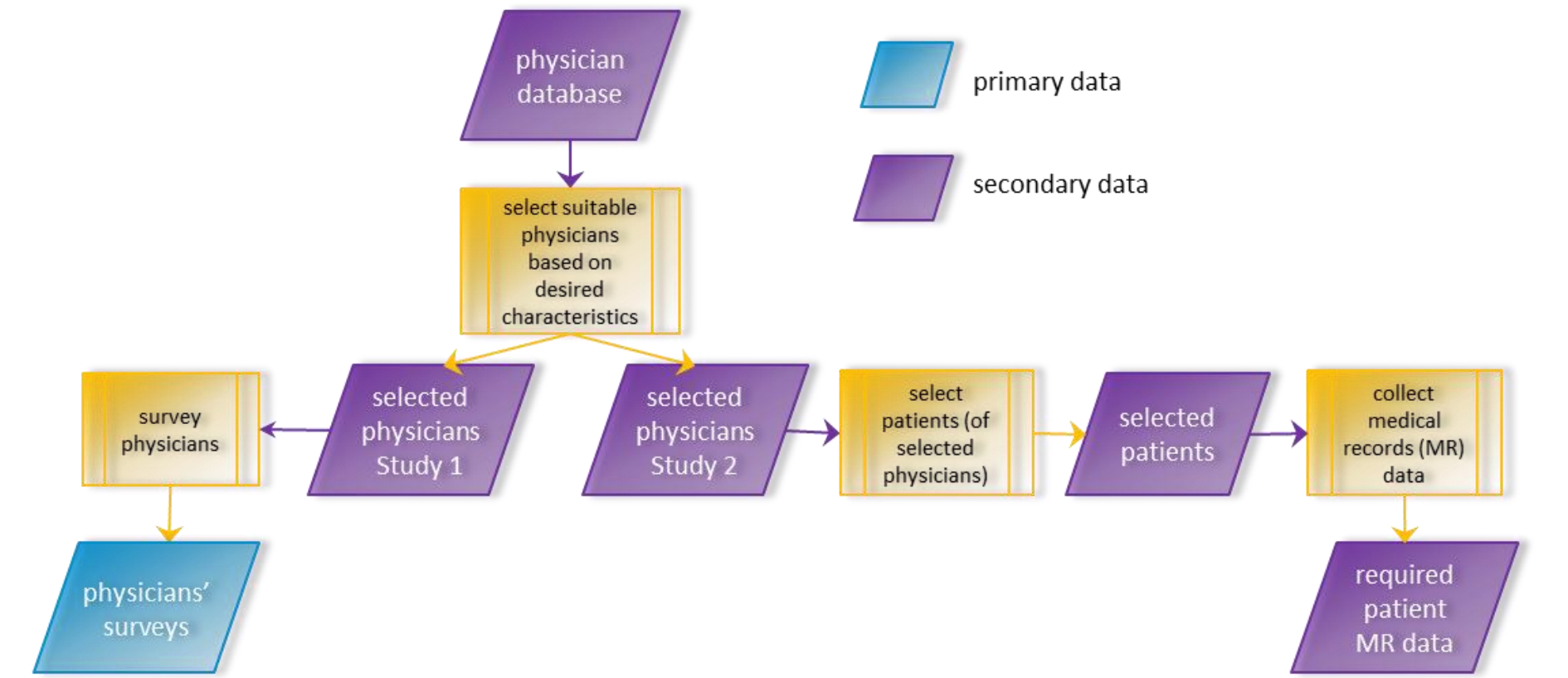


Figure 3: Data Flow for PASS

Study Design Challenges

- The questions posed by the competent authority can often be answered by many forms of PASS design. Whilst studies 1 and 2 met their aim, tweaks to the study design, at the initial design stage, would have made the studies easier to implement.
- The source database initially used for identifying physicians, whilst large and covered the required countries, once received it became apparent it was not accurate enough for our purposes. Out of date data, incorrect contact details and missing data fields meant we had to identify new data sources to complete the studies.
- Obligations usually provide minimal direction to take a study, so can be challenging to prevent the collection of more data than required. Careful review is important to prevent collection of unnecessary data that may add complexity to the study.

Programming Challenges

- Surveys are a snapshot at a point in time and therefore if incorrectly completed, it can be difficult or incorrect to verify responses. Depending on the survey, we either re-contacted the responder or adapted the TFL output to suit the missing or incomplete data.
- When data is incorrect or missing in the MR, the data needed by the study cannot be identified. The programming was updated to account for the data as it was collected in the MR.

Conclusion

As agencies become more focussed on PV, the need for PASS under all guises will increase, giving more biostatistical programmers and statisticians the opportunity to experience PASS. Understanding where these studies differ from pre-authorisation clinical trials will equip them with the necessary insight into how to implement a well-executed PASS.

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