

PASS and the Programmer

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ABSTRACT

A post-authorisation Safety Study (PASS) is designed to summarise the safety profile of a marketed drug and can be interventional or observational in nature. This may be voluntarily by the marketing authorisation holders or in response to an obligation imposed by a regulatory agency. In this paper I will discuss the characteristics of PASS, different methods of data collection for PASS and how they are overseen by regulatory committees. I will then go on to discuss some real-life examples of the challenges posed in implementing a PASS from a programming perspective.

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.”

A PASS for a medicinal product may be at the request of a regulatory agency such as the European Medicines Agency (EMA) or a local country agency, or initiated voluntarily by the marketing authorisation holder. If a PASS is imposed by an agency, it may be initiated as part of the initial marketing authorisation application, during the post-authorisation regulatory procedure or at a later date due to an emerging safety concern. The design of the study may be a clinical trial or non-interventional study and these are managed differently by the regulatory agency, the latter involving oversight by the Pharmacovigilance Risk Assessment Committee (PRAC). Whether the PASS is required to be included in the Risk management Plan (RMP) will be dependent on the conditions applied by the authorising agency.

PHARMACOVIGILANCE (PV)

PV 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 it may possess 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), EMA and regulatory authorities in the Member States. EU legislation around PV has been in place since July 2012 and its underlying objectives to contribute towards protecting patients’ and public health are:

- “preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public”.

The EMA has developed guidance to assist marketing authorisation holders with PV activities - good pharmacovigilance practices (GVP). This guidance has been developed by experts from the EMA and Member States and rolled out over a period of time in modules since July 2012. 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 (marketed drug or a biologic) which is performed to confirm the safety profile or detect a potential safety concern not detected in the controlled clinical trial population. GVP states that a post-authorisation study is classified as a PASS if the main aim of the study meets one of the following objectives:

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- “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 medicinal 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 medicinal 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 medicinal product (e.g. indication, dosage, co-medication, medication errors);
- to measure the effectiveness of a risk minimisation activity”.

A PASS may be initiated voluntarily by the marketing authorisation holder or pursuant to an obligation by the competent authority (EMA or Member State 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.

TABLE 1: Categories of mandated activities stipulated by the competent authority

Category	Type	Definition
1	Imposed obligation	Main aim of the study is to meet a requirement 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 that 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.

Requirements expected by the competent authority on a PASS pursuant to an obligation are also recommended to those initiated voluntarily, in order to maintain scientific and quality standards regardless of the type of PASS.

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 to be 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.

TIMING OF PASS REQUEST

A PASS may be imposed on a medicinal product any time after the initial marketing authorisation application. The competent authority (EMA or Member State authority as applicable as to the marketing authorisation application), may grant the marketing authorisation dependent on the implementation of a PASS to investigate further a safety concern identified during the assessment of the marketing authorisation application - PASS¹ (Figure 1). The need for a PASS may also be identified by a competent authority during the assessment of an extension, alteration or renewal of the marketing authorisation, sometime after the marketing authorisation - PASS² (Figure 1). A PASS may also be imposed 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).

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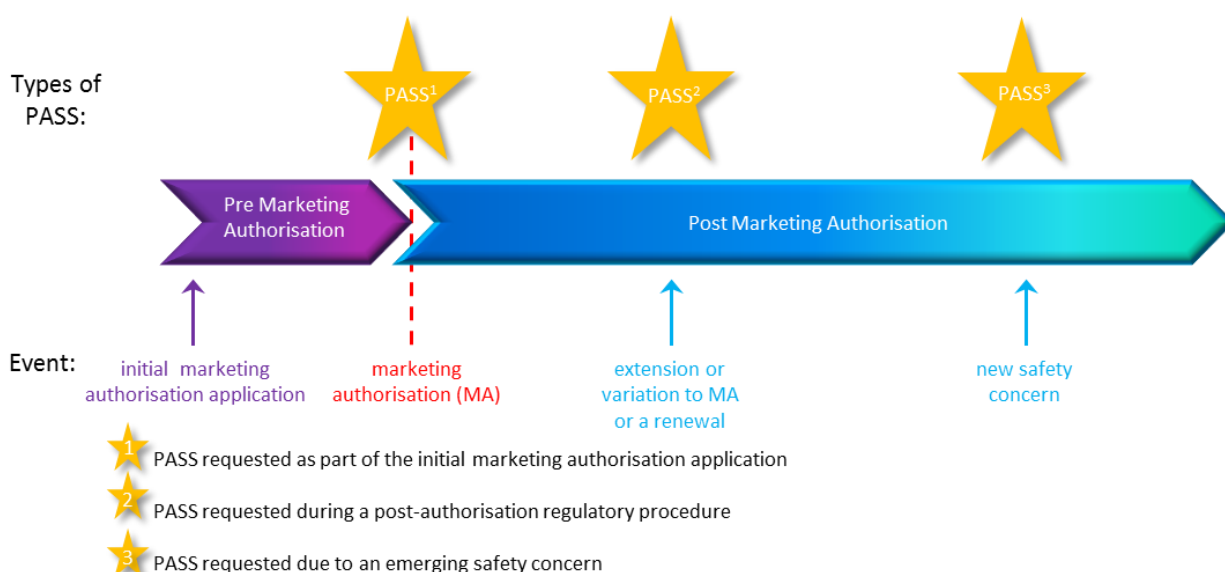


FIGURE 1: Timing of PASS in relation to marketing authorisation activities

RISK MANAGEMENT PLAN (RMP)

Details about a non-interventional PASS pursuant to an obligation (Table 1, category 1 or 2) or required to investigate a safety concern in the RMP (Table 1, category 3) should be described in the RMP for that medicinal product. The 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 drug'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. Additionally, a PAES may be imposed if there is a change to the knowledge about a disease or there is a need to amend previous clinical evaluations.

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 Member States for the evaluation, supervision and pharmacovigilance of medicinal products. It is responsible for oversight of all aspects of risk management of the use 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 marketing authorisation holder.

If the marketing authorisation application is submitted via the mutual recognition or the decentralised procedure to a single Member State and the PASS is authorised by the single Member State to be conducted only within that Member State, then the PASS will be overseen by the national procedures of that Member State and not by PRAC.

PASS DESIGNS AND DATA COLLECTION

The purpose of a PASS is to answer the question(s) posed by the competent authority and is not constrained to any specific study design. In fact, it need not be a study at all; if a literature review or meta-analysis suffices, these may be considered a PASS.

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).

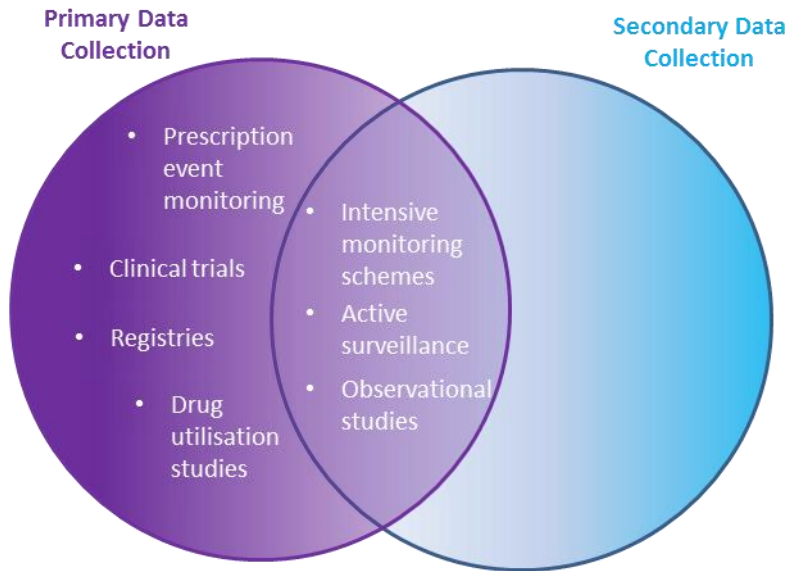


FIGURE 2: Primary and Secondary Data Methods for PASS

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.

CLINICAL TRIALS

Additional clinical trials are required post marketing authorisation if there are notable safety concerns that warrant further investigation and are not fully addressed in the pre-authorisation clinical trials. Sometimes this may be due to there being additional concerns about a specific population, who may metabolise the medicinal product differently. The elderly, children or patients with a specific condition (such as renal impairment) who were poorly represented or not included at all in the pre-authorisation trials may require further study to identify a specific risk (or benefit) in these populations.

A PASS clinical trial may differ from a pre-authorisation trial in that there may be a desire to collect a small amount of data from a large number of patients, with minimal monitoring. This may be referred to as a "large simple trial" but the simplicity is in relation to the structure of the data not necessarily that the data collection is straight forward. In reality, the data collection is likely to be as complex as any other clinical trial.

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. Three main types of observational study design include cross-sectional studies, case-control studies and cohort studies.

Cross-sectional studies involve the analysis of data collected from a population of patients, regardless of their exposure to a drug or disease status at one specific time point. They are commonly used to collect survey data or disease prevalence at that specific point in time. The singular time point means no conclusions can be drawn from the extent of drug exposure and the patient outcome.

A cohort study analyses a population that is at-risk but free from a specific adverse event, for a period of time for the occurrence of the adverse event. It uses correlations to determine the absolute risk of a patient succumbing to the event (the incidence rate). Cohort studies may be used to investigate the incidence rates within a specific population such as the elderly or children.

A case-control study uses a population with similar characteristics, split into two groups. One group possesses an adverse event or disease of interest, which is absent in the other group. The group without the adverse event or

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disease acts as the control group. The two groups are compared in order to derive an estimate of the relative risk of the event or disease occurring using the odds ratio. Large readily available population-based databases are often utilised for this type of study.

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. The study results can be used to determine rates of adverse events and highlight real world activities such as actual (versus advised) clinical practice, monitoring medical errors, risk of abuse of the medicinal product and unsuitable repeat prescribing.

ACTIVE SURVEILLANCE

Active surveillance is the process of identifying adverse events in an organised, proactive way as opposed to passive surveillance systems reliant on physicians or other medical staff and/or patients coming forward to report adverse events. Active surveillance is more likely to yield thorough adverse event reporting. It may be used to identify abnormal lab values through automated systems flagging out of range values. There are several different types of active surveillance, including intensive monitoring schemes, prescription event monitoring and registries.

An intensive monitoring scheme allows data collection within a specific environment, for example, data collected by monitors during a ward round within a hospital. The data collection may be focused on undesirable or unintended events thought to be causally related to the medicinal product or major drug related events such as renal failure or bleeding. The data may be collected by the monitor at the selected site through reviewing medical records or interviewing physicians or other medical staff and/or patients and so can be primary or secondary data collection.

Prescription event monitoring allows more detailed data on adverse events to be collected from a large number of physicians and/or patients. Following selection of patients from electronic prescription data or automated health insurance claims, the patient or their physician is sent a questionnaire at defined time points to collect the required data.

Registries are an organised collection of data outcomes for patients with a specific diagnosis, condition or procedure. They are usually defined by either the disease (disease registry) or by exposure to a medicinal product (exposure registry). They can be used as a data source within which studies can be performed (e.g. a case-controlled study within a disease registry).

PROGRAMMER EXPERIENCES OF PASS

In the past few years, as a biostatistical programmer I have gained experience of working on PASS and have noted differences and challenges they present. I will refer to two studies that were implemented to answer a specific obligation imposed by the EMA. These studies 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 reviewed (Study 2); primary and secondary data sources respectively.

STUDY DESIGN CHALLENGES

The design of a PASS, as previously discussed, can take many forms. There may be more than one study design that will answer questions posed by the competent authority and it is the responsibility of the marketing authorisation holder to decide what direction to take the study. Studies 1 and 2 were designed to answer a specific obligation and whilst both studies achieved their aim, tweaks to the study design, at the initial design stage, would have made the studies easier to implement.

The database initially implemented as the source for identifying physicians with required characteristics was large and covered the required countries; however once we received the database, it became apparent that the data held within it were not accurate enough for our purposes. Data were either out of date, contact details and physician disciplines were incorrect or necessary data fields were missing. We had to identify new data sources in order to complete the studies.

Designing studies is not an easy process, especially when the questions posed in an obligation offer only minimal direction. It can be a challenge for PASS to keep the design to the minimum requirements to answer the obligation and not expand the study away from the necessary information only, without good reason. Many people working on a clinical trial will have experienced mission creep in a trial; identifying this before implementation is the challenge to prevent unnecessary data collection that adds complexity to the study reporting process.

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Development of the survey questionnaires proved a particular challenge. Developing clearly defined questions, to gain all the required information without asking too many or too lengthy questions, or questions that are open to misunderstanding by the responder, took time and many reviews.

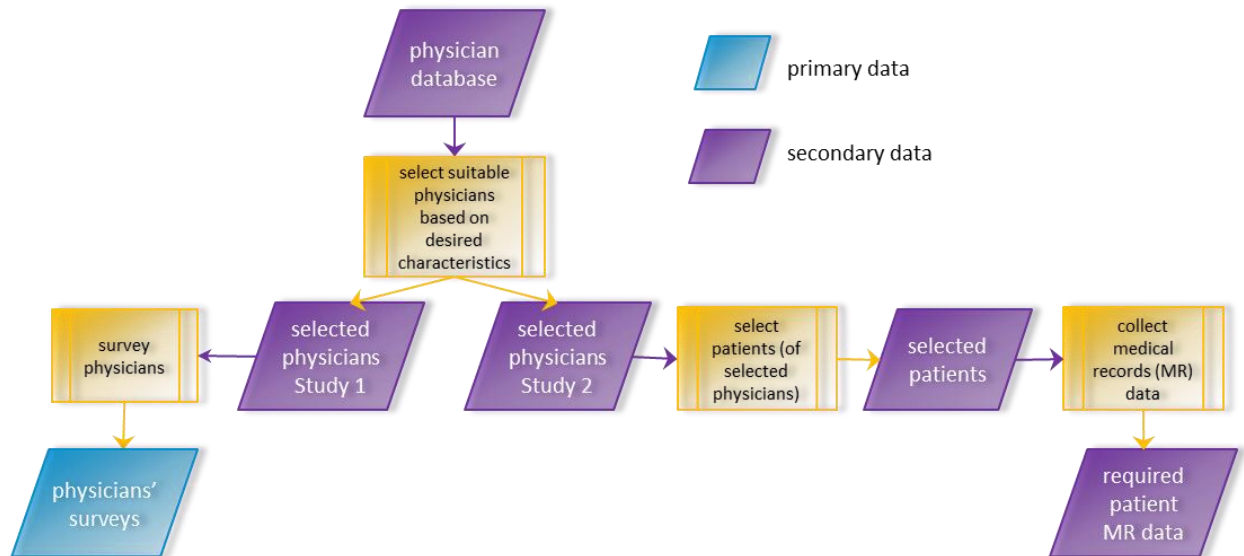


FIGURE 3: Data Flow for PASS

The studies involved areas of practical clinical knowledge in which the study team had little expertise, so a subject matter expert (SME) was sort to provide the required information. However, in this instance, the SMEs had limited knowledge regarding clinical practice across all the countries involved as the on-site processes were in a period of flux. During data collection, it became clear that the information we'd attained did not allow for all current processes and so amendments had to be made to the data collection device and programming in order to collect all the data correctly.

PROGRAMMING CHALLENGES AND DIFFERENCES

The primary and secondary data components of these studies brought up challenges that differ from those of clinical trials. Surveys are designed to be a snapshot at a point in time and therefore if the survey has been incorrectly completed or parts not answered, it can be difficult or incorrect to go back to the source and verify responses. Occasionally it was clear that the responder has misunderstood the question based on the responses they had given to other questions. Depending on the survey, this was either handled by re-contacting the responder to clarify their responses if the circumstances allowed, adapt the table, figure or listing (TFL) to suit some missing or incomplete data or the data was reported as planned and a footnote added to the TFL to explain any discrepancies so this could be written about in the study report.

Medical records (MR) also produce similar challenges. If data is incorrect or missing in the MR or the clinical site does not record the data in the same way as the study requires, the correct data required for the study cannot be identified. There is no way of querying for the data required and so the data as it was recorded in the MR must be accounted for in the programming or study report.

Despite these challenges of PASS, in general the data we collected brought up fewer data queries than a clinical trial. This could be due to no right or wrong answers in the case of some surveys and generally complete and consistently documented MRs. This especially made programming easier during the early stages of data collection as the data was more similar to clean final data.

CONCLUSION

As agencies become more focussed on PV, it is likely that the need for PASS under all guises will increase, giving more biostatistical programmers and statisticians the opportunity to experience these studies. 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.

From my experience, I would suggest considering the following when implementing a PASS:

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- confirm secondary data sources meet the requirements of the study. Obtain the database for review prior to agreeing to use it;
- keep in mind the questions the PASS is designed to answer to reduce complexity and mission creep;
- when designing surveys, keep the design team small, whilst incorporating information from experts and keep changes to “show stoppers” only;
- with surveys, keep the questions as concise as possible without reducing clarity;
- contact SMEs but be aware their knowledge may not be complete in all circumstances, especially if the topic is complex;
- if you have concerns about the potential need to make changes at a later date, build the study robustly so changes can be implemented with minimal impact;
- if using secondary data sources, expect some missing or incomplete data and build this into the study design;
- accept that you may need to make changes as your knowledge on the subject area increases and implement these with minimal impact to the study as a whole.

If you are going to be involved with a PASS or other PV study shortly, I would advise familiarising yourself with the purpose of the PV activities and reviewing the GVP documentation provided on the EMA website (details in reference section), especially module VIII relating to PASS.

REFERENCES

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