

The Challenges of Implementing Non-Interventional Studies in The EU



The European Medicines Agency (EMA) is piloting both adaptive pathways, to shorten time to market, and parallel scientific advice so that benefit and risk data requirements can be optimised for new medicines. Elements of both of these initiatives rely on real-world, post-authorisation data. There is a wider, growing need for post-authorisation data in general, for example through a post-authorisation efficacy study (PAES) or a post-authorisation safety study (PASS), the latter of which can be used to evaluate the effectiveness of additional risk minimisation measures (aRMMs). This article introduces the aforementioned aspects in more detail, and also highlights the need for harmonised regulations with respect to non-interventional studies to improve the efficiency of implementing these studies across EU member states, which can currently be unnecessarily complex.

Adaptive Pathways

The EMA are assessing adaptive pathways¹ to facilitate early discussion amongst stakeholders, sponsors, regulators, patient representatives and health technology assessment bodies (HTABs). Their aim is to optimise development pathways and accelerate patient access to medicines, for example in poorly-served therapeutic areas. Part of the acceptance criteria for this initiative includes expansion of the target population, i.e. from those with the highest medical need, and the collection of real-world post-authorisation efficacy data to complement data from clinical trials (CTs). In one case scenario (Figure 1), early approval is initially granted to a high-need medical group and, over time, the indication is expanded to a larger patient population as requisite data is obtained. This pathway accelerates patient access to new medicines.

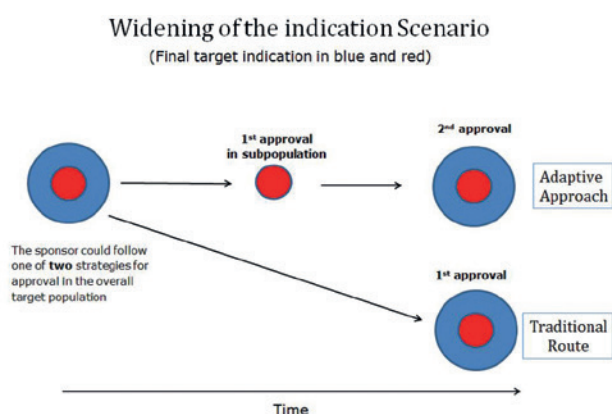


Figure 1 - Accelerated approval for a target indication under the proposed adaptive pathway route¹

Parallel Scientific Advice

Similarly, the EMA is also exploring parallel scientific advice as a method to enable sponsors to initiate joint dialogue with both regulators and HTABs.² Such advice can be used to assess the benefit-risk profile and value of a medicine earlier

in the development and approval processes. This can help stakeholders to guide the development plan for a medicine, determine which data would satisfy all parties, and overall shorten the market access process. The data can come from all stages of a product's life-cycle, including that generated from a PASS and/ or a PAES. The Committee for Medicinal Products for Human Use (CHMP) has established the Scientific Advice Working Party (SAWP) with the sole purpose of providing scientific advice and protocol assistance during the parallel scientific advice process.³

Post-authorisation Efficacy Studies

Recent guidelines for a PAES have been released in the EU⁴, reflecting that these studies are becoming more commonplace. A PAES aims to verify the real-world efficacy of a medicine already on the market, including efficacy in everyday medical practice, either to supplement efficacy data from pre-authorisation CTs or to address new information that may emerge post-authorisation.⁵ A PAES can be planned in a risk management plan (RMP) to assess efficacy knowledge gaps, or may be necessitated through previously unforeseen circumstances. For example, a surrogate endpoint such as a biomarker or tumour shrinkage may have been used to measure efficacy in CTs, while a subsequent PAES could be required to generate further efficacy data to verify the impact of the medicine on clinical outcomes or disease progression.

Risk Minimisation Effectiveness Evaluation

aRMMs are used to reduce the occurrence or severity of known risks associated with medicines. They may include active communication to healthcare professionals (HCPs) and patients, or other control mechanisms. These aRMMs need to be described in RMPs (e.g. EU-RMP in Europe), and in the EU the evaluation of the effectiveness of aRMMs is a regulatory requirement, covered by EU good pharmacovigilance (GVP) Modules V and XVI. It is common practice to register details of such studies on public websites such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and clinicaltrials.gov.

These evaluations may comprise a cross-sectional observational study, for example via surveys or other data collection techniques, to assess the effectiveness of aRMMs in HCPs and patients (or their caregivers), and are non-interventional. To qualify as a non-interventional PASS, participation in the study is voluntary and does not affect the participant's ability to prescribe or use the drug as an HCP or patient respectively.^{6,7} In this context it is also important to clarify that if surveys are used, answering the questionnaires may be considered as normal clinical practice, i.e. non-interventional. If falling outside normal clinical practice or standard of care, whilst still adhering to all other non-interventional study criteria, the study may be classified as clinical/interventional.

In the EU, non-interventional studies (including the protocol and questionnaires) must be reviewed centrally by the EMA Pharmacovigilance Risk Assessment Committee (PRAC). Once the study has been accepted by the PRAC it must then be endorsed by the CHMP, following which the study may be classified as a non-interventional PASS.⁸ Studies to assess the effectiveness of aRMMs, e.g. patient alert cards and educational material, are increasingly deployed as online surveys. These have many advantages over paper-based questionnaires and are considered appropriate for this research approach for several reasons, including:

1. Participants are becoming more familiar with online-based technologies – over 40% of hospitals in Western Europe are non-paper-based, with an increasing proportion each year⁹
2. Online surveys can be answered at the participant's convenience, therefore interview arrangements do not need to be made. This reduces the burden on participants and can increase participants' motivation to complete the survey, thereby improving response rates
3. Online surveys are programmed to ask standardised questions, and thus should elicit more consistent and reliable results¹⁰ than questions asked by telephone interviewers¹¹
4. Responses are gathered and analysed centrally, reducing the need for paper-based case record forms (CRFs) and local auditing and monitoring, which can be done remotely
5. Surveys can be designed to ask behavioural scenario-based questions in a manner dependent upon the participant's answers, e.g. a logical flow to ask or omit follow-on questions defined by previous responses, which can strengthen the value of the behavioural scenario line of inquiry. This can often be difficult to implement by other approaches. Also, question navigation (i.e. moving forwards or backwards through the scenarios) can collect additional information about participant behaviours that is not normally available through other means.

Surveys are usually designed to gain an understanding of a participant's aRMM utilisation, knowledge of appropriate medicine use, and/or potential adverse reactions and the correct courses of action to take, should these arise. Information about the effectiveness of the drug is not gathered through these surveys, and only a minimal amount of personal information is collected. The surveys cannot serve a promotional function and are not intended as a mechanism to collect adverse events (AEs) or minimise the numbers of AEs. However, standard pharmacovigilance (spontaneous reports) may be reviewed and correlated with knowledge of risks gained and measured from the surveys, although reaching meaningful conclusions is often difficult.

Regulatory and Quality Processes for Implementing a Non-interventional PASS

In a PASS, the study subjects are not humans but are, instead, the aRMMs being assessed for effectiveness. The main risk to participants is a breach of data privacy and the impact this may have on them. Care must be taken to only collect

the bare minimum of personal data needed for researchers to implement the study. This is usually limited to the collection of an individual's contact details so they may be provided access to the online survey.

Despite having central regulatory approval (i.e. PRAC and CHMP endorsement), there remain many regulatory hurdles to implementing a PASS efficiently across the EU. Whilst the legal and quality standards defining the requirements for implementing and reporting interventional clinical trials were harmonised through the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) – and subsequent interpretation and adoption into national legislation – the standards for non-interventional studies are not currently harmonised.

A non-interventional PASS differs from an interventional clinical trial in approach, design and potential risks and, as such, many of the requirements stipulated in ICH-GCP are not applicable to non-interventional studies. Currently, GCP and other standards cover a set of detailed ethical and scientific quality requirements for, *inter alia*, designing, conducting, monitoring and reporting predominantly CTs. However, as GCP is applied to any study that involves research with human subjects, many ECs have adopted and applied GCP standards to these types of non-interventional studies. This is despite GCP not applying to non-interventional post-authorisation studies.¹²

Together with GCP, there are various aspects of quality standards that could be applicable to non-interventional studies, including good epidemiological practice (GEP) or good pharmacoepidemiological practice (GPP). However, until harmonised guidelines are developed, non-interventional studies should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and local applicable regulatory requirements, namely:

- Participants provide their voluntary informed consent, or in the case of legal ineligibility/incompetence/incapacitation, consent should be obtained from their legal representative
- Participants are free to withdraw from the study at any time
- Benefit to the subject should outweigh the risk
- The rights, safety and welfare of subjects must be protected and their interests must always prevail over the interests of science and/or society
- The study must be scientifically valid and the purpose described in a protocol
- The protocol should always include a statement describing the ethical considerations.

There are many guidelines with varying degrees of relevance that also apply to non-interventional studies, including:

- The European Federation of Pharmaceutical Industries and Associations (EFPIA) Code of Conduct (HCP Code (Section 15.0)) and Marketing Practices
- EMA GVP Modules
 - ENCePP Guide on Methodological Standards in Pharmacoepidemiology

- The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines on Epidemiological Studies¹³
- ICH Guidance E2E for Pharmacovigilance Planning
- European Data Privacy Act
- Pharmacovigilance Directives (2001/83/EC and 2010/84/EU).

National Competent Authorities and IRBs/ECs interpret these guidelines and apply their legislation. However, since

the advent of these studies is relatively recent, few ECs (and other bodies) have experience in reviewing protocols for these studies. The current lack of harmonised guidelines means that individual countries govern non-interventional studies according to their own standards and requirements (summarised for selected countries in Table 1). For example, different rules may apply depending upon the individuals to be surveyed, e.g. HCPs or patients/caregivers. The approach of these bodies is likely to evolve with experience, particularly if harmonised guidelines are introduced.

Country	Competent Authority ^a	Ethics Committee	Other
Austria	Direct notification	Not required ^c	
Belgium	Via notification from EU PAS Register	Not required ^d	
Denmark	Via notification from EU PAS Register	Not required	
France	Via notification from EU PAS Register	Not required	CNOM, CNIL, CCTIRS
Finland	For classification ^b Variable	Depending upon classification from CA	
Germany	Direct notification	Single EC and sometimes LEC	Sick Funds
Italy	Direct notification via OsSC	Single EC	
Ireland	Via notification from EU PAS Register	LECs	
Netherlands	Direct notification	Single EC	
Norway	Via notification from EU PAS Register	Not required ^e	
Portugal	Direct notification	Site dependent	Data protection
Slovenia	Direct notification	CEC	
Spain	Direct notification ^b	Depending upon classification from CA	
Sweden	Via notification from EU PAS Register	Single EC	
United Kingdom	Via notification from EU PAS Register	Not required	

Table 1 - Selected Member States' requirements for transmission of information on non-interventional post-authorisation safety studies*

* Whilst reasonable efforts have been made to show the accuracy and completeness of the information provided, researchers and other individuals are advised to check with local authorities, National Competent Authorities or ECs before starting any non-interventional study in Europe.

CEC – central ethics committee; LEC – local ethics committee; Single EC – regional EC acting as a CEC; CA – competent authority; OsSC - Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali; CNOM - Conseil National de l'Ordre des Médecins; CNIL - Commission Nationale de l'Informatique et des Libertés; CCTIRS - Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé

a GVP Module VIII Addendum I Table VIII Add I.2.
b Competent authority classifies the study and this dictates the type of review required (including ECs committees)

c Prior to 2015, EC review was required. EC review may be required if the study results are to be published

d To be confirmed, conflicting messages regarding EC review are common

e Prior to 2015, EC review was required.

Once the study has been classified as non-interventional, the requirements per country need to be assessed and may include approvals, notifications and/or registration with any/all of the following:

- Competent authority
- Institutional review boards (IRBs) / research ethics committees (RECs)
- Data protection agencies
- Hospitals / institutions.

In some countries, healthcare professionals may need to request EC approval before they can participate in the study. In some cases, this can make the approval process time-consuming and may either delay or preclude an HCP from participating in the study, thereby impacting the collection of statistically meaningful data.

Summary

The scope of non-interventional post-authorisation studies carried out through adaptive pathways, parallel scientific advice, a PASS or a PAES is growing in both frequency and complexity. Adaptive pathways and parallel scientific advice have the potential to shorten market access timeframes and to streamline regulatory and payer requirements respectively, thus facilitating a more efficient approval process. Real-world post-authorisation data via a PAES and/or a PASS is often needed to supplement efficacy data gained through CTs to ensure that a medicine's benefit-risk profile remains sufficiently positive throughout its life-cycle. Unlike CTs, where regulations are well-established and harmonised, there are no current analogous regulations governing non-interventional studies. This results in unnecessary complexity in study implementation on a country-by-country basis within the EU. Therefore, harmonised guidelines for these studies would be beneficial for facilitating the efficient implementation of non-interventional studies in the EU.

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