Scientific guidance on post-authorisation efficacy studies

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Executive summary

To impose a post-authorisation efficacy study (PAES), there should be a well-reasoned scientific uncertainty to be addressed post-authorisation to enhance the understanding of therapeutic efficacy and the benefit-risk of a medicine with implications for better use in clinical practice. In addition, it should be ethical and feasible for a study to be designed with a suitable methodology, taking account of the post-authorisation setting and which can be conducted in a timeframe and manner that gives reliable and interpretable answers to the question at hand. Agreement should be sought as early as possible between the regulator and sponsor on the appropriateness of a study design to achieve this. To this end, scientific advice is recommended if the PAES objectives and key design features are not agreed during an assessment procedure.

1. Introduction

The granting and maintenance of a marketing authorisation (MA) in the European Union (EU) is dependent on data generated to that point in time supporting a positive benefit-risk within the therapeutic indication and terms of the MA as laid out in the Summary of Product Characteristics (SmPC). In general, to support a positive benefit-risk in an indication at the time of the initial MA, demonstration of benefit is required from pivotal, almost invariably randomised, trials that are appropriately designed and conducted in accordance with applicable guidance.

PAES of medicinal products are studies subsequently conducted within the authorised therapeutic indication to address well-reasoned scientific uncertainties identified by EU regulators on aspects of the evidence of benefits that should be, or can only be, addressed post-authorisation.

A PAES may, therefore, be needed at the time of the initial MA or the extension of an existing MA where there is a well-reasoned scientific uncertainty on an aspect of the established therapeutic efficacy and the resolution of this uncertainty is important for further understanding this aspect of benefit-risk. The uncertainty should also be such that it may be addressed post-authorisation by a study that can be designed and conducted to give interpretable results with the potential to impact on the MA status or product labelling.

Post-marketing evaluation of medicinal products is increasingly based on a benefit-risk management model encompassing emerging evidence relevant to both risks and benefits e.g. formal evaluation of benefit is a feature of Periodic Safety Update Reports. There may be circumstances where important uncertainties concerning a product's benefits become relevant in the context of such a post-marketing benefit-risk evaluation particularly where knowledge of the safety or benefit-risk profile has changed significantly since first MA. In such circumstances a PAES may be considered. A PAES may also be needed if an improved understanding of the disease or the pharmacology of a medicinal product has brought into question the criteria used to establish the efficacy of the medicinal product at the time of the initial MA.

The need for a PAES may therefore be seen as in keeping with the concept of life-cycle product benefit-risk profiling and monitoring through targeted research that translates into better labelling and better use of medicines.

2. Scope

This guidance has been developed in accordance with Article 108a of Directive 2001/83/EC which provides a mandate for European Medicines Agency (EMA) in cooperation with competent authorities and other interested parties to draw up scientific guidance on PAES.

The intention is to provide scientific guidance for MAHs and for competent authorities on PAES in the context of EU regulatory decision-making with regard to the general need for such studies and general methodological considerations. For specific scenarios where PAES may be considered, additional clarifications are given together with study designs which may be applied. Some principles of study conduct are also highlighted.

This guidance is not intended to replace or reproduce methods available in textbooks on various study designs but to highlight regulators' particular considerations and the potential role of mentioned study designs for the PAES setting.

3. Legal basis and relevant guidelines

In the EU, a PAES may be initiated, managed or financed by a marketing authorisation holder (MAH) voluntarily, or pursuant to an obligation imposed by a competent authority as follows:

– Within the scope of Delegated Regulation (EU) No 357/2014[1], PAES may be imposed for centrally (CAPs) and nationally authorised medicinal products (NAPs) either:

- at the time of granting the initial marketing authorisation (MA) where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed [Art 9(4)(cc) of REG / Art 21a(f) of DIR]; or

- after granting of a MA where the understanding of the disease or the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly [Art 10a(1)(b) of REG / Art 22a(1)(b) of DIR].

– Outside of the scope of Delegated Regulation (EU) No 357/2014, PAES may be imposed in the following specific situations:

- a conditional MA granted in accordance with Article 14(7) of Regulation (EC) No 726/2004;

- a MA granted in exceptional circumstances and subject to certain conditions in accordance with Article 14(8) of Regulation (EC) No 726/2004 or Article 22 of Directive 2001/83/EC;

- a MA granted to an advanced therapy medicinal product in accordance with Article 14 of Regulation (EC) No 1394/2007;

- the paediatric use of a medicinal product in accordance with Article 34(2) of Regulation (EC) No 1901/2006;

- a referral procedure such as initiated in accordance with Articles 31 or 107i of Directive 2001/83/EC or Article 20 of Regulation (EC) No 726/2004.

As this is a scientific guidance, it is not restricted to the situations falling within the scope of the Delegated Regulation (EU) No 357/2014.

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[1] Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required (OJ L 107, 10/04/2014, p. 1).

This guidance should be read in conjunction with Delegated Regulation (EU) No 357/2014, Regulation (EC) No 726/2004, Regulation (EC) No 1901/2006, Directive 2001/83/EC and Directive 2001/20/EC[2] and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations especially those on:

− The extent of population exposure to assess clinical safety for drugs (ICH E1A).

− Dose response information to support drug registration (ICH E4).

− General considerations for clinical trials (ICH E8).

− Statistical principles for clinical trials (ICH E9).

− Choice of control group in clinical trials (ICH E10).

− Clinical investigation of medicinal products in the paediatric population (ICH E11).

− Accelerated evaluation of products indicated for serious diseases (Life Threatening or Heavily Disabling Diseases) (CPMP/495/96 rev. 1).

− Points to consider on applications with 1.) Meta-analyses and 2.) One pivotal study (CPMP/2330/99).

− Points to consider on switching between Superiority and Non-inferiority (CPMP/EWP/482/99).

− Reflection paper on methodological issues in confirmatory clinical trials with flexible design and analysis plans (CHMP/2459/02).

− Guideline on Data Monitoring Committees (CHMP/EWP/5872/03 Corr).

− Clinical trials in small populations (CHMP/EWP/83561/05).

− Guideline on safety and efficacy follow-up- risk management of advanced therapy medicinal products (EMEA/149995/2008).

− Qualification of novel methodologies for drug development: guidance to applicants (EMEA/CHMP/SAWP/72894/2008).

4. General methodological considerations for PAES

The choice of study design will be based on the particular medicinal product and the scientific uncertainty to be addressed. In designing and conducting a PAES, consideration should be given to ensuring that the requested study will be feasible, ethically acceptable and of a design known to return reliable and interpretable results in relation to the primary objectives. The design should take particular account of the post-authorisation setting and be feasible to complete within the indicated timeframe.

There may be circumstances in which a PAES imposed in accordance with Delegated Regulation (EU) No 357/2014 could also include additional investigational arms and/or study cohorts, objectives, endpoints and /or analyses (e.g. data collection for health technology assessment purposes). This would be provided that this would not impact on the study integrity and the primary objectives of the study as defined in the condition of the MA.

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[2] To be repealed by Regulation (EU) No 536/2014 in accordance with Articles 96 and 99 thereof.

A PAES may be conducted as a randomised or non-randomised study. Note, as this is a scientific guidance, these terms are used without prejudice to the definitions pertaining to clinical trials that may be applied in European Union and national legislation, and related regulatory guidance.

Studies involving randomisation are the preferred design for PAES. Without randomisation, estimates of effects in relation to a control group (purporting to reflect only a difference in intervention) can be expected to be affected by confounding factors or biases in the population under evaluation. This is because a difference between treatment groups in non-randomised studies are likely to reflect both differences arising from the allocation of subjects into treatment and the subsequent patient management and any difference in the effects of the interventions. Randomisation also provides the basis for standard methods of statistical analysis and the results from non-randomised studies are generally more difficult to analyse and interpret. Nevertheless, for certain medicinal products (e.g. vaccines) and in certain situations (see section 4.2) the conduct of non-randomised comparative studies, where measures are included to minimise limitations/ biases, could be justifiable in the PAES setting.

Blinding should also be considered to support conclusions on efficacy being reliable, especially in conditions that involve subjective reporting (e.g. pain, depression) both for randomised and non-randomised studies. In the latter case, this will usually mean blinding the outcome evaluation to the exposure status of the patients.

All PAES should conform to applicable legislation and recognised international methodological and ethical standards for research.

4.1. Randomised trials

Trial designs, e.g. choice of control arm(s), objective (e.g. superiority or non-inferiority) will be determined by the uncertainty to be addressed, the nature of the intervention and the condition under treatment.

As far as is possible, the methods applicable for preauthorisation clinical trials should also be adopted in the PAES setting. One or more control arms, as appropriate, should be allocated to standard care (when standard care exists) and/or an established medicinal product of proven therapeutic value (see Section 5.5). Depending on the scientific uncertainty, a placebo control might also be a design option in the post-authorisation setting.

Clinical trial design options for the design of PAES could include explanatory and pragmatic trials. Explanatory trials generally measure the benefit of a treatment under ideal conditions to establish whether the treatment works. Pragmatic trials examine interventions under circumstances that approach real-world practice, with more heterogeneous patient populations, possibly less-standardised treatment protocols and delivery in routine clinical settings as opposed to a research environment. Minimal or no restrictions may be placed on modifying dose, dosing regimens, co-therapies or co-morbidities or treatment switching.

As the justification of each trial design feature in respect of trial objectives is more important than the distinction between pragmatic and explanatory clinical trials, these trials may be considered as a continuum rather than as a dichotomy. For example, some elements of explanatory trials could be made more pragmatic (e.g. by inclusion of a broad patient population or those with various baseline risks) without relaxing all of the design parameters associated with the most explanatory type of trials. Pragmatic trials may be more amenable to trial designs not commonly employed for explanatory clinical trials e.g. cluster-randomised or stepped-wedge designs.

4.1.1. Explanatory Trials

Such trials are expected to have a high degree of assay sensitivity and internal validity and designed to reflect the intended indication and treatment regimen, so that the errors and biases will influence the results as little as possible. Sources of bias (systematic errors) are controlled for by e.g. means of randomisation, blinding, allocation concealment and the use of clearly defined participant populations and analyses.

These trials play an important role in providing knowledge concerning the effects of precisely defined interventions applied to selected groups under controlled conditions. However, depending on the detail of the protocol, external validity may be limited. Thus in a PAES setting, these designs are best targeted at addressing those uncertainties that can be addressed most efficiently, with greatest sensitivity to drug effects, in a more homogenous population without limiting the generalisability of conclusions. Such trials will also need to be feasible post-authorisation and ethical considerations around the choice of control arm must be taken into account.

4.1.2. Pragmatic Trials

For the PAES setting, pragmatic trials may be used in situations in which randomisation is needed, and where there is a need to explore the use of the intervention in settings that are less restricted than the pivotal trials and whether that difference in usage, if any, affects the reported efficacy of the intervention. Pragmatic trials may also be used where non-adherence to treatment or relaxing of behaviours could be an issue or where population characteristics, co-morbidities and co-medications could have an impact on the benefits of the medicine. Such trials may also be appropriate if the comparator is usual care (if not, a more explanatory type of trial may be more appropriate).

The following are examples of expectations, or challenges of more pragmatic trials compared to traditional trial designs from a regulatory science perspective, and which should be addressed in any dialogue with regulators on the proposed use of a pragmatic trial design.

It is important to provide clear definitions of key terminology and pros and cons of study design options.

Robust randomisation processes with allocation concealment should be used as per explanatory trials. The length of follow up should be sufficient and the endpoints of interest should be ascertainable where 'real life' data collection systems are used.

Consideration should be given to the level of bias introduced if the outcome assessment is not blinded to the treatment allocation. Consequently, outcomes that can be robustly measured in the presence of knowledge of the intervention received are useful.

Consideration should also be given to whether or not the pragmatic approaches impact on the reliability of eligibility, treatment allocation or outcomes and whether the results are generalisable in different healthcare settings. As randomisation to treatment is performed in pragmatic trials, hypotheses testing for comparison of treatments should be possible. Consideration should be given as to whether there are other potential differences in patient management between treatment groups e.g. compliance, changes or switches in treatment which may impact on findings. In addition, populations may still be self-selecting and the demographic characteristics of the enrolled patients should be analysed for any impact on external validity.

The analysis plan should consider how to measure the effect of the treatment of interest on key study outcomes in the event of discontinuation of study drug, the use of rescue medications. The existence of substantial heterogeneity of effects should be considered. Investigators should report quality metrics

i.e. measures quantifying the mechanisms for operational control of the protocol and any extent to which inclusion criteria were relaxed. Clinical trials conducted for regulatory purposes should be reported in line with applicable legislation but from a scientific perspective pragmatic adaptation in the trial design should be clearly identified in the report as described in the CONSORT[3] statement extension for pragmatic trials.

4.2. Non-randomised studies

Non-randomised (for treatment) studies may be considered for investigating post-authorisation benefits where one or more of the following situations apply: randomisation is unethical or unfeasible, outcomes are infrequent, the generalisability of randomised trials is particularly limited, outcomes are highly predictable or effect sizes are very large. Observational PAES may additionally be useful to identify effect modifiers, namely factors that result in important differences in the level of efficacy of the drug between patients within the authorised indication and which may not have been detectable in the pivotal trials conducted prior to authorisation. Examples of effect modifiers are patient sub-groups defined by factors such as age, co-morbidities and use of concomitant drugs, disease severity, disease duration, treatment history, drug misuse and factors related to a defined country or health care system.

Observational studies to assess benefits require exposures and outcomes which can be measured with a high degree of accuracy (i.e. minimised risk of misclassification bias). Objective criteria should be adopted. The degree to which relevant confounding factors and effect modifiers are known and can be correctly measured will greatly impact on the confidence with which the results can be interpreted. This will, in general, be easier when comparing with another active treatment rather than no treatment.

Observational studies can also be more challenging to interpret due to e.g. time-varying confounders in chronic conditions and the role of factors that may influence prescribing trends, particularly on a local or national level e.g. treatment guidelines, re-imbursement policies or marketing. In observational studies of drug effects, confounding by indication and channelling of treatments are amongst the main sources of bias when evaluating benefit endpoints and these need to be addressed.

Observational studies involving secondary use of existing data (see Section 4.3) may be beneficial in situations where a rapid exploration of an efficacy question is needed. Control of confounding and bias is, however, especially difficult in this type of studies and there may be missing data (e.g. important confounders may not be measured or incomplete observation).

A detailed justification for conducting a non-randomised study should always be provided.

4.2.1. Studies with concurrent comparison data

The preferred comparison within a non-randomised study will be to a concurrent set of patients who have not or who are not currently receiving the treatment of interest but are similar in terms of disease progression to the patients receiving the treatment.

When it is possible to identify a subset of the observational study population that is broadly similar to that included in the explanatory randomised clinical trials, confidence in the overall study results may be increased if similar results are found in this sub-population. The importance of sensitivity analyses to test the robustness of study results is therefore emphasised.

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[3] Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, Oxman AD, Moher D for the CONSORT and Pragmatic Trials in Healthcare (Practihc) group. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008; 337; a2390.

4.2.2. Studies with historical comparison data

Comparison of currently treated patients with historically treated controls is difficult at least for two reasons. The decision to treat applies only to a selected patient group that may differ from the historical controls, and the clinical background may have changed over time.

However, comparison to historical datasets may have a role in the PAES setting where obtaining prospective data on concurrent controls are unfeasible; historical data should be well-characterised and relevant. These datasets are most likely to come from clinical trials for which the selection criteria were well documented and strictly measured and in which the known, important prognostic variables were recorded and can be matched to those of the treated patients. A major consideration is whether the selection criteria in the original trials have been applied in the subsequent observational study. There will also be circumstances under which historical comparison data are derived from large representative observational studies.

There is also the possibility of applying both concurrent and historical approaches at the same time e.g. disease risk scores may be calculated for concurrent controls based on weights generated from historical data. A patient may also be their own control for pre- and post-treatment comparisons.

4.3. Data sources

There are two main approaches for sourcing data i.e. primary collection of data or secondary use of existing data (e.g. as part of electronic records of patient health care). The use of these approaches are well described elsewhere in various textbooks. Two particular methodological issues of significance from a regulator's perspective are, however, highlighted in the following sub-sections:

4.3.1. Use of electronic healthcare data to facilitate the conduct of clinical trials

Clinical trials in general will rely on primary data collection. In contrast, using electronic healthcare record data to facilitate the conduct of clinical trials is relatively new and regulatory dialogue is recommended if the results of these studies are to be used to support regulatory decision-making. Potential value of using such databases may be realised when outcomes are clinically important acute events (e.g. death and onset of new disease) that are likely to be well recorded. Long-term low-cost follow-up could be possible and studying rare disease outcomes might be facilitated. The quality and completeness of data in the database must be sufficient to conduct a study that addresses research questions of the PAES. Important variations exist in data quality and focus between individual databases and consequently it should be assured that clinical trial processes can be implemented in a given database. Database screening or record linkage can be used to detect and measure outcomes of interest otherwise assessed through the normal process of care. Patient recruitment, informed consent, confidentiality, assuring of patient anonymity, and proper documentation of patient information are areas that still need to be addressed in accordance with the applicable (local) legal and ethical requirements for clinical trials. Administrative requirements, coding conventions, quality of data, the ability to link to additional data sources and the ability to provide further clinical details on request are all likely to be specific to a database.

4.3.2. Use of registries

Regulators can require marketing authorisation holders (MAHs) to establish or work with an existing registry i.e. 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. This is to support the post-authorisation collection of data on effectiveness and safety of medicinal products in the routine treatment of diseases.

Use of existing disease registries is recommended as they allow continued assessment of disease outcomes and a comparison of different treatment options using a similar methodology. Data of existing registries could be supplemented with additional data collection or linkage to external data sources. If it is necessary to start a new registry, its design should be based on relevant methodological standards and be described in a protocol.

Registries allow for a wide variety of observational study design options including prospective cohort studies with nested case-control analysis, inception cohorts, retrospective cohorts, natural history studies, and cohort studies with internal comparators, linkage and/or supplementary data collection. Capturing data on a set of variables and procedures (e.g. inclusion criteria, clinical and socio-demographic characteristics, exposure to treatment or vaccine, major outcomes, follow-up schedules) into a validated system can allow its subsequent extraction in a standardised form for observational studies. As for any source of data, data quality is crucial. Measures to ensure data quality include the use of common terminologies and data dictionaries/definitions, quality control of laboratory and measurements data and standards for collection of patient-reported information.

Registries with large numbers of subjects may allow for differences in efficacy by patient characteristics to be studied. Amongst the limitations is the confounding applicable to observational studies. Other limitations are situations where the disease or exposure classification is not specific enough, follow-up is missing, appropriate controls cannot be identified or when a suitable definition of an index event cannot be given for the control. Unless it aims to collect exhaustive data, it is important to describe the representativeness and generalisability of a registry and whether the relevant patients and periods of interest are covered.

5. Scientific guidance on specific situations

The following guidance expands on the situations where PAES may be imposed in the context of Delegated Regulation (EU) No 357/2014. As referred to in Section 3 there are other legal frameworks where the concepts are also applicable. There may also be a wide range of scenarios arising from change in understanding or the identification of new scientific factors that require a PAES to be imposed. These studies are not foreseen to be routine in that a PAES should only be imposed when there is a well-reasoned and clinically relevant scientific uncertainty, the resolution of which is important for understanding therapeutic efficacy and benefit-risk and it can be addressed post-authorisation. The uncertainty should also be such that a study can be conducted within a reasonable timeframe to give reliable and interpretable answers to the question at hand. The results of the study should have the potential to impact on the licensing status or product labelling. In all situations, the choice of design will need careful justification taking account of the precise question for which an answer is sought, the available evidence and the uncertainty.

5.1. Uncertainties concerning benefits stemming from (sub)-populations

An important well-reasoned scientific uncertainty may exist regarding aspects of the target population in the therapeutic indication and a PAES aimed at reducing such uncertainty may be required.

A wide range of potentially applicable sub-populations can be envisaged. These sub-populations may be defined by baseline demographic criteria or specific factors affecting disease prognosis or a drug's pharmacokinetic/pharmacodynamic profile, e.g. pharmacogenomic markers affecting treatment

response. Uncertainty may arise when the target population changes during the course of a development programme (including where new biomarkers are identified). It may also arise due to insufficient patient numbers in a given sub-population either due to the nature of the disease or unduly restrictive inclusion criteria in the pivotal trials and the consequent reliance on extrapolation of findings for the population studied to that sub-population within the therapeutic indication. Further study may, therefore, be aimed at establishing whether an effect is modified in a given sub-population.

Both randomised and non-randomised designs could be considered. Feasibility or otherwise of randomisation must be considered in all cases including for studying subgroups that were excluded from trials.

5.2. Uncertainties concerning benefits stemming from endpoints

Clinical intermediate or biomarker endpoint data have the potential advantage of providing evidence of efficacy before data are available from endpoints based on final clinical outcome, for example, effects on tumour progression in the area of oncology. Such data have been used in different therapeutic areas to define the efficacy of medicinal products in exploratory or confirmatory clinical studies. Understanding of the clinical relevance of any intermediate endpoints used to assess efficacy in support a positive benefit-risk is therefore essential. Thus, the use of intermediate or biomarker endpoints that are not the final clinical outcomes should only be the basis for granting an MA when agreed to be sufficiently informative by the scientific/regulatory community. However, there may be varying degrees of uncertainty in the strength or extent of relation between such endpoints and the final clinical outcomes. There may also be complex composite or key secondary endpoints that are considered important in supporting therapeutic efficacy, and in determining benefit-risk.

PAES may, therefore, be required to collect supplementary data to address such uncertainties e.g. with very rare or slowly progressive conditions, extended follow up in an extension study would be needed.

Both randomised and non-randomised designs could be considered.

5.3. Uncertainties regarding benefits of treatment over time

For treatments given on a continuous basis, the benefit-risk balance assumes that benefits established in the timeframe of pivotal studies persist. This assumption also applies for intermittent or repeated treatments e.g. where neutralising antibodies, which may abolish treatment effects, develop over time. Where uncertainty arises based on the clinical data or on considerations related to pharmacology that the response diminishes over time, a PAES could be required. Randomised clinical trials or observational studies could be used to address this uncertainty and the design should take particular account of the clinical pharmacology of the medicinal product. Randomised withdrawal designs could be considered and justified taking into account the timeframe of the effects.

5.4. Uncertainties in benefits regarding co-treatment with other products

At the time of its licensing, the use of a medicinal substance in combination with other treatments for the intended indication must be substantiated in terms of the safety and efficacy of the combination.

PAES may be required for additional potential combinations (simultaneous or sequential) that have not been assessed at the time of licensing for which uncertainties remain based on the accumulated scientific knowledge or for which theoretical uncertainties arise. This will be based on a case-by-case assessment. The study design will be dependent on the uncertainty, in particular whether the aim is to

establish the benefit of the new combination per se or to compare one potential combination with another.

In the post-marketing setting, treatment paradigms may change over time resulting in treatment combinations that are different to those that were originally studied for the MA and PAES may therefore be required if an uncertainty over the use of a particular combination arises.

Observational designs may suffice if justified and with consideration for whether factors determining co-administration of treatments are likely to impact the comparability of treatment groups.

5.5. Uncertainties stemming from benefits of the medicinal product in real life use

A PAES may be required where the benefits of a medicinal product demonstrated in clinical trials may be significantly affected by the use of the medicinal product under real-life conditions, e.g. where the efficacy demonstrated might not translate into a clinical benefit if the use of the drug provokes an effect on the behaviour of the recipients (risk compensation) or impacts negatively on other measures considered as important to prevent the disease. The results of such studies would allow determination of benefit in everyday medical practice and regulatory action if necessary.

A related scenario would be where the choice of control or background treatment is sub-optimal or, exceptionally, where a comparison to a particular standard-of-care, usually another medicinal product, is considered necessary even though positive benefit-risk has been established relative to a particular clinical trial control arm. The difficulties in defining standard of care are acknowledged including in the context of appropriate comparator arms, local definitions and the idea of multiple studies defining a number of 'standards of care'. For medicinal products where a major advancement in care has taken place whilst pivotal trials were ongoing and which also constituted a scenario where an active control would be needed to further inform on the benefit-risk of the product, consideration may be given to requiring a PAES with a relevant active comparator.

Another scenario where the need for PAES might be considered is where a specific scientific rationale questions the external validity of the data across various populations and settings despite a high degree of internal validity of the results from pivotal clinical trials e.g. impact of co-morbidities and polypharmacy on effectiveness of a specific intervention in a geriatric population.

A PAES may also be required in the case of vaccines where protective efficacy studies have not been feasible or if required to further determine the impact on strain, infection and disease epidemiology and herd immunity. PAES may also be used to estimate vaccine effectiveness where there is a well-reasoned scientific rationale for using study designs different to those that supported the initial MA to address an uncertainty. The information gained from assessment of vaccine effectiveness may also be particularly important to add knowledge on the most appropriate mode of use of a vaccine (e.g. need for booster doses in at least some segments of the population to maintain adequate protection over time).

Pragmatic trials and observational designs, with appropriate justification, may have a particular role in the study of a medicine in real-life use.

5.6. Change in the understanding of the disease or drug

The knowledge of the mechanism of action of a medicinal product develops throughout the product lifecycle. There may be many circumstances underlying a change in the understanding of the disease or drug. For example, investigation of dose-response is a critical aspect of the drug development

process and the initial understanding of a positive benefit risk balance may be improved through further investigation of posology. Also, with introduction of other therapies earlier in the treatment course, this may result in alterations of underlying disease biology, and or the patient population in question may present as more heavily pre-treated than at the time of licencing.

In the case where a change in the understanding of the standard of care for a disease or of the pharmacology of the drug has put into question the criteria used to establish the efficacy of the product at the time of authorisation, a PAES may be imposed. A change in a therapeutic efficacy guideline should not necessarily in itself be seen as a trigger for a PAES.

5.7. Change in scientific factors for previous efficacy evaluations

If new concrete and objective scientific factors (including regulatory or clinical guidance) emerge which significantly bring into question the criteria used to establish the efficacy of a medicinal product at the time the MA was granted, a requirement for a PAES may be considered.

6. Conduct of post-authorisation efficacy studies

MAHs and investigators should follow all relevant EU requirements and the national legislation and guidance of those Member States where the study is being conducted. The following section highlights principles that should be applied to the conduct of PAES. More detailed procedural guidance is available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000150 .jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580979eae.

6.1. Study protocol and report

Agreement on the protocol between sponsor and regulator needs to be reached for an imposed PAES and it is recommended that this is achieved as early as possible. Study protocols for PAES should take into account relevant scientific guidance applicable to the issue to be investigated and the study design to be applied. Input from patients and healthcare professionals should be sought, as appropriate. Scientific advice on the study protocol with respect to the proposed study design is also recommended.

Any substantial amendment to the protocol should be discussed and agreed in advance with the competent authorities.

The time frame for submission of the protocol/protocol amendments and interim/final study report should be agreed by the competent authorities, taking into account factors such as possible third party involvement. Timelines should be agreed at the time of study request and may be further refined at time of protocol finalization/amendment. If the study is discontinued, a final report should be submitted and the reasons for stopping the study should be explained.

6.2. Data protection and transparency requirements

The collection, use and trans-border transfer of personal data relating to patients enrolled in a PAES has to comply at all times with the requirements of the Data Protection Rules[4].

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[4] Data Protection Rules includes Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, the national laws, the laws of the European Union Member States transposing this Directive, the Opinions and guidance Developed by Article 29 Working Party and the guidance developed by the competent data protection authorities of the European Union Member States.

To support transparency on PAES that are outside the scope of Directive 2001/20/EC and which are conducted pursuant to a condition of the MA or voluntarily, study information (including for studies conducted outside the EU) should be made available in the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the Agency[5]. This recommendation is without prejudice to national transparency requirements.

6.3. Quality control and quality assurance

The MAH should ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. The MAH should ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection and adhere to CONSORT or STROBE reporting guidelines.

6.4. Safety aspects

Safety reporting from PAES which are clinical trials falls under the scope of Directive 2001/20/EC. The provisions set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 apply for studies falling outside the scope of Directive 2001/20/EC. For the latter, detailed guidance is provided in Module VI of the Good Pharmacovigilance Practice.

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[5] http://www.encepp.eu/encepp_studies/indexRegister.shtml