EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2016
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Human Medicines Research and Development Support Division

Scientific guidance on post-authorisation efficacy studies

Overview of comments from public consultation

1. List of Stakeholders

Stakeholder number	Name of organisation or individual
1	**ACRO**-Association of Clinical Research Organizations
2	**ACRP**-Association of Clinical Research Professionals
3	**AESGP**-Association of the European Self-Medication Industry
4	**Agenas**-Agenazia per I Servizi Sanitari Regionali, Dr Tom Jefferson
5	**BEUC**-The European Consumer Organization
6	**BPI**-German Association of Pharmaceutical Industry
7	**EFPIA**-European Federation of Pharmaceutical Industries and Associations, Pär Tellner
8	**ENCePP Centre (PEL)-**European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Centre-Unité de Pharmacoépidémiologie, Université Claude Bernard Lyon 1(PEL), Eric Van Ganse
9	**Eurordis**-European Organisation for Rare Diseases, François Houÿez, Tatiana Foltanova
10	**French Research Institute for Development & Paris Descartes University**, **Francois Simondon**-member of International Society for Pharmacoepidemiology / Vaccines Special Interest Group (VAXSIG)
11	**Gilead-**Gilead Sciences International Ltd.
12	**GPT**-German Society for Phytotherapy(Gesellschaft für Phytotherapie e.V.)
13	**IPFA**-International Plasma Fractionation Association
14	**ISDB**-International Society of Drug Bulletins, **Nordic Cochrane Centre**, **Prescrire**
15	**Kaiser Permanente Vaccine Study Center**, **Roger Baxter**-member of the Vaccines

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Stakeholder number	**Name of organisation or individual**
	Special Interest Group (SIG)
16	**Lundbeck**-H. Lundbeck A/S
17	**MEB**-Medicines Evaluation Board, the Netherlands
18	**MEDA**-MEDA Pharma GmbH & Co. KG
19	**Pfizer**-Pfizer Inc.
20	**REGenableMED**-REGenableMED consortium, Dr Aurélie Mahalatchimy, Prof. Alex Faulkner
21	**Vaccines Europe**-Vaccines Europe, Magdalena R. de Azero

2. General and specific comments

2.1. General comments

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1	The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 110,000 employees engaged in research activities around the world (including 30,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 research sponsors annually. ACRO welcomes and supports the draft guidance. In particular, ACRO appreciates the flexibility that the guidance allows in choosing the most appropriate study design to achieve the scientific objectives of a proposed post-authorisation efficacy study (PAES), and the emphasis placed on incorporating measures to improve the quality of data and the validity of studies. Throughout the draft guidance document, the words “trial” or “trials” are used in the context of clinical studies that may or may not meet the definition of a clinical trial in Directive 2001/20/EC. To avoid confusion with regard to the regulatory status of different types of PAES, ACRO recommends that the terminology in the draft guidance is revised so that any reference to a “trial” or “trials” means a clinical trial as defined by the Directive, and the term “study” or “studies” is used in other cases. This approach is consistent with the definitions in the new Clinical Trial Regulation (EU) No, 536/2014.	Not agreed - as this is a scientific guidance, terms such as randomised, non-randomised and observational are used without prejudice to the definitions pertaining to clinical trials that may be applied in European Union and national legislation.
2	ACRP appreciates the opportunity to provide EMA our comments regarding the Scientific guidance on post-market authorization efficacy studies. Overall we find the document clarifies situations under which such a study would be anticipated/ expected and provides useful information to help support adequate study design should such studies be conducted. However, we also recognize that in many jurisdictions globally certain types of post marketing trials do not require regulatory authority authorization and will not be	To clarify that the guidance refers to clinical trials conducted within the European Union, reference to ‘***In the EU***’ has been added to the text.

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	submitted to the regulator. For example in Canada, Health Canada doesn't need to be notified of clinical drug trials within approved label, although they must be done according to GCP. In the interest of global harmonization efforts, we request that clarification be added regarding applicability to clinical trials conducted within the jurisdiction of the EMA but which may fall outside regulatory requirements, particularly investigator initiated or academic studies. We would also like to suggest that clarification be added as to the applicability for independent ethics committees (institutional review boards, research ethics boards, etc.) during their evaluation of the proposed research.	Regarding the comment on Ethics Committees, this is considered addressed by the existing statement that "*All PAES should conform to applicable legislation and recognised international methodological and ethical standards for research.*"
3	AESGP overall appreciates this draft scientific guidance and believes that there is a fair balance given to the various study designs that can be used for generating post-authorisation efficacy data. We support the clear statements on the advantages and limitations of interventional and non-interventional clinical studies. Contrary to interventional clinical trials for which a wealth of ICH guidelines exist, there is limited guidance on non-interventional studies hence the reference to non-interventional studies is welcome but could be complemented by specific EMA guidance documents. The scope of the guideline would merit simplification and clarification – we would suggest referring simply to that described in “section 1.1 on legal basis and purpose” which corresponds to that of the delegated act. In our opinion, the specifications on quality management and quality assurance in non-interventional studies are reasonable. The same applies to the situations where a randomised trial is necessary and where a non-randomised trial is acceptable. Beyond this general appreciation, we would like to suggest some additional details on study design options and methodological options.	The comment on specific EMA guidance documents is noted but considered outside the scope of the present document.
4	The document is clear, concise, well written and avoids most methodologically controversial statements, which is a good thing as it keeps readers’ attention focused on the content. The lexicon used in some of the parts could be made more consistent with mainstream epidemiological lexicon.	General agreement

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5	BEUC welcomes the opportunity to comment on the EMA draft scientific guidance on post-authorisation efficacy studies. Post-authorisation efficacy studies (hereafter PAES) are very useful to complement already available efficacy data and to gain a better understanding of the efficacy of the medicine in real-life conditions. However the conduct of a PAES should not be considered as a sufficient reason to grant a marketing authorisation for a medicine whose efficacy has not been established yet. Article 21a (f) of Regulation 2001/83/EC as well as Article 9 (4) (c) of Regulation (EC) No. 726/2004 provide for the authorisation of medicine on the condition that additional evidence as to the efficacy of the product is provided after the authorisation by way of PAES in circumstances where concerns in regard to the efficacy, and in particular due to the product characteristics, can only be resolved after the authorisation. These provisions should be interpreted in the narrowest possible way in order to avoid shifting on consumers the risks of medicines whose efficacy is still not proven. Following the recent publication of a report1 from the US Government Accountability Office (GAO) which highlights the Food and Drug Administration (FDA) failure to properly monitor post-marketing studies, we think consumers need to be reassured that EMA has adequate resources to review post marketing studies (including PAES) and thoroughly assess the data and other information submitted to the Agency about the safety and the efficacy of medicines on the market. Most consumers are not fully aware of the regulatory approval process that a medicine follows before reaching pharmacies and hospitals and they trust regulators to ensure that the benefits of the medicines available on the market outweigh their risks. The scientific guidance document is mostly intended for marketing authorisation holders but it contains information that can be accessed also by the general public. In this context we suggest having a summary of the guidance document with a reader friendly language. EMA could also develop a question and answer document on the scientific guidance similar to the one developed for marketing authorisation holders but targeted to the general public (e.g. explaining why PAES are conducted).	The conduct of a PAES is not related to the early or premature granting of a marketing authorisation. The point is taken regarding. reader friendly language and will be addressed on the EMA website in any related press releases.

[1] http://www.gao.gov/products/GAO-16-192

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7	EFPIA welcome the development of scientific guidance on post-authorisation efficacy studies (PAES) and appreciate the pragmatic approach within the document. This is an important opportunity to achieve common interpretation on many key aspects of conducting research in this area and EFPIA would like to propose holding an EMA expert workshop with relevant stakeholders to support finalising the scientific guidance. Please note that input from the EFSPI working group on PAES has been incorporated into this EFPIA response. At start of the 'Introduction' (prior to 1.1 legal basis and purpose), an opening paragraph is needed to provide context on the broader scope of the scientific guideline beyond the specific mandated studies covered by the legal basis. Aspects to mention include the role and value of observational studies to address the broader aspects of efficacy evidence generation, observing the naturally prescribed population, link to GVP module for PASS studies and note that these are recommendations rather than requirements. Reference to specific existing definitions in the Clinical Trial Regulation and/or GVP modules should be included where appropriate. It is also suggested to swap the order of section 3 and 4 for readability. **Introduction/Legal basis** EFPIA recommends that the procedural/operational guidance in GVP VIII Post-Authorisation Safety Studies (PASS) be considered and adapted for separate procedural guidance for non-interventional (i.e. observational=non-experimental) PAES. PAES that meet the definition of clinical trial (experimental study) should follow requirements for such trials. In GVP VIII there is a general explanation, regarding "shall" and "should". A repeat/reference in the PAES guidance would be helpful. PAES are regulatory commitments that answer a specific scientific question following regulatory approval. Scientific Advice (which may optionally be EMA/HTA parallel advice – this should be reflected in 3, lines 73-375 and 396-397.) on PAES/PASS is recommended by EMA, however PAES should not be used to mandate studies that answer only to HTA questions. PAES may be used to answer similar scientific questions from HTA authorities. The guidance should allow for the opportunity to negotiate the study based on multi stakeholder discussions (e.g. HTA and patient bodies). In addition it should be permitted to collect data chosen by the MAH in addition to what CHMP requires.	An expert workshop is not planned for finalising the guidance. Agree. The introduction has been extensively re-worded and the legal basis moved to a new section. Detailed procedural guidance is considered outside the scope of the current scientific guide focussed on PAES but a link is included in Section 6 to the published Q & A on this 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. Also the text includes the statement that 'PAES…could also include additional

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	The importance of consistency in approach is in particular needed in situations where a given study is both a PASS and PAES. The use of GVP.VIII guidance should however not expand the number of mandated PAES, i.e. the scope of Delegated Regulation should be maintained. The link to Pharmacovigilance/GVP is important also with regard to benefit-risk evaluations (ICH E2C – should be listed in "Relevant guidance"). It would be useful to clarify what constitutes "scientific uncertainty" and lay down, if possible, some objective parameters (and/or thresholds) to describe such uncertainty so as to ensure that the imposition of PAES is not triggered indiscriminately by any new information about the disease or the medicinal product. This is also important in the context of the choice of the study design being driven by the scientific uncertainty to be addressed. **Structures and processes** It would be beneficial to address the opportunity for combining post-authorisation efficacy studies (PAES) and post-authorisation safety studies (PASS) into single study designs that aim to address both efficacy and safety uncertainties while promoting efficiencies in study logistics and time to complete. Although partially addressed in the associated Q&As provided, further clarity could be provided in the guidance on the governance and process for studies which do include assessment of both safety and efficacy; and in particular the involvement of the CHMP and PRAC. For studies that are being conducted to address only efficacy issues (and thus are considered to be PAES only studies), CHMP should retain oversight. **Scope** There is a need for better definition of the scope for this guidance, including principles expected to be applied to vaccines, orphan medicines, or different stage of the life cycle and different risk levels associated with the efficacy failures resulting in higher value of efficacy data in the benefit-risk ratio (OTC vs. HIV or Oncology drugs, mono-therapy vs. combination, etc.). The vaccines section should be expanded to address the specific situations for this product type (please refer to comments submitted by Vaccines Europe). Regarding biosimilars, these products are developed to be highly similar to their reference product and a comprehensive comparability package is provided as part of the submission. It is possible however that there may be an element of residual uncertainty to be addressed post-authorisation. For situations where	investigational arms and/or study cohorts, objectives, endpoints and /or analyses as proposed by the MAH and/or supported by the competent authorities e.g. data for health technology assessment purposes, provided this would not impact on the study integrity and the primary objectives of the study as defined in the condition of the MA.' This level of detail is outside the scope of the current scientific guide. This level of detail is considered outside the scope of the current scientific guide.

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	biosimilars are on the market, it also needs to be clarified if a PAES requested for the reference product would also be required for the biosimilar. The presented scope/definition - “Post-authorisation efficacy studies (PAES) of medicinal products are studies conducted within the authorised therapeutic indication to complement available efficacy data” (lines 3-4) - does not provide sufficient clarity on the scope of this Guideline. The introduction of “scientific uncertainty” as a legitimate trigger for PAES complicates this matter even further. Without a clearly defined scope this Guideline can potentially trigger increase in PAES requests without sufficient justification. It could be beneficial to establish a clear link between the need for PAES and the benefit-risk balance not being fully established, in case of the immediate post-approval commitments, or changed, in case of PAES required at later stages of the life cycle. The basis for requiring a PAES to “complement available efficacy data in light of well-reasoned uncertainties” seems vague. Something which is more directly linked to addressing gaps in the benefit-risk profile could be more precise.	This level of detail is considered outside the scope of the current scientific guide.
	Terminology Efficacy, effectiveness and effect need to be defined and used consistently in the document. Effect seems to cover both efficacy and effectiveness, but this need to be stated clearly. Alignment to the use of “Estimand” would be of an improvement as well. All terms above defines should be listed in the Keyword section. “risk-benefit” &” benefit-risk” is used almost on random. It is suggested to use ICH E2C: “benefit-risk” consistently.	‘Benefit-risk’ has been consistently used
	Study protocol: Central approval of studies It is important that the requirements make it possible to obtain approval of the protocol in all member states.	Requirements for e.g. trials are subject to relevant EU and national legislation.
	Study protocol: Data Collection / Sources Lines 196-198: "There are two main approaches for data collection. One is primary collection of data specifically for study. The other is to use data already collected for another purpose, e.g. as part of electronic records of patient health care (“secondary data collection”)” are not fully in alignment with the definitions of primary and secondary data collection used in the GVP Module VIII on PASS. Suggest using the GVP.VIII definition.	Agree. Text has been amended for consistency.

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	Study protocol: BIAS It could be valuable to remind the different type of biases related to observational studies and specify that the biases and measures set up to limit or control them should be discussed in the protocol and the CSR. Considerations on representativeness are not specific to registries and should also be discussed for explanatory, pragmatic trials and observational studies. It could be valuable to mention the possibility to have a comparator made up of several different treatments. **Format and content of the study protocol: Statistical/analytical elements of study design** The recommendations are very limited. It is suggested to adopt at minimum the level in GVP.VIII. It is appreciated that statistical analysis is under a continuous development and a very detailed guidance therefor risk becoming obsolete. At this point in time inferential statistics are limited for pragmatic trials and observational studies are more challenging to interpret. Considerations on sample size, power and multiplicity (type I, type II and type III errors) are missing and could be discussed in the guidance, where applicable (e.g. if hypothesis testing is intended and randomisation planned.) **Methods for post-authorisation studies: Observational PAES study types** Describe each major type of observational study that might be used for PAES (prospective cohort, Case control and case cohort if used) and provide strengths and weaknesses (biases). We recommend including examples. **Methods for post-authorisation studies: Observational study design & Outcome** Overall need to stress the value of observational study design and the importance of collecting outcomes. Observational studies important for understanding the prescribed population and understanding off-label use population comment in the section on outcome if an outcome is captured in usual practice or not. This potentially help designing the studies in a more efficient manner (i.e. less sample size) and reducing uncertainties. **Randomisation (for treatment) & Usual Practice** Studying usual practice using classical experimental clinical trial setup seems contradictory. As per the new EU Clinical Trial Regulations, a risk based approach (OECD - risk categories for clinical trials) is the basis for the clinical study types. In usual practice it is for example in UK permitted to	This is considered outside the scope of the current scientific guide which 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. This is level of detail is considered outside the scope of the current scientific guide. The

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	randomise but for treatment. With a PAS based on usual practice, within approved indication, the risk for the patients seems identical to what happened in usual practice i.e. it is as little experiment as how equipoise products are dispensed on “random” based on say reimbursement. A solution for randomisation of equipoise treatment followed by usual practise observational studies should be found. Till then patients could be randomisation within GCP setting (“low interventional trial”), just involving the randomisation, followed by an observational study setting. Studies involving randomisation are mainly those where there will be some comparison between groups. Indeed, as very well described later on in the PAES guidance, some of the question of primary interest may preclude the use of randomisation. Thus, it is important to re-emphasise that the question in hand is central and then the design follows. There is ambiguity/overlap in what constitutes and describes certain types of studies (e.g. observational, pragmatic, low interventional, large simple, explanatory and exploratory) and what characterizes their limitations, but also operational implications (e.g. consent, insurance, supply of medicine etc.). **General note:** It would be helpful throughout the document, where appropriate, if URLs could be inserted so that the reader could access the referenced document if needed/interested.	text has been amended in line with specific comments in the text below that are relevant. Agree.
10	In 1.1 it is stated that PAES are initiated by a MAH (either voluntarily or imposed). It is not clear how evidence provided from observational studies conducted by other entities (competent national bodies (e.g; UK, Denmark) academics, ECDC funded effectiveness networks etc.) will be taken into account for regulatory purposes (to simplify: based on scientific publications).	Evidence from all sources is used to monitor the benefit-risk profile of marketed drugs throughout the product life-cycle in various regulatory procedures. A PAES is conducted to address a well-reasoned specific research question to further inform on an aspect of the benefit.

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11	The stakeholder believes that the document would benefit from being restructured to provide more context earlier, followed by the "General methodological considerations for PAES". Many questions which arise from Sections 2 and 3 are addressed within Section 4. Proposal: Introduction; General guidance on the need for PAES; Scientific guidance on specific situations; General methodological considerations for PAES; Conduct of post-authorisation efficacy studies; Conclusions. Despite some text in the guideline that imposed PAES should be rare rather than routine, the occasions it lists for imposing PAES are many. Could the EMA comment on how on-going Registries / Prospective Phase IV trials will be handled. Will any changes/ updates be required? The stakeholder would appreciate information on how this proposal links and bridges to the Adaptive Pathway program and the expansion of patient populations and indications.	Agree. The document has been restructured to provide more context earlier. Linking to ongoing initiatives at EMA re registries and adaptive pathways is considered outside the scope of the current scientific guide.
12	The German Society for Phytotherapy (Gesellschaft für Phytotherapie, GPT; http://phytotherapy.org/de/) is engaged in scientific research and use of herbal medicinal products, i.e. for a scientifically based phytotherapy. GPT is member of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF). For centuries, phytotherapy has been used for the therapy of patients. In Germany, herbal medicinal products are available as authorized medicinal products or as registered traditional medicinal products (called "established herbal medicinal products" in the following). Like all other medicinal products they are covered by the basic principles of a rational, evidence-based medicine. The basic empirical evidence (bearing in mind the basic options of evidence, particularly its empirical part, as explained for instance by Sackett DJ in journals like Lancet, Br Med J, J R Soc Med, etc.) of a use for the treatment of patients partly for centuries has been falsified or verified within the most recent decades by systematic preclinical and clinical research, resulting in the existing marketing authorizations or registrations. However, for these established herbal medicinal products available as important option for treatment, further knowledge on efficacy and safety is desirable. The advantage in the development of established herbal medicinal products compared to new, not yet licensed medicinal products is the following: they can be clinically monitored under the terms of medical everyday practice. The representativeness of the results for efficacy and safety of such non-interventional studies (NIS) is much higher than the representativeness of the results of clinical studies, because they are close to the	General Agreement.

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	everyday practice of medical care. Knowledge on efficacy and safety gained from clinical as well as from non-interventional studies complement each other. Weaknesses of the respective other class of studies are compensated by own strengths. For future continuation of clinical research of established herbal medicinal products aiming at an increase of evidence, it is essential to maintain the diversity of options for gaining knowledge on efficacy and safety by interventional and non-interventional clinical studies and to acknowledge their results. The benefit and scientific acceptance of NIS-based knowledge on efficacy and safety of established herbal medicinal products has been proven in a number of positive decisions in marketing authorization procedures during the past decades. Against this background the GPT welcomes the Scientific guidance on PAES taking into account exactly this diversity and strengthening their acceptability by regulatory authorities in the member states of the European Union. The GPT suggests the following modifications for the draft dated 6 November 2015.	
13	The presentation of different situations that may justify the implementation of PAES is clear. Methodological considerations proposed in this paper are quite comprehensive and provides a broad overview of the different designs (interventional or observational) available to meet the demands of PAES. In this context, IPFA have no particular comments to share, this draft guideline promising to be quite useful.	General agreement
14	Paving the way to faster approvals but at what cost: EU pharmaceutical legislation provides that, as a general rule, before a medicine is authorised it has to undergo "extensive studies to ensure that it is safe, of high quality and effective for use in the target population". The requirement for the demonstration of solid evidence about benefits and harms before a medicine is approved protects patients' safety. It contributes to medical innovation by requiring companies to generate meaningful clinical data. During the discussions of the legislative proposals on pharmacovigilance, the European Parliament and the Council reiterated the need to ensure that “a strengthened system of pharmacovigilance does not lead to the premature granting of marketing authorisations”. Over the last 2 years, the European Medicines Agency has launched several initiatives that aim to change the interpretation of the current legal framework for market authorisations in the European Union (EU) and to promote faster approvals for “innovative” medicines in the EU. This concerted move is promoted under the guise of increasing access to patients, yet fails to address the	This is considered outside the scope of the current scientific guide. The need for PAES is separate to any concept or discussion on faster approval and is not linked to earlier granting of marketing authorisations.

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	underlying shortcomings of accelerated procedures and their over-reliance in post-marketing surveillance. Regulatory flexibilities for early market access should be applied only in fully justified circumstances, and must ensure patient safety and an advance as compared to best available treatment. To promote innovation in the pharmaceutical sector, the regulatory environment must send a clear signal to the pharmaceutical industry by setting the bar higher – and not lower as suggested – and demanding the delivery of relevant, comparative evidence of efficacy and safety. This includes providing scientific guidance that sets appropriate standards for the design, conduction and reporting of high-quality, useful and valid post-authorisation efficacy studies. Post-authorisation commitments are often not honoured: Years of experience also show that manufacturers fail to honour post-marketing commitments to provide missing data adding to concerns on patient safety. A frequent reason provided is that participants are too difficult to recruit. [i] [ii] [iii] Patients are less likely to participate in a clinical trial with all its constraints if the medicine is already available on the market. Also pharmaceutical companies have very little incentives to actually conduct post-marketing studies which could reveal that their drug is less effective or more harmful than initially presumed. According to a recent study on conditionally-approved drugs, the median time taken by companies to meet the specific obligations was four years (range 0.2 to 7.7) and there were delays or discrepancies in the fulfilment of obligations in more than one third of the authorisation procedures.[iv] In contrast to the approach proposed by the EMA in its consultation document, concrete measures to dissuade, penalties and sanctions should be applied to those marketing authorisation holders which do not comply with their obligations. The EMA must closely monitor marketing authorisation holders and apply sanctions in case of non-compliance (i.e. in the form of fines; revoking the conditional approval). Clearly, if a PAES is considered mandatory by the EMA, rigorous and proactive requirements must be ensured. In the EU, the new pharmacovigilance regulation explicitly allows drug regulatory authorities to withdraw marketing authorisations when pharmaceutical companies fail to conduct post-marketing studies. However, despite the results reported by Banzi et al 4, this provision has not been implemented till date. It is much more difficult for regulators to remove a drug from the market once it has been approved than to refuse approval in the first place. In the post-marketing scenario, even in the face of new evidence of higher risks or questionable efficacy, withdrawing drugs can be a lengthy and complicated process, often	

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	faced with opposition from patient groups.[v] [vi] According to an example from a US study, "this tension emerged (…) around bevacizumab, which was approved for the treatment of metastatic breast cancer on the basis of surrogate end points under the accelerated-approval pathway. When subsequent studies showed no increase in patient survival, withdrawing the indication took nearly a year and generated substantial opposition. Some insurers even still cover off-label use of the drug for this non–evidence-based purpose".[vii] The pre-market requirements for double-blind randomized controlled trials establish an indispensable level of scientific rigour that is often not present in the post-market period. The use of observational studies exploring national health services data has limitations and does not provide the required level of proof.[viii] Observational studies are of weaker quality than randomised clinical trials as differences in patient characteristics often affect outcomes; and there are fewer methodological standards. The scientific guidance under consultation suggests that observational studies and registers can be used to estimate the effectiveness of interventions. However, this is rarely true, particularly when the drugs being studies have very small effects. Observational studies are also more prone to confounders and can only be used to demonstrate causality in very limited situations. Randomisation reduces bias, produces a balanced comparison between treatment arms (drug being studies VS comparator) and enables a quantification of errors due to chance. Yet, as is mentioned throughout the document, randomisation can be difficult to achieve after authorisation. Therefore, the greater the evidence gap pre-approval, the greater is the need to rely on data that is less robust and coming from observational studies. In addition, the use of surrogate endpoints in PAES further decreases the reliability and usefulness of post-marketing efficacy data, making the matters worse. Use of surrogates: Surrogate endpoints do not guarantee that a drug will affect health status in a clinically meaningful way for patients. Nonetheless, they are commonly used, especially in expedited approval schemes.[ix]A study revealed that between 1995-2004 most cancer drugs were approved in Europe on the basis of surrogate endpoints such as ''tumour shrinkage [that] did not translate most of the time into significant survival benefit''.[x] Similarly, a recent US study revealed that the great majority of cancer drugs approved between 2008 and 2012 on the basis of surrogate endpoints (86%) had either unknown effects on overall survival or failed to show gains in survival. The authors concluded that most cancer drug	The section relevant to endpoints has been extensively amended.

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	approvals have not been shown to, or do not, improve clinically relevant endpoints.[xi] Transparency and Access to data: The EMA's transparency requirements are enshrined in the EU directive 200/83/EC which regulates pharmaceutical products, as well as in the EU freedom of information Regulation (Regulation 1049/2001)[xii] which governs public access to documents at European Union's institutions and agencies. The accountability and public scrutiny of Health Authorities' decisions are only possible when the public has access to both the body of evidence and the rationale on which decisions are based. However, the guidance document makes no mention to Regulation 1049/2001 and to the fact that under its provisions, European citizens are entitled to access any documents produced or received by European institutions, especially when an overriding public interest is at stake (article 2.3 of EC Regulation 1049/2001). This includes access to information about PAES studies. For more than 15 years, the EMA has failed to comply with a key measure of the European Freedom of Information Regulation (Regulation (EC) N°1049/2001), adopted in 2001: to set up a register of documents that it holds. This makes it very difficult for citizens to determine which document to request, leading to endless exchanges with the EMA before documentation is provided.	This is considered outside the scope of the current scientific guide.
15	In vaccines, we use the term "effectiveness", rather than efficacy, once the product is licensed and studied in general use.	While effectiveness is the term traditionally associated with study outside clinical trials, it may be that observational research can inform on aspects of efficacy in the context of PAES and benefit-risk.
16	H. Lundbeck A/S (Lundbeck) appreciates the opportunity given by the European Medicines Agency to comment upon this extremely relevant draft guidance for drug development and evidence generation in the context of medicines' lifecycle. Lundbeck believes that a clear scientific guidance on post-authorisation efficacy studies (PAES) will allow marketing authorisation holders to predict how to mitigate development uncertainties in the post-authorisation setting and how to optimise evidence generation plans to address questions related to effectiveness, outcomes and use in real world for other purposes (e.g. health technology assessment – HTA).Taking the above into account, it is absolutely key for Lundbeck that this	This is considered outside the scope of the current scientific guide.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	document is optimised to serve three key principles that impact how drug sponsors will plan and conduct PAES: • These PAES, being either required by the CHMP/PRAC or proactively proposed by the company throughout the regulatory assessment, should at best be aligned with HTA requirements in order to fit as possible effectiveness requirements relevant to further market access to patients in EU. For that, it is very important that EMA engages (and encourages sponsors to engage as well) in a proactive dialogue with partners such as HTA bodies and platforms such as the Registries Initiative by the CHMP in order to maximise how the evidence generated in through PAES satisfies requirements from multiple stakeholders benefiting patient access; • On the same note, drug development plans pre- and post-authorisation are nowadays a truly global activity. However, it still occurs that for the same medicine approved in major jurisdictions (e.g. US and EU) different post-authorisation requirements exist, making it sometimes a challenge to have a single PAES to satisfy both requirements. Even though this is a very subjective and case-dependent point, the fact that regulators from major ICH jurisdictions find different uncertainties and propose different solutions is a barrier to optimisation of a global lifecycle development; • The draft document is very rich in methodological considerations and this surely supports sponsors' expectations on how to conduct feasible PAES effectively. We would however like to call for a better alignment between how the uncertainties listed in the document and which types of studies can more effectively address each of them. For that it could be interesting to link each of the cases listed in Article 1 of the Delegated Regulation (EU) No 357/2014 with one or more methodology(ies) proposed in guideline's section 3. The underlying idea is to be able to predict which type of PAES would be required according to which type of uncertainty discussed during regulatory file development & review. • Finally, Lundbeck would like to ask clarification on which will be the level of public disclosure of the PAES (both imposed and proposed). Since PAES can be either interventional or non-interventional different levels of disclosure can be expected (e.g. registration in a public database for interventional studies) but it was not clear what EMA would disclose itself on these (e.g. disclosure in EPAR, CHMP/PRAC minutes, etc.). Both rationale for PAES requirements and study details should be considered in this question.	

Stakeholder number	General comment (if any)	Outcome (if applicable)
17	We support the need for a guideline concerning PAES that describes the circumstances in which this type of studies is required, and the methodological aspects that should be considered when designing PAES. However, the current draft guideline is very comprehensive and too detailed. We suggest to make a more compact and focused document, in order to provide clear guidance on the design and methodological considerations, including the feasibility of such a study. Regarding the design of the PAES, it is recommended to change the currently introduced classification of study designs and to use the distinction experimental vs non-experimental (or observational) studies. The guidance should further address the aspects of randomisation, blinding, generalisability of the results, the choice for control arms and methods to correct for confounding. Also, it should be made explicit that the overall aim and the design of the PAES should depend on the causal (pharmacotherapeutic) effect to be expected from the investigational product. Finally, in the discussion on the purpose and the design of the PAES, consideration should be given to involving the end user of the product, i.e. medical professionals and patients. Regarding Chapter 3 General methodological considerations for PAES, it may be questioned whether the current long introduction on different designs is necessary. It describes many general methodological principles, which are not necessarily specific for PAES (e.g. “the length of follow up should be sufficient and the events of interest should be detectable” (line 122)). Next, a distinction is made between explanatory and pragmatic trials, but we consider this reclassification of randomised clinical trials of limited value in the scope of PAES. In addition, the document does not describe the double-blind design nor the role of blinding, while these are very important aspects to consider when designing randomised clinical trials. Statements like “The choice of design will need careful justification taking account of the precise question for which an answer is wanted, the available evidence and the uncertainty” (line 274-276) are general statements and are recommended to be avoided. Alternatively, specific guidance should be provided to facilitate decision making on the trial design. Sentences are frequently very long, rather complex and the text contains a significant amount of jargon. It is proposed to break up sentences and to avoid the use of jargon where possible. Wherever possible, reference should be made to other sources (e.g. guidelines, guidance documents that describe methodological considerations). As the build-up of chapter 3 and 4 is different, we suggest aligning of the structure of the chapters and use of comparable subheadings.	The document has been restructured to provide more context earlier. More specific comments have also been addressed in response to specific comments on the text.

Stakeholder number	General comment (if any)	Outcome (if applicable)
19	Pfizer welcomes the guidance provided and overall considers that it provides a comprehensive and useful précis of the various approaches to evidence generation in the post approval space. It would be beneficial to address the opportunity for combining post-authorisation efficacy studies (PAES) and post-authorisation safety studies (PASS) into single study designs that aim to address both efficacy and safety uncertainties while promoting efficiencies in trial logistics and time to complete. Although partially addressed in the associated Q&As provided, further clarity could be provided in the guidance on the governance and process for studies which do include assessment of both safety and efficacy; and in particular the involvement of the PRAC. We consider that having PRAC review both PAES and PASS would be the efficient process. As stated in the title of this document, this is meant as a scientific guidance for PAES. However there are some operational requirements covered – e.g., public registration in lines 380-381. We would welcome comprehensive guidance on operational aspects of PAES – e.g. covering protocol formatting, review and approval requirements.	This is considered outside the scope of the current scientific guide. A link has been provided to the related procedural Q & A document.
20	All the partners of the REGenableMED project are aware of the existence of this draft guidance. We welcome the opportunity to review this scientific guidance on post-authorisation efficacy studies. Please find below general comments: Links between safety and efficacy follow- up: Could you please clarify whether they could be overlapping between efficacy and safety post- authorisation studies? Indeed, the previous or current guidelines on pharmacovigilance make clear the safety follow-up should be used as much as possible for the efficacy follow- up: - In Volume 9A (the reference until the availability of the respective new GVP modules), it appeared that that 'loss of efficacy' or 'less than expected efficacy' of a medicinal product used in life-threatening diseases was considered to be a safety issue. - In the EMA Guideline on safety and efficacy follow-up- risk management of advanced therapy medicinal products, 2008 (EMEA/149995/2008) provides: "For efficacy follow-up, the system that is or will be established for safety follow-up should be used as much as possible to save resources and increase the motivation of healthcare professionals that is the key to success of any such system. (…) The establishment of efficacy follow-up should only be considered in situations which require further study of the product's efficacy profile in the post-authorisation phase, and	This is considered outside the scope of the current scientific guide.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	when it is inappropriate to use the safety follow-up alone for this purpose." Although it is understandable that the new legal framework on pharmacovigilance distinguishes post-authorisation efficacy studies and post- authorisation safety studies, this guidance should clarify how the distinction is made or why there is no more necessity to consider such distinction. Link with adaptive licensing: The post- authorisation efficacy and safety studies should briefly be considered in the perspective of the pilot project on adaptive licensing. Link with guideline with ATMP: The links between this general guideline and the specific guideline for advanced therapy medicinal products (the EMA Guideline on safety and efficacy follow-up- risk management of advanced therapy medicinal products, 2008 (EMEA/149995/2008)) should be highlighted, especially regarding the potential contradiction between both texts regarding the maximum integration of efficacy follow- up within safety follow- up as explained above.	This is also considered outside scope. A reference to this guideline has been included.
21	Vaccines Europe (VE) notes well the general comment in section 4 that the requirement to conduct PAES will be rare rather than routine. In the case of vaccines for which large phase 3 efficacy studies were conducted prior to the initial MA, additional efficacy studies are not expected to provide substantial new efficacy information, whereas observational effectiveness/impact studies are needed. The conduct of post-authorisation studies using an effectiveness/impact study design is not a new concept for vaccines. Indeed, for prophylactic vaccines the concept of post-authorisation effectiveness studies existed well before the introduction of the new PV legislation, which formally introduced the concept of PAES. It is also important to note that some guidance on the type of studies that may be required for vaccines in the post-authorisation phase is currently already provided in the Committee for Medicinal Products for Human Use (CHMP) guideline on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/2005). Therefore and due to the vaccines specificities, Vaccines Europe proposes EMA to consider excluding prophylactic vaccines from the scope of this guidance. Vaccines Europe would propose that when the CHMP guideline on clinical development of new vaccines is revised additional guidance on PAES is included as appropriate.	Vaccines are within the scope of the Delegated Regulation. Text relating to vaccines has been amended in line with specific comments received.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	A main concern of Vaccines Europe is also that in the current draft guidance the feasibility aspect of conducting a PAES in the case of vaccines is not addressed and there seems to be insufficient recognition of the complex environment in which post-authorisation effectiveness studies for vaccines have to be conducted. Vaccines Europe would also like to point out that for vaccines PAES are mostly not clinical trials (generating efficacy data) but effectiveness studies, and this is not sufficiently reflected in the current draft guidance. Unlike for most medicinal products, there are specific aspects of conducting vaccine effectiveness studies that reflect both direct (vaccine-induced) and indirect (population-related) protection during routine use. Thus, for prophylactic vaccines, they provide practical "real world" data and a better estimate of the true protective efficacy of vaccination when introduced in the population under existing clinical practice conditions. Also, herd protection / indirect vaccine effects are difficult to be measured in efficacy trials. The tool to measure herd effects are post marketing effectiveness studies often part of nationwide disease surveillance. The herd effects can significantly contribute to the benefit of a vaccine, with documented additional disease reductions in the vaccinated and un-vaccinated age groups. Concerning clinical trials, it is also very important to note that for vaccines, there are specific limitations with regard to the possibility of conducting efficacy studies in the post-approval phase: • Incidences of vaccine preventable infectious disease are often very low (below 30 cases per 100,000 sometimes below 5 cases per 100,000 persons). In that case outcome randomised efficacy trials would result in study sizes above 100,000 subjects and are very challenging and sometimes not feasible. • When a vaccine is recommended in a country and a vaccine for the same disease is already on the market placebo controlled clinical trials are ethically not acceptable, as this may result in excluding a subpopulation from the national vaccination program. Furthermore comparing a new vaccine to an existing one in terms of relative efficacy may be highly challenging in terms of samples size. In addition, the confounding aspect of herd immunity will have to be taken into account. For vaccines, it should be noted that effectiveness studies most of the time require joint efforts by the industry and different governmental/research institutions to allow feasibility of the study. Therefore feasibility will depend on a large part on the possibility for industry to work with these governmental/research institutions. It is important to note that even if networks exist in countries that could be used to perform effectiveness studies, these may not necessarily agree to collaborate with	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	industry or provide access to data, which is an additional challenge to be taken into account. Most of the time the MAH will not have the ownership of the data. There will be a need to foster an environment of public-private partnership to be able to conduct such a study in a timely manner and not jeopardise access to vaccines. A good example of such complex situation is the current discussions on the monitoring of vaccine efficacy/effectiveness for influenza vaccines in a public private partnership. If vaccines remain under the scope of the guidance, this complexity should be reflected in the text. Nevertheless following on from the above stated views, Vaccines Europe would suggest excluding vaccines from the newly proposed guidance and include more specific guidance when the Guideline on clinical development of new vaccines is revised (EMEA/CHMP/VWP/164653/2005). The commission delegated regulation, the vaccine specific GVP and revised Guideline on clinical evaluation of vaccines would then provide together the guidance needed both for regulators and MAHs when PAES for vaccines are necessary. In the case EMA keeps prophylactic vaccines within the scope of the current proposed guidance on PAES, the vaccines specificities should be better addressed in all of the relevant sections as per the comments provided here below, and thus beyond section 4.5. as is currently the case. Vaccines Europe also noted that the terms efficacy and effectiveness are both used in the draft guidance without a proper definition of these terminology, and that there seems not to be a consistent approach in using either terms. As in the case of vaccines different interpretations can be given to the terms efficacy and effectiveness, Vaccines Europe deems it important that if vaccines remain under the scope of the guidance, specific phrasing should be included to clarify the meaning of these terms.	

2.2. Specific comments

2.2.1. Introduction

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
3 - 4	**7**	Comment: For observational studies, "in accordance with the terms of the marketing authorisation" may be a better term than "within the authorised therapeutic indication", in order to acknowledge the possibility of physician and patient influence on drug use in clinical practice. Proposed change (if any):'**in accordance with the terms of the marketing** authorisation'.	Do not agree. The issue being studies may not yet be reflected in the SmPC/marketing authorisation.
3 - 4	**9**	Comment: this is important, and maybe it is necessary to emphasize this definition, and maybe also to add what PAES aren't, e.g. not studies to obtain a marketing authorisation variation in order to add or enlarged the therapeutic indication. Proposed change (if any): 'Post-authorisation efficacy studies (PAES) of medicinal products are studies conducted within the authorised therapeutic indication. **They are not intended to enlarge the therapeutic indication or to add a new one**.'	Do not agree – this is implicit.
3 - 6	**7**	Comment: The Delegated Regulation addresses "well-reasoned scientific uncertainties" for imposed studies. Proposed change (if any): Suggest that the comment proposes more clarity for those situations not covered by the Delegated Regulation. Please provide examples of such uncertainties, how are they defined, who establishes such "uncertainties" within EMA? (CHMP, PRAC, Scientific Advice etc.).	Partially agree. Provision of examples of uncertainties and how they are defined is outside the scope of the present document however, the text has been amended to clarify how and when these uncertainties are identified with the addition of the statement '**identified by EU regulators'**.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
3 - 6	**17**	Comment: It may be emphasised here that PAES studies are not intended to resolve deficiencies in the clinical development plan.	Do not agree – this is implicit.
4, 45 - 46	**10**	Comment: For vaccines, studies might not be conducted within the authorised therapeutic indication. E.g. for HPV vaccines, efficacy against head and neck cancers could be an important endpoint. Last sentence in 4.2 line 289-290	Agree. Text has been amended to reflect the comment including reference to '**terms of the marketing authorisation".**
7 - 8	**9**	Comment: Regulation N (EU) No 536/2014 of the EU Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use states: Article 2, Definitions: (14) 'Sponsor' means an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial. Eurordis appreciates that for PAES, the sponsor of the study might be a different entity than the MAH, and this entity could initiate and manage the study, while the MAH would finance it. Therefore the definition of a sponsor for a PAES might differ from the definition above. The option of a third party to conduct the study could be made clearer. Proposed change (if any): 'A PAES may be initiated, managed or financed by a marketing authorisation holder (MAH) **or by a third party research organisation'**.	Do not agree with the proposed text change. While it is acknowledged that a third party may conduct a study, the scientific guidance is addressed to MAHs.
30	**7**	Comment: The guidance describes that a PAES may be imposed within the scope of the Delegated Regulation (EU) No 357/2014[2]. It is also specified that a PAES may be imposed outside the scope and list a few examples. Proposed change (if any): Clarification needed; What consequences this has in regards to a submission to PRAC. This is not really specified (in particular the operational consequences). PASS is categorised in 4 categories defined in GVP.V, and a similar situation is potentially to happen for a PAES – but this should somehow be mentioned.	These procedural aspects are considered outside the scope of the present scientific guidance.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
35	**21**	Comment: As explained in the general comments, Vaccines Europe suggests to exclude vaccines from this guidance. If adopted, the section on scope of the guidance should specify that vaccines are out of scope of this guidance. In case vaccines would remain in scope, VE proposes that the scope for vaccines is limited to imposed PAES only (RMP category 1 or 2).	Vaccines are within the scope of the Delegated Regulation (EU) No. 357/2014. The scientific principles in the guidance apply to imposed and non-imposed studies.
36	**16**	Comment: The document would improve by adding some statistical considerations with regard to choice of methods for causal effect estimation e.g. in situation of baseline confounding (observed / unobserved) and time-dependent confounding (observed / unobserved). Proposed change (if any): Please modify as above-stated.	Do not agree. Specific statistical considerations for causal effect estimation are outside the scope of this guidance.

2.2.2. General guidance on the need for PAES

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
43 - 57	**7**	Comment: It seems as a PAES, under some circumstances, potentially could be initiated to assess the clinical effectiveness of a risk minimization measures described/required in the RMP of a product. Proposed change (if any): If so, provide cross reference to the GVP modules on RMP and risk minimization.	Do not agree. Assessment of the effectiveness of risk minimisation measures is more within the scope of PASS and not PAES which are aimed at addressing scientific uncertainties on aspects of the evidence of benefits identified at the time of marketing authorisation or post-authorisation.
44 - 57	**17**	Comment: Different concepts are being merged in this paragraph: -PAES needed because of uncertainties in pre-authorisation data; -product benefit-risk profiling, better labelling and better use of medicines; -PAES as part of a planned strategy as in adaptive licensing. Proposed change (if any): In a PAES document, it should initially be clarified within which framework a PAES is to be done.	Partially agree. The text has been clarified to reflect the framework for the need for PAES at the time of initial marketing authorisation and post-authorisation if a change in understanding. PAES are not however part of a planned strategy around e.g. the timing of a marketing authorisation or in a clinical development programme.
4, 45 - 46	**10**	Comment: For vaccines, studies might not be conducted within the authorised therapeutic indication. E.g. for HPV vaccines, efficacy against head and neck cancers could be an important endpoint. Last sentence in 4.2 line 289-290.	Agree. Text has been amended.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
47	**7**	Comment: “a positive risk benefit” is inconsistent with previously used “a positive benefit risk balance”, which is a better wording. Proposed change (if any): Recommend to rephrase to “General practice is that to support a **positive benefit-risk balance** in an indication…”.	Agree. Text amended as proposed.
47	**4**	Comment: Risk-benefit is mentioned but the observation of harms is underdeveloped in the document, only making a cryptic appearance from line 246. This is very strange considering that assessment of harms is one of the key objectives of post marketing studies. Proposed change (if any): Develop the observations of arms throughout the document.	Partially agree. The focus of the current document is on benefit and the text has been amended to read ‘**benefit-risk balance**’ for consistency.
47 - 55	**5**	Comment: As mentioned in the general comments we suggest the guidance to further specify that PAES do not replace the conduct of ex-ante authorisation efficacy studies and that are only used to gather information where concerns in regard to the efficacy, and in particular due to the product characteristics, can only be resolved after the authorisation (or when the necessity to carry out PAES result from post-authorisation information, i.e. collected in a post-authorisation safety study ("PASS"), calling for additional confirmatory efficacy data).	Do not agree. This is implicit in the definition.
47 – 57	**7**	Comment: Section 2. has a long second paragraph which is important but hard to read. Proposed change (if any): Break up sentence starting in line 51 (“A PAES…) to make it more readable. Insert in line 47: “General practice is that **in order** to “ Insert in line 52: “scientific uncertainty **and** the” This is in keeping with the concept of life-cycle product benefit-risk profiling through targeted post-authorisation research that translates into better labelling and better use of medicines by patients and prescribers in clinical practice.	Agree. The proposed changes have been made and the text extensively revised.
47, 279	**21**	Comment: To be changed to “a positive benefit risk” (and not ‘risk benefit’).	Agree. Text amended as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
49	**14**	Comment: The text reads "*the demonstration of benefits therefore relies on persuasive and extensive data on the clinical outcome of interest*". The use of adjectives as persuasive and extensive is extremely vague and inappropriate to describe clinical data. Proposed change (if any): Replace persuasive and extensive by reliable and valid data.	Agree. Text amended by deletion of '~~*The demonstration of benefits therefore relies on persuasive and extensive data on the clinical outcome of interest or a validated surrogate in the patient population of interest.*~~'
50, 277-290	**14**	Comment: The document mentions "validated surrogates" as an established practice to support a positive harm-benefit balance in an indication. In the same way, the paragraph 4.2 (lines 277-290) considers surrogates to be a useful tool when they are considered to be sufficiently informative by the scientific/regulatory community. This is not acceptable. The use of surrogate endpoints warrants extreme caution. Hard outcomes should always be envisaged before licensing and PAES should not be used as a panacea to fix (after marketing) an inappropriate original drug trial design. The study cited by EMA by Svensson and Menkes (JAMA Intern Med, 2013) clearly states that only in very few exceptions (slowly progressing conditions without existing therapy or very rare diseases) the use of surrogate endpoints can be deemed reasonable. This article does not mention other potential examples as suggested by the EMA (such as complex or composite measurements or key secondary outcomes). Proposed change (if any): Remove the reference to validated surrogates.	Agree the whole line was deleted i.e. '~~*The demonstration of benefits therefore relies on persuasive and extensive data on the clinical outcome of interest or a validated surrogate in the patient population of interest.*~~'

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
51 - 57	**9**	Comment: during the scientific / regulatory discussion on whether or not a PAES if needed, it could be helpful to include patients at this stage for a better understanding of therapeutic efficacy and benefit-risk that is to be addressed post-authorisation, and even more if there is a potential to impact on the licensing status or product labelling. Proposed change (if any): to add '**Patients or their representatives can be invited to participate in the regulatory discussion on the relevance of a PAES and potential impact.**'	The point is well-taken but patient involvement is outside the scope of the current guideline.
55	**9**	Comment: The "authorisation" should be used, as provided for in the EU legislation on pharmaceuticals. It is not just a question of legality: the term "license" refers in fact to patent and intellectual property rights and here readers may be confused when the term "license" or "licensing" are used. Proposed change(if any): with the potential to impact on the '**authorisation** ~~licensing~~ status or product labelling'	Agree. Text amended as proposed.
55	**21**	Comment: There is the mention in lines 53-54 "… *for which a study can be designed and conducted." We believe that the feasibility assessment is indeed a critical factor that needs to be taken into account."* Proposed change (if any): We propose to add after line 55: ***'Prior to imposing the conduct of a PAES as post-approval commitment a feasibility assessment should be performed on whether such study can be designed and conducted.'***	We are reluctant to add the proposed text as a feasibility assessment as a formal step is open to interpretation and difficult to implement in practice and within timeframes for assessment.

2.2.3. General methodological considerations for PAES

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
58 - 250	**17**	Comment: Regarding the description of registries as a data source for PAES, it would be helpful to provide more guidance on which aspects need to be considered when registries are being suggested for PAES; issues such as the necessity of a disease-based registry rather than a product-based registry, type and quality of data to be gathered, registry (data) ownership, co-operation with regulatory authorities, accessibility of registry data, and privacy. We also suggest to refer to the EMA taskforce that is working on registries.	This level of detail on one study design is considered outside the scope of the present document.
59	**17**	Comment: The choice for the design of a PAES does not depend on the scientific uncertainty to be addressed, but on the causal (pharmacotherapeutic) effect to be expected from the investigational product. Proposed change (if any): Please, rephrase.	Agree. Text amended to clarify that the choice of study design will also depend on the particular medicinal product.
59, 73 - 75	**7**	Comment: While it cannot be argued that randomised studies have this advantage ("estimates of effects"), this statement sets high and potentially unrealistic expectations, considering the feasibility and acceptability of RCT for a marketed product is a main concern. The statement also contradicts the statement "The choice of study design will be based on the scientific uncertainty to be addressed." (Line 59). There is a need to clarify the situations related to the changes in the EU efficacy Guidelines for products which were approved based on the previous efficacy requirements. It could be helpful to make it clear that a change in a specific efficacy Guideline should not be seen as a trigger for a PAES. A scope for a new PAES request has to be limited to the actual changes to the risk benefit balance of the product. Proposed change (if any): Add on line 59: 'The choice of study design will be based on the scientific uncertainty to be addressed. **There will be scientific uncertainties that**	Agree but this acknowledgement that non-randomised studies may be the best approach is addressed in the existing wording that '*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.*' Also agreed to include a statement in the section on change in the understanding of the disease or

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		would be better addressed by non-randomised studies.'	drug to include the statement '**A change in a therapeutic efficacy guideline should not necessarily in itself be seen as a trigger for a PAES.**'
60 - 61	**9**	Comment: to help ensuring the study is feasible and ethically acceptable, it is important to consult with patients' representatives at scientific advice, if any, or via other consultation modalities. Proposed change (if any): '…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. **To achieve this, patients' representatives should be consulted.'**	Involvement of patients' representatives is considered outside the scope of the current guideline.
62	**16**	Comment: By "post-authorisation setting" do you refer to the participating physician's specialty (GP or specialist) or place of care (hospital or ambulatory) as well? The word "setting" is used throughout the document but may reflect different meanings. Proposed change (if any): Please clarify the meaning of "setting" if divergent throughout the document.	Agree. Text clarified to remove reference to 'setting'.
63	**7**	Comment: "Time" may also depend on uptake not just design".	Agree hence the reference to 'feasible' which will depend on a number of factors.
63	**5**	Comment: The time frame for the conduct of a PAES should be well defined. Proposed change (if any): 'The design should take particular account of the post-authorisation setting and be feasible to complete within ~~a reasonable~~ **the indicated** timeframe.'	Agree. Text amended as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
64 - 68	**9**	Comment: as national authorities could require comparison with medicines used off-label, this may be mentioned. Proposed change (if any): 'There may be circumstances in which a PAES imposed in accordance with Delegated Regulation (EU) No 357/2014 could also include additional investigational arms as proposed by the MAH and/or supported by the competent authorities e.g. data for health technology assessment purposes, provided this would not impact on the study integrity and the primary objectives of the study as defined in the condition of the MA**. In such circumstances, and depending on discussions with competent authorities, PAES might include a product used off-label as one or one of the comparators.'**	Do not agree that explicit reference to off-label use is needed here – the existing text allows for additional investigational arms as supported by competent authorities.
65	**7**	Proposed change (if any): "No 357/2014 could also include additional investigational arms and/or study cohorts, "objectives", "endpoints" and/or "analyses" as proposed by the MAH and/or" to allow for other circumstances, e.g. additional objectives are added to satisfy the requirements of an imposed PASS.	Agree. Text amended as proposed.
65	**19**	Comment: The phrase "…additional investigational arms …" indicates that only additional arms could be added under these circumstances. If this is the intention, we suggest adding "objectives", "endpoints" and "analyses" to allow for other circumstances, e.g. additional objectives are added to satisfy the requirements of an imposed PASS.	Agree. Text amended as proposed.
69	**3**	Comment: We appreciate the statement *"A PAES may be conducted as a randomised or non-randomised study"*. We suggest emphasising this by an additional clarification recommending that any of these study types should be accepted as evidence on efficacy by the EU Member States' regulatory authorities, however with further details on the strengths and limitations of each study type in lines 147-162 (chapter 3.2, therein our suggestion 3.2.4 c)).	Partially agree. The text was amended to include reference to interventional or non-interventional but acceptance as evidence of efficacy by regulators is considered as implicit in this.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): 'A PAES may be conducted as a randomised or non-randomised study, **as either interventional or non-interventional (such as observational) Such variety of study types should be accepted as evidence on efficacy by the EU Member States' regulatory authorities.'**	
69	**6**	Comment: We appreciate that a PAES may be conducted randomised or non-randomised (non-interventional=observational; and pragmatic trials). Nevertheless, we suggest to replace the word "may" by "should" to clarify that both of these study types should be accepted as evidence on efficacy by the EU member states' regulatory authorities. Proposed change (if any): A PAES ***should*** be conducted as a randomised or non-randomised ***(non-interventional)*** study.	Partially agree. The text was amended to include reference to interventional or non-interventional but acceptance as evidence of efficacy by regulators is considered as implicit in this.
69	**12**	Comment: We appreciate the statement "A PAES may be conducted as a randomised or non-randomised study". We suggest to emphasize this by an additional clarification which recommends that any of these study types should be accepted as evidence on efficacy by the EU member states' regulatory authorities, however, with further details on the strengths and limitations of each study type in lines 147-162 (chapter 3.2, therein our suggestion 3.2.4 c)). Proposed change (if any): 'A PAES may be conducted as a randomised or non-randomised study, **as either interventional or non-interventional (such as observational) study. Such variety of study types should be accepted as evidence on efficacy by the EU member states' regulatory authorities, however, with further details on the strengths and limitations of each study type in lines 147-162 (chapter 3.2).'**	Do not agree. As this is a scientific guidance the major distinction is considered to be between randomised/non-randomised. Acceptance as evidence of efficacy by regulators is considered as implicit in the existing text.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
69 - 72	**17**	Comment: Not clear what is meant by the sentence: "*Note, as this is a scientific guidance, terms such as randomised, non- randomised and observational 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."* Proposed change (if any): Please, clarify this sentence.	This sentence seeks to avoid confusion around terms that have specific scientific and legal interpretations.
69 - 72	**19**	Comment: If "… are used without prejudice to …" to mean that the terms "randomized", "non-randomized", and "observational" are not intended to align with interventional vs. NI, the subsequent section on observational studies seems confusing. This section essentially defines observational studies as studies with no randomization. However, per the Regulation, other criteria must be met for a NI designation – e.g., no additional monitoring/procedures. So theoretically, you could have an observational study per the PAES guidance that it not NI per the legal definition. We suggest that the same clinical study terminology given in the Regulation (i.e., interventional, low-interventional, and NI) are used in this PAES guidance.	Do not agree. This sentence seeks to avoid confusion around terms that have specific scientific and legal interpretations.
73	**8**	Comment: I tend to disagree with those statements. The choice of RCT or observational study primarily depends on the objective of the study. Besides, it should be emphasized that only observational study can study, in post marketing settings, actual drug use by patients (AND NOT standardized drug use as measured in the RCT).	This is considered addressed in the existing text where it is stated '*Nevertheless, in certain situations (see section 4.2) the conduct of comparative non-randomised studies, where measures are included to minimise limitations/ biases, could be justifiable in the PAES setting.*'

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
73 - 81	**12**	Comment: These lines are equitably balanced considerations on the necessity of randomisation or its dispensability in certain situations/circumstances.	General agreement.
73 - 75	**17**	Comment: The role of randomisation is to focus on one issue. Its role as a prerequisite for performing statistical inference is underemphasised. Proposed change (if any): Consider to add **'Randomisation provides the basis for standard methods of statistical analysis, i.e. statistical inference.'**	Agree. Text amended to reflect the role of randomisation.
74	**8**	Comment: Also, infrequent or delayed adverse events can be reasonably observed only in observational studies.	Agree but this is more applicable to post-authorisation safety studies.
75	**7**	Comment: Suggest "...expected to be more easily affected..." to acknowledge that randomized trials can also be affected by these biases, e.g. when randomization does not achieve total balance, and due to confounding post-baseline. Proposed change (if any): '**expected to be more easily affected'**.	Agree. Text amended to reflect the role of randomisation.
75 - 77	**17**	Comment: The following sentence can be formulated more clearly: "*This is because non-randomised studies, especially those comparing treatment with no treatment, may have a strong relationship between the decision to allocate a particular treatment and prognosis.".* Proposed change (if any): "*This is because a difference between treatment groups in non-randomised studies may be more a reflection of the process of allocation of subjects into treatment than of the actual treatment effect.".*	Agree. Text amended to reflect the role of randomisation.
76	**7**	Comment: "especially those comparing treatment with no treatment" Proposed change (if any): add "**or other comparator**"	Text amended in line with comment above.
77 - 79	**9**	Comment: not only results from non-randomised studies of efficacy are generally more difficult to interpret, but it usually take more time to obtain the information needed with non-randomised studies comparted to randomised ones, and the length of follow-up might be greater. This additional delay goes against the interests of patients.	Do not agree. Data from non-randomised studies might be already collected and results might be obtained more quickly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): 'It is widely acknowledged that results from non-randomised studies of efficacy are generally more difficult to interpret than those from similar studies of safety where confounding is likely to be less. **In addition, the time needed to obtain interpretable results from non-randomised studies might be longer**.'	
77 - 79	**17**	Comment: The following sentence does not seem to make sense: "*It is widely acknowledged that results from non-randomised studies of efficacy are generally more difficult to interpret than those from similar studies of safety where confounding is likely to be less.".* Proposed change (if any): Replace with: 'It is widely acknowledged that results from non-randomised studies of efficacy are generally more difficult to interpret than those from ~~similar~~ **randomised** studies of **efficacy** ~~safety~~ where confounding is likely to be less.'	Text amended in line with comment above.
78	**7**	Comment: Please provide a reference to the following statement:" It is widely acknowledged that results from non-randomised studies of efficacy are generally more difficult to interpret than those from similar studies of safety where confounding is likely to be less".	Text amended to remove reference to 'it is widely acknowledged' and statement now relates to new statement that '**Randomisation also provides the basis for standard methods of statistical analysis'**.
78 - 79	**19**	Comment: It would be helpful to add a reference or two to support this statement for those wanting to read further.	Text amended to remove reference to 'it is widely acknowledged' and statement now relates to new statement that '**Randomisation also provides the basis for standard methods of statistical analysis'**.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
79	**21**	Comment: We would like to clarify that in the case of vaccines a PAES will be most often an observational study like those referred to in line 150 (to obtain vaccine effectiveness estimates). Proposed change (if any): Replace lines 79-81 as from the word 'Nevertheless' by "*It is acknowledged that for certain medicinal products (like for example vaccines) the conduct of randomised trials might not generate the appropriate data and there may be additional value to conduct non-randomised studies to address scientific uncertainty that still exist to fully understand the product's benefit/risk profile and assess compliant vaccine use in real world settings. In these situations the conduct of non-randomised studies such as described under section 3.2, where measures are included to minimise limitations/biases, could be justifiable in a PAES setting*."	Agree. Text amended to read as follows: '*Nevertheless, **for certain medicinal products (e.g. vaccines) and** in certain situations (see section 4.2) the conduct of comparative non-randomised studies, where measures are included to minimise limitations/ biases, could be justifiable in the PAES setting'.*
79 - 81	**1**	Comment: ACRO welcomes and supports the flexibility that allows a PAES, when appropriate, to be of non-randomised design provided that measures are included to minimise limitations/biases.	General agreement.
80	**7**	Comment: Comparison between two groups is the driver for randomisation. Proposed change (if any): 'the conduct of non-randomised **comparative** studies'.	Agree. Text amended as proposed.
80 - 81	**14**	Comment: Non-randomized trials are considered of major importance in order to develop the adaptive pathways model. This document seems to be paving the way for the implementation of adaptive pathways, which is, at this stage only a pilot project, not an EMA policy.	Do not agree. This guidance has a specific legal mandate.
82	**17**	Comment: Without blinding, conclusions on efficacy may not be reliable. The role of blinding should not be underestimated in general and especially in conditions that rely on subjective reporting (e.g. pain, depression). Proposed change (if any): To add a section on blinding.	Agree. New statement added in line with the comment on blinding and subjective reporting.
84 - 145	**12**	Comment: These lines look fine and sufficient within the scope of the document.	General agreement

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
85-88	**9**	Comment: some products used off-label are sometimes part of the standard of care. Proposed change (if any): '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 should, as appropriate, be allocated to placebo (perhaps as 'add-on' to standard of care) and / or an established medicinal product of proven therapeutic value and any other design should be justified. **This might include a product used off-label.'**	Do not agree. This specific detail is considered outside the scope of the present document although the existing text allows for additional investigational arms as supported by competent authorities i.e. '*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.*'
85 - 88	**17**	Comment: "*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 should, as appropriate, be allocated to placebo (perhaps as 'add-on' to standard of care) and / or an established medicinal product of proven therapeutic value and any other design should be justified*". For an assessor this would be the crucial part of the guideline, and	Agree. Recommendation for scientific advice added.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		it should be stated more strongly. Proposed change (if any): This part can be more stressed, and this would be the place to encourage MAHs to ask for scientific advice about their PAES plans before starting the studies.	
85 - 88, 89 - 94	**7**	Comment: More logical order suggested Proposed change (if any): Consider switching the order to start with Line 89-94 which clarifies the role of these trials in PAES and then lines 85-89 which discusses their limitations and how to address them,	Agree. Text amended as proposed.
86	**14**	Comment: The text reads "*one or more control arms should, as appropriate, be allocated to placebo (perhaps as add-on to standard of care and/**or** an established medicinal product of proven therapeutic value*". Proposed change (if any): This sentence is unclear. There is no ethical or public health rationale to conduct a comparison of the medicine to be studied with placebo when an established medicinal product – standard of care – is available. The latter allows the assessment of therapeutic progress and should therefore be preferred.	Agree. Reference to placebo as comparison arm removed.
86 - 87	**5**	Comment: PAES should be run with standard care as a comparator when standard care exists. Proposed change (if any): One or more control arms should, as appropriate, be allocated to ~~**placebo (perhaps 87 as 'add-on' to standard of care) and / or**~~ an established medicinal product of proven therapeutic value and any other design should be justified.	Agree. Reference to placebo as comparison arm removed.
86 - 87	**10**	Comment: Standard of care (i.e. no care or for vaccines no prevention) is not an acceptable justification for placebo use as per Declaration of Helsinki (article 33), when serious conditions have to be prevented.	Agree. Reference to placebo as comparison arm removed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
86 - 87	**7**	Comment: The suggestion that "one or more control arms should, as appropriate, be allocated to placebo and/or an established medicinal product…" is absolute. The design of a study should be directly derived from the objectives, as stated in lines 89-94. It seems not to be realistic the situation where a product has been approved to run a clinical trial with a placebo arm. Recruitment could be tricky in that situation. Proposed change (if any): The need for a placebo arm should be strongly justified as the use of a placebo post approval raises potential ethical concerns and makes studies less feasible. Delete sentence starting line 86 or rewrite.	Agree. Reference to placebo as comparison arm removed.
86 - 87	**15**	Comment: It is considered unethical to give a placebo for an indication to which a licensed product is already available. Although it is mentioned, it appears uncommon. At least for vaccines, once recommended, it is an issue not to provide a vaccine.	Agree. Reference to placebo as comparison arm removed.
87	**7**	Comment: It would be helpful to clarify what is meant by "*as 'add-on' to standard of care"*	
87	**19**	Comment: It would be helpful if it is clarified what is meant by "as 'add-on' to standard of care".	Agree. Reference to placebo as comparison arm removed.
91	**14**	Proposed change (if any): Replace "It may be preferable to compare the medicinal product subject to PAES with that of an established medicinal product of proven therapeutic value", by "The medicinal product subject to PAES should be compared with an established medicinal product of proven therapeutic value; should this is not possible then it must be justified in detail".	Agree. The following was deleted '~~It may be preferable to compare the medicinal product subject to PAES with that of an established medicinal product of proven therapeutic value.~~'
91 - 92	**5**	Comment: PAES should run with an established medicinal product with proven therapeutic value and not with a placebo (whenever an established treatment exists) Proposed change (if any): ~~**It may be preferable to compare the**~~ medicinal product subject to PAES ***should be compared*** with that of an established medicinal product of proven therapeutic value.	Agree. The following was deleted '~~It may be preferable to compare the medicinal product subject to PAES with that of an established medicinal product of proven therapeutic value.~~'

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
95	**7**	Comment: It seems the recommendation is use of explanatory and pragmatic trial for PAES design. But observational studies can also able address certain efficacy question if confounders are measured accurately. In reality pragmatic trials can also be viewed as observational trial as many of the pragmatisms are driven by some effect modifiers (particular disease characteristics of the patients). Moreover given the complexity of the disease pragmatic trials can have more confounding effects than other designs. Especially properly chosen historical control can serve better comparison. In PAES setting observational studies may be ethical in most setting. With available modern statistical literature the challenges regarding indirect comparison and confounding can be handled.	Agree and the existing text allows for observational studies to potentially address certain efficacy questions if confounders are measured accurately to the extent that this is possible.
95	**3**	Comment: Cross-references to the following relevant ICH Efficacy guidelines E1 to E10 may be considered after line 95 – particularly E1, E4, E6, E8, E9 and E10. Proposed change (if any): Please add cross-references to the above-mentioned ICH guidelines.	These are included in the section on relevant guidelines.
95	**12**	Comment: After line 95 one may consider to cross-reference to the relevant ICH-guidelines (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000429.jsp&mid=WC0b01ac0580029590) E1 to E10, particularly E1, E4, E6, and E8 to E10. Proposed change (if any): Add such cross-reference to the relevant ICH-guidelines.	These are included in the section on relevant guidelines.
95	**15**	Comment: Explanatory" and "Pragmatic" Trials were made by inference. A more clear definition upfront, maybe with a bit of context, would be appreciated.	Partially agree. A definition was added for explanatory trials i.e. '**Explanatory trials generally measure the benefit of a treatment under ideal conditions to establish whether the**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			treatment works.' Pragmatic trials are considered sufficiently defined by the existing text.
96	**7**	Comment: One could consider an interim analysis in exploratory trial design. This may increase the appeal of this design from ethical point of view. Comment 2: It would be a possibility to include historical control information in exploratory trial setting. This can reduce the sample size (by means of unequal randomization) and increase feasibility of such a trial. This also supports ethical perspective when a drug is already known to be efficacious. So far historical control is only understood as observational trial in this guideline.	Both these points are considered a level of detail on considerations of the conduct of clinical trials in general that are outside the scope of the current guidance.
97-145	**7**	Comment: Some of the details and issues mentioned in 3.1.1-.3.1.2 subsections would seem to be relevant to both sections, and could be moved to 3.1 instead, with comments on differences in the subsections.	Agree. Text amended as proposed. Note the document has been restructured also.
97-162	**7**	Comment: In addition to the current discussions regarding confounding and other biases for trials and observational studies. Proposed change (if any): It would be helpful to add some statement regarding being aware of selection bias: 1) during follow-up (for randomised and non-randomised studies) as well as 2) at baseline (for observational, non-randomised studies – as randomised studies/trials)."	Do not agree. This level of detail is outside the scope of the current guidance.
99, 108 - 145, 329-332	**14**	Comment: Exploratory trials are defined as those where control of systematic errors is enabled through randomisation, blinding and allocation concealment. It seems that pragmatic trials cannot apply these standards, while in fact they can (and should).It is true that external validity of explanatory trials may be limited and pragmatic trials can add useful information in a post-authorisation scenario. But this cannot be a reason to lower standards in the first approval or to base approvals mainly in non-explanatory trials.	Do not agree. There is an existing statement that '*Robust randomisation processes with allocation concealment should be used as per explanatory trials*.'

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Correct text to also include that pragmatic trials can and should also be controlled for systematic errors through randomisation, blinding and allocation concealment.	
104, 114-116	**7**	Comment: Please clarify what is meant by "…where a need for tight control of heterogeneity is foreseen". It reads as in explanatory trials, the study population is selected in a way to avoid heterogeneity of the effect. Furthermore, this seems to be contradictory to the statement in lines 114-116: "For example, some elements (inclusion of a broad patient population or those with higher baseline risks) of explanatory trials could be made more pragmatic without relaxing all of the design parameters associated with the most explanatory type of trials." Proposed change (if any): "For example, some elements of explanatory trials could be made more pragmatic (such as inclusion of a broad patient population or those with various baseline risks) without relaxing all …"	Agree. Text amended to clarify.
104, 114 - 116	**19**	Comment: What is meant by "…where a need for tight control of heterogeneity is foreseen"? Does this mean that in explanatory trials, the study population is selected in a way to avoid heterogeneity of the effect? Or that if heterogeneity in the real world is anticipated, subgroups should be built into the protocol so that heterogeneity can be characterized explicitly? It seems to be the former, but the language is unclear. Furthermore, this seems to be contradictory to the statement in lines 114-116: "For example, some elements (inclusion of a broad patient population or those with higher baseline risks) of explanatory trials could be made more pragmatic without relaxing all of the design parameters associated with the most explanatory type of trials." We suggest revising to: "For example, some elements of explanatory trials could be made more pragmatic (such as inclusion of a broad patient population or those with various baseline risks) without relaxing all …".	Agree. Text amended to clarify. Also text amended as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
107	**17**	Comment: The section on pragmatic trials is too long. Proposed change (if any): Be referred to the general comments section for the proposal to change the setup of the study design paragraphs.	Agree. These sections have been amended.
108	**7**	Comment: Good definition of pragmatic trials. It may be worth commenting on some new pragmatic trial type study designs. It could be specified that pragmatic trials are expected to have a high degree of external validity Proposed change (if any): The definition of pragmatic trials should have been commented in line 69. The “cohort multiple randomised controlled trial” design (BMJ 2010; 340:c1066), should be commented to the extent this would be relevant for the intended guidance. Reference to a table that would describe the design types and their usual applicability, vulnerability to types of bias and confounding, statistical (analytical) and operational implications would help	Do not agree. This level of detail is outside the scope of the current guidance.
110	**7**	Comment: “Minimal restrictions may be placed on modifying dose, dosing regimens, co-therapies or co-morbidities or treatment switching.” Proposed change (if any): “Minimal or no restrictions may be placed on modifying dose, dosing regimens, co-therapies or co-morbidities or treatment switching.”	Agree. Text amended.
112	**7**	Comment: There is a spectrum between explanatory and pragmatic studies and they may not be that different. Both study types are however dependent on randomization. Proposed change (if any): This discussion seems academic and could probably be reduced to a few key points and made less narrative. Suggest inserting lines 139-145 before line 112 to explain the use of pragmatic trials for the PAES setting.	Agree. Text moved.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
112 - 114	**19**	Comment: We suggest simplifying the statement, as it is not very clear. Proposed change (if any): As the justification of each trial design feature 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.	Agree. Text amended.
112 - 118	**1**	Comment: ACRO welcomes and supports the flexibility that will allow for some elements of explanatory trial design to be made more pragmatic, when appropriate, without relaxing all of the design parameters associated with explanatory type trials.	General agreement.
112 - 118	**17**	Comment and proposed change: These lines concern both explanatory and pragmatic trials and should therefore be included in section 3.1 instead of 3.1.2.	Agree. Text amended.
114 - 116	**7**	Comment: “For example, some elements (inclusion of a broad patient population or those with higher baseline risks) of explanatory trials could be made more pragmatic without relaxing all of the design parameters associated with the most explanatory type of trials.” Proposed change (if any): ‘For example, some elements ~~(inclusion of a broad patient population or those with higher baseline risks)~~ of explanatory trials could be made more pragmatic **(for example inclusion of a broad patient population and less intensive patient monitoring)** without relaxing all of the design parameters associated with ~~the most~~ explanatory ~~type of~~ trials.’	Do not agree. Recommendations on patient monitoring are considered outside the scope of the current guidance.
114 - 116	**17**	Comment: "*For example, some elements (inclusion of a broad patient population or those with higher baseline risks) of explanatory trials could be made more pragmatic without relaxing all of the design parameters associated with the most explanatory type of trials.*" Proposed change (if any): "*Inclusion of a broad patient population*" would rather be an element of pragmatic trials.	Agree. Text modified to clarify that these elements reflect a pragmatic approach.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
116 - 118	**7**	Comment: Given that these designs have been less commonly encountered for regulatory purposes, please find below the proposed change. Addition of an explicit reference to the guideline would also be helpful. Proposed change (if any): It is important to provide clear definitions of key terminology, pros and cons of study design options as well as the challenges and pitfalls compared to traditional trial designs.	Agree. Text amended as proposed.
118	**21**	Comment: It is important to note that for vaccines, there are very few precedents of pragmatic trials (using cluster-randomised or stepped-wedged designs), because of the complexity of the implementation with very high sample size and long duration. Therefore the feasibility assessment prior to imposing such study on the vaccine manufacturers will be critical.	Agree. Statement added to this effect.
119 - 121	**17**	Comment: Sentence not clear – "*From a regulatory perspective, a number of methodological issues are highlighted given that these designs have been less commonly encountered for regulatory purposes: robust randomisation processes with allocation concealment should be used as per explanatory trial.".* Proposed change (if any): Clarify which are THESE designs?	Agree. The text has been amended.
122	**8**	Comment: This is the interest of observational studies as RCT cannot be performed over too long periods. In addition to delayed adverse events, RCTs are not well designed to detect infrequent adverse effects	Agree. The term 'events' has been replaced with 'endpoints' to avoid confusion.
122 - 123	**7**	Comment: Considerations on biases resulting from outcome assessment not masked to the treatment allocation are not specific to pragmatic trial and could also apply to explanatory trials. Proposed change (if any): please add general respective statement to a table proposed characterising trial types.	Do not agree. The scope of this guidance is not to replicate general methods.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
123 - 124	**7**	Comment: Suggest clarifying text Proposed change (if any): "Consequently, outcomes that **can be robustly measured in the presence of knowledge of the intervention received** ~~can be established to be accurate independent of the investigator or patients~~ are useful."	Agree. Text amended as proposed.
123 - 125, 135 - 138	**7**	Comment: The text in both sections addresses the appropriate selection of outcomes and would read well together. Proposed change (if any): The text sections are brought together in the text.	Agree. Text amended as proposed.
125	**7**	Comment: Management of treatment discontinuations could also apply to explanatory trials. Please clarify if the term 'Estimand' be introduced here is in anticipation of the ICH E9 addendum on Estimands. Proposed change (if any): This should not solely be discussed for this type of trial Proposed change (if any): "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 or use of rescue medications."	Do not agree to introduce the term 'estimand' at this stage. Agree. Text amended as proposed.
125	**19**	Comment: Should the term 'estimand' be introduced here in anticipation of the ICHE9 addendum on Estimands? This is effectively what is being described in this section.	Do not agree to introduce the term 'estimand' at this stage.
127-129	**7**	Comment: The two sentences seem to contradict each other as one is for no difference and the other refers to power (i.e. sensitive") to detect differences. Proposed change (if any): Suggest revising or deleting 125-129.	Agree. Text deleted as proposed.
128	**7**	Comment: Word missing Proposed change (if any): "...the interpretation of findings should take into account the level of noise and variability."	Text deleted.
130-131	**7**	Comment: "Investigators should therefore report quality metrics i.e. measures quantifying the control mechanisms and the extent to which they were relaxed". Proposed change (if any): Please clarify on what is meant by "control mechanism"... e.g. statistical control or operational control of the protocol.	Agree text clarified to refer to operational control of the protocol.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
135-137	**7**	Comment: ", as pragmatic trials tend not to do confirmatory tests" Seems to be an over-generalisation to state that pragmatic trials tend not to use confirmatory tests. Observational studies use confirmatory tests. Proposed change (if any): It should be clarified that whenever randomisation to treatment is performed in pragmatic trials, hypotheses testing for comparison of treatments should be possible and then as reliable as with RCTs. Alternatively explain why there would not be a role for confirmatory testing in a pragmatic trial. The above is different from the classical observational setting, where lack of randomisation is combined with potential unmeasured confounding, and estimate reliability dependent on the size of it. And please clarify "diagnostic approach to an indication".	Agree. Text clarified to include '**As randomisation to treatment is performed in pragmatic trials, hypotheses testing for comparison of treatments should be possible'**.
136	**16**	Comment: Given the broad definition of pragmatic trials, statistical tests will be performed to address objectives in some trials - how are the objectives otherwise to be evaluated? Please clarify what is meant by 'as pragmatic trials tend not to do confirmatory tests'. Proposed change (if any): Please clarify.	Agree. This statement has been deleted.
138	**7**	Comment: Please clarify "checking the demographic characteristics" regarding what it should be compared to. Additionally please clarify the impact if patients are selective (by definition for enrolment in a trial - even pragmatic) as this would not negate the internal validity.	Agree. Text amended to clarify including that the impact is on external validity.
139	**21**	Comment: The guidance states: *"For the PAES setting, pragmatic trials may be used in situations where there is a need to explore whether the intervention is used in the same way in the real-world setting as in the pivotal trials".* However the guidance also requires randomization, which would not fit with this objective. Assuming pragmatic trials are not observational studies and would by definition still involve treatment allocation per protocol (please refer to line 121), then the objective mentioned here	Agree. The text amended to reflect the comment regarding the the use of the intervention in settings that are less restricted than the pivotal trials.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		(i.e.*" to explore whether the intervention is used in the same way in the real-world setting")* is best assessed through an observational design. See also comments line number 118.	
139-140	**7**	Comment: Assessment of mere difference in usage can be done by a single arm study, looking at the pattern of care (usage) in routine clinical practice. Usage that will later be compared to what was considered in the registration RCT. So a traditional 'pragmatic trial' may not be needed. While if the objective is also to access its potential effect on the reported efficacy, which may be the case. Proposed change (if any): Add '... **and whether that difference in usage (if any), affects the reported efficacy of the intervention**.'.	Agree. Text amended as proposed.
139-142	**7**	Comment: Pragmatic trials are not designed to explore how drugs are actually used. Pivotal trial (like within diabetes) uses a treat to target approach with more frequent assessments and safety follow-up (as required by HA) than what is used in usual practices. Hence the intervention is not used in the same way as in a real world setting. Proposed change (if any): Delete line 139-142 or exemplify the need.	Agree. The text has been amended in light of similar comments on real-world use.
140	**7**	Comment: "real world" – pragmatic trials are more "real world" than clinical trials but less so than a true observational setting. If "use" and "adherence" to the intervention is the question, it would be better to do a utilization study and not a Pragmatic trial. When a study is not blinded to treatment, post randomisation selective drop out may occur- and it can be assumed that pragmatic trials are more vulnerable to this... Potential for this should be addressed in the statistical plan- e.g. in the context of estimand approaches.	Agree. The text has been amended in light of similar comments on real-world use.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
141-142	**7**	Comment: "....where there are concerns about whether trial results translate into this setting or where non-adherence to treatment could be an issue…" Proposed change (if any): "… an issue **or where co-morbidities present and co-medications used in the real world could have an impact on the efficacy of the medicine**".	Agree. Text amended in line with comment.
143	**19**	Comment: "Such trials" is used to begin the sentence but it is not specifically clear if "Pragmatic trials" is the intent. Proposed change (if any): Assuming pragmatic trials is the intention, we suggest modifying sentence to read: Pragmatic trials may also be sued if the comparator…	Agree. Text amended as proposed.
143-145	**7**	Comment: It is not clear why a pragmatic trial applies to usual care, since an explanatory trial could also include usual care as a treatment arm. Given the statement about trial continuum in lines 112-113, it is suggested that the first part of this sentence might be reworded. The sentence also suggests pragmatic trails may be used if randomisation (as opposed to non-randomisation) is needed to answer a particular question. This example may be confusing, as one might expect an explanatory trial to be used if randomisation (as opposed to non-randomisation) is needed, unless it is also stated that some level of observational follow-up is also intended. Proposed change (if any): "Such trials may also be ~~used~~ appropriate if the comparator is usual care (if not, a~~n~~ **more** explanatory **type of** trial ~~is needed~~ **may be more appropriate**)" ~~or if randomisation (as opposed to non-randomisation) is needed to answer a particular question or if strong modifying effects are anticipated~~. **For the PAES setting, pragmatic trials may be used in situations in which randomisation is needed, and where there is a need to explore whether the intervention is used in the same way in the real-world setting as in the pivotal trials or where there are concerns about whether trial results translate into this setting or where non-adherence to treatment could be an issue."**	Agree. The text has been extensively revised also in light of other comments.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
143 - 145	**19**	Comment: The statement suggests pragmatic trials may be used if randomisation (as opposed to non-randomisation) is needed to answer a particular question. This example may be confusing, as one might expect an explanatory trial to be used if randomisation (as opposed to non-randomisation) is needed, unless it is also stated that some level of observational follow-up is also intended. Proposed change (if any): Suggest removing "randomisation (as opposed to non-randomisation)" from the statement and further adding it to lines 139-142 as follows: "For the PAES setting, pragmatic trials may be used in situations in which randomisation is needed, and where there is a need to explore whether the intervention is used in the same way in the real-world setting as in the pivotal trials or where there are concerns about whether trial results translate into this setting or where non-adherence to treatment could be an issue."	Agree. The text has been extensively revised also in light of other comments.
146	**6**	Comment: A clarification should be added to the title of this chapter. In the European legal framework of clinical research, observational studies have usually been named "non-interventional studies". In contrast, scientific publications often use the name "observational studies". Proposed change (if any): "3.2 Observational ***(=non-interventional)*** studies"	Do not agree. As this is a scientific guidance terms are used without prejudice to definitions that may be applied in legal or other settings.
146	**3**	Comment: Clarification should be added to the title of this chapter. In the European legal framework of clinical research, observational studies have usually been named "non-interventional studies" throughout the more recent years. In contrast, scientific publications often use the name "observational studies". Proposed change (if any): "3.2 Observational **(=non-interventional**) studies"	Do not agree. As this is a scientific guidance terms are used without prejudice to definitions that may be applied in legal or other settings.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
146	**12**	Comment: Here a clarification should be added to the title of this chapter. In the European legal framework of clinical research, observational studies have usually been named “non-interventional studies” throughout the more recent years. In contrast, scientific publications often use the name “observational studies”. Proposed change (if any): “3.2 Observational (=non-interventional) studies”	Do not agree. As this is a scientific guidance terms are used without prejudice to definitions that may be applied in legal or other settings.
146	**14**	Comment: Observational studies have been widely promoted by drug companies in primary care as a promotional technique to increase prescriptions of new products among physicians (seeding trials). These types of studies should not be contemplated or considered appropriate as PAES.	The situations in which observational studies may be considered for PAES are defined in the existing text.
146-245	**7**	Comment: In the discussion of Secondary Data Analysis Studies to PAES, both the strengths and weaknesses of this approach should be discussed. Control of confounding and bias is especially difficult in this type of studies and is not specifically addressed in this document. This would be key for regulatory submissions. Proposed change (if any): Revise section: Describe each major type of observational study that might be used for PAES (prospective cohort, Case control and case cohort if used) and provide strengths and weaknesses (biases).	Partially agree. The scope of this guidance is not to replicate general methods. However a statement was added that ‘**Control of confounding and bias is, however, especially difficult in this type of studies.**’
147-149	**7**	Comment: “Non-randomised studies” is used as a synonym of “observational studies” (title of the section). Per UK guidance for example, one can randomise in usual practice but for treatment. Proposed change (if any): Add “Non-Randomised **(for treatment)** studies.” Please ad a reference and stronger justification for the proposed situations under which “Non-randomised studies” may be considered for investigating benefits” be provided. Suggest to clarify which outcomes are considered highly predictable (please give specific examples) and to clarify what is considered very large effect size studies (since these designs can have more noise than randomized studies). In some circumstances the very	Agree. Text amended as proposed to clarify non-randomised ‘for treatment’ studies. The addition of specific examples is considered too detailed for the current guidance. The reference cited was deleted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		large sample size that can be obtained by using large electronic databases can often be an advantage and for very rare outcomes this may be the most appropriate design. Highly predictable outcome and very large effect size are not reflected in the cited reference (Black, 1996).	
147 - 150	**17**	Comment: One of the reasons for an observational trial can be that "*outcomes are … far in the future*". This is in contradiction with the remark in line 62-63: *"The design should … be feasible to complete within a reasonable timeframe".* This is a general reason for conducting an observational trial, but it is not clear when this would be a reason for a PAES obligation. Proposed change (if any): Remove "*far in the future*" or explain when this is applicable.	Agree. Reference to 'far in the future' deleted.
147 - 162	**7**	Comment: Observational studies may be designed to describe outcomes in a cohort of patients treated, without any comparison. Such design has obviously some weaknesses but is not at all considered in these guidelines. We believe that the sample size calculation may be based on the precision around the expected change of outcomes measures and be reasonably justified.	The existing text allows for the possibility for observational studies to be designed without any comparative treatment.
147 - 162	**12**	Comment: Additionally to the existing lines, we would like to encourage adding more details at the end of this chapter by copying text from the chapter 1 to 15 from the publication by Sickmüller et al in the Regulatory Affairs Journal (2004, pages 247-250). The reason for this is that interventional clinical trials are well guided by the existing set of EMA-adopted ICH-guidelines, whereas detailed EMA-guidance on non-interventional studies is missing. Thus, the current scientific guidance may state some general details for the latter type of studies. Proposed change (if any): Addition of the sub-chapters 1 to 15 from the publication by Sickmüller et al in the Regulatory Affairs Journal (2004, pages 247-250) with modifications where necessary to accord with the current nomenclature in the EU-legislation framework:	The addition of more detailed guidance is considered outside of the scope of the current guidance which is not intended to replicate general methods.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		"Observational studies (non-interventional studies) are expressly exempted from the scope of the directives on good clinical practice. Therefore it is necessary to have a uniform definition of observational studies and the objectives that can be reached with this instrument. The following statements are intended to specify the term 'observational study', taking into account national and international proposals/ rulings, and to give recommendations for the planning, implementation and evaluation of such studies. 3.2.1 Definition: Observational studies are intended to gather findings in the use of marketable medicinal products. Their special feature is that they do not influence, as far as possible, the physician in charge of the treatment in his diagnosis or choice and implementation of therapy for the individual case. The aim is to observe therapeutic measures under the conditions of routine use of a medicinal product by physician and patient (in the context of these recommendations this comprises also healthy persons, e.g. in observational studies of vaccinations). Observational studies can be designed without a control group, i.e. product-oriented, or with two or more control groups, i.e. indication-oriented. They are conducted with commercial products. Observational studies are not clinical trials pursuant to Directive 2001/83/EC. Where certain specifications regarding indication are made, they must comply with the authorized indication. 3.2.2 General requirements to observational studies (= non-interventional studies, NIS): Observational studies (NIS) require planning, implementation, evaluation and assessment according to the state of the art in the relevant disciplines. They must pursue a medical-scientific objective (Section 4) formulated beforehand as a precise question. The chosen design (basis for comparison, time frame and scope of examination of the individual patient, number of patients) and planned methods (data	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		collection and evaluation) must allow this question to be answered. Observational studies are prospective, possibly with a retrospective starting date, and analogous to cohort studies in design and implementation. Also, they can be based on existing pharma-epidemiological data suitable for the given purpose. 3.2.3 Methodological character of observational studies (NIS): Observational studies (NIS) are one of several methodological instruments to gather information about medicinal products available on the market. Other instruments of post-marketing therapeutic research are clinical trials of Phase IV as well as case control studies, cross-sectional studies, correlation studies with aggregated data, evaluation of registers and spontaneous reporting systems. The choice of the suitable instrument is determined by the objective of the observations. Therefore, it must be substantiated for a given question that the chosen instrument is methodologically adequate, informative and efficient (number of patients) to answer the question. 3.2.4 Objectives of observational studies (NIS): Possible objectives of observational studies are: a) gathering information about prescription behaviour and prescription habits, compliance with summaries of product characteristics (SPCs) and product information leaflets (PILs), acceptance and general compliance, practicability, implementation of conditions imposed together with the authorization, etc.; b) gathering further data on known adverse reactions (ADRs) in routine use (e.g. verification of expected ADRs, frequency assessments, interactions); gathering data on previously unknown and particularly rare ADRs and interactions; and c) gathering further data on efficacy (e.g. under routine use conditions; in groups not included in clinical trials, in subgroups; to characterise non-responders; etc.). Proof of efficacy cannot be furnished by observational studies alone, apart from specially justified exceptional cases*.	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		* In cases of well-established medicinal products where reproducibly documented comprehensive and empirical knowledge is available, carefully planned observational studies can lead to the acceptance of statements on indications. In special cases where no clinical trials can be conducted, it must be decided on a case-by-case basis whether results from observational studies may be used. 3.2.5 Non-intervention: Non-intervention in the framework of observational studies refers to the fact that no stipulations specific to these studies are made to the physician in charge of the treatment as to: a) whether to use medicinal products in the therapy at all or which products to use; b) what the modalities of the therapy are (dosage, route of administration); and c) the circumstances in which the therapy must be discontinued or changed. A medicinal product must not be prescribed for the purpose of including a patient in an observational study. Prescription of a product and inclusion of a patient in an observational study are two aspects to be viewed separately from each other. This separation is achieved, for example, when the patient is only identified for the study after the decision on the therapy had been made. However, the systematic observation necessary to gather new scientific insight presupposes additional requirements to the collection of data, type and extent of documentation and their control. Depending on the findings to be gained, stipulations to the attending physician are inevitable to achieve a sufficient observational balance and an adequate quality and completeness of the collected data. A study-required systematisation of the documentation of therapy-required (i.e. also commonly study independent) procedures by using questionnaires (e.g. Kupperman Index, MRS, PASI, CGI, etc.) does not represent an additional observation or an intervention. Also questionnaires that promote physician-patient dialogue (e.g. MRS-II or other self-disclosure questionnaires, classical	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		anamnesis questionnaires, treatment diaries, etc.) do not represent an additional observation or an intervention. In contrast, a distinction must be made for questionnaires intervening with therapy (e.g. structured interviews intended to be used as therapy) if their intended usage exceeds the common medical practice in the observed patient-clientele. The latter type of questionnaires constitutes a study-related intervention. 3.2.6 Different forms of observational studies (NIS): Different objectives (4a - 4c) call for different designs and forms of observational studies. As a matter of principle, a differentiation must be made here between case series and single and multi-arm cohort studies. Where 4c) and partly also 4b) are concerned, comparative observational studies (NIS) designed like multiple-arm cohort studies provide more evidence than observational studies with only one treatment. Depending on the question to be answered, requirements concerning observation will differ. For the objectives under 4a), an attempt should be made to largely work without such requirements; here also the collection of data from past or ongoing treatments should be considered. For objectives under 4b) and 4c), measures must be taken for the standardised collection of the target parameters; here recommendations for the carrying out of diagnostic measures should be given or reference should be made to published recommendations (e.g. guidelines). 3.2.7 Study plan: Before the start of an observational study, a study plan reflecting the state of science in medicine and biometrics is to be drawn up. The essential parts of it are the observation plan and the evaluation plan. The observation plan should be oriented to routine practice and enable a structured and systematic observation. For objectives under 4b) and 4c), the observation plan should support the aim of observational balance. The study plan must include at least the following information:	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• formulation of one (or several) precise question(s) and reasons explaining why the observational study is the suitable instrument to answer this/these question/s; • description of patient recruitment and, if applicable, of the procedure in the selection of participating physicians (centres); • definition of patients to be included and, if applicable, of the procedure for the inclusion and exclusion of patients; • description of the measures to achieve representativeness (for physicians and patients); • determination of the parameters to be collected, description of their relevance and their role in answering the given question (target parameters, cofactors, covariates); • discussion of possible cofactors/ covariates and description of measures to control them; • time pattern of observation; • duration of the study and termination criteria; • description of the collection instruments needed for the observation (e g documentation sheets); • justification of the number of patients to be included; • description of type and scope of documentation; • determination of the ADR reporting routes giving due consideration to applicable legal provisions; • description of quality assurance measures; • description of the statistical evaluation; • determination of responsibilities (supervision and coordination of the study, biometrics, sponsor, etc); and	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• rules for reporting, including biometric and medical evaluation. 3.2.8 Quality assurance: The usual quality requirements applicable in epidemiological studies also apply to observational studies. The purpose of quality assurance is to minimise possible distortions through an adequate study design and/or an adequate data analysis, to ensure completeness and validity of data, and to identify and remedy shortcomings at an early stage. 3.2.9 Representativeness: As the aim of observational studies is to provide findings in the routine use of a medicinal product additionally to clinical trials, suitable methods must be applied to ensure that the patients and physicians included in a study as well as the therapeutic approach give an utmost representative picture of the medical practice. 3.2.10 Statistical evaluation: Evaluation of the data of an observational study is made by use of adequate biometrical methods. The planned approach is to be determined beforehand in the study plan; reasons must be given for deviations from this approach in the evaluation. 3.2.11 Patient information and consent: Regarding the decision on therapy, no information to patients beyond the usual information duty of physicians is necessary. The same is true for the documentation provided that patient data are handled in accordance with the data protection regulations. However, regarding the handling of patient data (e.g. quality assurance measures) and in respect of additional requirements for observation, there may be need to provide additional information to the patient. In such cases the patient's consent must be obtained. 3.2.12 Conflict of interest, ethics: Observational studies (NIS) have the potential for a number of conflicts of interest involving data protection, patient protection, protection and liability of physicians, and interests of the sponsor. Where such conflicts of interest	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		occur, counselling by an ethics committee can be helpful. Furthermore, sponsors should refer to relevant professional codes and laws and especially to the different legislations applicable to physicians in the individual member states. 3.2.13 Obligations of notification: Where applicable and according to national laws, observational studies (NIS) require immediate notification to distinct parties. 3.2.14 Report, archiving: A final report on the conduct and outcomes of an observational study is to be elaborated in due course; this report must include biometric evaluation and assessment from the medical viewpoint. The results of the observational study should be published according to scientific criteria. It is recommended that all documents of an observational study be archived for a period of at least ten years for subsequent access and evaluation. 3.2.15 Reimbursement and remuneration: The participation in an observational study is a medical activity. Efforts which go beyond standard medical care that may become necessary in observational studies are to be remunerated in analogy to national medical fee ordinances (e.g. ärztliche Gebührenordnung in Germany). The remuneration should be calculated with regard to the time needed for additionally necessary documentation and other measures. The reimbursement of services rendered beyond routine activities must be agreed upon separately. Reimbursement issues must not influence the scientific goal and the selection of patients to be included.”	
147-162	**16**	Comment: Observational studies may be designed to describe outcomes in a cohort of patients treated, without any comparison. Such design has obviously some weaknesses but is not at all considered in these guidelines. We believe that the sample size calculation may be based on the precision around the expected change of outcomes measures and be reasonably justified. Proposed change (if any): Please consider the above in the final document.	The existing text allows for the possibility for observational studies to be designed without any comparative treatment.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
150	**5**	Comment: the draft scientific guideline lists the situations where a non-randomised study maybe be conducted however we suggest making more explicit that a justification for running a non- randomised trial should always be provided. Proposed change (if any): *Addition:* A detailed justification for running a non-randomised trial should always be provided.	Agree. Text amended as proposed.
150	**21**	Comment: If large effect sizes are already expected, what would be the rationale for conducting PAES, if at the same time the guidance states that these studies would be required "*to complement available efficacy data in the light of well-reasoned scientific uncertainties on aspects of the evidence of benefits that should be, or can only be, addressed post-authorisation".*	In general, observational studies are more appropriate for large effect sizes and a statement has been added that a detailed justification for conducting a non-randomised study should always be provided.
150 - 153	**7**	Comment: In natural prescribed populations i.e. who actually get the drug, the Benefit-Risk should be maintained. Proposed change (if any): Prescriptions outside label should be split in last resort versus first line prescription outside label. Suggest to also mentioning that '**Additional data elements/effect modifiers/endpoints not studied in pivotal studies could be studied in PAES.'**	The current text allows for additional study arms and endpoints) provided this would not impact on the study integrity and the primary objectives of the study.
150 - 153	**17**	Comment: Not clear why observational PAES are especially useful to detect effect modifiers. Proposed change (if any): Explain the content of this statement.	Agree. The text has been clarified.
150 - 155	**7**	Comment: Although observational studies can help identify effect modifiers it would be important to distinguish between effect modifiers for many treatments (general treatment effect modifiers) and those that are only effect modifiers for a particular treatment of interest (specific treatment effect modifiers. This is a difficult issue which should be acknowledged in the guidance. The same comment is in fact relevant for trials.	Do not agree. Too much detail on a specific point.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
151 - 152	**9**	Comment: as explained above, avoid term “licensed indication”, use the appropriate term “authorised indication”. Proposed change (if any): differences between patients within the **authorised** ~~licensed~~ indication.	This has been deleted in light of another comment.
155	**8**	Comment: A major category of potential modifier factors should be cited: drug misuse This includes overuse, inadequate adherence and use outside the target population.	Agree. Text amended as proposed.
157	**5**	Comment: Criteria to measure outcomes should be always objective. Inclusion and exclusion criteria should also be provided. Proposed change (if any): objective data ~~**are preferred.**~~ ***Should be adopted. Inclusion and exclusion criteria should also be provided.***	Agree. Text amended as proposed.
158	**7**	Comment: Some relevant confounders and effect modifiers may be unknown and therefore are not measured. Proposed change (if any): Suggest modifying the sentence to the following: “… relevant confounding factors and effect modifiers **are known and** can be correctly…”.	Agree. Text amended as proposed.
159	**7**	Comment: Sentence starting with “This will, in general…” does not add any value. The need for comparative approach depends on the objectives and the link between this sentence and the previous one seems to be missing. Proposed change (if any): delete this sentence or provide additional explanations.	Do not agree. Inclusion of a comparator will help to identify confounders and effect modifiers.
161 - 162	**7**	Comment: The current wording seems too conservative. In fact, in case of possibility to control for biases (like indications bias), confounders and presence of robust outcomes, secondary use data may be appropriate. Proposed change (if any): ”… could be ~~considered~~ may be beneficial in additional assessments of post approval efficacy in situations…”; and specify that other methodological considerations are described below in the guidance.	Agree. Text amended as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
161 - 162	**16**	Comment: We believe this statement is flawed: use of secondary data collection may be appropriate for objectives other than efficacy, depending on availability of the outcomes measure. Also, such studies are not necessarily rapid: the time lag to access such data may be more than a year. Proposed change (if any): Please clarify according to the above.	Do not agree. The use of secondary data is further clarified in Section 4.3.
161 - 162	**21**	Comment: In the context of vaccine effectiveness monitoring, long term benefit data may be of interest, and the secondary use of existing data is a way to answer this question. Proposed change (if any): "*Post marketing observational studies involving secondary use of existing data … where a rapid exploration of an efficacy question is needed or long term data expected.*"	Agree. Text amended as proposed.
163	**19**	Comment: We suggest changing heading to: "Studies with concurrent comparison data" to be parallel with the following section heading.	Agree. Text amended as proposed.
164 - 165	**5**	Comment: Observational studies should be conducted according with STROBE[2] guidelines.	The references to specific guidance have been deleted.
164 - 165	**7**	Comment: Suggest reconsider 'in general'. The research question or indication should be the guidance. The concept to use only concurrent controls is not justified here. Proposed change (if any): Suggest changing heading to: "Studies with concurrent comparison data" to be parallel with the following section heading. Suggest edit line 165 as indicated "…have not (received) or who are not currently **receiving the treatment of interest but are similar in terms of disease progression to the patients** receiving the treatment of interest."	Agree. Text amended as proposed.

[2] http://www.who.int/bulletin/volumes/85/11/07-045120.pdf

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
165, 181 - 182	**21**	Comment: The guideline addresses studies in patients, however healthy subjects will be immunised in the case of vaccines. Proposed change (if any): Clarify in Section 2 of the guidance, in line 57, that also healthy subjects are in scope.	Agree. Reference to patients and prescribers deleted to allow for healthy subjects.
167 - 169	**17**	Comment: *"For well-measured confounders, there is little difference in results between different methods used to address confounding, although the impact of unknown":* "*little"* is rather vague, and it is not clear if this statement is true. Proposed change (if any): Please add a reference.	Statement has been deleted in light of other comments.
168	**7**	Comment: It is often but not always the case that various confounding control methods (of well measured confounders) produces similar results. Proposed change (if any): We suggest edit 165: “there is **often** little difference in”.	Statement has been deleted in light of other comments.
168	**16**	Comment: Suggest to add examples of which methods that typically provide ‘little’ difference in results. Proposed change (if any): Please clarify according to the above.	Statement has been deleted in light of other comments.
168	**19**	Comment: It is often but not always the case that various confounding control methods (of well measured confounders) produces similar results. Proposed change (if any): We suggest adding the word “often” before “little difference” to acknowledge this point.	Statement has been deleted in light of other comments.
169 - 170	**4**	Comment: this is the key concept underlying the primacy of randomised designs when testing for the effects of a drug and should be moved up to line 164. Proposed change (if any): Move to line 164 and explain that the impact of unknown confounders makes interpretation of any observational data a risky business.	The text has been amended in line with other comments.
174	**16**	Comment: Suggest adding that observational studies with time-varying confounders are also challenging because the appropriateness of the model assumptions are difficult to verify. Proposed change (if any): Please clarify according to the above.	This detail is considered outside the scope of the current guidance.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
174 - 179	**7**	Comment: This paragraph is for confounding control not specific to concurrent control. It applies to all types of controls. Hence the argument is not unique to concurrent controls and thus does not add to this section Some of the biases and challenges noted may also be operative for pragmatic trials. Proposed change (if any): Move into another section. i.e. The general statement in lines 174-179 about observational studies vs. (presumably) randomised studies should belong in the introductory section in 3.2 rather than in the section on 'concurrent controls'	Agree. Text amended as proposed.
180 - 183	**7**	Comments: The same could be said for concurrent controls (channelling bias). In fact, that is a main advantage to use historical over concurrent controls in certain situations. Proposed change (if any): Acknowledge that patient may be their own control for pre and post treatment comparisons.	Agree. Text amended as proposed.
181	**19**	Proposed change (if any): We suggest changing "controls" to "comparison patients" to avoid confusion with case-control study design terminology. Also applies to lines 190 and 194 and in other sections.	Do not agree. The term 'comparison patients' could be confusing in itself.
181	**8**	Comments: A specific situation is missing in this category: self-control designs in which each patient is his/her own control. Powerful design!	Agree. A statement has been added that a patient may be their own control for pre and post treatment comparisons.
181,190,194	**7**	Proposed change (if any): We suggest changing "controls" to "comparison patients" to avoid confusion with case-control study design terminology. Also applies to lines 190 and 194 and in other sections.	Do not agree. The term 'comparison patients' could be confusing in itself.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
185	**7**	Comments: Observational studies with secondary use of data often see data Gaps (e.g. important confounders not measured, or are associated with incomplete observation). Proposed change (if any): Considerations on the usefulness of such data for the intended purpose should be made in advance of the study; statistical techniques (e.g. sensitivity analyses with imputation of covariates) could be discussed as well if the gap is not considered critical.	Agree. A statement has been added that a detailed justification for conducting a non-randomised study should always be provided.
186 - 188	**7**	Comment: The statement “These datasets are most likely to come from formal clinical trials for which the selection criteria were well documented and strictly applied and in which the known, important prognostic variables were recorded and can be matched to the treated patient data” may not always apply. There will be circumstances under which historical comparison data should be derived from large representative observational studies which can be used as a reference to the proposed observational study assessing benefits. Proposed change (if any): Please address. Also consider adding that long term data collection on some endpoints is not possible anymore (because of ethical concerns of keeping patients on placebo for a long time).	Agree. Text amended to involve reference to historical data from observational studies. The difficulties of collecting long-term data are considered addressed by the current text referring to use of historical data where obtaining prospective data is unfeasible.
188 - 190	**17**	Comment: The problem is not necessarily if selection criteria are "*applied*", but if they are measured. When measured, a sub analysis can be performed. Proposed change (if any): Change "*applied*" to "*measured*".	Agree. Text amended as proposed.
189 - 190	**7**	Comment: Regarding “selection criteria” - this statement seems to confuse replicating the trial results with demonstrating usage in the real world. One assumes the latter is more relevant.	No change proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
191 - 194	**7**	Comment: The example here is not for historical control. Developing disease risk score (DRS) from historical data does not mean using a historical control. Most of time researchers calculate DRS for concurrent controls based on weights generated from historical data. The document leaves out the possibility of doing both concurrent and historical at same time.	Agree. Text amended to include the possibility of using both.
194	**19**	Comment: We suggest improved wording. Proposed change: If the new drug has been used extensively then again historical controls may need to be used.	Do not agree. Extensive use might not equate with market-share.
195 - 245	**3**	Comment: We appreciate that both approaches for data collection (i.e. existing databases and prospective collection of data specifically for a study) are taken into consideration.	General agreement.
195 - 245	**12**	Comment: We appreciate that both approaches of data collection are taken into consideration. Already existing data bases (e.g. tumour registers, health insurance data bases, electronic records of patient health care, etc.) on the one hand, and prospective collection of data specifically for a study. We agree with this chapter's fair balance between the diversity of data sources for clinical research.	General agreement.
196 - 198	**7**	Comment: The sentences:" There are two main approaches for data collection. One is primary collection of data specifically for a study. The other is to use data already collected for another purpose, e.g. as part of electronic records of patient health care ("secondary data collection")" are not fully in alignment to the definitions of primary data collection and secondary data collection used in the GVP Module on PASS. The dichotomy of clinical trial versus administrative healthcare database seems to leave out the possibility of prospectively collected data that is not a clinical trial. This is commonly done. Proposed change (if any): Please use similar language to the one used in the GVP Module VIII. In addition, This section (3.3) generally could benefit from the addition of	Agree. The text has been amended in line with the proposal to now read '*There are two main approaches for sourcing data i.e. primary collection of data or secondary use of previously collected data (e.g. as part of electronic records of patient health care).*' Agree on addition of sub-headings.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		some sub-sections and also a clear mapping of the different data sources to the different types of studies discussed in Sections 3.1 and 3.2. Further, a pragmatic trial is likely to use a combination of primary data collection and linking to electronic data sources, and this should be clearly stated for the reader.	Regarding the comment about pragmatic trials this is considered addressed by the current text which states that electronic healthcare records may be used to facilitate the conduct of clinical trials.
196 - 198	**10**	Comment: Anticipating the development of Immunisation information systems and other health information systems, this distinction might be less relevant, and rather a continuum is anticipated. Efforts should be devoted to build systems to frame and link data that would allow proper analyses without specific data collection.	No specific change proposed.
199 - 215	**1**	Comment: ACRO agrees with the comment that using electronic routinely collected healthcare record databases to facilitate the conduct of clinical studies is relatively new and raises some challenges if the results of such studies are to be used to support regulatory decision making. This is not an issue that is specific to PAES and applies equally to PASS and, to some extent, to clinical trials regulated by Directive 2001/20/EC, where it may be possible to auto-populate some, if not all, electronic case record form data elements directly from electronic healthcare record databases. ACRO supports the recommendation in the present draft guideline for regulatory dialogue in such cases and, additionally, recommends the Agency to develop a guidance document of more general applicability that addresses the issues associated with the use of electronic healthcare record databases in clinical research studies.	General agreement.
201	**7**	Comment: "…some challenges are likely…." is not very specific. Please provide 1 or 2 examples of these "challenges" to understanding what is meant. Change "trials" to "studies" to reflect the nature of non-trial data sources Proposed change (if any): "…if the results of these ~~trials~~studies are to…"	Agree. Reference to 'some challenges' removed and text amended as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
205	**7**	Comment: Sentence starting with “Any application to treatments…” is unclear, “large population coverage” could for example be multiple countries.	Statement deleted in light of other comment and the aspect of data collection in rare diseases is considered outside the scope of the current guidance.
205	**9**	Comment: use the term “rare disease” rather than “orphan disease”, as “rare disease” is now the preferred term, as referred to in the Communication from the Commission to the European Parliament and the Council, 11.11.2008, COM(2008) 679 and the Council Recommendation of 8 June 2009 on an action in the field of rare diseases. Proposed change (if any): Any application to treatments in **rare** ~~orphan~~ diseases is limited.	Statement deleted in light of other comment and the aspect of data collection in rare diseases is considered outside the scope of the current guidance.
205 - 206	**7**	Comment: Sample size is always an issue, no matter what the data source is. This statement is not really helpful in the way that it is currently used in the document. Proposed change (if any): Delete the sentence or develop more the aspect of data collection in orphan indications.	Agree. Statement deleted in light of the aspect of data collection in rare diseases is considered outside the scope of the current guidance.
206	**9**	Comment: furthermore, as few rare diseases benefit from a standard code (ICD), clinical healthcare record databases can rarely document on the exact nature of the rare condition. This might change when a new international classification of diseases will be released and when codes for rare diseases will be implemented in all healthcare systems. On this, see: Recommendation on Ways to Improve Codification for Rare Diseases in Health Information Systems Adopted at the 3rd meeting of the Commission Expert Group on Rare Diseases, 12-13 November 2014 http://ec.europa.eu/health/rare_diseases/docs/recommendation_coding_cegrd_en.pdf Proposed change (if any): To add the above-mentioned recommendations in annex 1.	This is considered outside the scope of the current guidance.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
206	**8**	Comment: By definition, in claims data, data are exhaustive (in contrast to EHRs, where part of data is often missing).	No specific change proposed.
206 - 207	**16**	Comment: Suggest adding that 'credibility may also be increased by replicating the results in two or more different secondary data sources'. Proposed change (if any): Please clarify according to the above.	Agree but the point here is that the data is being used to facilitate a clinical trial. This has been clarified by the addition of sub-headings.
206 - 207	**17**	Comment: Indeed the quality and completeness of data must be sufficient, but the available data should not guide the primary objective of the study. Proposed change (if any): Add a warning that secondary data can be used, but only if it fits the PAES-question, and not the other way around.	Agree. Text amended in line with proposal.
207	**4**	Comment: I am not sure if I got the sense right, but you appear to suggest that clinical trial equivalents could be run using data linkage or existing data. We do not think this is possible in any meaningful and ethical way. Proposed change (if any): clarify the meaning of the paragraph and section.	Do not agree. The suggestion is not for clinical trial equivalents per se but does relate to use of record linkage or existing data to supplement other data collection.
208	**4**	Comment: the sentence “it should be assured…” reads is not clear and there is a space after the final full stop. Proposed change (if any): As there are important variations in data quality and focus between individual databases, clinical trial processes should be implemented in a consistent way.	Agree. Text amended in line with proposal.
212	**7**	Comment: RCT abbreviation is used but full term is not defined. Proposed change (if any): Suggest writing out full term for RCT as the abbreviation is not previously defined.	Partially agree. Term deleted and replaced by clinical trials.
212	**19**	Comment: RCT abbreviation is used but full term is not defined. Proposed change (if any): We suggest writing out full term for RCT as the abbreviation is not previously defined.	Partially agree. Term deleted and replaced by clinical trials.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
216 - 217	**1**	Comment: ACRO recommends that the statement "The use of primary and secondary data collection sources for observational studies are well described elsewhere" is accompanied by relevant references. Proposed change (if any): Add the appropriate references.	This has been clarified by a reference to 'in various textbooks'.
216 - 217	**7**	Proposed change (if any): "~~The use of p~~ Primary collection and secondary data collection use sources…", and give a citation so that is clear where to go to get further information.	This has been clarified by a reference to 'in various textbooks'.
216 - 217	**10**	Comment: Please add main references.	This has been clarified by a reference to 'in various textbooks'.
216 - 218	**7**	Comment: The Draft Guidance seems to make a distinction between registries and primary data collection observational studies which is not clear, and registries are then discussed at length. Methodologically, it would seem that the two are essentially equivalent. In fact, lines 221-223 explicitly suggest this. If this is an important distinction for the Guidance, it would be good to have the distinction clarified and a rationale for this distinction given.	Registries may be a primary data collection for a given study/research question or a study/research question can use data in an existing registry. This is now clear in the text.
217	**5**	Comment: we suggested stating where primary and secondary data collection sources for observational studies are described and adding specific references or links.	This has been clarified by a reference to 'in various textbooks'.
218	**21**	Comment: More clarification is needed on the definition of registries that is provided in the footnote #10 of the document, as this is a very broad definition. Also, it is important to note that for vaccines, in order to obtain meaningful data it will be needed to have vaccines registries combined with disease related registries in a country or at above country level (for uncommon or rare patient outcomes of interest). Experience has shown that there are very few countries in EU or outside EU where this is possible. For vaccines the size of the birth cohort is often an additional limitation together with a poor reporting in the database of the vaccine brand/schedule/production batch used and low vaccine coverage in this age group. Therefore, feasibility	This level of detail is considered outside the scope of the current guidance and it is stated in the document that requested PAES should be feasible.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		assessments will be critical before requiring the establishment of registries compared to reinforcement of existing surveillance networks (at the same time acknowledging that these are mostly under governance of national public institutions and the MAH does not have data ownership, see also comments on section 5). Proposed change (if any): Amend line 218 as follows: "*Regulators can require marketing authorisation holders (MAHs), in case of positive feasibility assessment, to establish ….*"	
218 - 220	**5**	Comment: BEUC welcomes the possibility for regulators require marketing authorisation holders to establish post-authorisation registries to support collection of data on effectiveness and safety of medicinal products in the routine treatment of diseases, in particular in cases of paediatric use and orphan products.	General agreement.
218 - 220	**7**	Comment: Regulators require MAHs to use existing registries vs. requiring the initiation of a new registry. A question arises as to what will happen to the same class of products, for example, mTOR inhibitors. Will the data be judged on a case by case basis or as a class? How will this differ from the approach previously taken in immunology with TNFalpha inhibitors? With TNFalpha, all different companies set up a registry together. Please confirm that working in partnership with other companies is considered a viable option. Case by case is a good approach; additional guidelines on class effects i.e. registering the same type of drugs by more than one company would be helpful. Proposed change (if any): "…Regulators can require marketing authorisation holders (MAHs) to ~~establish post-authorisation registries~~ work with registries currently available or to be designed post approval jointly with concerned HTAs OR to facilitate joined registries (like Joined PASS) to support…"	Partially agree. Text amended to reflect the use of existing registries.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
218 - 220	**14**	Comment: This paragraph is very unclear. What types of registries are supposed to be established by marketing authorisation holders, under which circumstances? Taking into account that observational studies are mostly based on clinical records held by regional or national health services, are pharmaceutical companies to be allowed to have access to such data in order to carry out a particular study? Please clarify and provide specific examples.	This detail is outside the scope of the current guidance.
219	**15**	Comment: The discussion of registries was confusing. Please be more clear on what is defined as a registry.	The issue of defining a registry is complex and a working definition is included in the guidance.
220	**8**	Comment: or new, expensive treatments	Do not agree. This comment on costs is outside the scope of the current document.
223	**7**	Comment: The comment regarding "...not on an a priori decision on how patients will be recruited." is unclear. Please clarify what this means.	Agree. This has been deleted.
225	**7**	Comment: This type of registry might be useful for non-comparative studies of e.g. effect modification. See comment also on lines 150-153. Pre and post treatment comparisons may also be possible. It should be considered and referenced, that regardless, there are limitations for comparability of treatments, if appropriate index events cannot be defined on a common basis for treated and control subjects (e.g. if the treatment is only induced after some time of already received control treatment (switch). And when their disease status at index event cannot be constructed for either control or treated subject.	The statement on treatment comparison was deleted in light of being too much specific detail on registry design for the current guidance.
229 - 232	**7**	Comment: The potential usage of registries described is here. However, this very much depends heavily on how well the registries are designed. A poorly run registry will not allow many of these designs.	No specific change proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
230	**4**	Comment: the term retrospective should be used in para 3.3 as well to clarify that what the text calls “secondary data” (why not “existing data”?) is retrospective.	Agree. The term ‘existing data’ is now used.
230-231	**7**	Comment: “retrospective cohorts for events with short induction times” Proposed change (if any): The possibility of running a retrospective cohort study within a prospectively collected registry setting is not always restricted to the situation where study events have short induction times. In the case where a registry has been running for a large number of years, events with a longer latency period may be studied. This could be reflected in the study design options listed.	Agree. Reference to induction times deleted.
232	**7**	Comment: “common” is not clear Proposed change (if any): Suggest expand or use other word(s).	Agree. The term ‘common’ was deleted and the sentence has been re-worded.
233	**10**	Comment: Include exposure to the treatment or vaccine to the common set of variables (specific, by brand).	Agree. Text amended as proposed.
234 - 235	**7**	Comment: This point applies also to non-epidemiological data or any data collection.	Agree. Reference to ‘other epidemiological’ has been deleted.
236 - 238	**7**	Comment: The sentence is long and difficult to read. It needs to be simplified. Proposed change (if any): “~~Measures to improve the quality of data,~~ **In order to insure the quality of registries, several improvements need to be taken into consideration:** validity of studies, **quality of data captured into a validated system**, usefulness of results **from registries;** including common terminologies, data dictionaries definitions,...”	Agree. Sentence shortened by deleting reference to validity of studies and usefulness for results.
242	**7**	Comment: Should also state that limitations are given when a suitable definition of an index event cannot be given for the control.	Agree. Text amended as proposed.
242 - 244	**7**	Comment: The sentence (242-4) count for observational studies in general, not just registries. Proposed change (if any): “~~In terms of data interpretability~~ **As in any data source**...”	Agree. Text amended as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
245	**7**	Proposed change (if any): We suggest clarifying what is meant by “selection bias”. Assuming its means confounding due to non-randomisation. We suggest use “confounding” since other types of selection bias can occur in randomised studies.	Agree. Text amended as proposed.
245	**19**	Comment: We suggest clarifying what is meant by “selection bias”. Assuming it means confounding due to non-randomisation, we suggest using “confounding” since other types of selection bias can occur in randomised studies.	Agree. Text amended as proposed.
245	**8**	Comment: unless registries aim to collect exhaustive data	Agree. Text amended as proposed.
246 - 250	**7**	Comment: This section should perhaps be explained as out of scope for the current document (in section 1.2); nevertheless, efficacy will be in the context of benefit-risk assessment therefore safety will be a key component of it. This is not emerging from the prior text.	The sub-section on safety aspects has been moved to the section on conduct of studies.
246 - 250	**21**	Comment: In the specific case of vaccine effectiveness study, the outcome is the related preventable disease. By design, we look at "suspected” vaccine failure (lack of therapeutic efficacy) events that are reportable within a 15-days timeframe. Could the Authorities provide further details on how to handle this specificity in vaccine effectiveness studies, what are their expectations in terms of reporting?	This is considered outside the scope of the current guidance.
247 - 250	**19**	Comment: It might be useful to include a link to guidance on PASS studies, and to highlight different requirements of a PAES versus a PASS study.	This is considered outside the scope of the current guidance.

2.2.4. Scientific guidance on specific situations

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
251 - 261	**20**	Comment: Specific EMA, Guideline on safety and efficacy follow-up- risk management of advanced therapy medicinal products, 2008 (EMEA/149995/2008) should be mentioned.	
251 - 358	**7**	Comment: Section 4 as a whole is not easy to read/follow. The different uncertainties descried are not always fully clear and there seems to be overlap in the different scenarios presented. Proposed change (if any): Please address	It is acknowledged that overlap exists in the different scenarios and this reflects overlap in the situations defined in the Delegated Regulation.
256 – 260, 394 - 396	**7**	Comment: Both of these sentences indicate that when imposing a PAES, there should be a well-reasoned scientific uncertainly for which a study may be designed with a suitable methodology and conducted in a manner to give reliable and interpretative answers to the question at hand. In these statements, there is no discussion on the feasibility to complete the assessment within a reasonable timeframe. Agreeing on a design which is feasible to complete within a reasonable timeframe is important to produce interpretable results that address the uncertainty and benefit-risk in a timely manner. Proposed change (if any): Suggest adding language similar to lines 62-63: The design should take particular account of the post-authorisation setting and be feasible to complete within a reasonable timeframe.	Agree. The text has been reworded to better take account of feasibility and timeframe.
256 – 260, 394 - 396	**19**	Comment: Both of these sentences indicate that when imposing a PAES, there should be a well-reasoned scientific uncertainly for which a study may be designed with a suitable methodology and conducted in a manner to give reliable and interpretative answers to the question at hand. In these statements, there is no discussion on the feasibility to complete the assessment within a reasonable timeframe. Agreeing on a design which is feasible to complete within a	Agree. The text has been reworded to better take account of feasibility and timeframe.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		reasonable timeframe is important to produce interpretable results that address the uncertainty and benefit-risk in a timely manner. Proposed change (if any): We would suggest adding language similar to lines 62-63: The design should take particular account of the post-authorisation setting and be feasible to complete within a reasonable timeframe.	
262 - 347	**7**	Comment: Many of the mentioned uncertainties can be addressed using historical or relevant information. Use of indirect comparisons (meta-analysis, network meta-analysis) is particularly useful in these contexts. Proposed change (if any): Further emphasis on use of historical data. It has applicability beyond observational study.	The use of historical data is addressed in a separate sub-section.
263 - 264	**7**	Comments: Need to consider situation where RCTs are not feasible and observational studies may be the only choice for example, studying efficacy/effectiveness in subgroups that are excluded from RCTs.	Agree. Text amended as proposed.
268 - 276	**7**	Comment: Here a subpopulation could be defined by a biomarker Proposed change (if any): It should be further described what rules companion diagnostics or the ways to select a subgroup with an assay are applicable to follow.	This is considered outside the scope of the current guidance.
270	**17**	Comment: The text: *"lack of patient numbers in a given sub-population"* is not well formulated. Proposed change (if any): Should be replaced by: *"insufficient number of patients in a given sub-population"*.	Agree. Text amended as proposed.
271 - 272	**17**	Comment: The text: *"and the consequent reliance on extrapolation rather than clinical trial data to support a broader indication statement."* is not well formulated. Proposed change (if any): Should be replaced by: *"and the consequent reliance on extrapolation rather than on actual data to support a broader indication statement"*.	Partially agree. The statement has been modified.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
274, 296	**12**	Comment: We appreciate that both RCTs and observational clinical studies are taken into consideration.	General agreement.
50, 277 - 290	**14**	Comment: The document mentions “validated surrogates” as an established practice to support a positive harm-benefit balance in an indication. In the same way, the paragraph 4.2 (lines 277-290) considers surrogates to be a useful tool when they are considered to be sufficiently informative by the scientific/regulatory community. This is not acceptable. The use of surrogate endpoints warrants extreme caution. Hard outcomes should always be envisaged before licensing and PAES should not be used as a panacea to fix (after marketing) an inappropriate original drug trial design. The study cited by EMA by Svensson and Menkes (JAMA Intern Med, 2013) clearly states that only in very few exceptions (slowly progressing conditions without existing therapy or very rare diseases) the use of surrogate endpoints can be deemed reasonable. This article does not mention other potential examples as suggested by the EMA (such as complex or composite measurements or key secondary outcomes). Proposed change (if any): Remove the reference to validated surrogates.	The text has been amended to add more detail on the use of intermediate endpoints in line with what is stated in the Delegated Regulation. The reference cited has been removed.
277 - 290	**7**	Comment: May include the possibility of longer follow-up (than planned) to gain additional data of pivotal studies.	Reference is already may to extended follow-up.
47, 279	**21**	Comment: To be changed to “a positive benefit risk” (and not ‘risk benefit’)	Agree. Text amended as proposed.
279, 286	**4**	Comment: Risk-benefit is mentioned but the observation of harms is underdeveloped in the document, only making a cryptic appearance from line 246. This is very strange considering that assessment of harms is one of the key objectives of post marketing studies. Proposed change (if any): Develop the observations of arms throughout the document.	Assessment of harm is outside the scope of the current guidance which is focussed on efficacy.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
280-281	**5**	Comment: A valid surrogate should be used. When other surrogate is used a justification should be provided.	The current text refers to agreement as surrogates or considered sufficiently informative.
284	**7**	Comment: The statement "…PAES may therefore be required where supplementary data are needed to support the established positive benefit risk balance" could apply in numerous situations (a continuous re assessment of the established positive benefit risk balance of a product will be required during its full life cycle". Proposed change (if any): Please revisit this sentence / make it more specific.	Agree. The text has been amended to reflect the need for PAES to address uncertainty.
284 - 288	**9**	Comment: In rare diseases and in particular when the incidence of clinical outcomes is low over trial duration, some endpoints can be used and were used which were not fully validated as surrogate markers prior to the marketing authorisation. This situation should remain exceptional, but in case they would occur, the validation of the surrogacy could be made post marketing evaluation. Proposed change (if any): Examples include in the case of slowly progressive conditions necessitating extended follow up, or where there are complex composite or intermediate or key secondary endpoints that are important to establishing therapeutic efficacy and benefit-risk but cannot be fully understood on the basis of the clinical trial data presented, **or when the surrogacy of an endpoint has not been fully determined at the time of the authorisation.**	Agree. The text has been amended to include the proposed additional example.
291	**17**	Comment: *"Uncertainties in benefits regarding treatment over time"* is not well formulated. Proposed change (if any): Should be replaced by: *"Uncertainties regarding benefits of treatment over time"*.	Agree. Text amended as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
300 - 310	**7**	Comment: The section implies that PAES can be requested for additional potential combinations not substantiated in terms of the safety and efficacy at the time of MA. For such additional potential combinations uncertainties will nearly always be present as these have not been investigated at the time of MA. This seems to indicate that the guidance also is to be used outside the approved indication which goes against the legal basis and purpose. Section 4.4 line 308-310 Implies that when treatment paradigms change over time a PAES may be required to assess uncertainties over a particular combination used. This seems also to go against the legal basis and purpose. In addition it is unclear if changes in treatment paradigms will require PAES for one, two or more MA holders when assessing the safety and efficacy of the new or presently approved combination (e.g. if a SGLT2 inhibition is included as first line treatment in updates of present treatment guidelines (e.g. ADA's Clinical Practice recommendation) would PAES then be required for all combination previously approved with metformin as background treatment or would PAES only be required for the SGLT2 inhibition MAH on specific already approved combinations). Any requirement for appropriate dose finding for combinations should be addressed. Proposed change (if any): Only to incl. PAES requirements within the legal basis and purpose. At least it should be stated that this will be based on a case by case assessment.	Agree. Text amended as proposed by including a statement on the case-by-case assessment.
301	**7**	Comment: Suggest clarifying "…the use of a medicinal substance in anticipated combination with other treatments must…". Proposed change (if any): "the use of a medicinal substance in anticipated combination with other treatments **for the intended indication** must"	Agree. Text amended as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Title and throughout the document (e.g. from lines 301 and 308	**4**	Comment: the objective of the studies is ambiguous. The title of the document bears the word “efficacy” even when (as in line 140-141) the correct terms should be effectiveness. Proposed change (if any): explain in line 316 that the concept described is known as effectiveness.	Term ‘efficacy’ replaced with ‘benefit’.
311	**7**	Comment: It is suggested to add after the existing sentence: “It will be important to consider whether factors determining co-administration of treatments are likely to impact the comparability of treatment groups." Proposed change (if any): “Observational designs may suffice if justified. **It will be important to consider whether factors determining co-administration of treatments are likely to impact the comparability of treatment groups.**”	Agree. Text amended in line with proposal.
312 - 347	**17**	Comment: *"Uncertainties stemming from benefits of the medicinal product in real life use"*. This appears to be the ideal situation for an observational study as it focusses on real life use. This paragraph is another example for the comments that the guideline is very general, while it would be more helpful to give a suggestion on which type of PAES study to use in this case. Proposed change (if any): Add what type of study would be applicable in this situation.	Agree. Statement added ‘**observational designs, with appropriate justification, may have a particular role in the study of a medicine in real-life use**.’
320 - 332	**9**	Comment: Another reason why a PAES might be need is when the clinical trial setting is so much different from the routine organisation of care, and this can have an impact on the treatment observance, hence its efficacy. Special measures can be proposed to trial participants to help them coping with the trial constraints, even if the organisation of the trial should not differ too much from the standard care, there are settings where it does: counsellors during the trial (e.g. from a patient organisation) who provide support or who have consultations with the trial subjects to see any difficulty they might have in taking the treatment, or financial support to travel to the centre to receive treatment that is	Do not agree on the need for this level of detail given the existing text states that ‘*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.’*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		provided during the trial but not or only partly in real life etc. When measures exist in a trial but not in real life that could impact treatment observance and hence overall efficacy, then a PAES might be needed to verify the efficacy in the absence of such measures. Proposed change (if any): to add the following '**When measures exist in a trial but not in real life that could impact treatment observance and hence overall efficacy, then a PAES might be needed to verify the efficacy in the absence of such measures**.'	
99, 108 - 145, 329-332	**14**	Comment: Exploratory trials are defined as those where control of systematic errors is enabled through randomisation, blinding and allocation concealment. It seems that pragmatic trials cannot apply these standards, while in fact they can (and should). It is true that external validity of explanatory trials may be limited and pragmatic trials can add useful information in a post-authorisation scenario. But this cannot be a reason to lower standards in the first approval or to base approvals mainly in non-explanatory trials. Proposed change (if any): Correct text to also include that pragmatic trials can and should also be controlled for systematic errors through randomisation, blinding and allocation concealment.	Do not agree.
329 - 347	**17**	Comment: In these lines, the circumstances when a PAES may be necessary are outlined. However, it is unclear whether the design as mentioned in line 328 is also meant to be applicable to the scenarios of lines 329-347. Proposed change (if any): This needs to be clarified in the guideline. Of note: This comment reflects the general comment that the current guideline requires more focus.	No specific change proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
333 - 340	**7**	Comment: Whilst this text is important and relevant for the document, it is not clear that it should be included within Section 4.5 "Uncertainties stemming from benefits of the medicinal product in real life use." Proposed change (if any): Suggest that this text would perhaps seem more appropriate in Section 2.	Agree. This paragraph has been moved to the more general Section 2 as suggested.
337	**7**	Proposed change (if any): "Periodic ~~Safety Update~~ Benefit Risk Evaluation Report".	The Term PSUR is still applied.
341 - 342	**7**	Comment: Seems like "effectiveness" is meant here rather than "efficacy" Proposed change (if any): Should this be "impact of microbial epidemiology and/or herd immunity on ~~efficacy~~ effectiveness"?	Text amended to remove reference to either efficacy or effectiveness here.
341 - 344	**7**	Comment: "PAES may also be used to estimate vaccine effectiveness using study designs different to those that supported the initial MA." This statement needs rationale. The rationale for running a study in order to have a different design is missing. There should be a scientific rationale. This leaves open the question of whether a PAES would then be feasible.	Agree. The text has been amended to clarify the need for a scientific rationale to do this.
341 - 347	**10**	Comment: Preventive measures and specifically vaccines would justify a specific chapter. Justification for PAES for vaccines could also include schedule (e.g. change from 3 doses to 2 doses regimen for HPV), other outcomes (H&N for HPV, pneumo related outcomes…)	Do not agree. These changes to the initial MA would only be in light of supportive studies.
342	**21**	Comment: the wording 'microbial' epidemiology is not appropriate. Proposed change (if any): Replace **'***impact of microbial epidemiology'* by **'***impact on strain, infection and disease epidemiology'*	Agree. Text amended as proposed.
343 - 347	**21**	Comment: It should be acknowledged in the guideline that effectiveness studies may require joint efforts by the industry and regulatory bodies to allow feasibility of the study and to achieve a scientifically meaningful outcome, such as monitoring of vaccine efficacy for influenza vaccines by the ECDC and MAHs in a	This level of detail is considered outside the scope of the current guidance.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		public private partnership. The following aspects should be considered: • Changes in the epidemiological situation (due to the vaccine or not) and in this case the assessment of cross-protection. • Assessment of antibody persistence (related to the assessment of need for a booster dose).	

2.2.5. Conduct of post-authorisation efficacy studies

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
359	**7**	Proposed change (if any): Insert in beginning of section 5: "**in case the study is observational (i.e. non-experimental), the current EU GVP Module VIII should be followed. This includes the operational elements (protocol, reports) as for the analytical dataset (being kept de-identified) and contracting."**	This level of procedural guidance is outside the scope of the current scientific guide. It has been clarified that this section relates to principles and a link to the procedural Q & A on the EMA website has been added i.e. 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
359 - 398	**12**	Comment: Well done	General agreement
360 - 361	**11**	Comment: Could the EMA provide details on fees which will be imposed? Will these be in alignment with PASS staggered fees (protocol assessment followed by final CSR)? Proposed change (if any): Addition of PAES Application section within methodology.	This level of procedural guidance is outside the scope of the current scientific guide.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Comment 2: Could the EMA confirm if the same categorisation of PAES will exist as per PASS, i.e. Categories 1-4 and interventional / non-interventional.	
363 - 366	**9**	Comment: to help ensuring the study is feasible and ethically acceptable, it is important to consult with patients' representatives at scientific advice, if any, or via other consultation modalities Proposed change (if any): 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. Agreement on the protocol between sponsor and regulator needs to be reached for an imposed PAES. Any amendment to the protocol should be discussed and agreed in advance with the competent authorities. **To best achieve this, patients and clinicians should be consulted.**	Agree. Text amended to include reference to input from patients and healthcare professionals being sought as appropriate.
364	**21**	Comment: For observational vaccine studies it is important to note that the MAH often relies on the existing surveillance networks in countries, under the governance of national public institutions and the MAH does not have data ownership. Therefore the sponsor/MAH has to agree on the protocol/amendments and interim/final reports not only with the regulator but also with the partnering institution. This might impact the time needed for development of protocols and report and therefore it will be important to allow realistic timelines. In addition, it may be necessary to conduct these studies outside EU in order to obtain meaningful and interpretable results (true for primary and secondary data collection). Proposed change (if any): Change in section 5.1, line 367-369. Replace by : "*The time frame for submission of the protocol/protocol amendments, interim/final study report should be agreed by the competent authorities, taking into account possible third party involvements.* "	Agree. Text amended in line with the proposal.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
364 - 366	**18**	Comment: The use of “regulator” in line 365 and “competent authorities” in line 366 seems confusing. A PAES might be required by a national competent authority, the European Medicines Agency or the Commission (cf. Commission Delegated Regulation (EU) No 357/2014). However, the evaluation of the PAES protocol will be led by the CHMP with possible consultation of other committees. Therefore, the use of a more general term (e.g. CHMP appointed assessor) might be favoured. Proposed change (if any): Agreement on the protocol between sponsor and **CHMP’s appointed assessor** ~~regulator~~ needs to be reached for an imposed PAES. Any amendment to the protocol should be discussed and agreed in advance with the **appointed assessor** ~~competent authorities.~~	Do not agree. Ultimately the agreement of the more general ‘regulator’ will be needed.
364 - 366, 372 - 373	**20**	Comment: It should be highlighted that in case of advanced therapy medicinal product and where risk-based approach has been used, the latter may facilitate the agreement between the sponsor and the regulator on the study protocol.	This level of detail is outside the scope of the current scientific guide.
365 - 366	**7**	Comment: Inconsistency between how PASS and PAES are handled regarding amendments Proposed change (if any): Consider implementing "GVP.VIII.B.5.2. Substantial amendments to the study protocol" for observational PAES. For experimental clinical trials refer to Article 10(a) of Directive 2001/20/EC (or the new Clinical trial regulation).	This level of procedural guidance is outside the scope of the current scientific guide.
365 - 366	**18**	Comment: A restriction to substantial amendments might be more feasible and be in line with requirements for clinical trials imposed by the EU CT regulation. Proposed change (if any): Any **substantial** amendment to the protocol should be discussed and agreed in advance with the competent authorities.	Agree. Text amended as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
367 - 371	**7**	Comment: Delivery of interim report – incl. blinded data - Need to incl. a foot note: Blinded data not to be requested if transparency rules are applied. As summary is to be published and hence will reduce the validity of the trial. Proposed change (if any): Incl. a foot note.	This level of detail is outside the scope of the current scientific guide.
370	**21**	Comment: It is important to note that in the case of vaccines, the data may be owned by third parties and the MAH will not necessarily have full control over the format of the study report.	This level of detail is outside the scope of the current scientific guide.
370 - 371	**7**	Comment: "The format of study report should follow the conventional format as per ICH guidance" is inconsistent with GVP.VIII. Proposed change (if any): Please distinguish between experimental clinical trials and observational studies regarding protocol and study report requirements and make requirements for observational PAES consistent with those for observational PASS. I.e. repeat the guidance from GVP VIII.	Reference to the format of the study report deleted from here as this level of procedural guidance is outside the scope of the current scientific guide.
370 - 371	**19**	Comment: We suggest clarifying the specification about the ICH guidelines to apply only to interventional studies. Non-interventional PASS for example do not follow ICH but instead, the templates provided in PASS guidance. As these templates are very thorough and can easily apply to studies with primary efficacy objectives, it seems most efficient that non-interventional PAES would use the same protocol and study report templates with edits made as needed.	Reference to the format of the study report deleted from here as this level of procedural guidance is outside the scope of the current scientific guide.
372 - 375, 397 - 398	**14**	Comment: It is unclear why there should be an agreement between sponsor and regulator to decide the adequate study design to addressing a research question. This should be exclusively defined by the regulator, which should make that decision based on public health priorities. Resorting to scientific advice in this context might jeopardize EMA's independence and also result in studies which do not respond to the agency's needs.	The point is taken but ultimately the regulator will have to agree on the study design in line with the research question and what is proposed as feasible by the sponsor.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
379 - 383	**7**	Comment: According to this draft guidance study information should be made available in the EU PAS Register, but it is not clarified in this requirement which information should be included and timing for disclosure. For PASS which have to be registered in the EU PAS Register the final protocol, amendments, progress reports and the final study report have to be included. Proposed change (if any): Suggest the detailed requirements for contents and timing for PASS are applied.	This level of procedural guidance is outside the scope of the current scientific guide.
384	**7**	Comment: "5.3 Quality control and quality assurance" it is strongly suggested not only to relate to GCP, but also to GVP.VIII (when the study is observational). It is good practice/ needed to keep the dataset anonymised when kept for audit and inspection per EU data privacy regulations. Clarify that the anonymised analytical dataset as a minimum needs to be stored at the investigator, data privacy concerns may prevent storage at sponsor. Proposed change (if any): Copy from GVP Module VIII (PASS): I.e. if the study is experimental ("Interventional Clinical Trial") follow GCP. If the study is observational ("Non-interventional Clinical Trial") follow GVP Module VIII regarding protocol, reports, datasets/statistical program etc.	This level of procedural guidance is outside the scope of the current scientific guide.
386	**21**	Comment: As explained above for vaccines the MAH does not always own the data, and does not always have access to the analytical datasets and statistical programmes. Proposed change (if any): Add at the end of line 390: "*It is acknowledged that in some situations, the MAH will not have ownership of the database and possibility to access analytical datasets and statistical programmes*."	This level of procedural guidance is outside the scope of the current scientific guide.
389 - 390	**7**	Comment: The section mentions QC and QA far too superficial. STROBE and CONSORT should be adhered to and data protection laws. Proposed change (if any): Suggest a similar approach to PAES in regards to GVP module VIII as for non-interventional PASS. This	This level of procedural guidance is outside the scope of the current scientific guide.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		module and the GVP is the only enforced by law guidance which MAH can use besides the considerations of ICH guidelines.	

2.2.6. Conclusions

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
256 – 260, 394 - 396	**7**	Comment: Both of these sentences indicate that when imposing a PAES, there should be a well-reasoned scientific uncertainly for which a study may be designed with a suitable methodology and conducted in a manner to give reliable and interpretative answers to the question at hand. In these statements, there is no discussion on the feasibility to complete the assessment within a reasonable timeframe. Agreeing on a design which is feasible to complete within a reasonable timeframe is important to produce interpretable results that address the uncertainty and benefit-risk in a timely manner. Proposed change (if any): Suggest adding language similar to lines 62-63: The design should take particular account of the post-authorisation setting and be feasible to complete within a reasonable timeframe.	Agree. Text has been amended accordingly.
256 – 260, 394 - 396	**19**	Comment: Both of these sentences indicate that when imposing a PAES, there should be a well-reasoned scientific uncertainly for which a study may be designed with a suitable methodology and conducted in a manner to give reliable and interpretative answers to the question at hand. In these statements, there is no discussion on the feasibility to complete the assessment within a reasonable timeframe. Agreeing on a design which is feasible to complete within a reasonable timeframe is important to produce interpretable results that address the uncertainty and benefit-risk in a timely manner.	Agree. Text has been amended accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): We would suggest adding language similar to lines 62-63: The design should take particular account of the post-authorisation setting and be feasible to complete within a reasonable timeframe.	
396-398	**9**	Comment: idem Proposed change (if any): Agreement should be sought as early as possible between the regulator and sponsor on the appropriateness of a study design to achieve this and to this end, scientific advice is recommended **with the consultations of patients and clinicians**.	Input of patients and healthcare professionals has been referenced in the section relating to study protocol.
372 - 375, 397 - 398	**14**	Comment: It is unclear why there should be an agreement between sponsor and regulator to decide the adequate study design to addressing a research question. This should be exclusively defined by the regulator, which should make that decision based on public health priorities. Resorting to scientific advice in this context might jeopardize EMA's independence and also result in studies which do not respond to the agency's needs.	This has been previously addressed. The point is taken but ultimately the regulator will have to agree on the study design in line with the research question and what is proposed as feasible by the sponsor.
400	**20**	Comment: to add as a reference: EMA, Guideline on safety and efficacy follow-up- risk management of advanced therapy medicinal products, 2008 (EMEA/149995/2008).	Agree. Reference included.

[i] US Government Accountability Office "Drug safety – Improvement needed in FDA´s postmarket decision-making and oversight process" Report GAO-06-402, 2006. www.gao.gov: 63 pages.
[ii] Carpentier D "Can expedited FDA drug approval without expedited follow-up be trusted" JAMA Internal Medicine 2014; 174 (1): 95-97.
[iii] Lexchin J "Notice of compliance with conditions: a policy in limbo" Healthcare policy 2007; 2 (4): 114-122 (+ annexes: 5 pages).
[iv] Banzi R, et al, Approvals of drugs with uncertain benefit–risk profiles in Europe, Eur J Intern Med (2015), http://dx.doi.org/10.1016/j.ejim.2015.08.008
[v] Gibson SG , Lemmens T. Niche Markets and Evidence Assessmetn in Transition: A critical review of proposed drug reforms. Medical Law Review, Vol. 22, No. 2, pp. 200–220 doi: 10.1093/medlaw/fwu005
[vi] Light D, Lexchin J (2015) Why do cancer drugs get such an easy ride? » BMJ 2015;350:h2068 doi: 10.1136/bmj.h2068

[vii] Darrow JJ et al « New FDA Breakthrough-drug category-Implications for patients » N Engl J Med 2014 ; 370 (13) : 1252-1258

[viii] Moore T, Furberg C. "Electronic Health Data for Postmarketing surveillance: a vision not realized" *Drug Saf* 2015; **38**:601–610

[ix] Light D, Lexchin J "Why do cancer drugs get such an easy ride?" *BMJ* 2015; 350: h2068 doi: 10.1136/bmj.h2068

[x] Apolone G, Joppi R, Bertele V, et al. Ten years of marketing approvals of anticancer drugs in Europe: regulatory policy and guidance documents need to find a balance between different pressures. Br J Cancer 2005;93:504-9.

[xi] Kim C, Prasad V, 2015. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: An analysis of 5 years of US Food and Drug Administration approvals. *JAMA Internal Medicine* 2015;175(12):1992-1994

[xii] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents. Official Journal of the European Communities 31 May 2001: L 145/43-L 145/48.