29 January 2016

Submission of comments on 'Scientific guidance on post-authorisation efficacy studies' (EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015)

Comments from: EFPIA

| **Name of organisation or individual** |
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*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| **Stakeholder number**  ***(To be completed by the Agency)*** | **General comment (if any)** | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | 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.  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.  Please note that input from the EFSPI working group on PAES has been incorporated into this EFPIA response. |  |
|  | **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.  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 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. |  |
|  | **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. |  |
|  | **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.  **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.  **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.  **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](http://www.oecd.org/sti/sci-tech/oecdrecommendationonthegovernanceofclinicaltrials.htm) - risk categories for clinical trials) is the basis for the clinical study types. In usual practice it is for example in UK permitted to 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. |  |

1. Specific comments on text

| **Line number(s) of the relevant text**  ***(e.g. Lines 20-23)*** | **Stakeholder number**  ***(To be completed by the Agency)*** | **Comment and rationale; proposed changes**  ***(If changes to the wording are suggested, they should be highlighted using 'track changes')*** | **Outcome**  ***(To be completed by the Agency)*** |
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| Lines 3-6 |  | 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.). |  |
| Lines 3-4 |  | 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 ” |  |
| Line 30 |  | Comment:  The guidance describes that a PAES may be imposed within the scope of the Delegated Regulation (EU) No 357/2014². 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. |  |
| Lines 43-57 |  | 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. |  |
| Line 47 |  | 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…” |  |
| Lines 47 – 57  (comment addition |  | 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. |  |
| Lines 59, 73-75 |  | 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 would be better addressed by non-randomised studies.” |  |
| Line 63 |  | Comment:  “Time” may also depend on uptake not just design |  |
| Line 65 |  | 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. |  |
| Line 75 |  | 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” |  |
| Line 76 |  | Comment:  “especially those comparing treatment with no treatment”  Proposed change (if any):  ad “or other comparator” |  |
| Line 78 |  | 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”. |  |
| Line 80 |  | Comment:  Comparison between two groups is the driver for randomisation.  Proposed change (if any):  “the conduct of non-randomised comparative studies”. |  |
| Lines 85-88; 89-94 |  | 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, |  |
| 86-87 |  | 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. |  |
| Line 87 |  | Comment:  It would be helpful to clarify what is meant by “as ‘add-on’ to standard of care” |  |
| Line 95 |  | 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 |  |
| Line 96 |  | Comment:  One could consider an interim analysis in exploratory trial design. This may increase the appeal of this design from ethical point of view. |  |
| Line 96 |  | Comment:  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. |  |
| Lines 97-162 |  | 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)." |  |
| Lines 97-145 |  | 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. |  |
| Lines 104 and 114-116 |  | 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 …” |  |
| Line 108 |  | 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 |  |
| Line 110 |  | 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.” |  |
| Lines 112 |  | 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. |  |
| Lines 114-116 |  | 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. |  |
| 116-118 |  | 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. |  |
| Lines 122-123 |  | 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 |  |
| Lines 123-125; 135-138 |  | 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 |  |
| Lines 123-124 |  | 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.” |  |
| Line 125 |  | 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.” |  |
| Lines 127-129 |  | 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. |  |
| Line 128 |  | Comment:  Word missing  Proposed change (if any):  “...the interpretation of findings should take into account the level of noise and variability.” |  |
| Lines 130-131 |  | 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. |  |
| Line 135-137 |  | Comment:  “, as pragmatic trials tend not to do confirmatory tests”  Seems to be an over-generalization 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" |  |
| Line 138 |  | 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. |  |
| Line 139-140 |  | 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.’ |  |
| Lines 139-142 |  | 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. |  |
| Line 140 |  | 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. |  |
| Lines 141-142 |  | 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”. |  |
| Lines 143-145 |  | 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.” |  |
| Lines 147-149 |  | 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 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). |  |
| Lines 146-245 |  | 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). |  |
| Lines 147-162 |  | 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 |  |
| Lines 150-155 |  | 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. |  |
| Lines 150-153 |  | 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.” |  |
| Line 158 |  | 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 …”. |  |
| Line 159 |  | 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 |  |
| Lines 161-162 |  | 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. |  |
| Lines 164-165 |  | 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.” |  |
| Line 168 |  | 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”. |  |
| Lines 174-179 |  | 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’ |  |
| Lines 180-183 |  | 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  Acknowledge that patient may be their own control for pre and post treatment comparisons |  |
| Line 181, 190, 194 |  | 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. |  |
| Line 185 |  | 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. |  |
| Lines 186-188 |  | 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). |  |
| Lines 189-190 |  | 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. |  |
| Lines 191-194 |  | 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. |  |
| Lines 196-198 |  | 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 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. |  |
| Line 201 |  | 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…” |  |
| Line 205 |  | Comment:  Sentence starting with “Any application to treatments…” is unclear, “large population coverage” could for example be multiple countries. |  |
| 205-206 |  | 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. |  |
| Line 212 |  | 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. |  |
| Lines 216-217 |  | 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. |  |
| Line 216-218 |  | 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. |  |
| Lines 218-220 |  | 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…” |  |
| Line 223: |  | Comment:  The comment regarding “...not on an a priori decision on how patients will be recruited.” is unclear. Please clarify what this means. |  |
| Line 225 |  | 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. |  |
| Lines 229-232 |  | 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. |  |
| Line 230-231 |  | 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. |  |
| Line 232 |  | Comment:  “common” is not clear  Proposed change (if any):  Suggest expand or use other word(s). |  |
| Line 234-235 |  | Comment:  This point applies also to non-epidemiological data or any data collection. |  |
| 236-238 |  | 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,...” |  |
| Line 242 |  | Comment:  Should also state that limitations are given when a suitable definition of an index event cannot be given for the control |  |
| 242-244 |  | 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**…” |  |
| Line 245 |  | 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. |  |
| Line 246-250 |  | 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. |  |
| Lines 251-358 |  | 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 |  |
| Lines 256 – 260 and 394 - 396 |  | 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. |  |
| Lines 262-347 |  | 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. |  |
| Lines 263-264 |  | 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. |  |
| Lines 268-276 |  | 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. |  |
| Lines 277-290 |  | Comment: May include the possibility of longer follow-up (than planned) to gain additional data of pivotal studies |  |
| Line 284 |  | 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. |  |
| Lines 300-310 |  | 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 fist 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. |  |
| Line 301 |  | 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” |  |
| Line 311 |  | 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.” |  |
| Lines 333-340 |  | 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. |  |
| Line 337 |  | Proposed change (if any):  “Periodic ~~Safety Update~~ Benefit Risk Evaluation Report” |  |
| Lines 341-344 |  | 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 rational for run 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. |  |
| Lines 341-342 |  | 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”? |  |
| Line 359 |  | 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.” |  |
| Line 365-366 |  | Comment: Inconsistency between how PASS and PAES are handle 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). |  |
| Lines 367-371 |  | 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 |  |
| Lines 370-371 |  | 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. |  |
| Lines 379-383 |  | 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. |  |
| Line 384 |  | 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. |  |
| Line 389-390 |  | 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 module and the GVP is the only enforced by law guidance which MAH can use besides the considerations of ICH guidelines. |  |

Please add more rows if needed.