Non-imposed PASS final results assessment report sub-template for type II variations

*If considered helpful, please copy-paste the following section into the variation assessment report template and use it to describe and assess the results of the non-imposed non-interventional PASS. Not all subheadings have to be used/one can use only the relevant sub-headings.*

1. Non-interventional Post-Authorisation Safety Study (PASS) results

For detailed guidance on the scientific content and background on each section, please refer to:

*- the [Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/01/WC500137939.pdf" \t "_blank)*

- the [GVP Module VIII on Post-authorisation safety studies](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf).

* 1. <Title>
     1. Milestones

Copy here the table of section 5 of the final study report (Milestones).

<Text>

PRAC Rapporteur’s comment:

Comment on any difference between planned and actual dates of study milestones and the explanation provided.

<Text>

* + 1. Rationale and background

Summarise section 6 of the final study report.

<Text>

PRAC Rapporteur’s Comment

Comment only on any difference between initially planned and actual rationale and background and the justifications provided (which have not previously been assessed), including an assessment of the impact of these on the validity of study results. Reference should be given to the previous assessment of the study protocol and to the final approved protocol. If no differences have been found write **<No difference observed from the final approved protocol>**

<Text>

* + 1. Research question and objectives

Summarise section 7 of the final study report.

<Text>

PRAC Rapporteur’s Comment

Comment on any difference between initially planned and actual research question and objectives and the justifications provided, including an assessment of the impact on the validity of study results. Reference should be given to the previous assessment of the study protocol and to the final approved protocol.If no differences have been found write **<No difference observed from the final approved protocol>**

<Text>

* + 1. Amendments and updates to the protocol

Summarise section 8 of the final study report.

<Text>

PRAC Rapporteur’s Comment

Comment whether any substantial amendment and update to the study protocol after the start of data collection had impact on the validity of study results as initially planned in the final endorsed study protocol.

<Text>

* + 1. Research methods

Study design

Summarise section 9.1 of the final study report.

<Text>

PRAC Rapporteur’s comment

Was the choice of study design appropriate as regards the study research question and objectives?

<Text>

Setting

Summarise section 9.2 of the final study report.

<Text>

PRAC Rapporteur’s comment

Are locations and relevant dates for the study, including periods of recruitment, follow-up, and data collection described?

<Text>

Subjects

Summarise section 9.3 of the final study report.

<Text>

PRAC Rapporteur’s comment

Are the source population and eligibility criteria adequately described? Was their choice appropriate as regards the study research question and objectives?

<Text>

Variables

Summarise section 9.4 of the final study report.

<Text>

PRAC Rapporteur’s comment

Does the report adequately describe how exposure(s), outcome(s) and covariate(s) were defined and measured? Were measurement methods appropriate? Was exposure correctly classified as regards time windows, dose or duration? Was the validity of exposure and outcome measurement discussed?

<Text>

Data sources and management

Summarise section 9.5 of the final study report.

<Text>

PRAC Rapporteur’s comment

Does the protocol adequately describe strategies and data sources for determining exposures, outcomes and other variables relevant to the objectives, such as potential confounding variables and effect modifiers? Are coding systems described? Is there any evidence about the validity of the data source(s)? If data linkage was used, is the linkage method adequately described? Is data management adequately described, e.g. data collection and storage?

<Text>

Bias

Summarise section 9.6 of the final study report.

<Text>

PRAC Rapporteur’s comment

Does the final study report adequately describe sources and types of bias and the potential impact on study results?

<Text>

Study size

Summarise section 9.7 of the final study report.

<Text>

PRAC Rapporteur’s comment

Are the assumptions used for any calculation of sample size or precision of the study based on evidence? Are these assumptions acceptable? Is the sample size or study precision adequate?

<Text>

Data transformation

Summarise section 9.8 of the final study report.

<Text>

PRAC Rapporteur’s comment

Does the study report describe transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why? Were such data transformations acceptable?

<Text>

Statistical methods

Summarise section 9.9 of the final study report.

<Text>

PRAC Rapporteur’s Assessment

Does the data analysis plan provide sufficient details on the statistical methods that have been performed on the observed data in the study to generate the results that were interpreted, incl. correction of inconsistencies or errors, imputation of missing values, data transformation and presentation, calculation of point estimates and their precision, adjustment for confounding, sensitivity analyses? Are these statistical methods sound and appropriate?

If the analysis plan depended on the actual data and was not determined in advance (e.g. where several data sources were used and the analytical method depended on the heterogeneity of the data), was the process to identify the most appropriate method explained?

(see also Chapter 7 of the ENCePP Guide on methodological standards in pharmacoepidemiology)[http://www.encepp.eu/standards\_and\_guidances/documents/ENCePPGuideofMethStandardsinPE\_2.pdf]

<Text>

Quality control

Summarise section 9.10 of the final study report.

<Text>

PRAC Rapporteur’s comment

Will adequate mechanisms and procedures be in place to ensure data quality and integrity, and to allow accurate data reporting, interpretation and verification? Will methods of quality assurance be applied?

<Text>

Limitations of the research methods

Summarise section 9.9 of the final study report.

<Text>

PRAC Rapporteur’s Assessment

Have potential limitations of the study protocol been correctly identified and discussed in relation to the objectives of the study?

<Text>

* + 1. Results

Participants

Summarise section 10.1 of the final study report.

<Text>

PRAC Rapporteur’s Comment

Comments on the study participants section should mainly (but not only) take into account the following aspects:

- A clear accounting of study subjects who entered each stage of study (e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing followed and analysed) with an explanation for non-participation at every stage should be provided

- Exact number of subjects included in analyses of different objectives or hypotheses should be clearly presented

- In the case of a systematic review or meta-analysis, the number of studies screened, assessed for eligibility and included in the review (with reasons for exclusion at each stage) should be presented.

<Text>

Descriptive data

[Summarise section 10.2. of the final study report.]

<Text>

PRAC Rapporteur’s Comment

Comments on the descriptive data section should mainly (but not only) take into account the following aspects:

- Important characteristics of study subjects (e.g. age, sex, study site, categories of matching variables), potential confounders and/or other variables potentially relevant to the study question should adequately presented (by exposure or outcome categories if relevant) in table(s), with missing data for each variable of interest

- In case of cohort studies follow-up time (e.g. average and total) amount should be provided. In case of a systematic review or meta-analysis, descriptive information should include characteristics of each study from which data were extracted (e.g. study size, follow-up).

<Text>

Outcome data

Summarise section 10.3. of the final study report.

<Text>

Main results

Summarise section 10.4. of the final study report.

<Text>

Other analyses

Summarise section 10.5. of the final study report.

<Text>

PRAC Rapporteur’s Comment

Comments on the main results section should mainly (but not only) take into account the following aspects:

- The analyses for different study objectives or hypotheses should be clearly separated

- The absolute numbers of outcome events in each exposure category should be provided

- The results should be clearly and adequately presented, including unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval)

- If relevant, estimates of relative risk should be translated into absolute risks

- Sensitivity analyses should be performed if planned in the statistical plan

- Unplanned analyses, such as sub-group analyses or investigation of alternative exposure categories, should be clearly identified and the reasoning behind them explained

Comments should be also provided if some specific result presented in this section is likely to be affected by potential source of biases. **For a full overview of the biases encountered in the final study report, please refer to the Discussion**

<Text>

Adverse events/adverse reactions

[Summarise section 10.6. of the final study report.]

<Text>

PRAC Rapporteur’s Comment

Comments on the adverse events/adverse reactions section should mainly (but not only) take into account the following aspects:

- Is there an adequate presentation of solicited adverse events and reported adverse reactions in tabular format?

- Are relevant and serious adverse events/reactions discussed?

- Was causality assessment performed and presented in an adequate way, if relevant?

- Are reported adverse events already included in the Summary of Product Characteristics?

<Text>

* 1. Discussion

Summarise section 11 of the final study report, using the following sub-headings as appropriate.

<Key results>

<Text>

PRAC Rapporteur’s Comment

Key results should be discussed in relation to each of the study objectives with a particular focus on the safety concern(s) which triggered the initiation of the study.

<Text>

<Limitations of the study>

<Text>

PRAC Rapporteur’s Comment

The discussion on the limitations of the study should take into account:

* 1. circumstances that may have affected the quality or integrity of the data (e.g. methods of data collection, low response rate, missing or incomplete data)
  2. sources of potential biases (e.g. Selection bias, information bias, channelling/confounding by indication, exposure/outcome misclassification) and methods to control them (e.g. validation, imputation, sensitivity analyses)
  3. robustness of the statistical analysis, including any multiplicity issue;

<Text>

<Interpretation>

<Text>

PRAC Rapporteur’s Comment

Interpretationcriteria for assessment should mainly consider whether:

* 1. limitations of the study has been taken into account (see below)
  2. the interpretation arise logically from the main results or is far-fetched,
  3. the interpretation focus on positive results from primary and/or only secondary/subgroup analyses
  4. the results are substantiated by the MAH based on previous findings and/or relevant scientific literature
  5. mechanistic/pharmacological/physiological explanation has been provided to support the observed findings
  6. alternative explanations to the observed findings have been considered

<Text>

<Generalisability>

<Text>

PRAC Rapporteur’s Comment

The discussion on the generalisability of results should take into account data source, characteristics of the study population, inclusion and exclusion criteria. Findings from previous studies and/or relevant scientific literature might also be used to support the generalisability of the study results and discussions/conclusions from the initial assessment of the protocol may be useful for this section.

<Text>

* + 1. Other information

Summarise section 12 of the final study report and any additional information arising from the evaluation of the final study report.

<Text>

PRAC Rapporteur’s Comment

Provide an assessment of this additional information and of its impact on the study results and their interpretation.

<Text>

* + 1. Conclusion

Summarise section 13 of the final study report.

<Text>

PRAC Rapporteur’s Comment

Comment on the MAH’s main conclusion(s) derived from the study and on its evaluation of the impact of the results on the benefit-risk balance of the concerned medicinal product(s)

<Text>