Annex 15
of the Pharmacovigilance Procedure
(subitem 6 of item 8 of chapter 5
of section VI)

Structure of
protocol, final report and summary of post-registration safety study

I. Structure of protocol

1. Title (informative title including a commonly used term indicating the study design and the investigational medicinal product, vaccine, tuberculin (hereinafter - medicinal product), active substance or ATC code, and a sub-title with a version identifier and the date of the last version).

2. Name of registration certificate holder/applicant.

3. Information about study site.

4. Summary of the study protocol including the following sub-sections:

1) Title with subtitles including version and date of the protocol and last name and name of enterprise, institution, organization of author of the protocol;

2) Rationale and background;

3) Research question and objectives;

4) Study design;

5) Study population;

6) Variables;

7) Data sources;

8) Study size;

9) Data analysis;

10) Milestones.

5. Amendments and updates (any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made).

6. Milestones - table with planned dates for the following milestones:

1) Start of data collection;

2) End of data collection;

3) Study progress report(s);

4) Interim report(s) of study results (if applicable);

5) Final report of study results.

7. Rationale and background (short description of the safety hazard(s), the safety profile or the risk management measures that led to the imposition of the study).

8. Research question and objectives according to decisions of competent authority, which led to the study being imposed.

9. Research methods - description of the research methods, including:

1) Study design;

2) Setting (study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria and their effect on person number available for analysis. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained);

3) Variables;

4) Data sources (strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives. Where the study will use an existing data source, such as health records, any information on the validity of the recording and coding of the data should be reported. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described;

5) Study size (any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision);

6) Data management;

7) Data analysis;

8) Quality control;

9) Limitations of the research methods.

10. Protection of human subjects (safeguards in order to comply with national requirements for ensuring the rights of participants in non-interventional post-registration safety studies).

11. Management and reporting of adverse events/adverse reactions and other medically important events while the study is being conducted.

12. Plans for disseminating and communicating study results.

13. References.

II. Structure of summary of final report

1. Title and sub-titles with date of summary and full name and affiliation of main author.
2. Keywords (not more than five keywords indicating the main study characteristics).

3. Rationale and background.

4. Research question and objectives.

5. Study design.

6. Setting.

7. Subjects and study size, including dropouts.

8. Variables and data sources.

9. Results.

10. Conclusion (including, where relevant, an evaluation of the impact of study results on the risk-benefit balance of the product).

11. Registration certificate holder.

12. Names and affiliations of principal investigators.

III. Structure of final report

1. Title (title including a commonly used term indicating the study design; sub-titles with date of final report and full name and affiliation of main author).

2. Summary (stand-alone summary in the format presented in section II of this Annex).

3. Registration certificate holder/applicant, address.

4. Investigators (full names, titles, degrees, affiliations of the principal investigator and co-investigators, and list of all collaborating institutions and relevant study sites).

5. Milestones - planned and actual dates for the following milestones:

1) Start of data collection (planned and actual dates);

2) End of data collection (planned and actual dates);

3) Study progress report(s);

4) Interim report(s) of study results (where applicable);

5) Final report of study results;

6) Any other important milestone applicable to the study, including date of protocol approval in the list of studies.

6. Rationale and background (description of the safety concerns that led to the study being initiated, and critical review of relevant published and unpublished data and gaps that the study is intended to fill).

7. Research question and objectives **(**research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol).

8. Amendments and updates to the protocol (list of any substantial amendments and updates to the initial study protocol after the start of data collection, including a justification for each amendment or update).

9. Research methods:

1) Study design (key elements of the study design and the rationale for this choice);

2) Setting (locations, and relevant dates for the study, including periods of patient recruitment, follow-up, and data collection. In case a study design is a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale);

3) Study subjects (any source population and eligibility criteria of study subjects. Sources and methods of selection of participants should be provided, including, where relevant methods for case ascertainment, as well as number of and reasons for dropouts);

4) Variables (all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable);

5) Data sources and measurement (for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as health records, any information on the validity of the recording and coding of the data should be reported. In case of a systematic review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators should be provided);

6) Bias;

7) Study size (study size, rationale for any study size calculation and any method for attaining projected study size);

8) Data transformation (transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why);

9) Statistical methods: description of the following items:

Main summary measures;

Statistical methods applied;

Any methods used to examine subgroups and interactions;

How missing data were addressed;

Any sensitivity analyses;

Any amendment to the plan of data analysis included in the study protocol, with rationale for the change.

10) Quality control (mechanisms to ensure data quality and integrity).

10. Results:

1) Participants (numbers of participants at each stage of study; in the case of a systematic review or meta-analysis - number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage);

2) Descriptive data (characteristics of study participants, information on exposures and potential confounders and number of participants with missing data. In case of a systematic review or meta-analysis - characteristics of each study from which data were extracted);

3) Outcome data (numbers of participants across categories of main outcomes);

4) Main results (unadjusted estimates and (if applicable) confounder-adjusted estimates and their precision. If relevant, estimates of relative risk should be translated into absolute risk for a meaningful time period);

5) Other analyses;

6) Adverse events and adverse reactions.

11. Conclusions:

1) Key results (key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-registration safety study, and (where relevant) impact of the results on the risk-benefit balance of the medicinal product);

2) Limitations (limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods, sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases should be discussed);

3) Interpretation (interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence);

4) Generalisability.

12. References.