EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee

Checklist for prioritisation of EU regulatory network collaborative impact research

Background

A key deliverable of the Pharmacovigilance Risk Assessment Committee (PRAC) Strategy on Measuring the Impact of Pharmacovigilance Activities (EMA/790863/2015) launched in 2016 is the development of criteria for the prioritisation of collaborative impact research, and to establish a routine prioritisation process. Collaborative impact research in the context of the PRAC strategy includes studies initiated by the EU regulatory network and conducted by one or several research centres or by a consortium of research partners focussing on product or therapeutic class-specific regulatory actions adopted at PRAC plenary meetings.

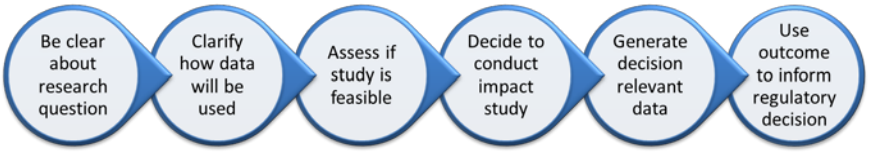
Objective

The criteria to prioritise collaborative impact research were developed with the following objectives:

- Guidance on the identification and selection of safety topics discussed at PRAC which require the generation of data to monitor impact of regulatory interventions in public health terms beyond the data submitted by marketing authorisation holders.
- Development and implementation of a selection process for EU collaborative impact research.

The decision on initiating a collaborative impact study for the above objectives should be based on a clear understanding of the research question (i.e. which information about a safety topic is required), on a clear understanding of how the data generated by the study will be used (i.e. does the study reduce uncertainty, will provide answers to relevant questions), clear understanding of the feasibility of the study and generalisability of the study outcome for better informed regulatory decisions (Fig.1).

Figure 1: Key considerations for initiating EU regulatory network collaborative impact studies.



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Prioritisation criteria

The prioritisation of PRAC safety topics for collaborative impact research take into account the following criteria, included as a checklist (see Annex 1).

I. Public health importance of the regulatory action

- Nature and severity of the risk in the affected population;
- Magnitude of the risk (absolute and relative) in the population where the product is used, taking into account the size of the affected population across Member States and product use in the context of clinical guidelines;
- Amount of public concern, for example due to risk in vulnerable populations (i.e. paediatrics, elderly, pregnant women), public debate on the regulatory decision or disagreement within the scientific community;

II. Potential impact on clinical practice

- Extent of the regulatory intervention (e.g. simple label changes from adding adverse reactions, warnings, contraindications to additional risk minimisation measures, restricting the indication and suspension or revocation);

III. Delivery of decision relevant data

- Is the nature of the regulatory action amenable to research that will ultimately generate decision relevant data?
- Are suitable data sources and methodologies available in several Member States to allow for generalisability of results across different healthcare systems?
- Does the study fill gaps in knowledge and understanding of the safety issue?
- Does the study provide evidence beyond the data of MAH's planned and/or ongoing studies?

Implementation and operational aspects

The PRAC strategy has a focus on major regulatory actions and expected (and unexpected) public health impacts. In line with the strategy the checklist with prioritisation criteria was tested and applicability to the following PRAC agenda items confirmed during a 6-month pilot (EMA/286748/2017):

- EU referral procedures for safety reasons: urgent EU procedures for finalisation (item 2.3)
- EU referral procedures for safety reasons: other EU referral procedures for finalisation (item 3.3)
- Signals assessment and prioritisation - Signals follow-up and prioritisation (item 4.3)

  The criteria are applied to signals where the PRAC assessment report recommends changes to the relevant sections of the product information(s) and/or risk management plan(s) including:

  - New contraindication(s) (SmPC section 4.3)
  - New warning(s) (SmPC section 4.4)
  - Restriction of the indication (SmPC section 4.1)

    - Additional risk minimisation measures in line with GVP XVI, section XVI.B.2.

- Results of post-authorisation safety studies (PASS) imposed (item 7.3) or non-imposed (item 7.4) in the marketing authorisation(s)

  The criteria are applied to PASS included in a risk management plan (RMP) where the PRAC assessment report recommends changes to the relevant sections of the product information(s) and/or risk management plan(s) based on the results, including:

    - New contraindication(s) (SmPC section 4.3)
    - New warning(s) (SmPC section 4.4)
    - Restriction of the indication (SmPC section 4.1)
    - Additional risk minimisation measures in line with GVP XVI, section XVI.B.2.
    - Lifting or changes of previously required additional risk minimisation measures

Reflection about the relevance of the checklist's criteria (high/yes, low/no or unclear) is expected to facilitate the prioritisation of safety topics for collaborative impact research. PRAC Rapporteur and Co-Rapporteur apply the criteria taking into account the evidence available at the time of finalisation of regulatory procedures. Operational challenges of regulatory measures across different healthcare systems, and possible unintended public health consequences and the need to evaluate these should also be taken into consideration.

The checklist in the Annex is a voluntary regulatory tool and other criteria may be relevant on case by case basis to decide on the need for a collaborative impact study.

Annex – Checklist with prioritisation criteria

Criteria	Explanation	High / Yes	Low / No	Not clear	Comment
Public health importance of the regulatory action					
1. Nature and severity of the risk in the affected population;	*How serious are the consequences for the patient? How is the risk perceived by the general public in terms of intensity (mild, moderate, severe)?*	☐	☐	☐	
2. Magnitude of the risk (absolute and relative) in the population where the product is used;	*How big is the risk in the treated, compared to the untreated population? How big is the population using the product in the EU taking into account exposure data from several Member States where the product is marketed, and if available recommendations in national clinical guidelines.*	☐	☐	☐	
3. Amount of public concern, e.g. due to risk in vulnerable populations, public debate, disagreement within the scientific community etc.;	*Are affected populations perceived as particularly vulnerable (children, pregnant women, elderly people)? Has the safety concern been subject to public debate in the media? Is there conflicting evidence about the safety concern in the scientific literature?*	☐	☐	☐	
Potential impact on clinical practice					
4. Extent of the regulatory intervention;	*Is the regulatory action expected to lead to changes in patient and/or HCP behaviour, to change the way the product is used in clinical practice or to changes in clinical guidelines? Regulatory interventions may include label changes e.g. addition of adverse reaction(s), warnings and/or contraindications to SmPC, additional risk minimisation measures, restriction of the indication, suspension or revocation.*	☐	☐	☐	
Delivery of decision relevant data					
5. Regulatory action is amenable to research generating impact relevant data?	*Are there any measurable effects of the regulatory intervention which allow assessing if the intended outcome (e.g. lower risk incidence) has been delivered in clinical practice or did any unintended consequences occur?*	☐	☐	☐	
6. Suitable data sources and methodologies are available in several Member States to allow generalisability of results?	*Are suitable data sources available and accessible for impact research or can they be generated within reasonable time frames? Do these data sources allow for generalisability of the results across different healthcare systems for the whole EU?*	☐	☐	☐	
7. Does the study fill gaps in knowledge and understanding of the safety issue?	*Are there clearly defined knowledge gaps about the risk to patients under real world conditions, about the effectiveness of risk minimisation measures or how the product is used in practice which could be answered by collaborative impact research?*	☐	☐	☐	
8. Does the study add to the evidence beyond the studies conducted by MAH(s)?	*Are there any other ongoing or planned studies from MAH(s) which provide evidence on the impact of the regulatory action in question?* *Are MAH(s) in the position to conduct such a study e.g. as joint study?*	☐	☐	☐	
Topic prioritised for impact research: ☐ **Yes** ☐ **No** **Comment:**					