28 November 2024
EMA/PRAC/490455/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

Guideline on specific adverse reaction follow-up questionnaires (Specific AR FUQ)

Draft agreed by PRAC drafting group on Specific AR FUQ	May 2023
Adopted by PRAC for release for consultation	31 August 2023
Start of public consultation	6 December 2023
End of consultation (deadline for comments)	9 February 2024
Agreed by PRAC drafting group on Specific AR FUQ	October 2024
Adopted by PRAC	28 November 2024
Date for coming into effect	1 February 2025

Keywords	***Specific adverse reaction follow-up questionnaire (Specific AR FUQ); Pharmacovigilance; Adverse drug reaction (ADR) reporting; Risk management (RM)***

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Executive summary

This paper aims at providing a guidance to the EU/EEA regulatory medicines network on when and how to use specific adverse reaction follow-up questionnaires (Specific AR FUQs) in routine pharmacovigilance activities (GVP module V, V.B.6.1.1.).

The completeness of information in Individual Case Safety Reports (ICSRs) is essential in many pharmacovigilance assessments. However, the information available in these reports is often limited and may lack essential data that would allow for better characterisation of the reported suspected adverse reactions. To address this issue, forms and questionnaires are commonly used to collect additional information when initial reports are incomplete. These include general follow-up questionnaires (FUQs), and Specific Adverse reaction Follow up questionnaires (Specific AR FUQs).

This paper provides guidance on Specific AR FUQs developed by the Marketing authorisation holders (MAHs) at the request of National Competent authorities (NCAs) or the European Medicines Agency (EMA) and does not intend to modify the MAHs internal policies for FUQs. It emphasizes the importance of obtaining structured and detailed information on reported suspected adverse reactions that may impact the benefit-risk balance of a product or have implications for public health.

Marketing authorisation holders (MAHs) should use Specific AR FUQs approved by National Competent authorities (NCAs) or the European Medicines Agency (EMA). Member States (MSs) could use these questionnaires as appropriate in the follow-up of any reports they receive (GVP VI, VI.C.2.1.).

The document identifies three main directions: providing general guidance on when and how to use Specific AR FUQs, guidance for MAHs on developing Specific AR FUQs, and considering discontinuation and removal of Specific AR FUQs.

The guidance outlines the requirements for a Specific AR FUQ and recommends that a Specific AR FUQ should be used for safety concerns that may impact the benefit-risk balance of a product. For important identified risks, FUQs should not be generally used, but in some special situations, a Specific AR FUQ may be necessary instead of the standard FUQ for further characterization of the risk.

The content of a Specific AR FUQ should focus on collecting the missing data of main importance for assessing the safety concerns. It should be prefilled with available information to avoid requesting the primary source to repeat information. A Specific AR FUQ should not be overly extensive and its completion by the reporter should be easy to minimize the burden on reporters and to avoid discouraging future spontaneous reporting.

The format of Specific AR FUQs and the way to contact the reporters should follow existing recommendations to optimize data collection. This includes having a common structure and contain a preface, basic content, and specific content with questions addressing essential aspects of the adverse reaction.

To facilitate knowledge sharing, approved Specific AR FUQs will be published on EMA website.

Overall, in addition to existing GVP guidelines, this guidance provides a framework for the use and implementation of Specific AR FUQs as part of risk management in routine pharmacovigilance activities to improve the completeness of information in pharmacovigilance.

1. Introduction (background)

The completeness of information in Individual Case Safety Reports (ICSRs) is essential in pharmacovigilance assessments. However, the information available in the ICSRs is sometimes limited and may not always provide important information that would allow to better characterise the suspected adverse reaction (AR) reported[1] (GVP Annex I).

Forms and questionnaires are used to collect additional information as part of routine pharmacovigilance when information in initial reports is incomplete. These include standard follow-up questionnaires (e.g., for pregnancy exposure to medicinal products) or companies' internal check lists that are used to collect more data on spontaneous reports or Specific Adverse Reaction Follow-up questionnaires (Specific AR FUQs) which aim to obtain standardised, structured, and detailed information from the reporter on a particular suspected AR.

For standard FUQs, the existing guidelines and the requirements from the GVP Module VI apply, e.g., for pregnancy FUQ the GVP P III: Pregnant and breastfeeding women or the guideline for medication errors[2].

2. Scope

To facilitate completeness of initial information, Specific AR FUQ refers to FUQs that are deemed necessary to obtain structured and detailed information on reported suspected adverse reactions (ARs) that may have an impact on the benefit risk balance of the product or have implications for public health.

The scope of this guidance is limited to specific (also known as targeted) AR FUQs requested by the competent Authorities. It does not intend to modify or change the MAHs' internal policy for standard FUQs.

In order to avoid duplicate work and unnecessary burden for the reporter, the MAH is expected to collect further information about case reports initially sent to them or captured by them from other sources (GVP VI, VI.C.2.2.). The MAH is not expected to perform follow-up for ICSRs made accessible to them from the EudraVigilance database[3] (GVP VI, VI.C.2.1.).

Three main directions have been identified for the present document:

- Providing general guidance (when and how to use Specific AR FUQs) to competent authorities in Member States (NCAs), Pharmacovigilance risk assessment committee (PRAC), pharmacovigilance

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-5_en.pdf
[2] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practice-guide-recording-coding-reporting-assessment-medication-errors_en.pdf
[3] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf

and clinical assessors, pharmacovigilance (GVP) inspectors, Marketing authorisation holders (MAHs) and the European Medicines Agency (EMA), using the opportunity of ongoing EMA work on updates of GVP guidelines;

- Developing guidance that can be used by MAHs and recommend if and how approved Specific AR FUQs could be published;
- Considerations on discontinuation and removal of Specific AR FUQs.

3. Legal basis

This guideline should be read in conjunction with all relevant information included in current and future EU guidelines based on the Directive 2001/83/EC [DIR] and Regulation (EC) No 726/2004 [REG], and ICH guidelines and regulations, especially:

- Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems
- Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management, and submission of reports of suspected adverse reactions to medicinal products
- Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report
- Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management
- Guideline on good pharmacovigilance practices (GVP) Annex I – Definitions
- Guideline on good pharmacovigilance practices (GVP) Product- or population- specific considerations III: pregnant and breastfeeding women
- Good practice guide on recording, coding, reporting and assessment of medication errors - EMA/762563/2014

4. Guidance on the use of the Specific AR FUQ

4.1. Requirements for a Specific AR FUQ

Suspected adverse reactions for which Specific AR FUQs are considered can be defined as those referring to safety concerns[4] (from RMP and/or PSUR) for which the collection of information should be as detailed as possible since their characterisation may have an impact on the B/R balance of the medicinal product.

For medicinal products requiring a Specific AR FUQ but without a RMP in place (e.g. for old products), the Specific AR FUQ could be associated to a safety concern followed-up in the PSUR. If there is a RMP already in place, the (new) Specific AR FUQ should refer to a safety concern and be included in the RMP (Annex 4).

As Specific AR FUQs are related to safety concerns which could impact the benefit/risk balance of a medicinal product, the number of situations requiring such questionnaires is expected to be limited. For

[4] Important identified risk, important potential risk and missing information

important identified risks Specific AR FUQs should in principle not to be used. However, in some special situations, where the reversibility, severity or other aspects of the important identified risk needs to be further characterised a Specific AR FUQ might be necessary.

When assessing whether a Specific AR FUQ should be recommended, consideration should be given to other tools in place which collect more data on the same risk (e.g., PASS) and to what extent a Specific AR FUQ would be of additional value.

Specific AR FUQs are considered as routine pharmacovigilance.

Specific AR FUQs used by different applicants/MAHs (including for generics and biosimilars) for the same suspected adverse reaction should be kept as similar as possible but should also take into account the specificity of the medicinal products as appropriate (e.g. therapeutic indication and context of use). MAHs are strongly encouraged to share the content of their questionnaire(s) upon request from other MAHs or use other tools as applicable, see also Chapter 5 of this Guideline.

4.2. Content of the Specific AR FUQ: aspects to be considered

Specific AR FUQs should focus on the collection of missing data of particular importance which were not initially provided by the reporter.

The Specific AR FUQ should be prefilled by the MAH with all the available information collected at the time of the initial report, to limit the burden on the reporters.

Additional questions should be strictly limited to the collection of standardised information and detailed information on a particular suspected adverse reaction to better characterise a safety concern.

In line with GVP Module VI, the length of the Specific AR FUQ should be as short as possible.

This guidance proposes a common structure of Specific AR FUQ which should be used and adapted to fit within existing MAH and NCA practices. These Specific AR FUQs should contain the following parts:

- A preface to explain the added value of this Specific AR FUQ (to increase the willingness of reporters to complete the Specific AR FUQ and thus provide relevant additional information) e.g., *"You have received this questionnaire because you have reported "adverse reaction" with "name of medicinal product". Please provide additional information below, if available to you. By providing this information, you are actively participating in safety monitoring of "name of medicinal product" use"*. The MAH could also consider a cover letter to address individual messages tailored for the reporter;
- Administrative part including privacy statement;
- A basic content (such as the patient age, gender, dates of drug intake, date of adverse reaction occurrence / resolution, outcome, actions taken with the medicinal product, medical history, concomitant medications);
- A specific content with questions covering essential aspects to be considered (i.e., detailed data on the adverse reaction) to allow the characterisation of an adverse reaction and/or assessment of the causality between the adverse reaction and the medicinal product. The aspects to be considered

should be identified when the need for this Specific AR FUQ emerges and should display the minimum content of information usually lacking but nevertheless essential to perform a causality assessment and a better characterisation of the adverse reaction. They could address the following points (but not limited to):

- Context of use (including the exact therapeutic indication),
- Risk factors related to the specific adverse reaction,
- Clinical/biological data including specific laboratory values (reference values should be asked for where relevant), histopathological results, imaging data, or any other relevant data (e.g., autopsy investigations in case of fatal outcome), that enable either the confirmation of the suspected adverse reaction or exclusion of other causes.

Regarding the approval of the content of the Specific AR FUQ, it is worth noting that the GVP Module V on the format of the risk management plan (RMP) in the EU provides the following guidance for Specific AR FUQs: "should be described in the routine pharmacovigilance activities section and copies of these forms should be provided in RMP annex 4" (see GVP Module V, Section V.B.6.1.1). Therefore, Specific AR FUQs within an RMP usually require a review of the exact content by the competent authorities. If there is no RMP in place, the specific AR FUQ could be approved within the regulatory procedure which identified the need for a specific AR FUQ.

Caution should be applied when choosing the name of the Specific AR FUQ in order to avoid terms at SOC level or vague medical concepts that could be considered too broad to characterise a safety concern. To simplify the collection and search of existing Specific AR FUQ, the heading of the Specific AR FUQ should be titled with the name of the medicinal product and the MedDRA term best reflecting the underlying safety concern (e.g. single/multiple preferred terms or standardised MedDRA query).

4.3. Format of the Specific AR FUQ

In general, the format, content and layout of the Specific AR FUQ should follow recommendations from GVP Module V and GVP Module VI to optimise collection of the additional information about the suspected adverse reaction, not originally included in the initial case report. Specific AR FUQs should use:

- A content as short as possible.
- Tick boxes where possible, to save time of the reporter.
- At least one free text field to enable responders to provide any additional information.

It is the responsibility of the MAHs to ensure that Specific AR FUQs are readable and understandable by the target recipients whom representatives could be involved by the MAH in the review before submission to competent authorities.

Specific AR FUQs should be sent by the MAHs to the reporters in the local language of the reporter. The translations in local languages are the responsibility of the MAHs. Member States could liaise with the MAHs to obtain translated specific AR FUQ.

4.4. Dissemination of the Specific AR FUQ

The dissemination of Specific AR FUQ to reporters is performed by the MAHs for suspected adverse reactions reports initially sent to them or captured by them from other sources.

Member States may disseminate Specific AR FUQ as appropriate in the follow-up of any reports they receive.

The tools used for the dissemination can include different means (e.g. emails, web-based questionnaires, apps, phone, letters). Measures should ensure that only the intended recipient can access this information. For example, information can be sent to the address from which the initial report was received, verified through a phone call, or shared via web-based questionnaires accessible using specific details from the initial report. Whenever possible, it is advised to use the same tools or channels through which the initial report was submitted for dissemination. Reminders should always be included, and timing should be defined[5].

5. Publishing of Specific AR FUQ

Specific AR FUQs approved by competent authorities and covered by the scope of this guidance will be published by the EMA.

6. Consideration on discontinuation and removal of Specific AR FUQ

Characterisation of risks through use of Specific AR FUQ might become necessary at any time throughout the lifecycle of a medicinal product.

The MAHs should ensure that the Specific AR FUQs are implemented in an effective and timely manner.

The MAHs are encouraged to regularly assess the effectiveness of the Specific AR FUQs, using process and outcome indicators:

- **Process indicators** (e.g., a response rate) can be used to monitor whether reporters respond to the request for more information. While process indicators cannot provide evidence on whether a Specific AR FUQ is effective, a low response rate should trigger further analysis. For instance, a low response rate could be related to the questionnaires not reaching the target (i.e., the reporter of the adverse reaction), the request not being identified as important by the target, an inadequate format or collection means, a lack of readability, or complex response process.
- **Outcome indicators** (e.g., details about the specific information collected after the implementation of the specific AR FUQ). Competent authorities may request to the MAHs to provide a detailed analysis of the level, extent and informative value of additional information provided and to substantiate how it contributes both to increase the quality of the data collected when compared with the initial information and to a better characterisation of the safety concern with a potential

[5] GVP VI.B.7.1. (Submission time frames of ICSRs)

impact on the benefit/risk balance of the medicine. The outcome indicators should reflect the added value of the information collected compared to what already existed in the initial ICSR.

Effectiveness results should be submitted upon request of the competent authorities.

Discontinuation and removal of a Specific AR FUQ should be regularly considered within any procedural framework (e.g. PSUR, RMP update) in light of effectiveness results and/or the characterisation of the safety concerns over time e.g. following reclassification of an important potential risk as an important identified risk or as a non- important risk (i.e. that would not warrant to be followed up through a safety concern in the RMP) or following the conclusion that there is no causal association and the important potential risk can be removed from the RMP and/or PSUR.

Definitions and abbreviations

Specific Adverse Reaction Follow-up questionnaires (Specific AR FUQs): Questionnaires which aim is to obtain standardised, structured, and detailed information on reported suspected adverse reactions of special interest and go beyond standard follow-up questionnaires.

B/R – Benefit/Risk

ADR reporting – Adverse drug reaction reporting

AR – Adverse reaction (synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect. A response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)]. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see GVP Annex I, GVP Annex IV, ICH-E2A Guideline))

EMA – European Medicines Agency

FUQ – Follow-up questionnaire

GVP – Good pharmacovigilance practices

ICSR – Individual case safety report

MAH – Marketing authorisation holder

MedDRA – Medical Dictionary for Regulatory Activities

NCA - National competent authority

PASS – Post-authorisation safety study

PRAC – Pharmacovigilance risk assessment committee

PSUR – Periodic safety update report

RM – Risk management

RMP – Risk management plan

SOC – System organ class

Specific AR FUQ – Specific adverse reaction follow-up questionnaire

References

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