ADVERSE EVENT REPORTING GUIDELINES

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EPHMRA ADVERSE EVENT REPORTING (AER) GUIDELINES - REVISED JUNE 2023

The EPHMRA AER Guidelines have been written for Marketing Authorisation Holders (MAH/CH) or Certificate Holders and market research agencies (MRA) on the collection and reporting of an Adverse Event (AE) of medicinal products and medical devices. The guidelines also include those working for a (MAH/CH), (MRA) or other organisations involved in Market Research (MR) activities, including employees and contractors working with or for a MAH/CH, MRA or other organisations engaged in MR.

TERMS AND DEFINITIONS

Term	Definition
Marketing Authorisation Holder / Certificate Holder (MAH/CH):	Organisation that is legally responsible for a medicinal product (medicine) or medical device; includes the MAH/CH contracting third party organisations who commission market research.
Market Research Agency (MRA):	Company that is commissioned to conduct market research on behalf of the MAH/CH; includes all subcontractors, fieldworkers, analysts, and interviewers engaged by the MRA.
Market Research (MR):	Its purpose is to gain insight through understanding and knowledge of customers, products, competitors, channels, and markets, to provide input or support decision-making. It involves the systematic collection, analysis, interpretation, and use of information about individuals, organisations or markets using the information gathering and analytical methods and techniques of the applied social, behavioural and data sciences, statistical principles, and theory. MR continues to evolve and adopt new methods, including usability testing, digital and social media sources; Generative Artificial Intelligence (Gen AI), Large Language Models (LLM), etc.
Syndicated Market Research:	Shared - both the findings and the costs - by a number of clients, but the data is owned by the MRA.
Adverse Event (AE):	Is an unintended and unfavourable response to a medicine, whether considered to be related to the medicine or medical device (i.e., causal relationship). Where it is reasonable to assume a causal relationship with a medicinal product this is referred to as an Adverse Reaction (AR). The MAH/CH PV will assess to determine if there might be a causal relationship or not for the purpose of AE reporting. It is not the role for market research to do this.
Special Report Situations (SPS):	Where a medicine is used outside of the marketing authorisation, including: • Overdose or Lower dose: use per administration or cumulatively above the recommended authorised maximum dose.

	• Off-label use: intentionally used for a purpose not within the intended use or authorisation for the medicine. • Misuse: intentional and inappropriate use outside of the marketing authorisation for the medicine. • Abuse: persistent or sporadic, intentional excessive use of a medicine accompanied by harmful physical or psychological effects [DIR Art 1(16)]. • Occupational exposure: contact with a medicine as a result of professional or non-professional occupation, e.g., splitting or cutting capsules and tablets. • Medication error: includes dispensing errors, accidental exposure, maladministration. • Lack of, or unexpected, therapeutic effect: where an additional benefit not previously known is reported. • Drug or drug-food interactions: effectiveness or toxicity of one medication is altered by the administration of another medicine(s), foods interfering with medication, e.g., grapefruit or grapefruit juice with some statins and other medicines. **Note:** MAH/CH/CH and MRA to agree additional SRSs, e.g., hospitalisation, pregnancy, breast feeding, transmission of infective agent, etc.
Product Quality Complaint (PQC):	Includes suspected failure of a medicine, damaged, missing, incorrect strength or colour of medicine, damaged packaging, missing patient information leaflet, broken or damaged needle or syringe, counterfeit medicine, etc.
Medical device[i]	Any instrument, apparatus, appliance, software, implant, reagent, material, or other article intended by the manufacturer to be used, alone or in combination, for human beings for specific medical purposes.
In-vitro diagnostic medical device[ii]	Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information.
Healthcare Professional (HCP)	A medically qualified person, such as a physician (e.g., primary, or secondary care), dentist, pharmacist, nurse, or as otherwise specified by local regulations.
Non-Healthcare Professional (Non-HCP)	A person such as a patient, relative of a patient or carer, payer who is not a healthcare professional.
Reporter	Data subject characterised by their qualification, e.g., physician, pharmacist, or patient, name or initials, address (e.g., organisation, department, street, city, zip or postcode, country), email or telephone/cell/mobile number.
Patient	Characterised by at least one of the following qualifying parameters: initials, data of birth, age/age group, or gender/sex.

i Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices

ii Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices

The principles relate to global PV requirements with reference to the European Medicines Agency's (EMA) Guideline on Good Pharmacovigilance practices (GVP), Module VI for the 'Collection, management, and submission of reports of suspected adverse reactions to medicinal products'[iii].

(ref. EMA 28 July 2017EMA/873138/2011 updated August 2017, Rev 2) and the Regulation (EU) 2017/745 on medical devices (CHAPTER VII; POST-MARKET SURVEILLANCE, VIGILANCE AND MARKET SURVEILLANCE) that became applicable on 26 May 2021 within the European Union (EU).

EPHMRA Members' Responsibilities

- MRAs and MAH/CH should comply with global, regional, and local regulatory Pharmacovigilance requirements, and with consideration to global, regional, and local codes and regulations, including data protection laws.
- These guidelines apply to MRAs, including subcontractors, fieldwork agencies, analysts, interviewers, and MAH/CH functions, e.g., global/regional/local market researchers, commercial/marketing, medical, health economics & outcomes research (HEOR), Market Access and others involved in MR activities.

1.INTRODUCTION

1.1 What is Pharmacovigilance?

Pharmacovigilance is 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem'.[iv] Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.

1.2 Basis of EPHMRA's AER Guidelines

These guidelines are to help those involved with healthcare market research, whether working for an MAH/CH or MRA or related contractors.

The guidelines offer best practice for an MAH/CH or an MRA or related contractors on collecting, forwarding, and managing Adverse Events (see Note below) for medicines and medical devices.

The following types of MR relating to medicines or medical devices where the commissioning company has responsibilities as a MAH/CH are in scope of these guidelines:

Primary Market Research (PMR): collected directly for the first time from the data subject to address a specific business issue or question.

Syndicated Research: is research funded by a MRA and the results are made available to anyone who wishes to purchase it. **Note:** an MAH/CH who purchases syndicated research data is responsible for reporting AEs associated with its medicines or medical devices to the relevant regulatory body.

Situations where AER arising during MR is not applicable:

- In-licensing opportunities or when the commissioning client is not the MAH/CH for a medicine(s) or medical device(s),
- Clinical trials.

Note: 'Adverse Events' is an umbrella term that covers Adverse Events (AE), Special Reporting Situations (SRS), and Product Quality Complaints (PQC). Refer Definitions.

iii https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf (accessed 05/02/2020)

iv The European Medicines Agency website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000258.jsp&mid=WC0b01ac0580b18c76 (accessed 05/02/2020)

2. RESPONSIBILITES FOR AE REPORTING IN MR STUDIES

Marketing Authorisation Holders / Certificate Holders (MAH/CH) have a legal and regulatory obligation to monitor, collect, report, and manage AEs associated with medicinal products (medicines), including prescription and non-prescription (e.g., over the counter (OTC), or medical devices for human use.

2.1 MAH/CH Responsibilities

- MAHs should take appropriate measures to manage all reports of suspected AEs associated with medicinal products for human use originating from unsolicited or solicited sources (see definitions).
- All MAH/CH employees - all functions, e.g., market research, business intelligence/information, marketing/ commercial, sales, etc), contractors and MAH/CH's representatives and third parties.
- Where a MAH/CH engages an MRA to provide services, it should require that the MRA reports AEs to the MAH/ CH.
- The MAH/CH's PV department is responsible for all associated follow-up actions, if appropriate.
- The MAH/CH's PV department is responsible for determining the severity of the AE and any causality.
- The commissioning MAH/CH should provide the MRA with a list of the brand and generic names of the medicines or devices for which they hold the marketing authorisation for the countries involved in the MR at the start of the MR.

2.2 MRA Responsibilities

- The MRA should agree the AE reporting requirements with the MAH/CH:
  - for medicines at the start of MR but before recruitment and fieldwork start
  - for medical devices as these may differ compared to medicinal products.
- Adverse Event reporting requirements associated with medical products should be checked with the Marketing Authorisation Holder before commencing any Market Research survey.
- AEs arising during MR where the MAH/CH medicine or medical device is mentioned by brand (trademark) name or its generic (International Non-proprietary Name /INN) should be reported.
- MRAs are not required to report AEs cited for a medicine or medical device where the commissioning client is not the MAH/CH, or a group of medicines or medical devices.
- Any type of AE, no matter the level of severity, should be reported by the MRA.
- The MRA can only provide the contact details of the data subject, whether a healthcare professional (HCP), e.g., physician, pharmacist, nurse, or non-HCP (e.g., patient, care giver, patient advisory group, payer, etc), where the MAH/CH if there is a lawful basis for this under the relevant data protection legislation.
- There may be different legal basis to process personal data depending on jurisdictions. Market research studies most commonly use the data subject's (Note 1) consent as a lawful basis for the transfer of personal data, but this is not the only option.
- If consent is used as the lawful basis for the transfer of personal data, this is a separate data processing operation and requires the data subject's[1] consent, whether a HCP, patient, carer or other.
- The MRAs should inform the data subject (i.e., HCP or non-HCPs) at appropriate times during the MR (e.g., recruitment, start of the interview) of the obligation to report AEs that may arise during MR to the MAH/CH
- Where the MRA subcontracts its MR obligations to a third party, e.g., a fieldwork agency, it should ensure the subcontractor undertakes AE reporting to comply with all legal, regulatory, and contractual requirements in general.
- In a co-promotion or co-marketing situation, the MRA should agree with the commissioning company the process for AE reporting.

Note 1: 'Data subject' is used in line with GDPR terminology for an individual, who may be an HCP or non-HCP, who participates in the MR interview.

3. COMPLETING AERs

- The AER may be completed at the end of recruitment or the MR interview - there is no need to interrupt the interview to do this.
- Provide as much detail as possible to complete the information required for AE reporting (refer reporting criteria below), preferably completing it with the help of the data subject.
- The MAH/CH should provide their PV department's contact details for the MRA (including sub-contractors, fieldwork) to forward AERs, i.e., email, fax number, other secure electronic method for the transfer of data. Note: Country level privacy rules for transfer of personal information should apply.
- AEs must be reported to the MAH/CH within one business day of the MRA or their subcontractor becoming aware of it.
- The only exceptions are:
  - Syndicated studies (either based on primary and/or secondary MR) where data are collected independently of individual companies and are available for purchase by multiple Healthcare companies. Refer Sources for AEs - Unsolicited - MAH/CH's responsibility to report unsolicited AEs
  - Longitudinal patient databases.

3.1 AE Reporting Criteria

The MAH/CH's PV is responsible for managing and reporting valid Individual Case Safety Reports (ICSR) of suspected AEs to the relevant regulatory authorities.

The MAH/CH's PV is expected to follow-up AERs where information is missing.

3.2 Four minimum criteria are required:

I. One or more identifiable reporter(s), i.e., data subject(s),

II. Identifiable patient or group of patients,

III. One or more suspected medicinal product(s) or medical device(s),

IV. Suspected Adverse Event (includes serious and non-serious AERs, SRSs and PQCs).

3.3 Sources for AEs

The two types of AEs that may arise for medicinal products or devices are classified as either 'solicited' or 'unsolicited' (see below). Both solicited and unsolicited AEs during MR interviews with HCPs or non-HCPs should be reported to the MAH/CH's PV department.

- **Solicited:** includes AEs "derived from organised data collection systems, including surveys of patients or healthcare professionals", e.g., personal/telephone/web-based interviews, surveys (paper, online, etc).

- **Unsolicited:** "not related to any organised data collection systems" e.g., European Medicines Agency (EMA) include internet or digital sources, including social media, as 'unsolicited'. Refer section 7.3 for MAH/CH's responsibility reporting unsolicited AEs associated with its own medicinal products or devices identified in syndicated studies (purchase of independent multi-company studies based on either primary and/or secondary MR).

4. CONSENT AND AE REPORTING

4.1 Transfer of personal information in AERs

The data subject's personal information, e.g., name, contact details, can only be forwarded to the MAH/CH if the data subject has provided consent or there is an alternative lawful basis in place (refer EU GDPR, UK GDPR, and any other applicable data protection legislation).

- If consent is being used this must be provided before any data are transferred by the MRA to the MAH/CH.
- Personal information must not be forwarded to the MAH/CH if consent has not been given, or there isn't another alternative lawful basis in place (e.g.: Legitimate Interests supported by a Legitimate Interest Assessment; note: the lawful basis must be agreed before any processing can take place) although the subject can still take part in the MR. Under these circumstances the MRA must forward AEs as an anonymous report.
- If the data subject has already notified the relevant authorities or MAH/CH, AEs from MR should still be forwarded to the MAH/CH.
- When relying on consent for receiving and transferring personal data the sponsoring organisation could be named when personal information is obtained during MR (EU GDPR, 2018). For very specific studies, such as in-licensing or requirement of local codes, e.g., Denmark, the sponsor should not be identified. The data subject should provide their consent to participate on this basis (preferably documented) or decline.
- Consent for processing personal data for AE reporting purposes may be obtained at the start or end of the interview, as it is not essential for participating in MR.
- Information about an AE from a MR subject that relates to someone else's experience e.g., a patient's carer, relative or friend, it must be reported to the MAH/CH without the personal details of the individual who experienced it as they have not consented to their details being forwarded.

4.2 Patient 'special category' personal data

- Personal data that is especially sensitive is classed as 'special category' and requires additional security.
- 'Special category' personal data (EU GDPR, 2018) includes race or ethnicity, sexual orientation, biometric or genetic data, religious beliefs, data on health problems.
- Patients must provide explicit consent if they are providing 'special category' personal data.

The above refers to EU GDPR, 2018 regulation for guidance. The MRA should check applicable local and regional data protection requirements and agree with the MAH/CH how this should be managed at the start of the MR. This should apply to the full data management process and documented (e.g., contract).

5.REPORTING FORMATS

The two common AE reporting formats are:

- **AER Form:** collecting information during a MR interview, e.g., personal or group interviews. There is no need to interrupt the flow of the interview as the form can be completed at the end. Collect as many details as possible for minimum reporting criteria. The MRA employee/interviewer/agency fieldworker collecting the information or the person filling in the reporting form is responsible to sign the AE reporting forms before these are forwarded to the MAH/CH.
- **Tabulation of aggregate data:** information provided in tables for review in aggregate or a large volume of AEs is anticipated, e.g., online surveys, particularly those collecting data on prescribing behaviour and potentially conjoint studies. The reporting format typically includes the number of MR subjects citing AEs but should be agreed with the MAH/CH before the MR starts.

5.1 Format of AE Tabulations

AER tabulations, e.g., structured, or semi-structured surveys, should include:

- Number of MR subjects where an AE was cited.
- Question base i.e., how many MR subjects answered the question.

The **format** should be agreed with the MAH/CH in **advance of data processing.**

5.2 AE Reconciliation Process

Confirmation and/or reconciliation of AEs is a requirement upon completion of a MR study.

A summary of all AEs identified during the MR is to be 'reconciled' with or checked against the individual AEs forwarded to the MAH/CH's PV during the MR to ensure all AEs are accounted for. The MRA should agree the reconciliation process as some MAH/CHs use a digital AER system.

The reconciliation form should be completed at the period agreed at the start of the study or contract with the MAH/CH's PV (e.g., end of fieldwork or study), even if no AEs were reported, i.e., report as "0" or "No AEs".

This applies to irrespective of whether information is collected using AE Report Form or tabulation of aggregate data.

The AER Reconciliation form should include for each country where MR was undertaken, the number of AEs identified (not just reported), summary by each AE of MR subject's ID, the medicine or medical device, and the AE details.

5.3 Syndicated Studies

Syndicated research (refer section 1 Introduction) is conducted by the MRA independently of any healthcare company (e.g., pharmaceutical, Biotech) and the results and data purchased by multiple clients, and there is no legal responsibility for the MRA to report AEs.

Responsibility to collect AEs lies with the MAH/CH that purchases the syndicated data.

The MAH/CH should forward any AEs identified from a purchased syndicated data to their PV department. The MAH/CH may however request the MRA to provide the data in an appropriate AE reporting format.

Where confidential or proprietary questions are added to a syndicated survey by a MAH/CH, the data from these questions must be treated in the same way as MR commissioned from the MRA by the MAH/CH, i.e., the MRA should forward AEs to the MAH/CH PV department.

5.4 Longitudinal Patient Databases

Longitudinal patient databases e.g., GPRD (General Practice Research Database) are out of scope.

The Council for International Organisation of Medicinal Sciences (CIOMS) suggests that there is no obligation to search through such databases for individual AEs as this will give rise to spurious signals and conclusions however if they are found (deliberately or co-incidentally), they should be forwarded to the MAH/CH.

Data from longitudinal patient databases are different to tabular AE summaries collected from MR as they have not arisen from a defined project and are for multiple users, not just acquired by an MAH/CH for internal use (unlike commissioned MR).

5.5 AE reporting where social media is used in MR

- AE reporting requirements apply where social media, or social media associated techniques (e.g., online communities) are used as a source of MR data, i.e., treated as any other type of MR study. The MAH/CH and MRA should agree the process for collecting and reporting AEs associated with their medicinal products or medical devices before the start of the study.
- This applies to public and private sites, passive, and active approaches and to company sponsored and non-company sponsored websites, which should be monitored during fieldwork for AEs.

- If a company chooses to listen-in to or 'scrape' from non-company sponsored sites, whether public or private (with consent) it is recommended that the 'listened' to pages should be monitored for AEs for the period of the listening-in activity only.
- There is no obligation for researchers to monitor non-company sponsored sites routinely for AEs if they are not being used for a MR purpose.

5.6 Who to Direct Queries To?

MRAs should direct queries relating to the AER process to the MAH/CH PV department, or MR contact for guidance.

6. DATA RETENTION

6.1 Responsibility for AER data retention

- The MAH/CH is responsible for retaining certain types of AE data for as long as necessary.
- The MAH/CH and MRA should agree on data retention periods for all relevant AER data and material, including measures to be followed at the end of the agreed retention period, i.e., deletion and/or transfer of AER data and material being returned to the MAH/CH if longer retention is required.

6.2 Longer PV retention and Personal Data Processing

- It is recommended that appropriate technological or operational measures are taken to minimise the risk of processing personal data for longer period of times, if not strictly necessary and in compliance with relevant data protection legislation.
- Where possible MAH/CH and MRAs shall agree that relevant AER data and documentation is either anonymised or pseudonymised at the earliest opportunity.

7. DISCLOSURES OF TRANSFER OF VALUE (TOV)

In general, disclosure requirements under European Federation of Pharmaceutical Industries and Associations (EFPIA) code, 2019 and the US Physicians Payment Sunshine Act, 2010 relating to Transfer of Value (TOV) do not require MRAs to identify the names of the HCPs who report AEs during MR studies.

These are considered as solicited AE reports. The HCP's personal data are provided to the MAH/CH's PV for the purpose of AE reporting only and is dependent on the HCP's consent to pass the information.

8. QUALITY MANAGEMENT AND TRAINING

- The MAH/CH and MRAs should have clear and comprehensive operating procedures in place for the collection, forwarding and management of Adverse Events.
- PV training requirements including AERs should be agreed between the MAH/CH and MRA before the start of the MR.
- PV training including AER should be undertaken to ensure all individuals directly involved understand the requirements and what actions is needed.

The MAH/CH should supply their AER form, or the EPHMRA AER template may be used.

RESOURCES

Websites:

- European Medicines Agency: https://www.ema.europa.eu/en
- European Medicines Agency Pharmacovigilance training materials: https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance/pharmacovigilance-training-materials
- EPHMRA (European Pharmaceutical Market Research Association): https://www.ephmra.org/
- EPHMRA Code of Conduct, AE Guidelines & AER Proformas: https://www.ephmra.org/code-conduct-aer
- BHBIA (British Healthcare Business Intelligence Association): https://www.bhbia.org.uk/
- Centers for Medicare and Medicaid Services (CMS) final rule on the Sunshine Act 02/08/2013 : Federal Register: Medicare, Medicaid, Children's Health Insurance Programs; Transparency Reports and Reporting of Physician Ownership or Investment Interests
- CMS 42 CFR Parts 402 and 403 Medicare, Medicaid, Children's Health Insurance Programs; Transparency Reports and Reporting of Physician Ownership or Investment Interests; Final Rule https://www.cms.gov/OpenPayments/Downloads/Affordable-Care-Act-Section-6002-Final-Rule.pdf
- Open Payments Law and Policy | CMS

Glossary of abbreviations

AE	Adverse Event
AER	Adverse Event Reporting
AR	Adverse Reaction
EMA	European Medicines Agency
EU	European Union
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
MAH/CH	Marketing Authorisation Holder / Certificate Holder
MR	Market Research
MRA	Market Research Agencies (including company and/or individuals conducting MR, including subcontractors, fieldwork analysts and interviewers)
PQC	Product Quality Complaint
SRS	Special Reporting Situations