ephmra

Adverse Event Reporting (AER) Guidelines -

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These guidelines provide the principal requirements of Pharmacovigilance (PV) reporting for individuals or organisations involved in market research (MR) activities within the healthcare industry. This includes those working for a Marketing Authorisation Holder (MAH), Market Research Organisation (MRA) or other organisations involved in MR activities. It applies to employees and contractors working with or for a MAH, MRA or other organisations engaged in MR.

The principles relate to global PV requirements with particular 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'[1].
(ref. EMA 28 July 2017EMA/873138/2011 updated August 2017, Rev 2) and also 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.

EPHMRA Members' Responsibilities

- MRAs and MAHs 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 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

Pharmacovigilance

Pharmacovigilance (PV) is '*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem*'.[2]

Before a regulator authorises a medicine or medical device for use, evidence on the safety and efficacy is limited to clinical trials conducted in defined patient population(s) and for relatively short time periods. After regulatory authorisation the medicine or the medical device may be used in a broader patient population and for longer time periods where new or an increase in known side effects may appear.

The Marketing Authorisation Holder (MAH) is responsible for monitoring, collecting, and reporting suspected adverse events associated with medicinal products (medicines) or medical devices for human use including prescription and non-prescription, e.g. over-the-counter (OTC), and managing the safety of all its medicines and medical devices during their use in healthcare practice.

Basis of Guidelines

EPHMRA's Adverse Event Reporting Guidelines detail the scope of the responsibilities and requirements of the process for Adverse Event reporting for market research activities.

These Guidelines outline best practice for MRAs on collecting, forwarding, and managing Adverse Events, Special Reporting Situations, and Product Complaints for medicines and medical devices (refer Definitions). It applies to market research connected with medicinal products or medical devices in therapeutic areas authorised for human use where a company has responsibilities as a Marketing Authorisation Holder (MAH) / Certificate Holder. It does not apply to:

- In-licensing opportunities or when a company is not the MAH/Certificate Holder;
- Clinical trials.

The term 'Adverse Event' is used as an umbrella term within these guidelines. It encompasses Adverse Events (AE), Special Reporting Situations (SRS), and Product Complaints (PC). Refer Definitions.

2.DEFINITIONS

2.1 Adverse Event (AE)

An Adverse Event is an unintended and unfavourable response to a medicine, whether or not 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 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 and as such the term AE is used in the EPH MRA AER Guidelines.

2.2 Special Reporting Situations (SRS)

Situations 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 and MRA to agree additional SRSs, e.g. hospitalisation, pregnancy, breast feeding, transmission of infective agent, etc.

2.3 Product Complaint (PC)

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.

2.4 A medical device[3]

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.

2.5 In vitro diagnostic medical device[4]

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.

3.RESPONSIBILITIES FOR AE REPORTING FOR MARKET RESEARCH STUDIES

Who is responsible?

- **All MAH personnel** (e.g. market research, business intelligence/information, marketing, etc) and including representatives and contractors.
- **All Market Research Agency (MRA) personnel** working on behalf of the MAH, including the agency, sub-contractors, recruiters and fieldwork, interviewers, analysts, etc.
- MRAs should have a contract in place with all their suppliers on the required AE reporting process.

Responsibilities and processes

- The MAH is primarily responsible for compliance with global, regional, and local PV regulations and for assessing whether MR studies may generate AEs, SRSs, or PCs.
- Where a MAH engages an MRA to provide MR services, explicit procedures and detailed agreements for AE reporting should be put in place, i.e. contractual arrangements, to ensure the MAH can comply with regulatory requirements.
- The MAH's PV is responsible for managing reporting of the Individual Case Safety Report (ICSR), recording incomplete AE reports (not a valid ICSR), and all associated follow-up actions, if appropriate.
- The MRA can only provide the contact details of the AE Reporter, whether a HCP, patient, carer or other, to the MAH 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 (refer Note below) 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 participant's consent, whether a HCP, patient, carer or other. This may be done at the end of the interview.
- 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.
- Co-promotion or co-marketing situation: the MRA should agree with the commissioning company the process for AE reporting.

Note: 'Data subject' is used in the EPHMRA guidance in line with GDPR terminology rather than participant or research subject.

Responsibilities to Data subjects

All data subjects, whether HCPs or patients, should be informed at appropriate times (e.g. at recruitment, start of interview), of the requirement for MAH's to report AEs arising during MR.

Disclosure of Transfer of Value

- In general, disclosure requirements under European Federation of Pharmaceutical Industries and Associations (EFPIA) code, 2019[5] and the US Physicians Payment Sunshine Act, 2010[6] 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's PV for the purpose of AE reporting only and is dependent on the HCP's consent to pass the information.

4.AE REPORTING REQUIREMENTS

- The MRA should agree the AE reporting requirements with the MAH at the start of MR but before recruitment and fieldwork start.
- The MRA should also agree AE reporting requirements with the MAH associated with **medical devices** as these may differ compared to medicinal products.
- AEs for any medicines or medical devices where the commissioning client holds the marketing authorisation need to be reported to the MAH's PV.
- AEs should be forwarded where the reporter uses either the company's brand or a generic name.
- The commissioning MAH can provide a list of the medicines and devices for which they hold the marketing authorisation for the countries included in the study, including brand and generic names, to the MRA at the start of the MR.
- MRAs are not required to collect AEs cited for other companies' medicines, or report AEs cited in groups of drugs.

Any type of AE, no matter the level of severity, should be reported by the MRA.

4.1 When and how to complete 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 reporter.

The MAH should provide 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.

4.2 Quality Management and Training

The MAH and MRAs should have clear and comprehensive operating procedures in place for the collection, forwarding and management of Adverse Events.

PV training requirements including AER should be agreed between the MAH and MRA before the start of the MR (some differences between MAH's requirements).

PV training including AER must be undertaken to ensure all individuals directly involved understand the requirements and what actions is needed.

The MAH should supply their AER form, or the EPHMRA AER template may be used (access to the electronic system can be arranged).

4.3 Categories of AE sources for Market Research studies

There are two types of AE reports in the post-authorisation phase: "*reports originating from unsolicited sources and those reported as solicited*."[7]

Usually AEs reported during MR studies are solicited, but it's important to recognise those that arise as unsolicited, spontaneous AEs.

- **Solicited**: includes AEs "*derived from organised data collection systems, including surveys of patients or healthcare professionals*"[8], e.g. personal/telephone/web-based interviews, surveys (paper, online, etc).
- **Unsolicited**: *"not related to any organised data collection systems"*[9] e.g. syndicated studies, social media/ digital listening (EMA classify as internet/digital media as unsolicited spontaneous).

Solicited and unsolicited AEs during MR studies with healthcare professional and / or consumers (refer definitions below) should be reported to the MAH's PV.

4.4 Primary sources of AEs: Healthcare Professionals and Consumers

Healthcare Professional (HCP): *"defined as a medically qualified person, such as a physician, dentist, pharmacist, nurse, coroner or as otherwise specified by local regulations"*[10]

Consumer: *"is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, relative of a patient or carer"*.

NOTE: EPHMRA guidelines use **patient** as the more familiar and most used term in the healthcare industry, rather than consumer. However, it is important to note AE reporting still applies other types of 'non-HCP' participating in MR studies, e.g. a relative, friend or carer of the patient.

4.5 AE Reporting criteria

The MAH's PV is responsible for managing and reporting valid Individual Case Safety Reports (ICSR) of suspected AERs to the relevant regulatory authorities. Four minimum criteria are required for a valid ICSR (see below).

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

4.6 Minimum criteria for valid ICSRs

a. One or more identifiable reporter(s),
b. Identifiable patient or group of patients,
c. One or more suspected medicinal product(s) or medical device(s),
d. Suspected Adverse Event.

- **Reporter:** 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.
- **Medicinal product or medical device**: medicine(s) or medical device(s) where the commissioning client is the MAH (identified by brand or generic name).
- **Suspected Adverse Event**: includes serious and non-serious AERs, SRSs and PCs.

5.CONSENT AND AE REPORTING

5.1 Transfer of personal information in AERs

- The reporter's personal information, e.g. name, contact details, can only be forwarded to the MAH if the participant has provided consent or there is an alternative lawful basis in place[11] (refer GDPR, 2018).
- If consent is being used this must be provided before any data are transferred by the MRA to the MAH.
- Personal information must not be forwarded to the MAH 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 has to 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 reporter has already notified the relevant authorities or MAH, AEs from MR should still be forwarded to the MAH.
- When relying on consent for receiving and transferring personal data the sponsoring organisation could be named when personal information is obtained during MR (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 respondent 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 without the personal details of the individual who experienced it as they have not consented to their details being forwarded[12].

5.2 Patient 'special category' personal data

- Personal data that is especially sensitive is classed as 'special category' and requires additional security.
- 'Special category' personal data (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 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).

6.REPORTING AEs

- AEs must be reported to the MAH within one business day of the MRA or their subcontractor becoming aware of it.
- The only exceptions are:
  - Syndicated studies (either based on primary or secondary MR) where data are collected independently of individual companies and are available for purchase by multiple Healthcare companies.
  - Longitudinal patient databases.

7.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. **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 before the MR starts.

  Refer EPHMRA AE Reporting Form template

7.1 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 in **advance of data processing.**

7.2 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's PV during the MR to ensure all AEs are accounted for. The MRA should agree the reconciliation process as some MAHs use a digital AER system.

The reconciliation form should be completed at the time period agreed at the start of the study or contract with the MAH'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.

7.3 Syndicated Studies

There is no legal responsibility for the MRA to forward AEs for syndicated studies. Syndicated primary market research studies are conducted by the MRA independently of any healthcare company (e.g. pharmaceutical, Biotech) and the results and data purchased by multiple clients.

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

The MAH should forward an AE identified from a purchased syndicated study to their PV. The MAH may however request the MRA to provide the data in an appropriate AER format.

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

7.4 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.

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 for internal use (unlike commissioned MR).

7.5 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 MR study. The MAH 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.

7.6 Who to Direct Queries To?

MRAs should direct queries relating to the AER process to the MAH's PV or MR contact as this is the most important source for guidance.

RESOURCES - WEBSITES:

- EPHMRA website
- BHBIA website (UK)
- CMS's final rule on the Sunshine Act: www.federalregister.gov/ articles/2013/02/08/2013-02572/medicare-medicaid-childrens- health-insurance-programs-transparency-reports-and-reporting-of
- European Union website
- European Medicines Agency
- https://www.cms.gov/OpenPayments/Downloads/Affordable-Care-Act-Section-6002-Final-Rule.pdf
- Physician Payment Sunshine Act Final Rule: Definitions, Policy and Medicine, Feb. 5, 2013: www.policymed.com/2013/02/physician- payment-sunshine-act-final-rule-definitions.html
- US Government Sunshine Act

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	Marketing Authorisation Holder
MR	Market Research
MRA	Market Research Agencies (including company and/or individuals conducting MR, including subcontractors, fieldwork analysts and interviewers)
PC	Product Complaint
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
SRS	Special Reporting Situations

Footnotes:

1 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)

2 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)

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

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

5 https://www.efpia.eu/media/413022/efpia-code-2019.pdf Transfers of Value (ToV), p8 (Direct, or indirect where the Member Company knows or can identify the Recipient who will benefit from the ToV

6 https://www.govinfo.gov/content/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf (accessed 23/02/2020), SEC. 6002. PUBLIC LAW 111–148—MAR. 23, 2010 TRANSPARENCY REPORTS AND REPORTING OF PHYSICIAN OWNERSHIP OR INVESTMENT INTERESTS.

7 EMA GVP, Module VI (Rev 2), EMA/87138/2011, Section VI.B.1. Collection of individual safety reports

8 EMA GVP, Module VI (Rev 2), EMA/87138/2011, Section VI.B.1.2. Solicited reports

9 EMA GVP, Module VI (Rev 2), EMA/87138/2011, Section VI.B.1.1.1. Unsolicited spontaneous reports

10 EMA GVP, Module VI (Rev 2), EMA/87138/2011, Section VI.A.1.4. Primary source, healthcare professional, consumer

11 European Union (EU) Regulation (EU) 2016/679, (April 2016). General Data Protection Regulation. Came into force May 2018. https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1532348683434&uri=CELEX-:02016R0679-20160504 (accessed 26/02/2020).

12 https://www.bhbia.org.uk/guidelines-and-legislation/AE-PC-SRS-Guidance (accessed 21/02/2020). BHBIA/ABPI (2018). Guidance notes on collecting adverse events, product complaints and special reporting situations during market research. August 2018, Section 4.2, p7