EphMRA Adverse Event Reporting Guidelines 2015

Based upon the Guideline on good pharmacovigilance practices (GVP)
Module VI – Management and reporting of adverse reactions to medicinal products
European Medicines Agency 22 June 2012 EMA/873138/2011

Introduction

EphMRA's Adverse Event Reporting Guidelines detail the scope of market researchers' adverse event reporting responsibilities and the requirements of the process.

Details of suspected adverse events (including adverse reactions) that meet the qualifying and minimum reporting criteria should be forwarded by the market research agency and their sub-contractors to the nominated contact within the market authorisation holder that commissioned the market research. This information is assessed by the pharmacovigilance department and if appropriate it will be reported to the regulators as an individual case safety report and/or within a periodic safety update report.

Legal Basis

EphMRA's Adverse Event Reporting Guidelines are based upon legal requirements

- Detailed in Directive 2001/83/EC and Regulation (EC) No 726/2004, as regards the collection, data management and reporting of suspected adverse reactions associated with medicinal products for human use authorised in the European Union
- Interpreted within the European Medicines Agency's Guidelines on good pharmacovigilance practices, particularly volume VI Management and reporting of adverse reactions to medicinal products

EphMRA Members' Responsibilities

EphMRA members should understand and adhere to the EphMRA Adverse Event Reporting (AER) Guidelines and ensure others involved in market research (MR) abide by the guidelines too – such as suppliers and sub contractors as well as colleagues in marketing, sales and national/local market researchers.

The AER Guidelines apply irrespective of which functional area or organisation/department within the marketing authorisation holder (MAH)/pharmaceutical company initiated the work i.e. whether the work is commissioned by the department responsible for market research, marketing or another function.

Responsibility to Respondents

All respondents whether healthcare professionals or not should be informed at recruitment of the requirement for MAHs to report adverse events that arise during MR.

Glossary & Terminology

AE	Adverse Event
AER	Adverse Event Reporting
AR	Adverse Reaction
EU	European Union
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MR	Market Research
PSUR	Periodic Safety Update Report
PV	Pharmacovigilence

EMA Guidelines:

"All applicable legal requirements detailed in this Module are usually identifiable by the mod verb "shall".

Guidance for the implementation of legal requirements is provided using the modal verb "should"."

Important Background Information

The European Medicines Agency categorises adverse event reports as solicited or unsolicited depending upon their source. With regard to market research sources solicited reports include AEs from MR studies except when social media/digital listening is used, AEs arising from digital listening are classified by the EMA as unsolicited reports.

Adverse events may be collected within Individual Case Safety Reports or as Signals within Periodic Safety Update Reports collated by the marketing authorisation holders' pharmacovigilance department and forwarded to the regulators.

Solicited reports are *"derived from organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, compassionate use or name patient use, or information gathering on efficacy or patient compliance."* The European Medicines Agency (EMA) state that *"safety reports originating from market research (MR) programmes should be considered as solicited reports. A MR programme refers to the systematic collection, recording and analysis by a marketing authorisation holder of data and findings about its medicinal products, relevant for marketing and business development.*

Unsolicited reports include spontaneous reports, literature reports, other sources e.g. lay press and those from the internet or digital media. The EMA states that:

- *"MAHs should regularly screen internet or digital media under their management or responsibility, for potential reports of suspected ARs. In this aspect, digital media is considered to be company sponsored if it is owned, paid for and/or controlled by the MAH*
- *If a MAH becomes aware of a report of suspected AR described in any non-company sponsored digital medium, the report should be assessed to determine whether it qualifies for reporting"*

Consequently AEs arising from the use of social media to gather market research information i.e. digital listening will be unsolicited reports whilst those cited during any other form of online market research, face to face, telephone or postal market research will be solicited reports. This does not make any difference to market research activities.

Individual Case Safety Report (ICSR) refer "*to the format and content for the reporting of one or several suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time. A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction and at least one suspect medicinal product*."

Signals are "*information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action*."

ICSRs are forwarded directly to regulators and ICSRs and signals are incorporated into **periodic safety update reports** these are the"*format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase*."

Source: Module VI – Management and reporting of adverse reactions to medicinal products, European Medicines Agency 22 June 2012 EMA/873138/2011

	EMA Guidelines	EphMRA Guidelines
Scope	Suspected adverse reactions (serious and non-serious) and emerging safety issues associated with medicinal products for human use authorised in the EU. A medicinal product is for: – Treating or preventing disease in human beings – Restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis Applicable to medicinal products authorised in the EU but also to any such medicinal products commercialised outside the EU by the same marketing authorisation holder (MAH) All ARs suspected to be related to any of the active substances being part of a medicinal product authorised in the EU. The pharmacovigilance (PV) rules laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004 do not apply to investigational medicinal products and non-investigational medicinal products used in clinical trials conducted in accordance with Directive 2001/20/EC21. Independent of the strengths, pharmaceutical forms, routes of administration, presentations, authorised indications, or trade names of the medicinal product. Where a case of ARs is reported to be related only to a therapeutic class, it is considered incomplete and does not qualify for reporting.	AER Guidelines apply to authorised medicines for human use. AER applies to both prescription and non-prescription bound (over the counter) medicines. AER requirements associated with medical devices should be agreed with the MAH. AEs that relate to any product for which the drug company has or expects to have EU marketing authorisation need to be forwarded. Market researchers are not required to collect events cited for other companies' products. Serious and non-serious adverse reactions should be included. It is not the market researcher's responsibility to decide what is and is not serious. AEs should be forwarded whether cited in the company's brand or generic name. AEs cited in groups of drugs should not be forwarded. Companies should provide agencies with a list of products for which they hold or are applying for the marketing authorisation.
Definition of an Adverse	Any untoward medical occurrence in a patient or clinical trial subject	The definition of an adverse event is taken from the EMA's Guideline on

Event **Definition of an Adverse Reaction**	administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors. Plus: – Suspected or confirmed falsified product or quality defects – Suspected transmission via a medicinal product of an infectious agent – Misinformation in the product information – Use of a medicinal product during pregnancy or breastfeeding – Lack of therapeutic effect . . . unless the reporter has specifically stated that the outcome was due to disease progression – For vaccines , cases of lack of therapeutic effect should be reported – Drug interactions – drug/drug, drug/food, drug device and	good pharmacovigilance practices (GVP) Annex I – Definitions 2012. Adverse event is an 'umbrella term' that includes adverse reactions and product complaints. An adverse reaction is directly linked to the medicine i.e. is caused by the medicine, the adverse event may not be. Lack of efficacy whether unexpected or expected needs to be reported unless it is due to disease progression i.e. the drug would have been expected to work but the patient's disease worsened.

	drug/alcohol	
Causality	The definition of an AR implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event If the primary source has made an explicit statement that a causal relationship between the medicinal product and the adverse event has been excluded and the receiver (competent authority or marketing authorisation holder) agrees with this, the report does not qualify as a valid ICSR since the minimum information is incomplete.	It is not the market researcher's responsibility to assign causality AEs should be reported even if the reporter states that there is no link/causal relationship between the event and the drug. This may be the case but the decision not to forward the event can only be taken by the MAH.
Minimum Reporting Criteria	A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction and at one suspect medicinal product. 1. Identifiable reporter One or more identifiable reporter characterised by qualification (e.g. physician, pharmacist, other HCP, lawyer, consumer or other non-HCP) name, initials or address. There are several types of primary sources [reporter]: – A healthcare professional is defined as a medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner or as otherwise specified by local regulations. – A consumer is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, relative of a patient or carer.	For the purpose of reporting suspected AEs, the minimum data elements for a case are: 1. Identifiable reporter 2. Identifiable patient or patients 3. Suspected adverse event 4. Suspected medicinal product. Researchers should identify events based on the information cited, they are not required to probe for missing reporting criteria. THE FOLLOWING GUIDELINE HAS BEEN AGREED WITH THE EMA BUT THE ISSUE OF AER FOR UNIDENTIFIABLE AND UNTRACEABLE PATIENTS IS STILL UNDER CONSIDERATION AND EphMRA IS AWAITING FURTHER GUIDANCE FROM THE EMA If a potential adverse event is mentioned in the context of a group of patients it is essential to establish that the patients actually exist i.e. they are/were real patients actually seen. Reporters should be able to state how many patients have been impacted if it is suggested there is more than one. If

	2. Identifiable patient One single identifiable patient characterised by initials, patient identification number, date of birth, age, age group or gender. The information should be as complete as possible. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular population. When collecting reports of suspected ARs via the internet or digital media, the term "identifiable" refers to the possibility of verification of the existence of a reporter and a patient via verifiable contact details (e.g. an email address under a valid format) 3. Suspected medicine One or more suspected substance/medicinal product Biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the name of the product and the batch number MAH responsibilities apply to reports related to medicinal products for which ownership cannot be excluded on the basis of one the following criteria: medicinal product name, active substance name, pharmaceutical form, batch number or route of administration. 4. Suspected adverse reaction One or more suspected AR. The report does not also qualify as a valid ICSR if it is reported that the	this information is not available, the adverse event does not need to be forwarded. When forwarding AEs arising from the use of social media to gather market research information i.e. digital listening (spontaneous AEs), for both the reporter and patient (it may be the same person) it should be possible to verify the individual's existence via contact details even if these are not to be used. AEs should be reported even if the details are incomplete: 1. Reporter – in MR research there will always be a reporter and it will generally be known if the reporter is at least a HCP or a non-HCP 2. Patient – there should be a patient or a specific number of patients. Patient details should be collected if possible 3. Drug – there must always be a drug for which the company commissioning the MR is the MAH 4. Adverse Event – there must always be an AE of some type even if the detail is sparse Describe the AE as clearly and carefully as possible, try to avoid paraphrasing

	patient experienced an unspecified AR and there is no information provided on the type of AR experienced. Reports, for which the minimum information is incomplete, should nevertheless be recorded within the pharmacovigilance system for use in on-going safety evaluation activities Reports should include the verbatim text as used by the primary source or an accurate translation of it	
Passing on Reporter Contact Details	Whenever possible, contact details for the reporter should be recorded so that follow-up activities can be performed. However, if the reporter does not wish to provide contact details, the ICSR should still be considered as valid providing the organisation who was informed of the case was able to confirm it directly with the reporter.	Researchers must ask the reporter if they are willing to provide their contact details and allow these to be passed to the MAH so that if required PV follow up is possible. Contact details (i.e. personal data) cannot be passed on without permission. When asking for permission to pass on contact details, it must be clear that the MAH can only use the personal data for AE investigation purposes and reporters must be made aware that they may be re-contacted with regard to the AE by the MAH. Potential AEs can be forwarded without contact details if permission to pass these on is denied. In Germany MR industry guidelines prohibit requesting personal data to pass to the client company. It may be practical to request that the MR agency

		facilitates any follow up between the MAH's PV department and the reporter (so protecting the reporter's anonymity) by allowing questions and answers to be passed via the agency with no personal data passed to the MAH.

Consent for Further Follow Up from a Consumer	Attempts should be made to obtain consent to contact a nominated HCP to obtain further follow-up information	Non-HCPs/consumers should be asked if they are willing to consent to supply contact details for the relevant HCP. If they do not consent, the AE should still be forwarded
Duplication of AE Reports	If the primary source may also have reported the suspected AR to another concerned party, the report should still be considered as valid	Even if the primary source/reporter has already reported the AE directly to the authorities or the MAH, it must be reported from the MR
Who Should Forward AEs	Any personnel of the marketing authorisation holder, including medical representatives and contractors.	All employees of the commissioning pharmaceutical company/MAH - market researchers, sales representatives, clinical research associates etc. All organisations and individuals contracted to work on behalf of the MAH including MR agencies Any sub-contractors used by the MR agency e.g. freelance recruiters, interviewers, coders – MR agencies should have a contract in place with all their suppliers too
Reporting Timetable	The clock for the reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the national or regional PV centre of a competent authority or of any personnel of the marketing authorisation holder, including medical representatives and contractors. This date should be considered as day zero. In practice this is the first business day the receiver becomes aware of the information.	AE reporting forms should be completed and forwarded to the MAH within one business day of the first awareness of the potential AE - EMA guidelines refer to "next working day", "first business day" and AER to be "done immediately when becoming aware of them"
Reporting Formats		There are two potential AER formats: – AE Reporting Form - generally used when responses are generated or

		analysed on a respondent by respondent basis e.g. from one to one interviews or group discussions – Tabulations of aggregate data - appropriate when AE data are only reviewed in aggregate so AEs can only be detected at the point of coding or analysis at intervals during fieldwork or at the end of data collection e.g. an online survey The reporting format should be agreed with the MAH at the project start

AE Reporting Form		The MAH should supply the AER form EphMRA provide a standard AER form that can be used
When and How To Complete AER Forms		Complete the AER form at the end of the interview – there is no need to interrupt the interview to fill it in Collect as many details on the form as possible, ideally complete it with the help of the reporter The company should provide an email or fax address to which completed AER forms should be sent
The Format of AE Tabulations		AER tabulations should show: – Number of respondents citing event – Question base i.e. how many respondents answered the question The format should be agreed with the MAH in advance of data processing
Quality Management and Training	Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant	Both client companies and market research agencies should have clear and comprehensive operating procedures in place for the collection of adverse events – these should be exchanged upon project commissioning at the latest and AER responsibilities built into contracts. Training should be undertaken to ensure that all those directly involved

	with applicable requirements. Personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse event collection and reporting in accordance with internal policies and procedures. Where the MAH has set up contractual arrangements with a person or an organisation, explicit procedures and detailed agreements should exist between the MAH and the person/organisation to ensure that the MAH can comply with the reporting obligations. These procedures should in particular specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities and should avoid duplicate reporting to the competent authorities.	in AE reporting have a clear understanding of how to recognise an AE and what action is required

Confirmation and/or Reconciliation Process	When transfer of PV data occurs within an organisation or between organisations having concluded contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken.	Confirmation and/or reconciliation involves production of a summary of all AEs identified during the project to be 'reconciled' with/checked against the individual AEs received during the MR study ensuring all AEs are accounted for An AE reconciliation form should be completed at the end of each MR study (not at the end of fieldwork) even if no AEs were forwarded and irrespective of whether data collection forms or tables were used Reconciliation form should include: – Number of AEs identified (not just reported) – Summary by each AE of respondent ID, product (s) and event details
Syndicated Studies	MAHs have no obligations [to collect AEs] if the programme is not commissioned, financed or influenced by them. In this example* GVP VI does not apply, since it concerns only MAHs and Competent authorities in the EEA. However local requirements may be applicable to the organisation who is conducting the programme. You need to check directly with the competent authorities of the Member State where the programme is conducted. Source: EMA Comment to EphMRA * "this example" refers to market research studies that are designed and run independently by a market research agency and the findings then sold to several pharmaceutical manufacturers, so there is no MAH involved during design, data collection or processing.	For syndicated studies e.g. patient diary studies, there is no legal responsibility for the supplier to forward AEs as the supplier is not the legal agent at the time of data collection Responsibility to collect AEs lies with the MAH that purchases the syndicated data, the MAH's market researcher should forward the AE data to the PV department, the supplier may be requested to prepare the data in the appropriate format for the MAH If confidential questions are added to a syndicated survey by a MAH, the data from these questions must be treated in the same way as an ad hoc study i.e. the agency should forward AEs generated by these questions

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) V 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. 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 uses, not just acquired by an MAH for internal use (unlike commissioned MR)
If You Have Questions		The MAH's PV department is a most important source of guidance on requirements for forwarding AEs

EphMRA Adverse Event Reporting Form – TEMPLATE			
MR Agency Information			
Agency name			
Telephone number			
Researchers name			
Date aware of Adverse Event			
Project title/reference number			
Respondent ID/AE number			
Patient Information			
Number of patients			
Availability of patient information	YES	NO	
Age and Gender	AGE	FEMALE	MALE
Pregnant	YES	NO	
Patient's initials			
Drug and Event Information			
Drug name			
Description of Adverse Event			
Indication/condition for which drug prescribed			
Daily Dose		DON'T KNOW	
Lot/batch number.		DON'T KNOW	
Frequency		DON'T KNOW	
Route of administration/form		DON'T KNOW	
Reported to local regulator	YES	NO	DON'T KNOW
Does reporter think drug caused event	YES	NO	DON'T KNOW
Respondent/Reporter details			
Reporter/respondent name			
Reporter type (E.g. doctor, patient)			
Respondent's address/contact information if willing to provide			
	NOT WILLING TO PROVIDE		
Willing to be contacted for follow up	YES	NO	
	SIGNATURE		
Doctor's name & address if patient is a respondent/reporter			