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Overview of comments received on ICH E2D(R1) Guideline on post-approval safety data: definitions and standards for management and reporting of individual case safety reports

(EMA/CHMP/ICH/59123/2024)

Please note that comments will be sent to the ICH E2D EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	0	0		EFPIA find the document helpful in that it adds clarity on the requirements, although the expectation that this revision will take a more balanced approach towards safety data collection (commensurate to the likelihood of receiving good quality data) is not met.	
EFPIA	0	0		EFPIA identified themes relating to concepts where we believe EWG should place a specific focus on: 1. References to local/regional legislation: The principle of ICH should be the harmonization across regions. There is concern that the frequent reference to local/regional legislation is rather encouraging further deviations than driving harmonization. 2. Definition of ODCS: The definition of ODCS is too broad and should be limited to activities where medical information from patients on treatment is actively collected by the MAH. Specifically, for data from digital platforms not owned by MAH the proposed approach appears to be overly complex. 3. Digital Platforms: Software applications are included as an example of digital platforms in section 4.3. More detailed guidance on how data collected via these apps should be handled would be appreciated. 4. The reporting of 'important safety findings' (section 428-435) is not in scope of ICH E2D. 5. Patient gender identity should be addressed.	
EFPIA	0	0		EFPIA identified themes relating to to potential implementation impediments where we believe EWG should place a specific focus on: 1. Reference to local/regional legislation: In some instances, deviating local/regional requirements could not be implemented, e.g. it is not feasible for MAHs to categorize the same case as 'spontaneous' in some and 'solicited' in other regions. 2. Data received in the context of ODCS: The new requirement for MAHs to have documentation in place that describes the objectives of the ODCS and the dataset collected/analyzed creates confusion. Should AEs that are not in scope of the objectives/defined dataset consequently be handled spontaneous cases? 3. Digital platforms: Follow-up requirements for digital platforms not under the responsibility of a MAH are not realistic/feasible.	

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EFPIA	0	0		A few general comments regarding implementation not specified in the document - whilst the need for specificity is needed, implementation concerns need to be addressed if we are introducing new report types for the E2B XML file to differentiate these concepts, PSP, Market research etc - would MAHs need to re-categorize existing cases in their databases? at the point of implementation? how would this affect signal detection/signal assessment if all of the data in the MAH database is not re-categorized?	
EFPIA	0	0		The proposed text assumes that a patient's gender is binary (male/female). The current data conventions do not support the collection of data from people who are transgender or gender nonconforming. This limits the ability to accurately capture data from these populations which in turn may inhibit pharmacovigilance activities that could identify issues relating to the safety and efficacy of medicines.	It is recommended that routine data capture includes: the gender identity of a patient at the time of reporting; AND whether their gender is the same or different to their gender assigned at birth. This would facilitate the capture of data from people who are transgender or gender nonconforming; and would further "ensure that reports are authentic, accurate, as complete as possible".
EFPIA	0	0		Overarching comment to the entire document: it seems contradictory (and mis-aligned with the ICH concept) to state this document is to standardize and harmonize, yet in almost every section it is ok to refer to local/regional requirements?	
EFPIA	0	0		General comment regarding the mentioning of following the local and regional requirements. This version (rev 1) of the guideline has overall increased references to local/regional requirements in mulitple sections compared to the previous version. It is acknowledged that local/regional regulations can be needed and should always be followed when required. However, we would recommend reducing the use of this phrase in the guideline as this could be seen as opening up for local/regional variations of the guideline which seem to be counter productive and not in line with the objective of the guideline i.e. to establish international standards and harmonise the gathering and reporting of information. Currently, pharmacovigilance is a rapidly developing focus area of health authorities across the world. At the same time new technologies and digitalisation are impacting the pharmacovigilance landscape and creating an even greater need for harmonised standards for both MAHs and Authorities. Therefore, the need for internationally accepted standards and harmonisation is of increasing importance. We therefore, strongly recommend to avoid opening up for additional and/or differing local requirements in this guideline.	
EUCOPE	0	0		Eucope welcomes the opportunity to provide comments on this important draft ICH Guideline. Eucope members have been following the progress of this update closely as over the last few years many discussions have been held about the value of data gathered from patient support programmes, market research programmes and social media. Several publications have identified that the large amounts of data generated from these activities are not necessarily bringing additional insights for signal detection activities and subsequently patient safety. However, EUCOPE recognises that harmonised definitions should support appropriate categorisation of safety data and could help to filter out relevant data for signal detection and risk management.	
EUCOPE	0	0		Particularly the concept of harmonisation is of concern for EUCOPE members. ICH guidelines should strive for harmonisation but as already noticed in the introduction, a caveat has been introduced that local and regional requirements may vary allowing divergence instead of harmonisation. Throughout the document, several statements are included that MAHs should take into account that locally or regionally the requirements may differ and should accommodate these. EUCOPE member companies are and have been operating across different countries and regions for many years and have noticed that many countries have adopted regulations based on 'global' regulations such as the EU but these adopted guidelines are been modified to cater for some local requirements. This leads to an exponentially growing complexity of regulations which EUCOPE members are having to deal with, while national regulatory agencies only have to deal with one set of rules. Therefore, EUCOPE would like to urge regulatory agency ICH members to strive for harmonisation instead of allowing customisation of guidelines at local or regional level. This will help to achieve the goal of this guideline to create harmonised data requirements for post-marketing safety collection.	

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EUCOPE	0	0		EUCOPE notes that this draft guideline is introducing further categorisation of safety data in the post-marketing space which may lead to further complexity and divergence as these requirements are subject to interpretation. Several aspects in the draft guideline would need further clarification or revision. Although it might be helpful to provide definitions for certain activities such as PSP or MRP, it can also lead, as already obvious from the document, to different approaches in different countries where certain activities are considered to generate 'spontaneous' cases while in other countries these cases should be coded as 'solicited'. In addition, the introduction of a requirement to have documentation on all aspects of the conduct of such programmes needs further discussion or clarification. If the intent is that MAHs have the appropriate processes in place to guarantee complete and accurate collection of safety data, EUCOPE recommends to update the text to that regard. On the other hand, if the intent is that the MAHs should have such documentation available for all activities, this is nothing less than expecting protocols for each and single activity thereby introducing additional bureaucracy, complexity and divergence in interpretation. In addition, this could lead to additional expectations during inspections.	
EUCOPE	0	0		EUCOPE would like to propose to engage with ICH and the regulatory authorities to consider changing the approach and definitions rather significantly while allowing to use the existing legal frameworks. In the post-marketing phase of products, two different scenarios can be envisaged on how MAHs become aware of safety data, firstly, through research activities (interventional clinical trials, non-interventional studies, other research) and secondly through non-research activities (spontaneously reported data, PSP activities, other activities with the possibility of interaction between HCPs, caregivers or patients).	
EUCOPE	0	0		For research activities, a protocol is required outlining the research objectives and most importantly for this discussion, data collection requirements. This would imply that for non-interventional studies and other research activities, the category of 'solicited report' would remain and these AE reports would require a proper causality assessment as per protocol.	
EUCOPE	0	0		For non-research activities, the second category would apply: spontaneous. Safety data identified through social media posts, literature, PSPs or other non-research activities are collected not through a specific soliciting process but are usually quite random (spontaneous reports by patients or HCPs, contact with patients where a 'random' question is asked 'how are you?', social media posts originating spontaneously, receipt of medical records which probably should be considered secondary data) and therefore should be considered spontaneous. However, as there is evidence that case reports from PSPs and social media are creating noise in the signal detection process, EUCOPE proposes to use the category 'spontaneous-other' for such case reports enabling to filter these report while performing statistical analyses on the large safety databases for the purpose of signal detection.	
European CRO Federation (EUCROF) Pharmacovigilance Working Group (PVWG)	0	0		PV WG at EUCROF welcomes further development of the guideline.	
Gedeon Richter Plc. (BK)	0	0	5.1.1	The same AE/ADR can be reported at various levels of specification (e.g., "I took the drug and something bad happened", "this drug caused severe side effects", "while on the drug, I developed a skin condition", "it caused a rash", "noticed itchy pimples on my back", "the patient had an acute maculo-papular pruritic rash over her left scapula two days after drug initiation"). While the proposed guideline defines what an ADR is, it does not address the necessary level of specification at which a reported event should be considered to provide sufficient basis for a valid ICSR. Inclusion of such guidance would prevent the capturing of meaningless, uninterpretable information in safety databases.	Proposed change: insert following at end of section 5.1.1: Reports of AEs/ADRs that do not allow for qualitative characterization of the events beyond the mere fact that they fulfill the definition of an AE/ADR do not qualify cases as valid ICSRs. A sufficient level of characterization is one that allows for the event to be confidently placed at least within an organ-specific MedDRA System Organ Class (SOC) category. Accurate characterization of insufficiently specified events should be attempted through follow-up.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	0	0	4.6	Can there be guidance added around follow-up responsibility for such cases? This is currently a grey area as to who is responsible for following-up for cases received from Regulatory Authority sources as some local regulations allow follow-up by MAH and some do not.	
Medicines for Europe	0	0	6.5	Propose to include guidance on day 0 for such cases in the following situations: a. When there is a direct contract agreement between the parties - Day 0 is shared b. When One company (eg. A) has agreement for same product with 2 companies (eg. B and C), what should be the MRD taken for a case by company C received from company B by company A and then transfered to the company C. Since there is no direct contract between Company B and C, MRD need not be shared in this situation between Company B and C. There are different interpretations we see in industry for such scenario leading to challenges in timeline negotiations for exchange of cases in such complex arrangements.	
Medicines for Europe	0	0	2.10/4.5	In order to categorize a project as market research, can number of participants be the deciding factor (for ex: if the participant of the project is more than 100, only then we can term it as market research). Can we have some clarity around this in the guidance?	
Medicines for Europe	0	0	2.9/4.4	Can clarity be added regarding the following situations of PSPs/Patient Assistant Programs (PAPs)? 1. PAP programs for reimbursement process, executed over a web portal with limited patient information & has the option to upload Rx, should this be under the scope of PSP / organized data collection? 2. Copay programs, executed by the licensed HCP's (esp. US) should this be categorized under PSP's under ODCS? 3. PSP / PAP executed over web portals, with no free text option but information is included around patient drug adherence or drug disposal, would these come under the scope of ODCS?	
Prescrire	0	0		This guideline is a complex document whose scope is sometimes difficult to gauge, in view of the numerous situations where national legislation prevails. In three areas (pregnancy, off-label use and medication errors), pharmacovigilance cases that have not given rise to an adverse event or an adverse drug reaction need only be reported if required by local or regional legislation. Information and knowledge about these three areas are limited. In the interests of protecting vulnerable populations, learning more about under-documented or under-analysed areas, and preventing medical errors, we propose that all cases should undergo systematic analysis, including those that have had no clinical consequences.	

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
European CRO Federation (EUCROF) Pharmacovigilance Working Group (PVWG)	20	20	2.1.1.	align with applicabiity to variety of indication and uses	Proposed new text: An adverse event is any untoward medical occurrence in a human exposed to a medicinal product ....
EFPIA	21	21	2.1.1	"which does not necessarily have to have a causal relationship (...)" is redundant	Suggest to simplify the wording to "which does not necessarily have a causal relationship (...)". It is also aligned with other ICH definitions (e.g. ICH E2B).
EFPIA	26	27	2.1.2	Why is the ADR definition plural ("reactions")? Not in E2a; also AE is singular ("event")	An adverse drug reaction, as defined by local and regional requirements, concerns noxious and unintended responses to a medicinal product.

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EFPIA	28	30	2.1.2	In defining causal relation, the current draft guidance makes reference to ICH E2A which includes in its ADR definition the concept of 'relationship cannot be ruled out.'' And in the same time, the expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship. Of note, the guidance of the CIOMS VI working group provides the following recommendation: ''The CIOMS Working Group believes that it is virtually impossible to rule out with any certainty the role of the drug on the basis of a single case. "The use of "cannot-be-ruled-out" to imply drug relatedness would lead to excessive over-reporting and excess noise in the system. It is virtually impossible to completely rule-out the role of a drug in causing an adverse event in single-case reporting." Therefore, removal of the reference to ICH E2A is preferable to have any reference with ''relationship cannot be ruled out.'' Addtional rational and comment are provided in comment for line 425.	Recommend removing reference to ICH E2A: The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility ~~(refer to the ICH E2A guideline)~~.
BPI	30	31	2.1.2	This and the following lines (420-425) both refer to the definition of an ADR in opposition to an AE. However, they are partially contradictory: Spontaneous reports are per se ADRs, on the other hand at least a reasonable suspicion of a causal relationship is required.	It becomes clearer if the definition will be changed to "a causal relationship cannot be excluded" to qualify as an ADR.
AESPG	30	33		This and the following lines (420-425) both refer to the definition of an ADR in opposition to an AE. However, they are partially contradictory: Spontaneous reports are per se ADRs, on the other hand at least a reasonable suspicion of a causal relationship is required.	It becomes clearer if the definition is changed to "a causal relationship cannot be excluded" to qualify as an ADR.
BPI	34	52	2.1.3	European GVP considers any suspected transmission via a medicinal product of an infectious agent also a serious adverse reaction. Harmonisation would be appreciated.	Consider adding a sentence the like: "Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction."
European CRO Federation (EUCROF) Pharmacovigilance Working Group (PVWG)	42	42	2.1.3.	Align with practice	Proposed to add to the definition: "…..if not because of social circumstances"
BPI	47	54	2.1.3	The part suggested to be omitted as described in column G has led to much confusion and an undue incrementation of serious ADRs due its lavishly wide interpretability without any avail. The prevention part that follows is sufficient to explain the intention of the seriousness criteria.	Omit "but might jeopardise the patient or".
AESPG	47	54	37623	The part suggested to be omitted as described in column G has led to much confusion and an undue incrementation of serious ADRs due its lavishly wide interpretability without any avail. The prevention part that follows is sufficient to explain the intention of the seriousness criteria.	Omit "but might jeopardise the patient or".
BPI	54	56	2.1	In addition to the examples given, which are much appreciated, perhaps a more general instruction could be added	In general, whenever an intervention is required, without which a deterioration would be very likely to occur, and this potential consequence fulfils the criteria for seriousness, such a situation should be assessed as serious. However, the probability of occurrence should be greater than the probability of non-occurrence.
EFPIA	54	54	2.1.3	Why is an unclear PT (Substance use disorder) instead of the more clear "abuse", as also in E2a?	abuse [to replace substance use disorder]
European CRO Federation (EUCROF) Pharmacovigilance Working Group (PVWG)	54	54	2.1.3.	Align with EU GVP thinking	Proposed to add from EU GVP "Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction"
BPI	56	58	2.1.4	The first sentence of the sections reads: "MAHs should treat AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not included in any section of the local/regional product labelling." Instead of using "included in " the better term might be "consistent with". E.g. an event of anemia might be included in the SmPC, however low RBC should also be considered expected, even if the term has not explicitely been mentioned in the SmPC.	Consider changing the sentence to: "MAHs should treat AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not consitent with any section of the local/regional product labelling"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	56	56	2.1.4	MAHs do not "treat" AEs/ADRs differently if they are expected or unexpected, esp. in the database; difference may be in reporting.	MAHs should consider (...)
EFPIA	56	58	2.1.4	Propose to remove reference to "in any section of the local/regional product labelling" and replace with e.g., "in the undesirable effects / adverse reactions section (or equivalent) of the local/regional product labelling". It is important to clarify that an event presented only in another section (e.g., contraindications, pharmacological properties) is not a listed event.	in the undesirable effects / adverse reactions section (or equivalent) of the local/regional product labelling
EFPIA	56	58	2.1.4	Not included in any section of the product labeling is not correct, as for example renal impairment may be mentioned as part of the dosing recommendation	Is not included as an AE/ADR in any section of the local/regional product labelling
EFPIA	56	58	2.1.4	Several authorities have provided conflicting advice with regards to the statement that "MAHs should treat AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not included in any section of the local/regional product labelling"	We have been previously advised that only terms and associated synonyms contained in specific sections of the labelling document such as the "Undesirable Effects" or "Adverse Reactions" sections are considered labeled. Other sections, such as the "Warning and Precautions" section, can also be referenced to assist with medical judgement, but the term must still be contained in the "Undesirable Effects" or "Adverse Reactions" section to be considered labeled. Consider adapting this sentence to "MAHs should treat AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not included in the appropriate section of the local/regional product labelling"
EFPIA	56	58	2.1.4	"MAHs should treat AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not included in any section of the local/regional product labelling (e.g., Prescribing Information or Summary of Product Characteristics)" Not logical: The entire PI should not be used as expectedness reference, for example sections 4.4, 4.6, 4.9 can include information on AEs without causal association, which are still unexpected	"MAHs should treat AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not included in the targeted ADR section of the local/regional product labelling (e.g., Prescribing Information or Summary of Product Characteristics)"
EFPIA	56	57	2.1.4	MAH should treat AE/ADRS in ISCRs as unexpected if the reported AE/ADR is not included in any section of the local/regional product labelling. The sentence is very US oriented. Some potential AE/ADR might be included in some sections for warning purpose however it does not mean that they should be considered expected for the product. We suggest to remove "any section" to make it more neutral and adaptable to all countries/region.	MAH should treat AE/ADRS in ICSRs as unexpected if the reported AE/ADR is not described in ~~included in any section of~~ the local/regional product labelling
European CRO Federation (EUCROF) Pharmacovigilance Working Group (PVWG)	56	58	2.1.4.	It is not clear if the definition also refers to sections presenting non-clinical data. More precise definition is needed.	Proposed change: MAHs should treat AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not included in any section of the local/regional product labelling (e.g., Prescribing Information or Summary of Product Characteristics) aiming at describing AEs/ADRs associated with use of the product.
EUCOPE	56	58		not included in any section of the product labeling is not correct, as for example renal impairment may be mentioned as part of the dosing recommendations.	is not included as an AE/ADR in any section of the local/regional product labelling
BPI	58	59	2.1.4	Terms, which are not mentioned by verbatim.	Terms in SmPC/PI should also be considered as expected if the clinical concept or synonyms are described in the product text.
EUCOPE	60	62		This statement is not helpful as the the definition for an unexpected AE/ADR seems quite clear from sentences 56-60 (with the addition as proposed in the comments relating to lines 56-58). EUCOPE suggest to delete the sentence	When an MAH is uncertain whether an AE/ADR in an ICSR for a country or region should be treated as expected or unexpected, the AE/ADR should be treated as unexpected for that local country or region.

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EFPIA	63	65	2.1.4	Sentence to be incorporated into above paragraph after "should be considered unexpected" (line 60), as this is an example of the situation described in the preceding sentence.	"In addition, an AE/ADR in an ICSR whose nature, severity, or specificity is not consistent with the term or description used in the local/regional product labelling should be considered unexpected. For example, an ADR included in the local/regional product labelling should be considered unexpected when it is reported with a fatal outcome in an ICSR unless the labelling specifically states that the ADR might be associated with a fatal outcome.
EFPIA	66	70	2.1.4	Product labelling may include information related to ADRs for the pharmaceutical class to which the medicinal product belongs. This situation is often referred to as ‘‘Class ADRs’’, and such class ADRs should not automatically be considered “expected” when reported in an ICSR for one of the medicinal products. In this instance, MAHs should refer to the relevant local or regional requirements. Class effect are not considered by default as expected unless it is explicity stated in the local product labelling. This specification was added.	Product labelling may include information related to ADRs for the pharmaceutical class to which the medicinal product belongs. This situation is often referred to as ‘‘Class ADRs’’, and such class ADRs should not automatically be considered “expected” when reported in an ICSR for one of the medicinal products unless it is consistent with the term or description used in the relevant sections of local/regional product labelling. In this instance, MAHs should also refer to the relevant local or regional requirements.
BPI	71	73	2.1.4	A great opportunity to give importance to the CCSI as the reference document for the MAH's signal managing activities is missed here by merely referencing (as traditionally done) to ICH E2E. Its importance transcends the PBRER concept.	Add a definition as done in ICH E2C or GVP-annex IV of the EU.
AESPG	71	73	37988	A great opportunity to give importance to the CCSI as the reference document for the MAH's signal managing activities is missed here by merely referencing (as traditionally done) to ICH E2E. Its importance transcends the PBRER concept.	Add a definition as done in ICH E2C or GVP-annex IV of the EU.
BPI	74	74	2.1.5 / 5.1.3	For the "other observations" listed in this sections also the term "special situations" is commonly used. Also, adding a reference to the sections where the definitions can be found might be beneficial for users of this guideline.	Consider changing header to also include the term "Special Situations" Add reference to section 5.1.3 (line 436)
EUCOPE	77	79		This sentence does not add value to this guideline there EUCOPE suggests to delete this sentence	In some cases, “other observations” can occur without any associated AEs/ADRs, while in other cases “other observations” can occur with an associated AE/ADR.
BPI	80	80	2.1.6	Whilst it is appreciated that the defintion for the term "reporting" given only applies to this specific guideline the term "reporting" is used in so many different ways in pharmacovigilance as well as in this guideline. In order to better differentiate between these meanings the term "submitting" or, if applicable "submission", has been introduced in other guidelines to described the regulatory reporting.	Consider changing "reporting" in this context to "submitting" or, as applicable "submission", throughout the guidance
EFPIA	85	87	2.1.6	As the purpose of this guidance is to set standards and harmonise, we suggest to use the term ADR(s) only as only AEs with a suspected causal relationship i.e. an ADR (as defined in 2.1.2) qualifies for reporting.	
EFPIA	87	88	2.1.6	it seems that AE/ADRs terms include as well other situations	keep other situations separated even if in some regions there are reporting requirements.
EFPIA	88	88	2.1.6	To make guidance clear and avoid confusion, we suggest to leave out "or other observations, unless specifically stated otherwise", by using "or" it is unclear when it would include other observations and when it would not. Furthermore, as "other observations" is a separate definition described in section 2.1.5 with separate reporting requirements, it should not be mixed with the terminology "AE(s)/ADR(s)"	
EFPIA	89	103	2.2 + footer page	N/A	the term suspect medicinal product includes interacting medicinal products or substances. "Interacting" medicinal products are products for which the reporter indicates a suspected interaction with other medicinal products or substances.

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EFPIA	93	93	2.2	We suggest to rephrase "At least one AE/ADR" to "At least one ADR" as this relates to minimum criteria for reporting. AEs should not be reported unless they have a suspected causal relationship in which case it would be defined as an ADR. Furthermore, we suggest to remove the part "or other observations - see Section 5.1.3" since it would imply that all other observations are to be reported even if occurring without an ADR.	
EFPIA	99	99	2.2	"Cases missing…" are often termed 'invalid reports' and are worthwhile to collect, e.g. for analysis 'en groupe' for trends and/or includion in Periodic reports	These, often called invalid, reports should be collected for other purposes than expedited reporting.
EFPIA	100	102	2.2	"While these criteria....." In order to achieve internationally harmonised standards, we suggest to leave this sentence out to avoid local differences leading to deharmonisation.	
EFPIA	107	109	2.3	For clarity, consider add also here the negative (non-expedited). This way it will be clearer that ICSRs that meet the requirements for reporting with timelines greater than 15 calendar days are non-expedited (e.g. NS cases to be reported to Eudravigilance in 90 calendar days; these still have critieria for reporting, but the timeline does not qualify to expedited).	An expedited report is an individual case safety report that meets the requirements for reporting as soon as possible, but no later than to be reported within 15 calendar days after day zero. Timelines greater than 15 calendar days are considered non-expedited (see Section 5.2, Reporting Timeframes).
BPI	117	117	2.4	Please specify/add and be reffered to line 226	In the case of a literature article the country of first author is regarded as the primary source and defines the primary source country of the ICSR. This in turn defines the reporting obligations of the ICSR.
EFPIA	127	129	2.7	Need of a clearer definition on whether it refers to external facing platform, who the users are, and if it is only applicable to actively reported events (i.e., human reported event, rather than sensor collected data)	N/A
EFPIA	128	129	2.7	It looks surprizing that definition of digital platform is provided in ICH PV guidelines. Recommendation would be to use an official definition used in other guidance. Anyway, "A digital platform is the software and technology used..." is misleading as it is rather an interface supported by a software and technology.	Suggest to change wording to "A digital platform is an interface supported by a software and technology which enables transmission of information between users".
EUCOPE	130	130		The definitions in this section may not be helpful, but rather the basic requirement should be reinfored that MAHs should have processes in place to collect safety information from ODSC that do not follow a protocol. EUCOPE suggests to delete lines 155 through to 176.	
EFPIA	131	154	2.8	ODCS Definition and scope to be updated to remove the terminology around "planned" manner as this can be attributed to many initiatives of the MAH, yet these could be non structured way of collecting data by the MAH. Add further descriptive terms into the ODCS definition to ensure its scope is clear and this also fit with the actual wording of: Organized Data Collection In addition, the definition of ODCS 'in the context of this guideline' should exclude activities that according to the objective (line 139) and the specification of the dataset (line 141) do not systematically collect any safety or efficacy related information. Information received incidentally/at random should be handled as spontaneous reports. Note: Row 151-154, example to be revised to fit the above proposal. For example, "MAH organizing forum on a digital platform with two-way interaction to collect and assess...."	Proposed ODCS Definition and scope: An organised data collection system (ODCS) is an activity that gathers data in a systematic and organized manner from activities or programs where two way interaction with external participants happen and there is a likelihood that the MAH receives Adverse Event/Special Situation or Product Complaints related to its marketed products.
EFPIA	131	154	2.8	Clarity is needed on which types of Data collection are to be considered ODCS. Are there activities of retrospective data collection in digital platforms that should be not considered ODCS?	N/A

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCOPE	137	144		Although it is stated that these activities are not conducted according to a protocol, the documentation required is almost as detailed as a protocol. Therefore, a suggestion would be to clarify that the MAH should have processes in place that cover these points	For MAH ODCS …, the MAH should have processes in place that describe the:
Gedeon Richter Plc. (EB)	144	144	2.8	GVP VI Rev 2 Section VI.C.1.2.1.1., allows MAHs to limit the range of safety information that is actively collected in non-interventional studies (NIS) based on "due justification". At the same time, GVP guidance also recommends that the possibility to notify MAHs or concerned regulatory authorities of such protocol-excluded events through spontaneous reporting be clearly communicated to doctors and patients alike. An explicitly provided option to lay down similar criteria for PSPs and MRPs would be beneficial to avoid the collection of large amounts of data that are of limited or no real drug safety value and may lead to the creation of invalid cases for which missing information often cannot be obtained through follow-up and a meaningful medical assessment is not possible. Performing follow-up activities is especially difficult and of questionable ethical standing in social media listening activities (e.g., sentiment analysis) where there is no prior notification of users that their posted or other data may be scrutinized for pharmacovigilance purposes and follow-up options are often technically or otherwise limited. Specific examples of exclusion criteria generally accepted by Health Authorities would also be appreciated because ODCS documentation does not undergo formal approval by National Competent Authorities or Ethics Committees.	Original: 5. Process for collection and management of any AEs/ADRs that may be identified Proposed change: 5. Process for collection and management of any AEs/ADRs that may be identified and the overall rules and scope of safety data collection (e.g., whether the program will foreseeably collect any safety data at all and if not, then why routine pharmacovigilance activities are sufficient to handle program-related safety information, included/excluded AEs/ADRs/other observations, included/excluded medicinal products, extent of due diligence in follow-up activities, how any imposed limitations on safety data collection will be counterbalanced by information provision on spontaneous reporting options, etc.)
BPI	149	155	2.8	It would be helpful to have a decision included whether studies acc. to German Drug Law, Art. 67 (6), are covered by this otherwise well worded definition. Furthermore, it will be helpful to know whether retrospective data collections are included or not.	Clarify the wording as to whether studies acc. to Art. 67 (6) German Drug Law are included or not, likewise clarify the wording with regard to retrospective data collections.
EFPIA	149	151	2.8	It looks surprizing that definition of ODCS is provided in ICH PV guidelines. Current definition of ODCS is very broad and can include different programs, like IT User Experience research, or EU labelling readability testing or reputational projects run by Communication team. In the context of these guidelines, recommendation would be to use an official ODCS definition extracted from other guidance if exists and to limit the scope of ODCS only to programs with a data collection about registered company drug/or therapeutic area where company drug is present and also to programs, where collection of patient medical data is planned (as detailed in Patient Programs definition line 162 to 166). Programs without the collection of medical information should not considered as PSPs. Please include this same specifity in the ODCS definition and not only in PSPs.	In the context of this Guideline, we propose to limit the definition of ODCS only to programs with a data collection about registered company drug/or therapeutic area where company drug is present.
CCMO	149	151	2.8	Clinical trials are mentioned as a type of Organised Data Collection System. It is not clear from the guideline that for clinical trials with approved products other requirements could apply for sponsors of those clinical trials (e.g. 7 or 15 days reporting requirement for SUSARs)	Suggestion to add additional explanation and/or reference to the relevant ICH guidance either in section 2.8 or already in the introduction
AESPG	149	155		It would be helpful to have a decision included whether studies acc. to German Drug Law, Art. 67 (6), are covered by this otherwise well worded definition. Furthermore, it will be helpful to know whether retrospective data collections are included or not.	Clarify the wording as to whether studies acc. to Art. 67 (6) German Drug Law are included or not, likewise clarify the wording with regard to retrospective data collections.
EFPIA	151	154	2.8	Suggest include social listening as an example of ODCS activity through social media, this is very comon among the industry and currently misunderstood if cases originated from this activity is spontaenous or solicited.	Other examples include: an activity where the MAH observe, collect and analyze communications taking place on social media, without participating in those communications (e.g., social or digital listening),an MAH activity using a patient forum on a digital platform to assess patient perceptions of the safety of disease treatments; and a product-specific analysis of consumer positivity or negativity about the product (i.e., a sentiment analysis) conducted by an MAH using posts on social media networking sites.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	155	176	2.9 2.10	PSP and MRPs are ODCS so it could have been defined with section 2.8	put PSP in section 2.8.1 and MRP in section 2.8.2
EFPIA	155	157	2.9		PSPs are ODCSs where a marketing authorisation holder receives and collects information relating to the use of its medicinal products or the management of their medical condition,
EFPIA	160	160	2.9	Too many commas, e.g. it should be read as "certain reimbursement programs and educational programs", shoretend to reimbursement and educational programs. The comma suggests that PSPs may be reimbursement.	disease management and certain reimbursement and educational programs
EFPIA	174	174	2.10	MRPs are ODCSs which are used for planned collections of healthcare professional...: The term "planned" is not clear in this respect	Simplify the sentence: MRPs are ODCSs which are used for collections of healthcare professional…
EFPIA	175	175	2.10	"MRPs are ODCSs which are used for planned collections of healthcare professional and/or consumer insights by an MAH, on medicinal products and/or a disease area, for the purpose of marketing and business development." What consumer insights means ? Only patients ? What about: - insights collected from patient's caregivers that can be patient's family for example. - key opinion leaders (former HCPs, influencers), payers etc ?	"MRPs are ODCSs which are used for 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"
EFPIA	178	186	3.1	It is not uncommon for an HCP or a patient to make the MAH aware of an AE/ADR that is associated with the use of a company medicinal product, but not the product that is the subject of the ODCS. For example, the ODCS could be for product X and in the course of speaking to the patient, they inform the MAH about an ADR experienced while taking company product Y. In that case, the ADR experienced with company product Y would be a spontaneous case report. Suggest adding this clarification to the draft document.	
EFPIA	178	182	3.1	Not all spontaneous reports are reported directly to a MAH. For instance, by the ICH's own admission in section 4.2, MAH's are encouraged to monitor the world wide literature, i.e. the MAH is obtaining this information using an indirect method such as a programmatic database search. Later in the same section MAH's are advised to apply context as to whether the report should be considered spontaneous (which we agree with), but they are still not directly reported.	Consider returning to the previous use of the term "Unsolicited" rather than reported 'directly' to the MAH for this definition. Or consider rephrasing to "A spontaneous report is typically a direct communication by an HCP or consumer to an MAH..."
EFPIA	178	188	3.1	According to CIOMs V, the reporter of a spontaneous report suspects ‘at least the possibility of a causal relationship to a drug product`, which differentiates a spontaneous report from a solicited report. This concept is lost by adding ‘AE’ to the definition.	Suggest to delete ‘AE’ from the definition of a spontaneous case which has implied causality.
EFPIA	179	179	3.1		A spontaneous report is an unsolicited communication by an HCP or consumer to an MAH, regulatory
EFPIA	187	188	3.1	Draft text:Local or regional regulatory requirements may require HCPs to report AEs/ADRs not gathered as part of an ODCS to regulatory authorities; these reports should also be managed as spontaneous reports. Suggest adding an example to this statement, for context.	
EFPIA	187	188	3.1	"Local or regional requirements may require HCPs to report AEs/ADRs not gathered as part of an ODCS to regulatory authorities; these reports should also be managed as spontaneous reports." - Examples should be provided to clarify	Suggest to provide examples

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	190	192	3.2	Could we examine scenarios in which safety reports coming from ODCS are not solicited ? (e.g., data collection not related to disease or product)	N/A
Jazz Pharmaceuticals	208	209	4.2	Literature reports: MAHs should assess literature to see if AEs from published abstracts from meetings and draft manuscripts require reporting.	Suggest removing the requirement to assess draft manuscripts for AE reporting as MAHs routinely do not have access to draft manuscripts.
EFPIA	212	215	4.2	Separate the 2 sentences to improve readability	if a case in the literature arises from spontaneous observations, “Type of Report” in ICH E2B format should be classified as “spontaneous report”. Conversely, if a case in the literature arises from a study, “Type of Report” in ICH E2B format should be classified as “report from study”
European CRO Federation (EUCROF) Pharmacovigilance Working Group (PVWG)	214	215	4.2.	To improve detection of duplicates	Suggested addition: add requirement to include study identifies (trial ID from EudraCT, Clinicaltrials.gov, etc.) if available to support duplicate identification
EFPIA	220	222	4.2	The use of the 'Other' category as of today seems to be very limited (we do not use it as a company but would default to spontaneous when it is not clear from the article). Whilst it is understood that this category currently exists in E2B, mentioning it here would then necessitate further explanation as to how "other" cases are managed, with regard to causality assessments etc, and whether they fall under the reporting requirements of spontaneous cases or solicited cases. "Other" is also not referred to in Section 3 (Types of individual Case Safety Reports). Inclusion of this sentence seems to create more questions than answers.	Propose to remove this sentence since this case type is so infrequently used.
EFPIA	220	222	4.2	Clarity is needed for using 'Other' report type. What are the different scenarios which the regulations are expecting under Category 'Other'?	N/A
Medicines for Europe	220	222	4.2	1. It is difficult to understand which circumstances would a report from literature source be classified as "Other". Either there is a study reference cited in the literature or there is no study reference. In latter situation it will be classificed as Spontaneous Literature and in former a report from study. Can an example be added where it is expected to be classified to be "Other" for clarity? Do we need this for Literature section? 2. For the study cited in the literature, what is expected report type for non company sponsored ODCS by the MAH Screening the literature. Can that clarity be added for consistency in interpretation?	Remove the last sentence starting from row 220 until 222.
EUCOPE	220	222	4.2	The use of the 'Other' category as of today seems to be very limited (we do not use it as a company but would default to spontaneous when it is not clear from the article). Whilst it is understood that this category currently exists in E2B, mentioning it here would then necessitate further explanation as to how "other" cases are mananged, with regard to causality assessments etc, and whether they fall under the reporting requirements of spontaneous cases or solicited cases. "Other" is also not referred to in Section 3 (Types of individual Case Safety Reports). Inclusion of this sentence seems to create more questions than answers.	Propose to remove this sentence since this case type is so infrequently used.
EFPIA	232	233	4.2	"MAHs and/or the third parties acting on their behalf should review the literature search results without undue delay to identify AEs/ADRs" -> "Undue delay" is too broad, a minimum delay should be specified (knowing that local/regional requirements prevail)	Suggest to modify the wording to: "MAHs and/or the third parties acting on their behalf should review the literature search results without undue delay, and no later than 7 calendar days, to identify AEs/ADRs"
EFPIA	233	233	4.2	"...should review the literature search results without undue delay to identify AEs/ADRs." "…without undue delay…" is quite vague and could be interpreted as everything from one day to several weeks	"...should review the literature search results without undue delay (within X calendar days) to identify AEs/ADRs."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	236	240	4.2	1. The wordings could lead to different interpretations with respect to date of searching versus date of screening of search results. See proposed edits.	The regulatory time clock for the reporting of ICSRs from the scientific literature starts (day zero) as soon as the MAH or third party acting on their behalf receives sufficient information to determine that the criteria for ICSR 238 reporting (i.e., the minimum criteria for reporting (refer to Section 2.2, ICSR, and 5.2, Reporting 239 Timeframes)) are met, and not necessarily on the date of the initial search.
European CRO Federation (EUCROF) Pharmacovigilance Working Group (PVWG)	237	237	4.2.	The EU recently updated its guideline with respect to defining day 0 of local literature cases (https://www.ema.europa.eu/en/coordination-pharmacovigilance-inspections-0). It is explained that "The marketing authorisation holders should review the received information without delay ... This should be done within a week of the date of receipt....Therefore, the clock start (day zero) for the regulatory reporting of valid ICSRs identified in relevant published abstracts from meetings and draft manuscripts as well as publications in local medical journals should not be beyond 7 calendar days of the date of receipt (electronic/ hard copy) of that information by marketing authorisation holders." E2D (R1) does not take this new EU guideline on local literature monitoring into account, which willintroduce a gap between EU defined D0 and E2D (R1)international expectations. We suggest to apply the EU view on D0 for literature cases in E2D (R1).	Suggested change: add definition of Day 0 for ICSRs identified in local literature sources in line with the definition provided by EU PV Inspectors group under: https://www.ema.europa.eu/en/coordination-pharmacovigilance-inspections-0
SciencePharma	243	247	4.2	A request to clarify whether the term "marketing status" refers to obtaining marketing authorization or the launch of the product on the market. Clarifying the term will enable correct exclusion of cases based on the date of obtaining marketing authorization or the date the product was launched on the market (a product may obtain marketing authorization and not be launched on the market for many years).	NA
EFPIA	249	250	4.2	It is unclear how this needs to be specified and if it is required. For example, if there was not a brand value in the relevant E2B fields, then we believe that is enough detail to indicate that the specific brand was not identified.	suggest clarifying or removing this statement.
BPI	251	256	4.2	It is hard to understand whether the good pharmacovigilance spirit is covered here: If there are e.g. 20 people affected by an ICSR it does not fulfil the attention purpose by waivering the submission.	Define a better way of reporting for group findings, ideally a special one that distinguishes it from single patient reports.
EFPIA	251	260	4.2	Whilst the passage is clear with respect to an article which references several products, there is no guidance with respect to an article which only mentions a single product. Similar to the cited example, authors may also not necessarily suspect the product to be causally related to the event(s) described in the article, but because there is often no direct or implied causality statement provided it results in a conservative assessment by the MAH even when the product taken is not the focus of the article.	Include a clarification that where an article makes reference to a single product which is not implicated directly or indirectly to the reported event, then the MAHs should not submit these as an ICSR.
EFPIA	251	259	4.2	In an article, if the author doesn't specify if an event is associated with the medicinal product (author's causality is not reported), should the case be processed and submitted conservatively ?	Give guidance to manage this kind of publication
EFPIA	251	259	4.2	If it is reported in an article that, during a study, patients took either a company drug (group A) or another drug (goup B) and AEs are listed but it is not specified if the AEs occured in group A or in group B, should we process and submit the case conservatively ?	again, add guidance in the section to support harmonization in the management of these publications
Medicines for Europe	251	256	4.2	The text suggests that only if author explicitely states in an article that an event if not associated with a medicinal product, MAH should not submit it as an ICSR. However, later in the paragraph it says that ICSR should be submitted by the MAH(s) whose product(s) is/are suspected by the article author. This is contradictory to the statement before this and leading to different interpretations by different agencies and MAH in literatures where either causality is not provided but other contributory factors are provided. See suggested wordings for sentence starting from line 254.	If an author explicitly states in an article that an event is associated with a medicinal product, the MAHs should submit it as an ICSR.
AESPG	251	256		It is hard to understand whether the good pharmacovigilance spirit is covered here: If there are e.g. 20 people affected by an ICSR it does not fulfil the attention purpose by waivering the submission.	Define a better way of reporting for group findings, ideally a special one that distinguishes it from single patient reports.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	252	256	4.2	"as authors may reference many events and many medicinal products, and the author may not necessarily suspect the products to be causally related to the events described in the article; MAHs should consider the relationship between products and events in this context. If an author explicitly states in an article that an event is not associated with a medicinal product, or the event occurred before the patient was exposed to the product, the MAHs should not submit it as an ICSR. "	Recommendation is also to add guidance when causality is not explicited by author and in this scenario, to collect/submit only if MAH does assess as related
EFPIA	253	254	4.2	The sentence proposed provides more clarity with regards to expectations in relation to articles with multiple products	necessarily suspect the products to be causally related to the events described in the article; only those which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected adverse reaction should be considered for literature review by the concerned marketing authorisation holder(s).
EFPIA	254	256	4.2	Draft text: If an author explicitly states in an article that an event is not associated with a medicinal product, or the event occurred before the patient was exposed to the product, the MAHs should not submit it as an ICSR. Propose to add clarification on collection of ICSRs from literature as well as reporting. In line with GVP Module VI (VI.B.1.1.2. Literature reports), only products mentioned in the publication as having possible causal relationship with the adverse reaction should be considered for literature review.	Proposed updated text: If an author explicitly states in an article that an event is not associated with a medicinal product, or the event occurred before the patient was exposed to the product, the MAHs should not process or submit it as an ICSR.
European CRO Federation (EUCROF) Pharmacovigilance Working Group (PVWG)	254	256	4.2.	Align with practice	Suggested change: replace the sentence with the following: If an event occurred before the patient was exposed to the product, or the author neither states nor implies a causal relationship between any of the listed medicinal products and any event occurring, and the MAH does not identify at least a reasonable possibility that the event is related to the medicinal product, the MAH should not submit it as an ICSR.
Gedeon Richter Plc. (BK)	254	256	4.2	The primary objective of the publication of many, if not most, case reports in the medical literature is not the communication of adverse drug reactions, therefore authors often do not discuss the drug safety implications of their article's contents. Furthermore, even if there are events highlighted by the authors as adverse drug reactions in a publication, extensive medical documentation of the case may lead to the inclusion in the article of many diseases, symptoms and laboratory values that are of highly variable drug safety relevance: they may be in an uncertain or neutral temporal relationship with the drug, have varying seriousness and severity, and have varying commonality with the known safety profile of the medicinal product in question. To avoid capturing large amounts of data that are of highly questionable relevance, if an event is not highlighted as a potential AE/ADR by the authors, decisions about which of the various other events have notable relevance to the safety profile of their medicinal product should be explicitly assigned to the discretion/medical judgement of MAHs. The original text in the highlighted section is of almost no practical value, since MAH's are rarely, if ever, in a position to make more accurate assessments on causality than the publication authors, therefore, if an author explicitly states that an event is not related to a drug, MAHs are extremely unlikely to disagree and there is no rationale for reporting. Similarly, if temporality between drug and event rules out causality, MAHs are highly unlikely to report it as a suspected ADR in a valid ICSR. Consequently, recommend replacing the original text entirely.	Original: If an author explicitly states in an article that an event is not associated with a medicinal product, or the event occurred before the patient was exposed to the product, the MAHs should not submit it as an ICSR. Proposed change: If an author does not explicitly state in an article that an event is associated with a medicinal product, causality assessment by the author should be considered missing information. In such instances, the event should not be considered to meet the definition of an adverse drug reaction (section 2.1.2) even if "Type of report" ” in ICH E2B format is classified as “spontaneous report”, unless the MAH determines that a causal relationship between its product and the event has at least a reasonable possibility and the event is relevant to the benefit-risk balance of its product.
EFPIA	288	291	4.3	The document is silent on digital devices, wearables etc. and only focuses on social media in the digital section. Whilst it is understood that the principles within this document can be extrapolated to those other sources of information (i.e. based on whether the MAH actually has access to the data and whether it is 'spontaneously' arising or is gathered as part of an ODCS) it would seem helpful to mention these sources of adverse event information and the principles that should be applied to collect, manage and report ICSRs coming from them and when they should be managed accoridng to medical device requirements.	
EFPIA	288	293	4.3	Clarity is needed in expectation for passively collected data (i.e., no human reporter but a collection of data from the application for example through sensors)	N/A

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCOPE	288	291	4.3	The document is silent on digital devices, wearables etc. and only focuses on social media in the digital section. Whilst it is understood that the principles within this document can be extrapolated to those other sources of information (i.e. based on whether the MAH actually has access to the data and whether it is 'spontaneously' arising or is gathered as part of an ODCS) it would seem helpful to mention these sources of adverse event information and the principles that should be applied to collect, manage and report ICSRs coming from them and when they should be managed accoridng to medical device requirements.	
EFPIA	289	290	4.3	See comment in section 2.7 (lines 128-129) It looks surprizing that definition of digital platform is provided in ICH PV guidelines. Recommendation would be to use an official definition used in other guidance. Anyway, "A digital platform is the software and technology used..." is misleading as it is rather an interface supported by a software and technology.	See comment in section 2.7 (lines 128-129) Suggest to change wording to "A digital platform is an interface supported by a software and technology which enables transmission of information between users".
EFPIA	290	291	4.3	"Digital platforms include but are not limited to social media, web sites, internet forums, chat rooms, and software applications (apps)."	It's not clear in the definition what will be the requirements about software applications (apps) in case they or their components fall unders the scope of definition of SaMD (software as medical device)?
EFPIA	294	310	4.3.1	This section does not clearly articulate when the regulatory clock begins for information posted on a digital platform under the responsibility of the MAH despite being mentioned in section 4.3.2 (sites not under MAH responsibility).	To avoid doubt, it is recommended the following statement to be included in this section: "[…]. The regulatory time clock for reporting starts (day zero) as soon as sufficient information to determine that the criteria for reporting (i.e., the minimum criteria as defined in section 2.2., ICSR incldluing minimum criteria for reporting) was posted on the digital platform; day zero is not the date the digital platform data was accessed."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gedeon Richter Plc. (EB)	295	300	4.3.1	The highlighted section may leave open questions involving seemingly ambiguous scenarios such as when MAHs publish content on a digital platform owned and controlled by an independent third party and the platform allows for reader feedback in the form of comments. For example, if an MAH sponsors an article on a website which serves as an independent source of information for patients about various medical topics (diseases, treatments, how to read lab data...etc.). Here, the MAH has control over the content of a subpage where its article is published but not over the communication via the webpage or even via the specific subpage where the article is published. Additionally, when an MAH operates websites which are not directly connected to its pharmaceutical sector activity (e.g., pages for social engagement such as awards or competitions funded by the MAH via its own foundations or carrier pages), although specific contact channels are provided, the nature of the website are such, that safety monitoring seems inappropriate or redundant.	Original: The MAH is responsible for the content of, and communication made available via digital platforms, that are owned, controlled, or operated by, or on behalf of, the MAH. A donation (financial or other) by an MAH to an organization that owns the digital platform does not necessarily mean that MAH is responsible for for the content of and communication made available via that digital platform, provided that the MAH does not control any content or communications made available via the digital platform. Proposed change: The MAH is responsible for the content of, and communication made available via digital platforms, that are owned, controlled, or operated by, or on behalf of, the MAH. A donation (financial or other) by an MAH to an organization that owns the digital platform does not necessarily mean that MAH is responsible for for the content of and communication made available via that digital platform, provided that the MAH does not control any content or communications made available via the digital platform. When an MAH publises content on an independent third-party platform that it does not control or operate, its pharmacovigilance responsibilities as source of the content may be fulfilled by providing information on the possibilities related to the spontaneous reporting of suspected ADRs. MAHs do not have specific pharmacovigilance responsibilities with respect to digital platforms that are owned, controlled or operated by the them, but which do not include information on or related to any of their medicinal products (e.g., social engagement, charity, environmental conservation, etc.).
EFPIA	301	301	4.3.1	"MAHs should regularly screen digital platforms"	Change the term "screen" to "monitor" as it is better fit for digital platforms. Screening is usually used for listening activities
EFPIA	301	303	4.3.1	More clarity on what the Day 0 is needed. It is not clear from the text and reference to Section 5.2 whether Day 0 is date of screening or date in which report was posted in Digital platform / received by the MAH within the platform.	N/A
EFPIA	314	317	4.3.2	Is this activity considered a social listening? If yes, can this be explained by adding in the brackets (i.e., social listening)?	However, if a MAH screens or accesses data from a digital platform not under its responsibility (i.e., conducting social listening), and the MAH’s data collection activity is conducted in a planned manner consistent with an organized data collection the MAH should consider the activity to be an ODCS (see Section 2.10 ODCS).
EFPIA	325	329	4.3.2	Whilst it is understood that there are currently different reporting requirements for global health authorities (hence the mention of local/regional requirements throughout the document), it is operationally impossible to introduce the concept/flexibility of following local/regional requirements in this section. This would result in a seperate case having to be created for different Health Authorities i.e. those that require it to be managed as a spontaenous case vs. those that require it to be managed as a solicited case.	
EUCOPE	325	329	4.3.2	Whilst it is understood that there are currently different reporting requirements for global health authorities (hence the mention of local/regional requirements throughout the document), it is operationally impossible to introduce the concept/flexibility of following local/regional requirements in this section. This would result in a seperate case having to be created for different Health Authorities i.e. those that require it to be managed as a spontaenous case vs. those that require it to be managed as a solicited case.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	327	327	4.3.2	In digital listening activities (ODCS) where e.g. social media posts are scraped from different platforms, the requirement for obtaining the reporters causality may be challenging in practise. Please clarify whether MAH is expected to attempt follow-up via posting public comments to the individual social media posts.	
EFPIA	330	344	4.3.2	The text from line 330 to 344 is placed under the header of 4.3.2. "Digital Platforms Not Under the Responsibility of the MAH", but seems to provide guidance also relevant for AE/ADR obtained from Digital Platforms under the responsibility of the MAH (section 4.3.1). It would therefore be desirable to present the information from line 330 to 344 under a new subheader 4.3.3. or to amend 4.3.1 with relevant information on day zero and the report type in case of differences between digital platforms under or not under the responsibility of an MAH. Lines 345 to 352 are applicable to digital platforms not under the responsibility of an MAH and should be moved up in case lines 330 to 344 would be presented under a new subheader	
EFPIA	330	344	4.3.2	This guidance should also be applicable for digital platforms under the MAH responsibility	Recommendation is to move this guidance after line 293 since applicable also to digital platforms under the MAH responsibility
Gedeon Richter Plc. (EB)	345	352	4.3.2	In lines 323-325, it is made clear that "When accessing data from a digital platform not under its responsibility in the context of an ODCS, an MAH is not expected to search for AEs/ADRs beyond conducting its planned review of the dataset collected for the activity as detailed in its documentation." A similar caveat is not provided in the highlighted section, therefore recommend adding further detail.	Original: If an MAH becomes aware of AEs/ADRs on a digital platform not under MAH's responsibility, and the MAH received the information outside of the context of an ODCS (e.g., an MAH employee is viewing a website to identify possible answers/solutions to a business question and sees an AE/ADR mentioned), the MAH is expected to review the safety information and collect AEs/ADRs; although these cases are not direct communications to the MAH, they should be managed as spontaneous report unless local or regional requirements indicate otherwise (see Section 5, Standards for Reporting, for information on standards and timeline for reporting). Proposed change: If an MAH becomes aware of AEs/ADRs on a digital platform not under MAH's responsibility, and the MAH received the information outside of the context of an ODCS (e.g., an MAH employee is viewing a website to identify possible answers/solutions to a business question and sees an AE/ADR mentioned), the MAH is expected to review the safety information and collect AEs/ADRs (but is not necessarily expected to search for further AEs/ADRs on the platform); although these cases are not direct communications to the MAH, they should be managed as spontaneous report unless local or regional requirements indicate otherwise (see Section 5, Standards for Reporting, for information on standards and timeline for reporting).
EFPIA	349	352	4.3.2	Whilst it is understood that there are currently different reporting requirements for global health authorities (hence the mention of local/regional requirements throughout the document), it is operationally impossible to introduce the concept/flexibility of following local/regional requirements in this section. This would result in a seperate case having to be created for different Health Authorities i.e. those that require it to be managed as a spontaenous case vs. those that require it to be managed as a solicited case.	
EUCOPE	349	352	4.3.2	Whilst it is understood that there are currently different reporting requirements for global health authorities (hence the mention of local/regional requirements throughout the document), it is operationally impossible to introduce the concept/flexibility of following local/regional requirements in this section. This would result in a seperate case having to be created for different Health Authorities i.e. those that require it to be managed as a spontaenous case vs. those that require it to be managed as a solicited case.	
EFPIA	357	384	4.4	If AE/ADR reported for a MAH product not in scope of the PSP/MR but during the conduct of the PSP/MR, should this be also considered solicited and reported under PSP/MR case type?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	358	359	4.4	If - according to the PSP documentation described in section2.8 – the data set collected/received to meet the objectives of the program does not include AE information, incidental AEs received should not be handled as solicited cases (incidental data not collected in a solicited manner.	same as for the comment / rationale
EUCOPE	358	359		the situation is more complex than just reviewing all information received. Three types of data can be received through such programmes, (1) solicited data as part of the programme, (2) spontaneous data as the patient or caregiver may report AEs to programme administrator in an unsolicited way and (3) secondary data in the form of medical records	should be managed as solicited reports or spontanous reports as predefined in the programme documentation and as primary or secondary data usage. Solicited reports should include an appropriate causality assessment…
Medicines for Europe	373	377	4.4	The text suggests an introduction of a new Study type element of PSP. What are the industry recommendations of existing processed and submitted data in the database prior to this study type becoming effective? The distinguished analysis can only be facilitated if there is an update to ongoing programs with the new study type, is this going to be recommended approach? This will lead to additional efforts of implementation. What is the value add of this distinction as opposed to existing "Other study" study type?	
EFPIA	388	389	4.5	Whilst it is understood that there are currently different reporting requirements for global health authorities (hence the mention of local/regional requirements throughout the document), it is operationally impossible to introduce the concept/flexibility of following local/regional requirements in this section. This would result in a seperate case having to be created for different Health Authorities i.e. those that require it to be managed as a spontaenous case vs. those that require it to be managed as a solicited case.	
EUCOPE	388	389	4.5	Whilst it is understood that there are currently different reporting requirements for global health authorities (hence the mention of local/regional requirements throughout the document), it is operationally impossible to introduce the concept/flexibility of following local/regional requirements in this section. This would result in a seperate case having to be created for different Health Authorities i.e. those that require it to be managed as a spontaenous case vs. those that require it to be managed as a solicited case.	
EUCOPE	404	406		it should be recommended that case reports from regulatory authority sources should not up-graded or down-graded	add sentence on line 399: These reports should not be modified unless the MAH has obtained or received new information about the case from a primary source.
EFPIA	408	411	4.7	If an MAH becomes aware of an AE/ADR from non-medical sources, e.g., the lay press or other media, although not a direct communication to the MAH, it should be managed as a spontaneous report unless local or regional requirements indicate otherwise. Reports received by the MAH as a result of litigation should also be managed as spontaneous reports. MAH collect and assess reported suspected adverse reaction from non-medical sources (spontaneous reports imply ADRs)	If an MAH becomes aware of an AE/ADR from non-medical sources, e.g., the lay press or other media, although not a direct communication to the MAH, it should be managed as a spontaneous report unless local or regional requirements indicate otherwise. Reports received by the MAH as a result of litigation should also be managed as spontaneous reports.
EFPIA	409	410	4.7	Whilst it is understood that there are currently different reporting requirements for global health authorities (hence the mention of local/regional requirements throughout the document), it is operationally impossible to introduce the concept/flexibility of following local/regional requirements in this section. This would result in a seperate case having to be created for different Health Authorities i.e. those that require it to be managed as a spontaenous case vs. those that require it to be managed as a solicited case.	
EUCOPE	409	410	4.7	Whilst it is understood that there are currently different reporting requirements for global health authorities (hence the mention of local/regional requirements throughout the document), it is operationally impossible to introduce the concept/flexibility of following local/regional requirements in this section. This would result in a seperate case having to be created for different Health Authorities i.e. those that require it to be managed as a spontaenous case vs. those that require it to be managed as a solicited case.	
EFPIA	415	415	5.1.1	We suggest to leave out "AEs" as only causally related AEs (ADRs) should be reported. By including AEs in this sentence it could be perceived as open for introducing additional/different local requirements leading to de-harmonisation which is conflicting with the objective of the guideline. We believe it is important that this guideline sets clear expectations to the harmonised standards and that it does not open up for local/regional differences and variations	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	415	419	5.1.1	Cases of AEs/ADRs that are both serious and unexpected are subject to expedited reporting. The reporting of serious expected AEs/ADRs in an expedited manner varies according to local or regional requirements. Non-serious AEs/ADRs, whether expected or not, would normally not be subject to expedited reporting but may be reportable as ICSRs per local or regional requirements and timelines. AE does not fall in the definition of expedited reporting	Cases of AEs/ADRs that are both serious and unexpected are subject to expedited reporting. The reporting of serious expected AEs/ADRs in an expedited manner varies according to local or regional requirements. Non-serious AEs/ADRs, whether expected or not, would normally not be subject to expedited reporting but may be reportable as ICSRs per local or regional requirements and timelines.
EFPIA	416	417	5.1.1	We suggest to align so that this guidance clearly sets expectations whether serious expected ADRs should be reported rather than leaving this up to local/regional requirements. We believe this sentence will lead to different local /regional requirements leading to de-harmonisation which is conflicting with the objective of the guideline. It is important that this guideline sets clear expectations to the harmonised standards and that it does not open up for local/regional differences and variations.	
BPI	417	418	5.1.1	The EU as one of the three large ICH regions legally requires expedited reporting of non-serious ADR within 90-days.	Consider changing the sentence to "Non-serious AE/ ADRs, whether expected or not, may be expeditedly reportable ICSRs as per local or regional requirements and timelines."
BPI	420	425	5.1.1	see line before, i.e. 18.	
AESPG	420	425	36896	see line before, i.e. 18.	
EFPIA	425	425	5.1.1	The guidance of the CIOMS VI working group and ICH E2A recommend using a binary approach to causality assessment for solicited cases (see comment lines 28-30). As stated in the CIOMS VI working group report: ‘‘the various gradients of relatedness offer little or no advantage in data analysis or regulatory reporting. (…) Furthermore, there is very little agreement among different people on the meaning and weight of the terms (probably vs. possibly vs. likely, etc.) even within the same language, but is even more disparate across languages.’’ However, in practice, many health authorities are asking for the use of causal assessment algorithms, such as the WHO-UMC algorithm. The use of the WHO-UMC system for standardised case causality assessment is promoted by WHO UMC. This criteria for causal assessment is apparently made available in Vigiflow and more and more countries is using Vigiflow with the support of UMC. Submission with ICH E2B submission does not include the WHO causality assessment. ICH E2D(R1) binary causal assessment statement is highly recommended. It will help to harmonize the approaches to causality assessment and dissuade HAs from requesting the use of other algorithms	The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.”
EFPIA	426	427	5.1.1	Please consider removing 'Hospitalisation' as an example. The term 'Death' provides significant clinical information if it is the only information provided, however, a Hospitalisation could have occurred for a number of reasons which may have included observation and monitoring as opposed to requiring a significant medical intervention.	Please consider removing 'Hospitalisation' as an example.
EFPIA	426	427	5.1.1	Cases that contain only an outcome (e.g death/hospitalization) may be subject to reporting per local or regional requirements. Sentence not very clear with regard to the purpose. Could be deleted since anyway ICH does not provide any consensus on reporting and MAH needs to follow local or regional requirements.	Cases that contain only an outcome (e.g death) may be subject to reporting per local or regional requirements
Medicines for Europe	426	427	5.1	The cases that contain only an outcome with Fatal makes medical relevence for reporting, however, for the cases with only hospitalization reported generally do not contain any medical AE until the reason for hospitalization is known. Any specific reason for including Hospitalization only reported reports? These are generally accepted as invalid cases in the industry and interactions with Health Authorities during inspections.	Cases that contain only an outcome of death may be subject to reporting per local or regional requirements.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	428	435	5.1.2	"Safety findings which do not qualify for ICSR reporting and which may lead to changes in the known risk-benefit balance of a medicinal product and/or impact on public health should be communicated as soon as possible to the regulatory authorities in accordance with local or regional requirements. Examples include any significant unanticipated safety findings from an in vitro, animal, epidemiological, or clinical study that suggest a significant human risk, such as evidence of mutagenicity, teratogenicity, carcinogenicity, or immunogenicity or increased mortality." We suggest to move this section to ICH E2C/E2F since major safety findings from non-clinical in vivo and in vitro studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) and for findings from non-interventional studies e.g. epidemiological studies is included in e.g., ICH E2C PEBRER guideline	
EFPIA	428	435	5.1.2	Clarification about ''important safety finding'' : does it refer to Emergent Safety issues? how should it be managed (as signals?)	confirm if important safety findings refer to Emergent safety issues and confirm how t should be managed (refer to module IX) suggest removing this section from ICH E2D (not in scope of this guideline)
EFPIA	436	477	5.1.3	Each of the subsections of 5.1.3 refers to local or regional legislation. As the principle of ICH should be the harmonization across regions, the expectation is that ICH regions implement the good practice standards as recommended by the ICH working groups. Reference to local or regional legislation is not helpful in an ICH document as it rather encourages deviations than driving harmonization.	Please consider removing the references to local or regional legislation.
EFPIA	438	440	5.1.3	The sentence "These cases should be recorded by the MAH and followed up to obtain information needed for evaluation of the case" indicates that all these cases should be followed up though some might have all necessary information in the inital report. therefore, a modified wording is recommended. Please see also the comment referring to line 606-608	These cases should be recorded by the MAH and followed up as applicable to obtain information needed for evaluation of the case.
EFPIA	449	450	5.1.3.1	For some life threatening conditions like cancer disease progression does not mean lack of efficacy	exlcude, natural disease progression from lack of effficacy
EFPIA	454	455	5.1.3.1	Reports associated with AEs/ADRs are subject to ICSR reporting requirements.	Reports associated with ~~AEs/~~ADRs are subject to ICSR reporting requirements.
BPI	456	477	5.1.3.2	The section is formed in a manner that it implies that any term focussed on in 5.1.3.2 might not be off-label-use which is generally wrong according to the specific definitions.	Either make the terms in 5.1.3.2 specific sub-terms of off-label-use or name 5.1.3.4 "further off-label-use".
Prescrire	456	462	5.1.3.2	"Reports associated with overdose, abuse, misuse, medication error, or occupational exposure, with no associated AE/ADR should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions." Cases involving overdose, abuse, misuse, medication error or occupational exposure must be reported in detail and systematically analysed, so that measures can be put in place to prevent these risks and to rectify any contributory factors, such as packaging flaws. The fact that no adverse event or adverse drug reaction occurred does not rule out the risk of such consequences. In particular, the systematic analysis of medication errors must make it possible to identify packaging-related risk factors (involving the primary or secondary packaging or the package leaflet), an area that falls under the remit of health regulators. Systematic reporting and the analysis of reported cases will enable regulatory authorities, including the EMA, to fulfil their role of making the market safer, by asking marketing authorisation holders to implement corrective or preventive measures.	"Reports associated with overdose, abuse, misuse, medication error, or occupational exposure, with no associated AE/ADR should only be reported as ICSRs, with a detailed description of the circumstances under which they occurred so that they can be analysed if required by local or regional regulations, guidelines, or other regulatory authority conditions."
AESPG	456	477		The section is formed in a manner that it implies that any term focussed on in 5.1.3.2 might not be off-label-use which is generally wrong according to the specific definitions.	Either make the terms in 5.1.3.2 specific sub-terms of off-label-use or name 5.1.3.4 "further off-label-use".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Prescrire	463	470	5.1.3.3	"Reports of exposure through a parent, such as the use of medicinal products in pregnancy or breastfeeding, with no associated AE/ADR in either the parent or the child should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions." Exposure through a parent during pregnancy or breastfeeding must be systematically reported, even when there are no clinical consequences, in line with section 6.4.1.2. Given that the data on medication use during pregnancy or breastfeeding are usually sparse, it is useful to report cases in which exposure had no clinical consequences, in order to estimate the frequency at which adverse effects occur.	"Reports of exposure through a parent, such as the use of medicinal products in pregnancy or breastfeeding, should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions even if there is no associated AE/ADR in either the parent or the child."
EFPIA	464	464	5.1.3.3	Draft text: *Reports of exposure through a parent,…* " Suggest noting that this applies to both maternal and paternal exposure, which aligns this section with section 6.4.1.2.	Proposed updated text: Reports of exposure through a parent (through maternal or paternal exposure)…
EFPIA	464	470	5.1.3.3	Reports of exposure through a parent, such as the use of medicinal products in pregnancy or breastfeeding, with no associated AE/ADR in either the parent or the child should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions. AEs/ADRs, such as abnormal outcome following parental exposure, including congenital anomalies, potential epigenetic responses, developmental disorders in the foetus or child, foetal death/spontaneous abortion, or AEs/ADRs in the mother or new-born, are subject to ICSR reporting requirements.	Reports of exposure through a parent, such as the use of medicinal products in pregnancy or breastfeeding, with no associated AE/ADR in either the parent or the child should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions. AEs/ADRs, such as abnormal outcome following parental exposure, including congenital anomalies, potential epigenetic responses, developmental disorders in the foetus or child, foetal death/spontaneous abortion, or AEs/ADRs in the mother or new-born, are subject to ICSR reporting requirements.
EFPIA	471	477	5.1.3.4	There is an opportunity to provide clarity on the definition of off-label use. In the EU, off-label use is differentiated from misuse by who made the determination to use the product outside the use described in the approved product label. For example, a product prescribed by an HCP at a dose that is higher than the dose range approved in the approved product label, would constitute off-label use. However, if the HCP prescribed a dose consistent with the approved product label and the patient decided to take a higher than prescribed dose, that would be misuse. Outside of EU, guidance is not clear on the difference between off-label use and misuse and as a result, off-label use could be coded when the correct term is misuse.	
Prescrire	471	477	5.1.3.4	"Off-label Use Reports of intentional use of a product not in accordance with the terms of the marketing authorisation with no associated AE/ADR should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions. MAH should apply judgement when determining if a case report represents off-label use with consideration of the local product labelling." Off-label use must be systematically reported, even in the absence of clinical consequences, to enable regulatory authorities to evaluate and regulate them if necessary, and to prevent the potential risks of off-label use.	"Off-label Use Reports of intentional use of a product not in accordance with the terms of the marketing authorisation with no associated AE/ADR should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions. MAH should apply judgement when determining if a case report represents off-label use with consideration of the local product labelling."
EUCOPE	471	477		EUCOPE agrees that off-label use cases associated with an AE should be collected and reported if required; however, EUCOPE recommends to add guidance in this section about how MAHs should monitor off-label use with their products. It is highly unlikely that significant off-label use will be detected through individual reports collected in the filed. Therefore, MAHs should be recommended to monitor off-label use through literature screening and potentially by screening medical information enquiries instead of being encouraged to collect these off-label use cases not associated with an AE.	
EFPIA	472	473	5.1.3.4	"Reports of intentional use of a product not in accordance with the terms of the marketing authorisation with no associated AE/ADR should only be reported as ICSRs" Need to specify that reporter for OLU is an HCP (as if the reporter is a consumer it would be considered Misuse)?	Reports of intentional use of a product by a HCP not in accordance with the terms of the marketing authorisation with no associated AE/ADR should only be reported as ICSRs

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	474	476	5.1.3.4	Suggest updating to align with MedDRA and to ensure a consistent approach on what is considered Off-label (as well as the existing text which guides us to the local product labelling).	Suggest additional bolded text to be added: "MAH should apply judgement when determining if a case report represents off-label use with consideration of the local product labelling. Off-Label use terms should only be selected when off label use is specifically mentioned in the reported verbatim information. For information that is suggestive of off-label use but not reported, attempt to obtain clarification"
EUCOPE	474	476	5.1.3.4	Suggest updating to align with MedDRA and to ensure a consistent approach on what is considered Off-label (as well as the existing text which guides us to the local product labelling).	Suggest additional bolded text to be added: "MAH should apply judgement when determining if a case report represents off-label use with consideration of the local product labelling. Off-Label use terms should only be selected when off label use is specifically mentioned in the reported verbatim information. For information that is suggestive of off-label use but not reported, attempt to obtain clarification"
BPI	479	481	5.2	Timeframes for expedited reporting meanwhile vary, depending on country/ region and/ or type of report. Therefore this section should not, or at least not only, make refrence to 15-day reports.	Consider changing the sentence to a more general wording in order to refelect different timelines for expedited reporting. E.g.: "In general, ICSRs that fulfil local or regional criteria for expedited reporting (see Section 5.1, What Should Be Reported?) should be submitted as soon as possible, and in any case within the legally required timelines. The definition of day zero is described further below."
BPI	481	484	5.2	In the EU 90-day reports also qualify as expedited treports (see GVP VI.C.3)	Consider changing the sentence to reflect ICRS to be submitted within more than 15 days also to qualify as expedited reports. E.g.: "Timeframes for reporting AEs/ADRs that are expeditedly reportable as ICSRs, including non-serious AEs/ADRs, may vary according to local or regional requirements.
Medicines for Europe	497	499	5.2	Can we propose a specific scenario of when there is splitting of an already submitted case with no new information, the clock start date to be date of splitting. The rationale for proposing that is that the information is already submitted under the existing case, however, it requires a split due to administrative reasons (eg. some agencies unable to accept large piece of information). This kind of split unnecessarily leads to global compliance challenges for some agencies (eg. the ones which are still accepting E2B R2 submissions which have file size limitations).	
Medicines for Europe	522	525	6.1	Can this scenario on second hand reports be clarified further? What about reports received from institutions for compensations etc? Should all those reports be considered as incomplete? This can lead to a lot of different interpretations.	
Medicines for Europe	526	528	6.1	Has FDA and Health Canada accepted this wording? As per FDA and Canada regulations, knowledge of patient is sufficient for reporting a case even if the identifiers are not present. If FDA and Canada expectations remain different from EMA, then please see proposed modified text.	For cases where the patient identifiers are not reported, the ICSR could still be reported if required by local regulations, as long as the existence of an individual patient is known.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gedeon Richter Plc. (BK)	535	539	6.1	If a report refers to a single patient, identifiability of the patient is implicitly supported by the patient's inclusion in that specific, unique report. If a report refers to multiple patients who are not uniquely distinguishable, this additional support is not present and patients cannot, in fact, be uniquely identified based on qualifier-report combination data.	Original: In the absence of qualifying descriptors, a report referring to a definite number of patients should not be regarded as a case until the four minimum criteria for reporting are met. For example, “Twenty patients experienced…” or “a few patients experienced” should be followed up for patient-identifiable information before creating an ICSR. To qualify for ICSR reporting it should be possible to associate an AE/ADR or AEs/ADRs with a specific identifiable patient. Proposed change: In the absence of unique patient identifiers, a report referring to a definite number of patients should not be regarded as a case even if qualifying descriptors are present or can reasonably be inferred for each patient and the four minimum criteria for reporting would formally be met. For example, “Twenty adult patients born between 1990 and 2000 experienced…” or “a few elderly female patients experienced” or "three patients with uterine myomas experienced" should be followed up for patient-identifiable information before creating an ICSR. To qualify for reporting, ICSRs originating from multi-patient reports should include an individual patient who is not only identifiable by various qualifiers, but also clearly distinguishable from all other patients in the source report.
SciencePharma	535	539	6.1	An inquiry on how to proceed when quantitative data was provided, e.g. "five adult patients who presented with headaches after taking a certain medication. Among these patients, two had also taken other medications, and three were smokers." Consequently, it becomes challenging to match this information to any particular patient.	NA
EFPIA	539	539	6.1	We suggest to remove" AEs" from the sentence as only AEs with a suspected causal relationship to the drug (i.e an ADR) are reportable.	
EFPIA	540	548	6.1	Regarding identifiability of the reporter/patient on digital platforms, the draft text requires 'existence of a real person' and not a 'handle'. For many people, their 'handle' is their actual name. Does the proposed text mean that any handle, even handles that are people's names, cannot be automatically considered as a valid reporter until contact can be made with that person and confirmatory information is received?	
Gedeon Richter Plc. (EB)	546	548	6.1.	The meaning of the terms "permissible" and "feasible" applied to follow-up attempts involving cases originating from digital platforms not falling under MAH responsibility is not always straightforward. Examples of expected levels of due diligence would serve as helpful guidance. For example, to what extent are MAHs expected to pursue posts in specific private user groups or in forums requiring registration? Recommend adding proposed passage to either section 4.3.2, or the highlighted part of section 6.1.	Original: Where follow-up is feasible, MAHs should attempt to obtain evidence of the existence of a real patient and reporter (e.g., via requesting at least one identifiable characteristic such as gender, age, or age category). Proposed: Where follow-up is feasible, MAHs should attempt to obtain evidence of the existence of a real patient and reporter (e.g., via requesting at least one identifiable characteristic such as gender, age, or age category). However, MAHs are not expected to follow up AE/ADR reports identified on digital platforms if such follow-up would, for example, require registration to that platform or joining specific user groups.
EFPIA	549	549	6.2	Added value brought by narratives of non-serious ICSR is very limited.	Recommendation to provide guidance on the necessity to capture a narrative for non-serious ICSR

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCOPE	554	557	6.2	The guidance here to present in chronological order and to clearly identify new information seems a little challenging and could result in very 'messy' narratives.	
EFPIA	558	559	6.2	"Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units." Not the same acronyms for lab parameters/units in different territories. Suggest clarification.	"Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units, which are international standard units or widely used acronyms"
EFPIA	597	599	6.4	"For serious AEs/ADRs, it is important to continue follow-up and report new information until the outcome has been established or the patient's condition is stabilised.": Continue follow-up can be challenging and useless in some scenarios, suggest to add back the original sentence from ICH E2D "How long to follow up such cases is a matter of judgment."	Suggest to change the wording to: "For serious AEs/ADRs, it is important to continue follow-up as much as possible and report (...)" to bring some flexibility.
EFPIA	606	608	6.4.1	To follow up all reports of other observations without an AE will impose significant burden on MAHs and primary sources and might be impossible (eg for intercepted medication errors where no patient was administered a medicinal product). In addition, it is not expected that such extensive follow-up would aid significant new safety information not offered in the initial report. Follow-up should be conducted based on medical judgement taking into consideration trends/patterns of reports of other observations relevant to the interpretation of safety data.	As per Section 5.1.3, Other Observations, reports of other observations (without an AE), should also be followed up to obtain complete information based on medical judgement taking into consideration the specific observation reported and to ascertain if an AE/ADR has occurred.
European CRO Federation (EUCROF) Pharmacovigilance Working Group (PVWG)	615	615	6.4.1.2.	Similar if the product mode of action implies a long, sustained impact on the patient e.g. immunosuppressive drugs where, even after the drug is no longer present in the body, the effects on the immune system may persist for some time.	Suggested change: add reference to "mode of action" of a drug and provide as an example "immunosuppressive drugs".
EFPIA	617	618	6.4.1.2	To improve readability. Alternatively remove "if" from the beginning.	(e.g., if medicinal products were taken before the gestational period commenced should be considered). OR (e.g., ~~if~~ medicinal products taken before the gestational period commenced should be considered).
EFPIA	620	621	6.4.1.2	"Consideration should be given as to whether the product is specifically indicated for use during pregnancy": What does "consideration" mean?	Suggest to clarify what "consideration" means in this context
BPI	622	635	6.5	The different rules in different world regions are duly addressed. However, it is difficult to follow stricter rules for literature search such as weekly, whenever there are regions with less strict rules.	Add a phrase demanding that stricter rules apply for the agreement in the exchange section as to exchange timelines to be agreed if two regions differ.
AESPG	622	635		The different rules in different world regions are duly addressed. However, it is difficult to follow stricter rules for literature search such as weekly, whenever there are regions with less strict rules.	Add a phrase demanding that stricter rules apply for the agreement in the exchange section as to exchange timelines to be agreed if two regions differ.
EFPIA	645	645	6.6	This situation is more applicable for multiple co-suspect drug articles	Literature reporting of the same AE/ADR or other observations by multiple MAHs, such as articles with multiple co-suspect drugs.
Medicines for Europe	647	647	6.6	Should this not also apply to Regulatory Agencies (RA)? We see some agencies relying on Worldwide Uniquie Case Identification Number (WUCIN) being utilized for duplicate identification. This may not be sufficient in certain scenarios and is leading to duplicate in Regulatory databases. The scenarios commonly seen are for reports received from literature where there are multiple MAH for generic products and are screening the same journals in parallel and processing data thereby generating different WUCINs. This is also seen when reporter reports same case to different MAH/RA due to co-suspect products, thereby leading to duplicates in RA Databases if they rely on WUCIN for duplicate identification.	MAHs and Regulatory Agencies may utilise duplicate management strategies that are most suitable for their individual