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Data Analytics and Methods Taskforce

Detailed guidance on ICSRs in the context of COVID-19

Validity and coding of ICSRs

Revision 3: Detailed guidance updated to clarify the recording in ICSRs of vaccine dose schedule received by patients and to easily distinguish reactions linked to mixed vaccines administration. Recommendations are also provided for the coding of lack of therapeutic efficacy notification referring to COVID-19 vaccines and for the management of cases when no information is available on the COVID-19 vaccine name received by the patients. The new guidance introduced through Revision 3 is recommended to be applied prospectively to newly received and follow-up cases and the amendment of ICSRs already submitted to EudraVigilance is not required.

Introduction

This detailed guidance document provides recommendations relevant to the processing and submission of Individual Case Safety Reports (ICSRs) associated with medicinal products used for the treatment or prevention of COVID-19 infection, taking into account:

- the Notice to stakeholders published by the European Commission[1];
- the guidance regarding COVID-19 related terms[2] published by the MedDRA MSSO; and
- the introduction of COVID-19 related terms since the updated MedDRA version 23.0.

Reporting principles

Organisations are reminded to comply with their legal obligations to report suspect adverse drug reactions in line with Articles 107 and 107a of Directive 2001/83/EC and to adhere to the guidelines in GVP Module VI[3], ICH E2B Guidelines[4] and the current version of MedDRA term selection: Points to Consider[5]. In particular:

[1] Notice to stakeholders - Questions and answers on regulatory expectations for medicinal products for human use during the covid-19 pandemic
[2] MedDRA MSSO COVID-19 Information Page
[3] Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2):
[4] ICH E2B(R2) guideline and ICH E2B(R3) guideline
[5] https://www.meddra.org/how-to-use/support-documentation

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- GVP Module VI Chapter VI. C.6.2.2. Preparation of individual case safety reports
  - the complete information (medical and administrative data) for a valid ICSR that is available to the sender should be submitted in a structured manner in the relevant ICH-E2B data elements (which should be repeated as necessary when multiple information is available) and in the narrative section for serious cases;
- GVP Module VI Chapters VI.A.1.3. Active substance, excipient, medicinal product, and VI.C.6.2.2.2. Information on suspect, interacting and concomitant medicinal products
  - Reports should not be submitted for the misuse of non-medicinal products which may contain substances also present in medicinal products, such as swimming pool cleaner containing chloroquine phosphate;
  - When a case of adverse reactions is suspected to be related only to a therapeutic class, it is considered incomplete and does not qualify for submission as ICSR. Efforts should be made to follow-up the case in order to collect the missing information regarding the suspected medicinal product (see VI.B.3. for follow-up guidance). Taking this guidance into consideration, where the information on the suspected COVID-19 vaccine received by the patient is not specified in the report (e.g., A 20-year-old male patient experienced fatigue with COVID-19 vaccine), and if it is not possible to know which vaccine the patient was administered (e.g., based on information on national vaccination campaign and/or on patient's identifier), the case should not be considered valid for submission to EudraVigilance. It should be followed-up and should be recorded within the pharmacovigilance system for use in on-going safety evaluation activities.
- GVP Module VI Chapter VI.C.2.2.12. Reporting of off-label use
  - Reports of off-label use with no associated suspected adverse reactions (this includes reports of unexpected therapeutic benefit) should not be reported to EudraVigilance; they should be discussed in the Periodic Safety Update Report and/or addressed in the product Risk Management Plan in line with the requirements provided in GVP Module VI chapter VI.C.2.2.12;
- GVP Module VI Chapter VI.B.6.4. Lack of therapeutic efficacy
  - If a medicinal product is being used in accordance with its authorisation to prevent or treat COVID-19 infection and a lack of therapeutic efficacy is reported with no associated suspected adverse reaction, then, because COVID-19 is a potentially life-threatening disease, this should be submitted within 15 days to EudraVigilance as an ICSR (see guidance further down for adding MedDRA LLT 'Vaccination failure' in the ICH E2B 'Reaction(s)/Event(s)' section of the ICSR),
  - If a medicinal product is being used off-label to prevent or treat COVID-19 infection and a lack of therapeutic efficacy is reported without an associated ADR, then, in accordance with the principle outlined in Chapter VI.B.6.4, this should not be submitted as an ICSR[6]. It should instead be discussed in the Periodic Safety Update Report and/or addressed in the product Risk Management plan,

[6] "For example, a report of lack of therapeutic efficacy with an antibiotic used in a life-threatening situation where the use of the medicinal product was not in fact appropriate for the infective agent should not be submitted."

- Reports with a valid Adverse Drug Reaction[7] which also have of lack of therapeutic efficacy reported should be submitted as ICSRs, regardless of whether the medicinal product was used off-label or not;

- GVP Module VI.C.1.2.2. Compassionate use and named patient use

  - If authorisation has been granted for a medicinal product to be supplied in accordance with Article 83(2) of Regulation (EC) No 726/2004 (compassionate use) or Article 5(1) of Directive 2001/83/EC (named patient use), and the organisation or a healthcare professional supplying this medicinal product is notified or becomes aware of an adverse event, the requirements in the concerned Member State should be followed:

    - If the active collection of adverse events occurring in these programmes is required, then any ICSRs should be considered as solicited and only causally related ICSRs should be submitted to EudraVigilance,

    - If the active collection of adverse events occurring in these programmes is not required, then any ICSRs should be considered as spontaneous reports;

- GVP Module VI Chapters VI.B.1.1.2. Literature reports, VI.C.2.2.3.1. Monitoring of the medical literature by the European Medicines Agency, and VI.B.1.1.3. Reports from non-medical sources

  - It is expected that the number of publications related to substances used to treat or prevent COVID-19 will increase significantly. Marketing authorisation holders shall not create duplicates in EudraVigilance by submitting ICSRs which should be submitted by the Medical Literature Monitoring service[8]. QPPVs will be informed when the scope of substances is updated.

  In addition, the following points should be taken into consideration:

  The exclusion criteria provided in Chapter VI.C.2.2.3.2 should be followed. Particular attention should be paid to exclusion criteria d to f, which concern literature which:

  d. refers to data from publicly available databases (e.g. poison control centres) and where the cases are presented in aggregate tables or line listings. The submission requirement remains for valid cases described individually,

  e. presents the results from post-authorisation studies, meta-analyses, or literature reviews,

  f. describes suspected adverse reactions in a group of patients with a designated medicinal product and the patients cannot be identified individually for creating valid ICSRs (see VI.B.2. for ICSRs validation),

  One case should be created for each single identifiable patient while respecting the exclusion criteria provided in Chapter VI.C.2.2.3.2. ICSRs based on information from the medical literature, lay press or other media should have as complete as possible patient and reporter information to aid in the detection and management of duplicates;

[7] See GVP Module VI, Chapter VI.B.2. Validation of reports, section d. one or more suspected adverse reaction for details on valid ADRs.
[8] In accordance with Article 107(3) of Directive 2001/83/EC and to avoid the submission of duplicate ICSRs, the marketing authorisation holder shall only submit those ICSRs described in the medical literature which is not reviewed by the Agency, for all medicinal products containing active substances which are not included in the list monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004

- GVP Module VI Chapter VI.B.1.1.4. Information on suspected adverse reactions from the internet or digital media
  - Marketing authorisation holders (MAHs) should regularly screen the internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions. MAHs are not expected to search non-company sponsored digital media for potential reports of suspected adverse reactions where their product is being used in COVID-19 infection; however, if a MAH becomes aware of a report of suspected adverse reaction described in any of these sources, the report should be assessed to determine whether it qualifies for submission as ICSR.

MedDRA COVID-19 coding guidance

Specific COVID-19 terms have been included in MedDRA since version 23.0. Stakeholders should ensure that they select the relevant precise COVID-19 related term when coding ICSRs in accordance with the MedDRA term selection Points to Consider[5].

In line with the MedDRA MSSO Best Practices document the decision to re-code historical data is left to the discretion of each individual organisation. Amended versions of the ICSRs should be submitted when the re-coding significantly impacts on the medical evaluation of cases already submitted to EudraVigilance. When transmitting in E2B(R3) format, this should follow the principles for 'Amendment reports' in line with GVP module VI guidance[3] section VI.C.6.2.2.8. Amendment of cases.

From MedDRA version 23.1 a new COVID-19 SMQ (Special MedDRA Query) was released. The MedDRA MSSO has advised to apply this SMQ not only in Reaction(s)/Event(s) data elements, but also in other relevant data elements such as those for medical history, indications, laboratory tests, etc. Furthermore, since this SMQ has been designed to be specific to COVID-19, users are advised to consider applying other SMQs in combination to perform a more comprehensive search of the various clinical manifestations of the infection if desired.

ICH-E2B data element 'Dosage text'

When a vaccine is required to be administered in multiple doses, or when booster doses need to be further administered, there is no dedicated data element in ICH E2B to capture which dose schedule the patients received before they experienced a suspected adverse reaction. The following guidance has been developed in order to easily recognise reactions potentially linked to the first, second, or third/ booster dose. It will also facilitate the retrieval of reactions linked to the administration of different vaccines (e.g., 1st dose adenovirus vaccine and 2nd dose mRNA vaccine).

Information concerning the suspected vaccine dose schedule is recommended to be recorded in the 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8), E.g., "Dose 1", "Dose 2", etc. If the reaction is following the second or subsequent vaccine dose with no information regarding the previous received dose(s), then only the information concerning the suspected dose should be recorded. The fact that it is the second or subsequent dose should be provided in the 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8), where the number corresponds to the known dose schedule for the administered vaccine. E.g., A patient experienced a reaction after administration of a third vaccine dose schedule and no information is reported regarding the first dose: "Dose 3" should be recorded in the 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8).

- **Where the patient received multiple doses of the same COVID-19 vaccine**

  Two situations are considered – when the previous vaccine dose is suspected and when it is not:

a. If a previous vaccine dose is also suspected in the reaction occurrence:

   The 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8) should be used to capture information on the dose schedule number for each suspected dose.

   In ICH E2B(R3) format, information concerning the suspected dose should be captured under the 'Dosage and Relevant Information' section (ICH E2B(R3) G.k.4.r) for the suspected COVID-19 vaccine, and the 'Dosage and Relevant Information' section should be repeated for each suspected dose.

   In ICH E2B(R2) format, information concerning each suspected dose should be recorded through the 'Drug(s) information' sections (B.4), which should be repeated for each of the suspected COVID-19 vaccine dose.

b. If the previous vaccine dose is not suspected in the reaction occurrence:

   The 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8) should be used to capture information on the dose schedule number for the suspected dose.

   Information concerning the non-suspected dose schedule should be recorded under 'Relevant Past Drug History' data element/ section (ICH E2B(R2) B.1.8/(R3) D.8.r).

- **Where the patient received multiple doses of mixed COVID-19 vaccines (e.g., 1st dose Vaxzevria, 2nd dose Comirnaty)**

  Two situations are considered – when the previous vaccine dose is suspected and when it is not:

  a. If the previous vaccine dose is also suspected in the reaction occurrence:

     Both the suspect vaccines should be structured in accordance with normal case processing, and the 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8) should be used to capture information on the dose schedule number for each suspected vaccine.

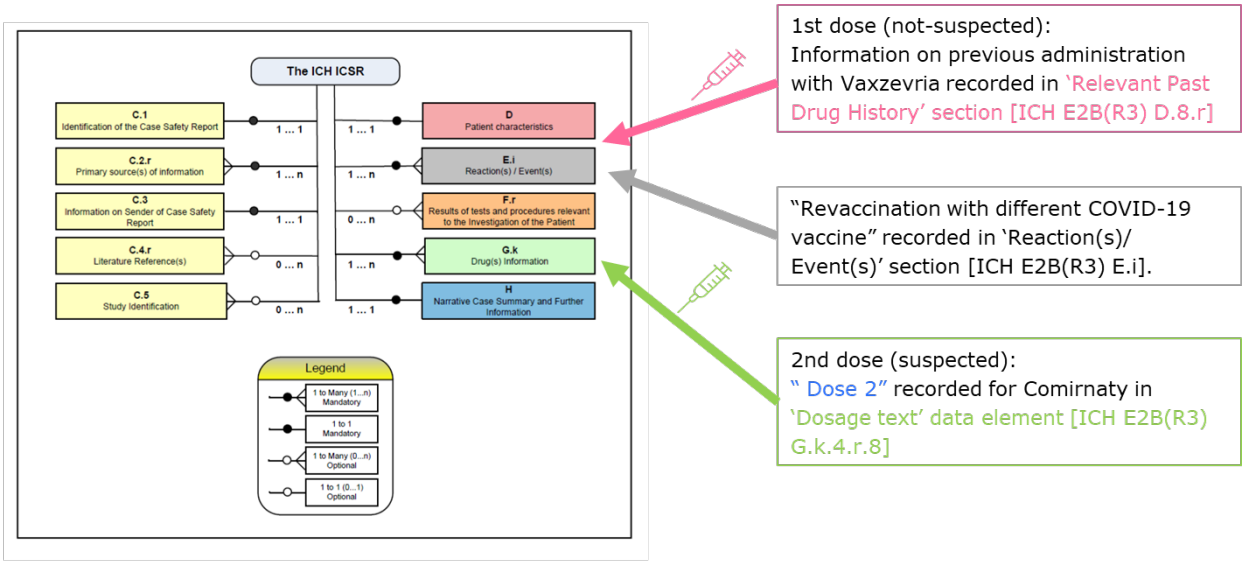
  b. If the previous vaccine dose is not suspected in the reaction occurrence:

     The 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8) should be used to capture information on the dose schedule number of the suspected vaccine.

     Information concerning the non-suspected vaccine should be recorded under 'Relevant Past Drug History' data element/ section (ICH E2B(R2) B.1.8/(R3) D.8.r).

  In order to easily distinguish reactions linked to mixed vaccines administration, the MedDRA LLT "Revaccination with different COVID-19 vaccine" is also recommended to be recorded in the 'Reaction(s)/ Event(s)' section [ICH E2B(R2) B.2/(R3) E.i], in addition to the reported suspected adverse reaction(s).

  E.g., vaccine dose schedule data entry in ICH E2B for 1st dose Vaxzevria not-suspected and 2nd dose Comirnaty suspected, see figure hereafter:



Stakeholders may already have implemented procedures to specifically record in ICSRs the information on vaccine dose schedule. These measures may also be linked to dedicated fields in structured electronic forms developed to collect within websites safety information in the context of COVID-19 pandemic.

Some flexibility is acknowledged in the ways to record information on previous dose schedules either in the 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8) (e.g., where a product may be entered as concomitant), or in the 'Relevant past drug history' data element/ section (ICH E2B(R2) B.1.8/(R3) D.8.r). It is recommended however to record at least the information on the suspected dose schedule received prior to the reaction in the 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8).

Similarly, since the 'Dosage text' data element (ICH E2B(R2) B.4.k.6/(R3) G.k.4.r.8) is a free text field, different terms may already be used by stakeholders to record the corresponding dose schedule number. Flexibility is permitted in the terms to be recorded in this data element, however the use of mixed alpha-numerical values is recommended (i.e. combination of alphabetical and numerical characters instead of only alphabetical characters) in order to easily identify the number corresponding to the dose schedule; E.g., 1st dose; Dose 1; Dose # 1; Dose no. in series: 1; etc...

ICH-E2B section 'Reaction(s)/Event(s)'

Codding of disease aggravation

In line with GVP Module VI Chapter VI.C.6.2.3.4., the indication for which the suspected medicinal product was administered should not be included in the ICH-E2B section 'Reactions/Events' unless aggravation of the medical condition occurs.

If a patient experiences an aggravation or exacerbation of their condition, then usually the 'Reaction (MedDRA)' data element should be populated with either the MedDRA LLT "COVID-19 aggravated" (LLT Code 10084657) or MedDRA LLT "COVID-19 pneumonia aggravated" (LLT Code 10084658).

If neither of those terms is sufficiently precise, then, in accordance with the principles of MedDRA term selection: Points to Consider[5], two reactions should be entered:

- The most precise COVID-19 related LLT

  and

- "Condition aggravated" (LLT code 10010264)

If a suspected adverse reaction occurs in the setting of off label use, the guidance provided in GVP Module VI chapter VI.C.6.2.3.3. should be followed for the provision of the information in the ICSR.

Coding of lack of therapeutic efficacy notification referring to COVID-19 vaccines

In line with GVP Module VI Chapters VI.B.6.4 and VI.C.6.2.3.4, reports of lack of therapeutic efficacy should be collected and recorded when notified and followed-up if incomplete. They should normally not be submitted as ICSRs if there is no associated suspected adverse reaction, but they should be discussed in periodic safety update reports. In certain circumstances, reports of lack of therapeutic efficacy with no suspected adverse reaction may require to be submitted within a 15-day time frame. Medicinal products used in critical conditions or for the treatment of life-threatening diseases, vaccines, contraceptives are examples of such cases.

While some degree of protection is expected from vaccines even after the first dose, full protection can only be claimed after the correct vaccination regimen has been administered (e.g. after the second does if it is a 2-dose schedule) in line with the recommendations given in the product information.

General guidance regarding the definition of vaccination failure is available in the Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance[9]. As stated in this document, multiple approaches exist regarding the definitions of vaccination failure due to the fact that it can be characterised by a variety of criteria (e.g. disease prevention, disease mitigation, immune response) or clinical endpoints against which vaccine should protect (e.g. infection, versus disease, versus serious (complicated) disease). The vaccination failure can also be linked to multiple causes such as:

- Host related (e.g. immunodeficiency; pre-existing infection with targeted pathogen; concurrent immunosuppressive therapy; waning immunity);
- Vaccine related (e.g. vaccine not 100% efficacious; incomplete coverage of strains, serotypes, genotypes, antigenic variants or escape mutants; batch variation or quality defect);
- Usage related (e.g. administration error; vaccination series incomplete; non-compliance with recommended schedule/ booster vaccination; inappropriate storage; use beyond expiry date).

Taking these variables into consideration, together with the guidance given in the MedDRA Term Selection: Points to Consider, which specifies not to infer that lack of efficacy has occurred unless specific information is provided, the following is proposed when the notified information refers to a potential lack of therapeutic efficacy of a suspected COVID-19 vaccine:

The MedDRA LLT 'Vaccination failure' is recommended to be added in the 'Reaction(s)/Event(s)' section (ICH E2B(R2) B.2/(R3) E.i) when the following 3 conditions are met:

- Associated symptoms are reported;
- The reported events occur after the normal time period for the protection to be acquired as a result of immunisation in line with the suspected vaccine product information; and
- A positive diagnostic test for COVID-19 is also reported in the case.

The monitoring of COVID-19 vaccines effectiveness has shown that the conferred protection wanes over time and further dose administrations are recommended to sustain and improve the protection.

[9] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.

Therefore, the MedDRA LLT 'Vaccination failure' should not be added if the reported event occurred after the time interval recommended for a new COVID-19 vaccine dose to be administered in line with

- The guidance provided in the National immunization plan against COVID-19 of the occurrence country, or if not available
- The product information of the COVID-19 vaccine used in the previous immunization.

ICH-E2B data element 'Indication for Use in Case'

Each medicinal product used to treat confirmed or suspected COVID-19 infection should have an indication (ICH E2B(R2)B.4.k.10/(R3)G.k.7.r.2b) populated with the most precise COVID-19 related MedDRA LLT.

If the medicine is used as prophylaxis against COVID-19 infection, the indication should be populated with the MedDRA LLT "COVID-19 prophylaxis" (LLT code 10084458).

If the medicine is used as immunisation against COVID-19 infection, the indication should be populated with the most precise MedDRA LLT under the PT "COVID-19 immunisation".

If the medicine is used as treatment for COVID-19 infection, the indication should be populated with the most precise MedDRA LLT under the PT "COVID-19 treatment", unless a more precise term is available.

ICH-E2B data element 'Relevant Medical history and Concurrent Conditions'

The data elements for medical history should also be used to capture concurrent conditions. This is particularly relevant for ICSRs concerning COVID-19 patients, for which the suspected medicinal product was not used for the treatment and/or prevention of the COVID-19 infection.

If a patient has confirmed COVID-19 infection, then the ICH-E2B data elements patient medical history (ICH E2B(R2)B.1.7.1a.2/(R3)D.7.1.r.1b) should be populated with the most precise COVID-19 related MedDRA LLT.

For ICSRs where the suspected medicinal product was not used for the treatment of COVID-19 infection and where it is explicitly reported that the patient has known exposure to COVID-19 without developing infection (e.g. healthcare workers), the most precise MedDRA LLT under the PTs "Exposure to SARS-CoV-2" or "Occupational exposure to SARS-CoV-2" should be entered.

The two paragraphs above also apply to parent medical history.

ICH-E2B data element 'Results of tests and procedures relevant to the investigation of the patient'

MedDRA LLTs such as "Coronavirus test positive" (LLT Code 10070255) or "SARS-CoV-2 test negative" (LLT Code 10084273) reflect test results and should not be used in the ICH-E2B data elements for test name (ICH E2B(R2)B.3.1c/(R3)F.r.2.2b). The data element for the test name should be populated with the most precise MedDRA LLT under the PTs "Coronavirus test", "SARS-CoV-2 test" or "SARS-CoV-2 antibody test" as applicable.