Detailed guidance on ICSRs in the context of COVID-19

Validity and coding of ICSRs

Revision 2: Detailed guidance updated to acknowledge that COVID-19 related terms are made available from the updated MedDRA version 23.0 onwards and to notify the release of a COVID-19 SMQ with MedDRA version 23.1.

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 Commission¹;
- the guidance regarding COVID-19 related terms² 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 applicable legislation Articles 107 and 107a of Directive 2001/83/EC and to adhere to the guidelines in GVP Module VI³, ICH E2B Guidelines⁴ and the current version of MedDRA term selection: Points to Consider⁵. In particular:

- 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

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
(which should be repeated as necessary when multiple information is available) and in the narrative section for serious cases;

- **GVP Module VI Chapter VI.A.1.3. Active substance, excipient, medicinal product**
  - 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;

- **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,
  - 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. It should instead be discussed in the Periodic Safety Update Report and/or addressed in the product Risk Management plan,
  - Reports with a valid Adverse Drug Reaction 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 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.1.3. 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

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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.”

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.
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;

- 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

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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.
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 ‘Reaction(s)/Event(s)’**

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)’ field 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.

**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.