

28 July 2017
EMA/405655/2016

Guideline on good pharmacovigilance practices (GVP)

Module VI Addendum I – Duplicate management of suspected adverse reaction reports

Draft finalised by the Agency in collaboration with Member States	21 July 2017
Draft agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	25 July 2017
Draft adopted by Executive Director as final	28 July 2017
Date for coming into effect	22 November 2017

Note: This document is the revision 1 of the CHMP Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) published on 7 November 2011, and is now issued as a new GVP guideline, replacing the CHMP guideline as of 22 November 2017.

The revision contains the following changes:

- Alignment with revision 2 of GVP Module VI;
- Update of electronic reporting modalities of ICSRs in the new ICH-E2B(R3) format;
- Update overall with the revised pharmacovigilance legislation as regards the roles and responsibilities of the Agency, the competent authorities in Member States as well as marketing authorisation holders in relation to the operation of duplicate detection and management of reports of suspected adverse reactions;
- Guidance on how to inform the Agency of suspected duplicates in EudraVigilance;
- Changes for consistent presentation of GVP documents.

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

The European Medicines Agency is
an agency of the European Union



Table of contents

VI. Add I.1. Introduction	3
VI. Add I.2. General aspects of duplicate cases	4
VI. Add I.3. Detection of duplicate cases	5
VI. Add I.3.1. What to do if possible duplicates in EudraVigilance have been detected	7
VI. Add I.3.2. Confirmation of duplicates cases	7
VI. Add I.4. Management of duplicates cases	8
VI. Add I.4.1. Process of managing duplicates detected during periodic screening	9
VI. Add I.4.1.1. Allocation of a master case.....	9
VI. Add I.4.1.2. Creation of a master case	11
VI. Add I.4.2. Process maps and descriptions for allocation or creation of a master case	11
VI. Add I.4.3. Sending nullifications	19
VI. Add I.4.4. Duplicates received from the same sender organisation	19

VI. Add I.1. Introduction

Duplicate case reports of suspected adverse reactions can pose significant problems for analysing signals arising from pharmacovigilance databases, both artificially inflating and masking signals of disproportionate reporting (see [GVP Module IX Addendum I](#)). The applicable reporting rules cannot avoid duplicate reporting. Databases should therefore be routinely screened to detect and eliminate duplicate cases and the European Medicines Agency (the 'Agency'), competent authorities in Member States and marketing authorisation holders shall all collaborate in the detection and elimination of duplicates in the EudraVigilance database [Articles 107(5) & 107a(3) of Directive 2001/83]. The guidance in this document proposes methods for detecting, confirming and managing duplicate cases suitable for organisations receiving pharmacovigilance data in various different formats and describes methods for stakeholders to collaborate with the Agency in the detection and management of duplicate cases. This guidance is part of the good pharmacovigilance practices (GVP) and an Addendum to [GVP Module VI – Management and reporting of adverse reactions to medicinal products](#).

Guidance is also provided for situations where individual cases might be reported by different senders e.g. where a marketing authorisation holder is aware that a healthcare professional or a patient has reported an adverse reaction to one of the medicinal products, for which they hold a marketing authorisation, to the competent authority of a Member State. [GVP Module VI](#) states that when one party is made aware that the primary source(s) may also have reported the suspected adverse reaction to another concerned party, the report should still be considered as a valid individual case safety report (ICSR). All the relevant information necessary for the detection of the duplicate case should be included in the ICSR.

A duplicate refers to the same individual case reported by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point of time. This individual case may be reported by different senders, through different routes, whereby the case information may be handled differently by the processor of the case, which makes it difficult to identify the reported cases as duplicates. Case handling refers e.g. to coding practices, obtaining follow-up information and processing of personal data in line with EU Data Protection legislation^{1,2}.

Detection and handling of duplicates by competent authorities and marketing authorisation holders form an important element of good case management and the collaboration of marketing authorisation holders and competent authorities in Member States with the Agency in the detection of duplicates in EudraVigilance (EV) is mandated by Directive 2001/83/EC^{3,4}. The presence of duplicates in any pharmacovigilance database can create misleading signals and therefore impact on the safety monitoring and potential regulatory actions. How duplicates can impact on the identification of potential new safety issues can be illustrated by an example of duplication in the US FDA Adverse Events Reporting System (AERS) database. In an evaluation of quinine-induced thrombocytopenia, researchers identified 20% of 141 reports as duplicates.⁵ Norén et al.⁶ highlighted that since commonly used data-mining procedures may highlight associations with as few as three reports, one or two duplicates may severely affect their utility.

¹ Regulation (EC) No 45/2001

² Directive 95/46/EC

³ Directive 2001/83/EC Article 107(5) "Marketing authorisation holders shall collaborate with the Agency and the Member States in the detection of duplicates of suspected adverse reaction reports"

⁴ Article 107a (3) "Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports."

⁵ Hauben M, Reich L, DeMicco J, Kim K. 'Extreme Duplication' in the US FDA Adverse Events Reporting System Database. *Drug Safety*. 2007; 309(6): 551-554

⁶ Norén GN, Orre R, Bate A, Edwards I R. Duplicate detection in adverse drug reaction surveillance. *Data Mining and Knowledge Discovery*. 2007, 14: 305-328

The simplified reporting rules will come into effect on 22 November 2017, and this is expected to significantly reduce the number of duplicate cases, although they can never be completely excluded.

As an initial step in 2006 to investigate which procedures exist for handling potential duplicates, the EudraVigilance Expert Working Group (EV EWG) collected some information on the various aspects of duplicate detection and management through a questionnaire to Member States, marketing authorisation holders as well as clinical trial sponsors. Based on the feedback received, the EV EWG prepared the Guideline on Duplicate Detection and Management of Individual Cases and Individual Case Safety Reports (ICSRs), which was published in 2011 and has provided competent authorities in Member States, marketing authorisation holders, sponsors and any other organisations involved in case handling and processing (e.g. third party service providers) with clear directions on the management of duplicates. The aforementioned guideline is now replaced by this GVP Module VI Addendum I, which updates the original guideline to take account of the simplified reporting rules and the changes to the responsibilities of competent authorities in Member States, marketing authorisation holders and sponsors.

The objective of this new guidance is to promote accurate detection and handling of duplicate cases, with the ultimate aim of achieving a duplicate-free database. Organisations need to implement duplicate management strategies that are most suitable for their individual situation, while taking into account that the electronic exchange of ICSRs in ICH-E2B(R2) and E2B(R3) formats⁷ may require specific actions to be taken upon detection of duplicates.

There are various ways in which individual case information and the related ICSRs can be recorded. In most circumstances, the method will depend on the complexity of the organisation's database and the amount of data received. Therefore, it should be acknowledged that this document is not able to address every situation and that alternative approaches might exist. However, the key principles and processes as outlined in this guidance should be adhered to.

VI. Add I.2. General aspects of duplicate cases

Regardless of the system used for collecting and collating ICSRs, there should always be an appropriate mechanism in place for identifying duplicates. The potential causes for duplicates should be carefully taken into account, as well as the appropriate processes to detect and manage them. If duplicates are identified, analysis of the root cause should be performed and corrective action taken, where appropriate.

Examples of common causes of duplicate reports are:

- A consumer and a healthcare professional reporting the same reaction occurrence;
- Multiple health care professionals treating the same patient reporting the same reaction occurrence;
- An reaction occurrence being reported to EV by the original reporter to both the marketing authorisation holder and a competent authority in a Member State;
- Literature reporting of the same reaction occurrence for generics.

Handling duplicate reports typically involves three steps:

(1) searching/detection of duplicates;

(2) confirmation of duplicates; and

⁷ Hereafter, ICH-E2B(R2) or (R3) formats shall be referred to as "ICH-E2B format", unless it is necessary to specify which format is being discussed

(3) management of duplicates.

The identification of potential duplicates in collections of individual cases is a challenge. Duplicates will often either have been submitted by different senders or processed in different reporting systems, and as such case information can be in many instances dissimilar: different terms may have been used to code the same incident, patient information may be of different level of specificity due to differences in the implementation of the personal data protection rules in Member States or the listed medicinal products may be coded differently related to the same incident due to the absence of an international standard on identification of medicinal products. This makes the identification of duplicates a challenging and resource intensive task. It appears to be clear that the problem of duplicate reports is fairly common in spontaneous reporting systems, although there is certainly a lack of published research, both on the extent of the problem and the methods employed to detect them. Even upon the confirmation that reports are indeed duplicates it is not always obvious how to proceed: should the duplicates be maintained in the database or should one of them perhaps be removed from the data set; if so, which one(s)?

Reviewing pharmacovigilance systems for potential duplicates is also considered necessary when evaluating signals e.g. signals of disproportionate reporting (SDR). Such review may be necessary in addition to routine duplicate and data quality checking. Although databases should be screened regularly for potential duplicates, there may be situations when an individual case was reported more than once in the database and may have not appeared initially as a potential duplicate.

All stakeholders are reminded about the duplicate handling provisions laid down in GVP Module VI, whereby the most relevant sections will be also referenced in this document where applicable. The detection and management of duplicates is also an element that needs to be addressed by applicants and marketing authorisation holders as part of their pharmacovigilance system master file (PSMF) (see GVP Module II).

VI. Add I.3. Detection of duplicate cases

Databases should be reviewed regularly to identify duplicates. As a general rule, every newly received ICSR referring to an individual case should be considered a potential duplicate and should be checked thoroughly against the cases that are already present in the database. Therefore, screening for duplicates should be done at the time when a new report arrives in the database i.e. during data entry or during the process of loading ICSRs that have been received electronically. Some IT systems offer lookup and duplicate detection features to assist the identification of an identical case during data entry procedures, based on automated and semi-automated search criteria. Similar tools can be used for e.g. automatic flagging of potential duplicates at the time of importing ICSRs that are received electronically in ICH-E2B(R2) or ICH-E2B(R3) format (see GVP Annex IV - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for pharmacovigilance).

Duplicate searches are generally based on similarities in patient, adverse reaction and medicinal product data. Different search criteria may be suitable for different datasets. For pharmacovigilance systems that do not have to deal with large datasets, a simple table which sorts the reports by age, sex, suspected/interacting medicinal products and adverse reactions can be suitable to detect similarities. Adding 'country' to this search can be valuable, depending on the dataset. For cases received in ICH-E2B format, screening of the case ID numbers and duplicate fields (see below for ICH-E2B (R2) & (R3) field names and codes) may offer a quick start.

Table VI. Add I.1. ICH-E2B data field names with R2 & R3 codes

Field name*	E2B(R2) code	E2B(R3) code
Sender's (case) safety report unique identifier	A.1.0.1	C.1.1
Worldwide unique case identification	A.1.10.1 or A.1.10.2	C.1.8.1
Source(s) of the case identifier	A.1.11.1	C.1.9.1.r.1
Case identifier(s)	A.1.11.2	C.1.9.1.r.2

*Useful fields for quick identification of duplicate cases

In large databases like EudraVigilance, there is a strong need to eliminate duplicates. Therefore, an initial grouping of ICSRs is performed based on the primary source country, sex and age of the patient. The EudraVigilance algorithm further quantifies the difference of ICSRs from a statistical point of view taking into account additional parameters related to the patient, the primary source, the reported medicinal product(s)/active substance(s) and adverse reaction(s) as well as the fact that case information may vary e.g. due to differences in coding practices.

There are many options for using patient, adverse reaction and medicinal product data and their specific data-elements for duplicate detection purposes. Other data fields (e.g. reaction end/start date) can be used to make the assessment more likely. Whatever algorithm is applied, it should be taken into account that information in the cases may differ, and that the main purpose of this step is to seek for similarities in the cases, thus highlighting potential duplicates for manual review. If no match is found upon the initial search, the search can be broadened e.g. by expanding the criteria to include null values (e.g. a new report concerning a female patient will be checked against other cases with a female patient cases and where the patient's gender is unknown).

Differences in coding practices based on MedDRA (see [GVP Annex IV](#)) can be addressed by taking into account that the medical concepts need to be consistent, rather than searching for an exact match of terms. Furthermore, it is important to be aware of the natural course of reported reactions and that these can become more serious (for example: a rash can develop into a Stevens Johnson Syndrome). Therefore, a search for duplicates can be based on the MedDRA Preferred Term (PT) Level, but moving up to the associated Higher Level Term (HLT) or even HLTG (Higher Level Group Term (HLGT)) might be appropriate.

Individual cases originating from clinical trials are usually well-documented and duplicate detection can include other criteria which will be more reliable, e.g. Research centre ID and study details (EudraCT number, protocol number).

It is recommended to carefully validate the duplicate detection algorithms of databases and to evaluate the need for tuning the algorithms over time e.g. the quality/level of details of ICSRs may differ over time. For example, when specific data fields have been made mandatory, these might be considered for inclusion in the duplicate detection algorithm.

It is apparent that duplicates might involve more than two individual cases, and can be considered a cluster i.e. if case A is a potential duplicate of case B and case B is a potential duplicate of case C. Bearing this in mind, throughout this document the term "duplicate cluster" is used to denote two or more cases which have been identified as potential duplicates of each other.

VI. Add I.3.1. What to do if possible duplicates in EudraVigilance have been detected

If, when reviewing cases obtained from EudraVigilance, there is a suspicion that two or more cases are duplicates of one another; the reviewer should send an email to duplicates@ema.europa.eu with information on which cases are suspected to be duplicates. The Agency will not routinely send feedback on whether or not the cases are duplicates. To receive such feedback, the sender of the email should request this in the email.

The information that the Agency needs is either the case numbers (either Worldwide unique case safety IDs or Safety report IDs) or local report numbers (those starting with EU-EC-) of the suspected duplicates in a cluster.

To report suspected duplicates, the agency encourages that the sender sends each suspected cluster of duplicates as a single row in a table similar to the format below:

Table VI. Add I.2. EMA preferred format for receiving notification of suspected duplicates

Cluster 1	EU-EC-1234567	EU-EC-3456789		
Cluster 2	EU-EC-1564838	EU-EC-2254839	EU-EC-5742358	EU-EC-9137568
Cluster 3	EU-EC-5748548	EU-EC-2563147	EU-EC-9876543	

If the Agency confirms that the cases are duplicates, then, as described in VI.Add I.4.1.2., a master case will be created, with the duplicates merged underneath and the case numbers of the duplicates in the report duplicates section of the master. The master case will be transmitted to EV and, if necessary, rerouted to competent authorities in Member States within the usual rerouting timelines. The master case will be immediately available to marketing authorisation holders for downloading for Level 1 access and will be available the following day for Level 2 access as described in the EudraVigilance Access Policy⁸. The awareness date for marketing authorisation holders and competent authorities in Member States of the confirmed duplication will then coincide with the day zero for the master for marketing authorisation holders & competent authorities in Member States.

VI. Add I.3.2. Confirmation of duplicates cases

Upon identification of potential duplicates, a manual confirmation will always be necessary. A well-documented case, including a case narrative, is a prerequisite to confirm if two cases are duplicates and it is of utmost importance that all stakeholders adhere to the principles set out in GVP Module VI, regarding data quality of individual case safety reports transmitted electronically and duplicate management. This also applies for cases that are reportable in line with Directive 2001/20/EC.

Directive 2001/83/EC, Articles 107a(3) and 107(5) require Member States and marketing authorisation holders, respectively, to collaborate with the Agency, and each other, in the detection of duplicates of suspected adverse reaction reports. In addition GVP Module VI emphasises the need for marketing authorisation holders and competent authorities in Member States to ensure the highest quality of the ICSRs transmitted electronically to the EudraVigilance database within the correct time frames, and which enable the detection and management of duplicate ICSRs in their system. Those transmitted ICSRs should be complete, entire and undiminished in their structure, format and content. Judgement will always need to be applied especially for certain types of medicinal products and adverse reactions such as cases related to vaccines in 'neonates/infants' or widely used medicinal products amongst 'elderly' patients (e.g. vaccine reports in a 'neonate' with an adverse reaction of 'injection site

⁸ European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use (EudraVigilance Access Policy), revision 2

reaction', even if the dates of administration, primary source, medical history and concurrent drug fields match, one cannot be certain that reports are true duplicates as it is a common reaction possibly reported for many 'neonates' with similar history from the same clinic).

Population of the 'Linked reports' section (ICH-E2B(R2) data field 'A.1.12')/ICH-E2B(R3) data field 'C.1.10.r') with the numbers of other cases that are linked by a common element or elements, but are distinct from one another, is a particularly effective method of enabling confirmation that cases are not duplicates of one another. Conversely, population of the 'Report duplicates' section (ICH-E2B(R2) data field 'A.1.11'/ ICH-E2B(R3) data field 'C.1.9.1') with all other reference numbers by which the case is known is a particularly effective method of enabling detection and confirmation of duplicates.

If there is conflicting or limited information, which on first review does not allow determination that the cases are duplicates, additional information from the reporter or sender needs to be sought. It is recommended to keep track of all duplicate investigations, also if cases are confirmed not to be duplicates.

If the individuality of cases cannot be confirmed without compromising legal expedited reporting timelines, it is recommended to enter the potential duplicated case into the database as a valid case. However, investigations to confirm or clarify the information submitted should be continued. Once the individual case is confirmed as a duplicate or otherwise, appropriate steps should be taken to manage the duplicates as described in VI.Add I.4..

VI. Add I.4. Management of duplicates cases

Duplicate cases are generally managed through a process of merging two or more cases into one master case. This process can consist of one of the following approaches:

- The master case can either be based on one of the existing cases, with information from the other subordinate duplicate cases added unless the same, or more precise, information is already present in the master case (this is referred to in this document as "Allocation of a master case"), or;
- The master case can be created as a new case combining the information from the subordinate duplicate cases (this is referred to in this document as "Creation of a master case").

Regardless of the approach chosen, the master case should always contain all case reference numbers from all subordinate duplicate cases, such that they can be easily traced. The master case should reflect the most accurate and up-to-date information available to the organisation.

Both concepts are acceptable; however, whatever method chosen, the process should be well-documented. Proper record management should ensure that all received ICSRs for all individual cases can be tracked adequately, including all information as reported by the primary sources, the reporters and the report senders. The 'Date report was first received from source'⁹ and 'Date of receipt of the most recent information for this report'¹⁰ of the duplicates must remain unchanged unless new information is received.

A challenge to be faced in duplicate management relates to situations where conflicting or divergent information is provided by different senders. Attempts should be made to obtain clarification. If this is not possible, the case narrative should reflect information from both sources.

The master case should be a complete representation of the case, whereby all information should be presented in full compliance with ICH-E2B and the guidance provided in GVP Module VI. Regarding the

⁹ 'Date report was first received from source' (ICH-E2B(R2) 'A.1.6' or ICH-E2B(R3) 'C.1.4')

¹⁰ 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) 'A.1.7' or ICH-E2B(R3) 'C.1.5')

adverse reactions, one can choose to merge all reported reactions as presented in the duplicated cases in the master case. However, if the reactions reflect similar concepts, but one is more specific (e.g. 'liver injury' versus 'fulminant hepatitis'), one may choose the more specific term. Medical judgement should always be applied in these and other decisions which are based on whether the extra specificity is clinically important. If there is conflicting information, it is not considered appropriate to reflect this twice in the structured fields of the master case as this would impede calculation of cumulative doses. Since the completeness of the cases can vary (e.g. one case may have follow-up information clarifying and amending certain points, whereas the other simply has the initial information), the most accurate information should always be used.

It may, however, not be possible to determine which case is the most accurate and complete, and so in some cases, where it is necessary and possible and where a field has been populated differently in the duplicate cases, either one value or another may be chosen, or an average be stated, with clear reference in the case narrative that there is conflicting information obtained from different sources and what the conflicting information is. It will not always be appropriate to do this, especially in cases of suspected overdose or underdose, and medical judgement is always required in such cases.

If information has been populated in one case, but not in another, and there is no reason to believe that the lack of such information is necessarily correct, then it is appropriate to add the extra information, e.g. case 1 has no concomitant medication, whereas case 2 has paracetamol as concomitant medication; unless case 2 is the more recent case, and clearly states that the patient was not, contrary to previous information, receiving paracetamol, then the paracetamol should be included as concomitant medication in the master case.

VI. Add I.4.1. Process of managing duplicates detected during periodic screening

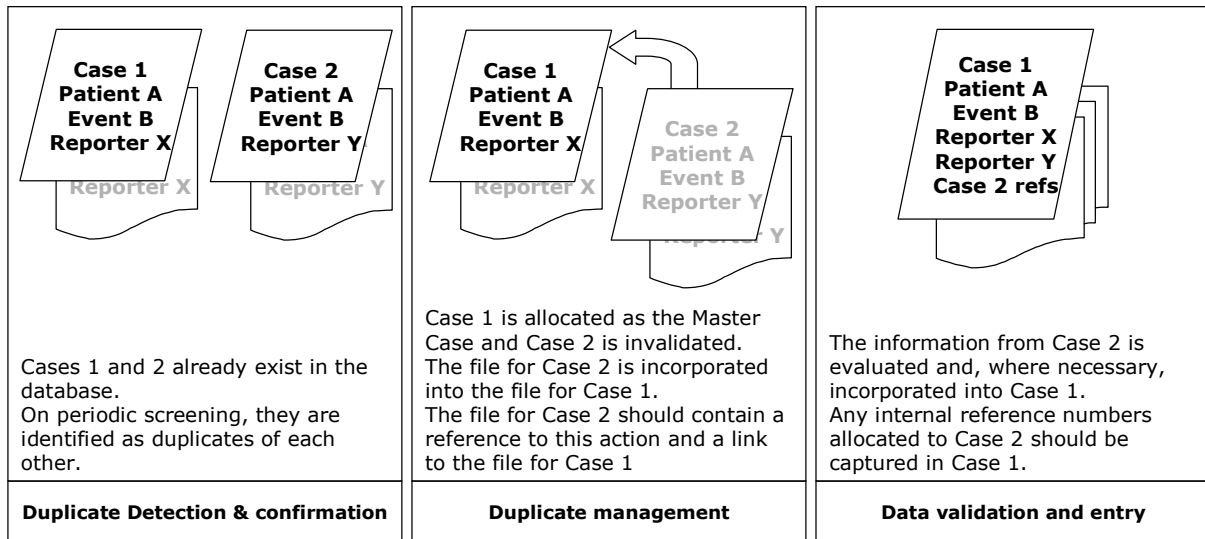
Confirmed duplicates that have been detected after data entry are usually managed through a merging process. By merging cases, usually a master case is created in a database, which refers to the case chosen or created to represent the duplicated information. When creating a master case it is important to capture the case-identifiers and the sources of the duplicated cases in the ICH-E2B(R2) data field 'A.1.11'/ICH-E2B(R3) data field 'C.1.9.1'.

VI. Add I.4.1.1. Allocation of a master case

The allocation of a master case refers to the procedure where one of the confirmed duplicate cases is allocated as the master case and retains its classification as a valid case. The master case should support all pharmacovigilance activities such as signal detection and medical review of ICSRs.

The allocation of a master case procedure necessitates the "invalidation/inactivation" of the subordinate duplicates. This means that subordinate duplicate cases remain in the database for the purpose of audit trails, but will not be used for any other pharmacovigilance purpose. **Figure VI. Add I.1.** provides a pictorial representation of the allocation of a master case.

Figure VI. Add I.1. The allocation of a master case when duplicates have been detected during periodic screening



Follow-up information received for any of the subordinate duplicate cases will need to be evaluated and, incorporated into the master case unless the same, or more precise, information is already present in the master case.

This concept is most suitable for:

- Organisations (e.g. marketing authorisation holders, regional pharmacovigilance centres) which mainly receive cases in non-ICH-E2B-format, and where manual data entry is performed for the majority of the cases; and/or
- When the duplicate detection process is taking place at the time of data entry.

The Worldwide unique case identification number (ICH-E2B(R2) data field 'A.1.10.1' or 'A.1.10.2'/ICH-E2B(R3) data field 'C.1.8.1') of the individual case that is allocated as the master case should be maintained. The other subordinate duplicate case reference numbers should not be reused, but should be recorded in the 'Other case identifiers in previous transmissions' (ICH-E2B(R2) data field 'A.1.11'/ICH-E2B(R3) data field 'C.1.9.1').

When allocating the master case based on the identified duplicates either the case that was first received, the case that contains the most detailed information or the case that was already transmitted to external partners can be selected. If there is no significant new information (see [GVP Module VI](#) for clarification of significance regarding follow-up information), the master case does not need to be transmitted to external partners (e.g. competent authorities in Member States, EMA). Case identifiers from previously transmitted cases should always be considered as significant new information, however case identifiers from non-transmitted cases need not be considered as significant new information.

All subordinate duplicate cases and related ICSRs should be retained and there should be adequate cross-referencing between case files and/or database entries.

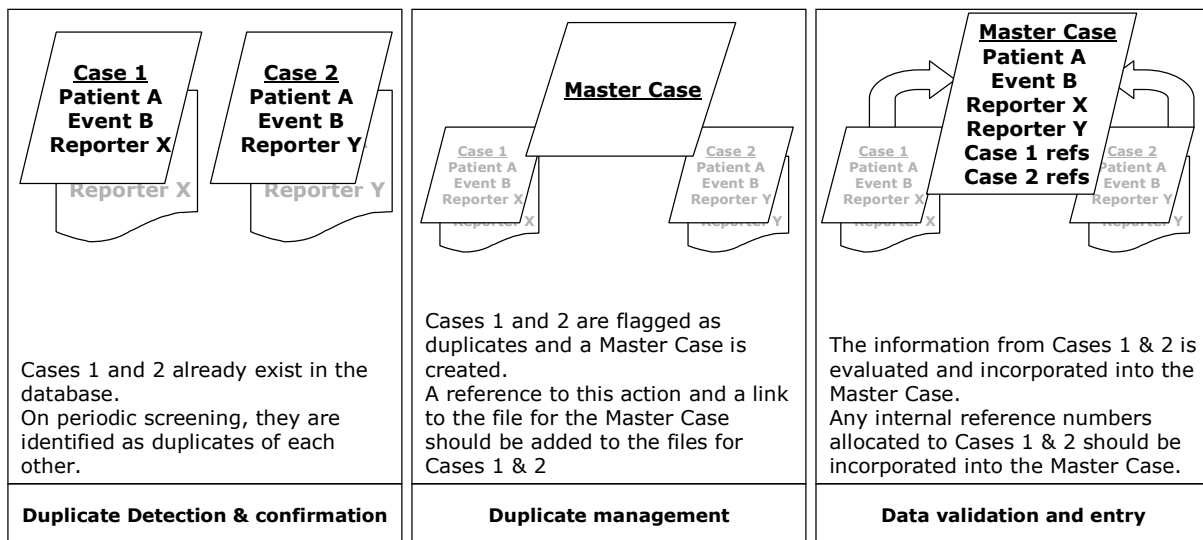
If follow-up information is received for any of the duplicated cases, the master case should be updated accordingly.

VI. Add I.4.1.2. Creation of a master case

The Creation of a master case refers to the procedure where a master case is created with a new Worldwide Unique Case Identifier (ICH-E2B data field 'A.1.10'), based on all the information contained in the subordinate duplicate cases. All of these subordinates are flagged as duplicates and linked to the master case and remain valid for the purposes of receiving follow-up information; only the master case, will be used for pharmacovigilance activities such as signal detection and medical evaluation.

If there is no significant new information related to the case (see [GVP Module VI](#) for guidance on Follow-up information), the master case does not need to be transmitted to external partners (e.g. competent authorities in Member States, EMA). [Figure VI. Add I.2.](#) provides a pictorial representation of the Creation of a master case.

Figure VI. Add I.2. The Creation of a master case when duplicates have been detected during periodic screening



If follow-up information is received for any of the subordinate duplicated cases, they should be updated automatically based on the newly obtained ICSRs. All new information should be evaluated and the master case manually updated accordingly.

This is the method employed in EudraVigilance.

This concept is most suitable for:

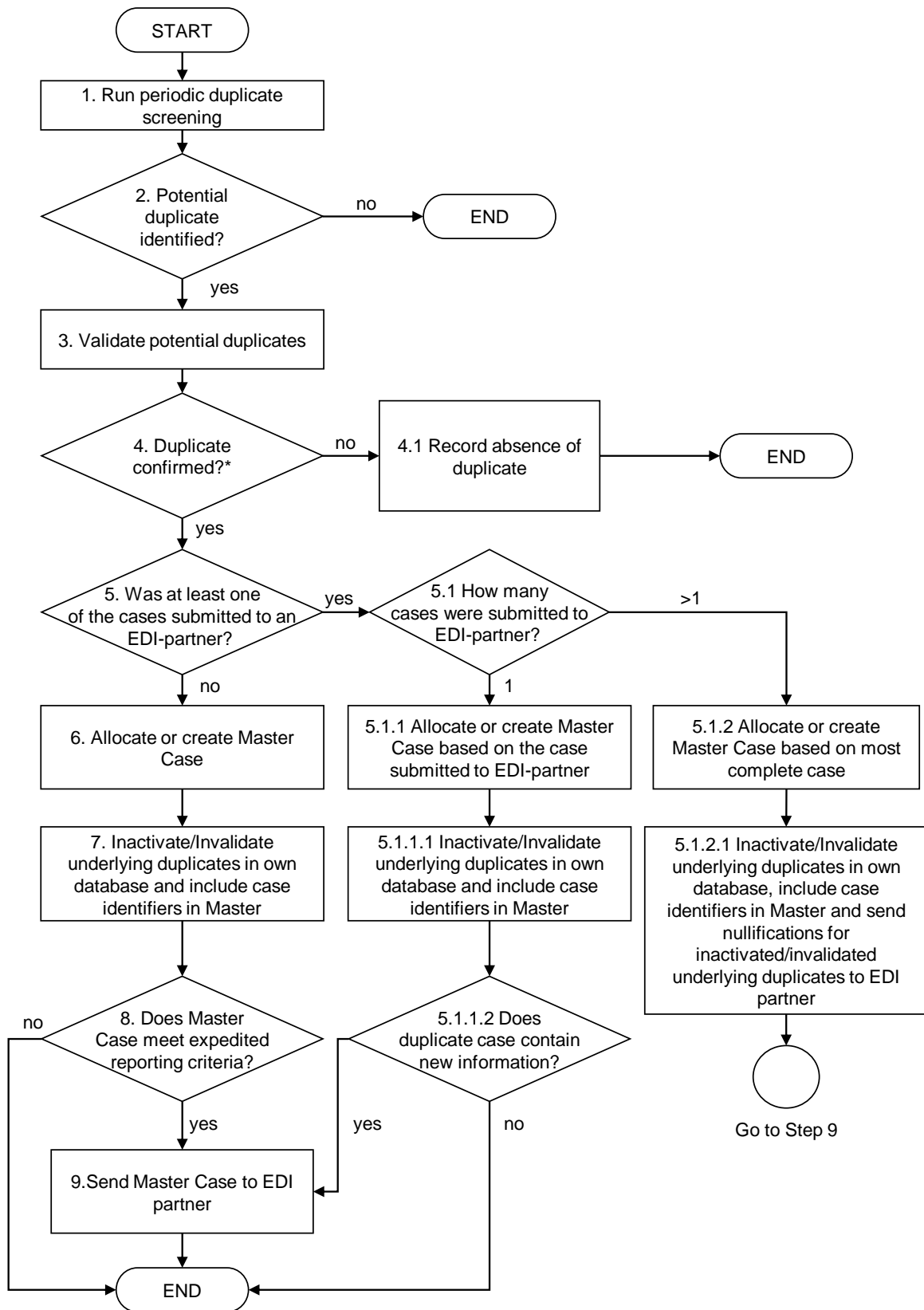
- Organisations (e.g. competent authorities in Member States, EMA), which mainly receive individual cases electronically in ICH-E2B-format from multiple Electronic Data Interchange (EDI) partners as it allows maintenance and traceability of all ICSRs as received originally from the Sender.

VI. Add I.4.2. Process maps and descriptions for allocation or creation of a master case

A detailed description of the process flow for the Allocation or Creation of a master case based on duplicates existing in a database is presented in the flowchart in [Figure VI. Add I.3.](#)

A detailed description of the process flow for the Allocation of a master case based on duplicates detected at the time of data entry is presented in the flowchart in [Figure VI. Add I.4.](#). This process refers mainly to situations where a case has been reported on paper, and it has been identified as a duplicate of another case before any data has been entered in the local database.

Figure VI. Add I.3. Business process map – allocating or creating a master case of duplicates existing in a database



* assessment is valid only at this point in time and can change upon receipt of new information. Receipt of new information should trigger a new check for duplicates

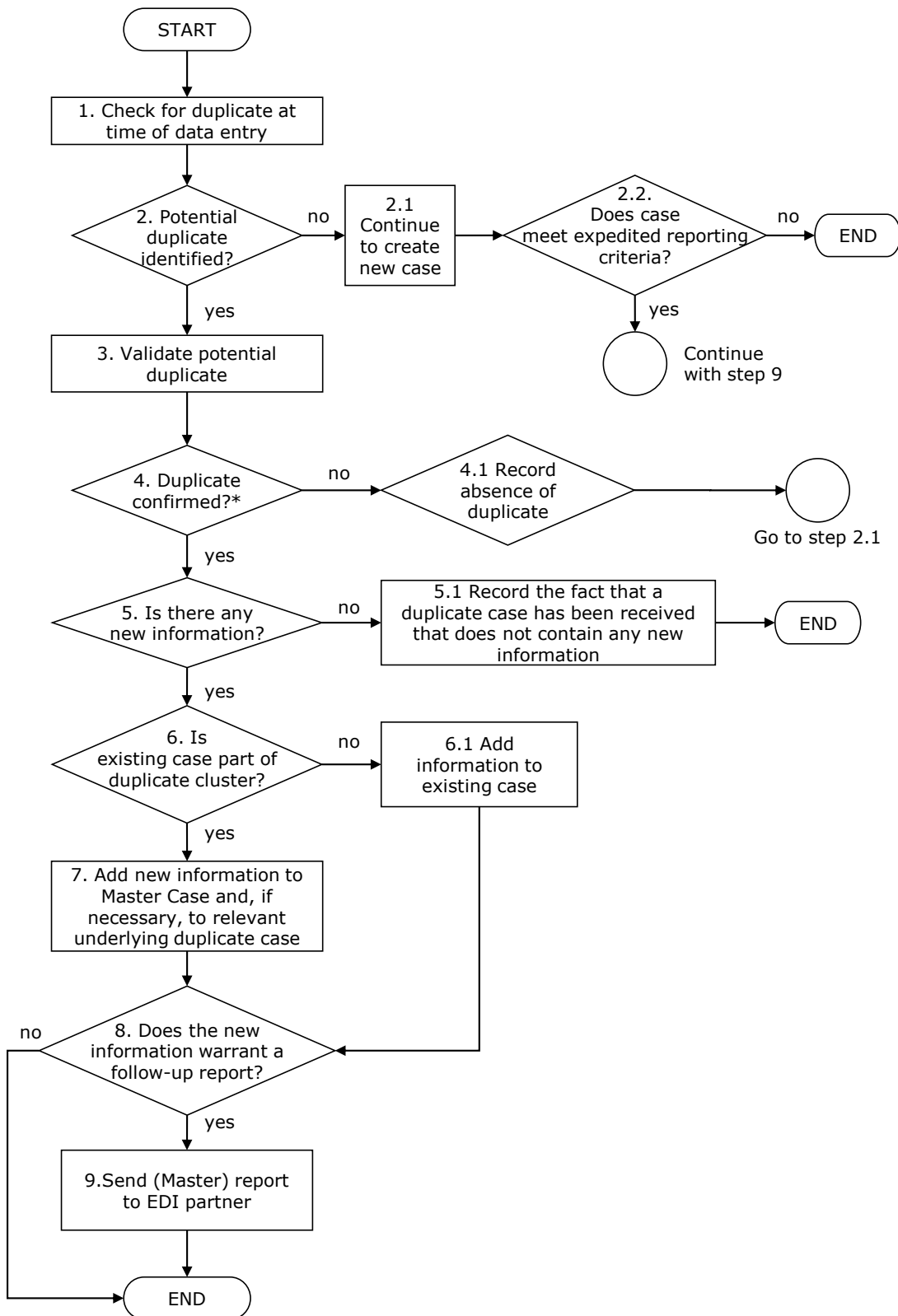
Table VI. Add I.3. Process description – allocating or creating a master case of duplicates existing in a database

Step	Action
1.	<p>Run periodic duplicate screening</p> <p>Periodically search the database for potential duplicates.</p> <p>Databases should be reviewed regularly to identify duplicates. It is best practice to perform these reviews on a daily basis, to ensure timely identification of duplicates, and to prevent a large backlog of duplicates developing.</p> <p>If receipt of cases is not a daily occurrence, then the database should be reviewed whenever cases have been received and processed.</p>
2.	<p>Potential duplicate identified?</p> <p>If no, end process</p> <p>If yes, continue with Step 3</p>
3.	<p>Validate potential duplicates</p> <p>Manually verify whether the automatically identified potential duplicates are actual duplicates.</p>
4.	<p>Duplicate confirmed?</p> <p>Is the case a duplicate of a case that already exists in the database?</p> <p>This decision is only valid at this point in time and must be based on the information presently available. The assessment of whether or not cases are duplicates of one another can change upon receipt of new information. Receipt of new information should trigger a new check for duplicates.</p> <p>If it is not possible to be certain that cases are duplicates of one another, continue as though they are not.</p> <p>If no, continue with Step 4.1</p> <p>If yes, continue with Step 5</p>
4.1	<p>Document absence of duplicate</p> <p>Record the decision that this case is not a duplicate of the automatically identified potential duplicates, in order to avoid re-assessing these potential duplicate clusters during periodic duplicate screening.</p> <p>End process</p>
5.	<p>Was at least one of the cases submitted to an EDI-partner?</p> <p>Were any of the most recent versions of the cases in the duplicate cluster previously submitted to an EDI partner?</p> <p>If yes continue with step 5.1</p> <p>If no, continue with step 6.</p>
5.1	<p>How many cases were submitted to EDI partner?</p> <p>How many of the cases in the duplicate cluster were submitted to an EDI partner?</p>

Step	Action
	<p>If only 1 of the cases was submitted, then base the master case on that one. If more than 1 case was submitted, then base the master case on one of those which was submitted.</p> <p>When allocating a case, the worldwide case safety ID (ICH-E2B(R2) data field 'A.1.10.1' or 'A.1.10.2'/ICH-E2B(R3) data field 'C.1.8.1') of the master case should be that of one of the submitted cases.</p> <p>If only 1 case was submitted, continue with step 5.1.1</p> <p>If more than 1 case was submitted, continue with step 5.1.2</p>
5.1.1	<p>Allocate or create master case based on the case submitted to EDI partner</p> <p>Depending on the method of duplicate management in the system, create or allocate a Master case based on the case already submitted to an EDI partner. The Worldwide case safety ID (ICH-E2B data field 'A.1.10') of the case already submitted to an EDI partner should be retained, if possible.</p>
5.1.1.1	<p>Inactivate/Invalidate the underlying duplicates in own database and include case identifiers in the master case</p> <p>All underlying duplicates in the database should be inactivated, invalidated or otherwise marked as part of a duplicate cluster. Case identifiers from the underlying duplicates should be included in the duplicates section (ICH-E2B(R2) data field 'A.1.11'/ICH-E2B(R3) data field 'C.1.9.1') of the Master case.</p> <p>Go to Step 5.1.1.2.</p>
5.1.1.2	<p>Does duplicate case contain significant new information?</p> <p>Do(es) the duplicate case(s) contain any significant new information as described in GVP Module VI?</p> <p>If yes, go to step 9.</p> <p>If no, end process.</p>
5.1.2	<p>Allocate or create master case based on most complete case submitted to EDI partner</p> <p>Depending on the method of duplicate management in the system, create or allocate a Master case based on the most-complete case already submitted to an EDI partner.</p>
5.1.2.1	<p>Inactivate/Invalidate the underlying duplicates in own database, include case identifiers in Master and send nullifications for inactivated underlying duplicates to EDI partner</p> <p>All underlying duplicates in the database should be inactivated, invalidated or otherwise marked as part of a duplicate cluster. Case identifiers from the underlying duplicates should be included in the duplicates section (ICH-E2B(R2) data field 'A.1.11'/ICH-E2B(R3) data field 'C.1.9.1') of the Master case.</p> <p>For the underlying duplicates that were created in your database, and have already been transmitted to an EDI partner, nullification reports should be transmitted to the same EDI partner(s).</p> <p>Since at least 2 of these cases have been transmitted to an EDI partner, then the master case will certainly contain new information relevant to case management for the EDI</p>

Step	Action
	<p>partner. Therefore, the master case should be transmitted.</p> <p>Go to Step 9.</p>
6.	<p>Allocate or create master case based on most complete case</p> <p>Depending on the method of duplicate management in the system, create or allocate a Master case based on the most-complete case.</p>
7.	<p>Inactivate/Invalidate the underlying duplicates in own database and include case identifiers in Master</p> <p>All underlying duplicates in the database should be inactivated, invalidated or otherwise marked as part of a duplicate cluster. Case identifiers from the underlying duplicates should be included in the duplicates section (ICH-E2B(R2) data field 'A.1.11'/ICH-E2B(R3) data field 'C.1.9.1') of the Master case.</p>
8.	<p>Does Master meet expedited reporting criteria?</p> <p>Does the Master case, now meet expedited reporting criteria or warrant transmission to an EDI partner?</p> <p>If no, end process If yes, continue with step 9.</p>
9.	<p>Send Master report to EDI partner</p> <p>Send the Master case to the relevant EDI partners.</p> <p>If one, or more, of the cases has already been transmitted to an EDI partner, then the Master case should be transmitted to those same EDI partners*.</p> <p>If the cases merged under a Master case were transmitted to the receiving database by more than one EDI partner, then the information that the receiving organisation considers these cases to be duplicates does not need to be shared with the transmitting EDI partners.</p> <p>* If the original case was sent to an NCA before 22 Nov 2017 and the latest version is to be sent on or after 22 Nov 2017, then you should send it to EudraVigilance and not to the NCA.</p>
	End

Figure VI. Add I.4. Business process map – managing duplicates at the time of data entry



*assessment is valid only at this point in time and can change upon receipt of new information. Receipt of new information should trigger a new check for duplicates

All of the steps in this flowchart assume that preliminary data entry on the newly-arrived data has been performed, and a new case has therefore been created. If duplicate detection is performed prior to the creation of a new case, then one should consider the "potential duplicate" referred to in steps 2, 3 & 4 to be an "existing case" and, in Step 5.1, the arrival of a follow-up with no new information should not be captured in the duplicates section (ICH-E2B(R2) data field 'A.1.11'/ICH-E2B(R3) data field 'C.1.9.1'), but in another relevant field in one's pharmacovigilance database.

Table VI. Add I.4. Process description – managing duplicates at the time of data entry

Step	Action
1.	<p>Check for duplicate at time of data entry</p> <p>During data entry, search your database for potential duplicates.</p>
2.	<p>Potential duplicate identified?</p> <p>If no, continue with Step 2.1</p> <p>If yes, continue with Step 3</p>
2.1	<p>Continue to create new case</p>
2.2	<p>Does case meet expedited reporting criteria?</p> <p>If no, end process.</p> <p>If yes, continue with Step 9</p>
3.	<p>Validate potential duplicate</p> <p>Manually verify whether the automatically identified potential duplicates are actual duplicates</p>
4.	<p>Duplicate confirmed?</p> <p>Is the case a duplicate of a case that already exists in your database?</p> <p>This decision is only valid at this point in time and must be based on the information presently available. The assessment of whether or not cases are duplicates of one another can change upon receipt of new information. Receipt of new information should trigger a new check for duplicates.</p> <p>If you cannot be certain that cases are duplicates of one another, you should continue as though they are not.</p> <p>If no, continue with Step 4.1</p> <p>If yes, continue with Step 5</p>
4.1	<p>Record absence of duplicate</p> <p>Record the decision that this case is not a duplicate of the automatically-identified potential duplicates, in order to avoid re-assessing these potential duplicate clusters during periodic duplicate screening.</p> <p>This step may not be relevant depending on the systems available and the volume of data processed by the organisation.</p> <p>Go to Step 2.1</p>
5.	<p>Is there any new information?</p> <p>Do(es) the duplicate(s) contain any new information that you do not currently hold?</p> <p>If no, continue with step 5.1</p> <p>If yes, continue with step 6.</p>
5.1	<p>Record the fact that a duplicate case has been received that does not contain any new information</p>

Step	Action
	<p>This information should be captured in the duplicates section (ICH-E2B(R2) data field 'A.1.11'/ICH-E2B(R3) data field 'C.1.9.1') and also the case narrative (ICH-E2B(R2) data field 'B.5.1'/ICH-E2B(R3) data field 'H.5.r.1a') of the existing case.</p> <p>If the date that the most recent information for the duplicate case was received is different to that of the master case, this may be recorded in the case, but it should not be recorded in the 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) data field 'A.1.7b'/ICH-E2B(R3) data field 'C.1.5')</p> <p>End process</p>
6.	<p>Is existing case part of duplicate cluster?</p> <p>Is the existing case already part of a duplicate cluster?</p> <p>If no, continue with step 6.1</p> <p>If yes, continue with step 7.</p>
6.1	<p>Add information to existing case</p> <p>Add the new information to the existing case as follow-up information.</p> <p>Continue with Step 8.</p>
7.	<p>Add new information to Master case and, if necessary, to relevant underlying duplicate case</p> <p>Add the new information to the master case and, if necessary, also add it to the relevant underlying duplicate case.</p>
8.	<p>Does the new information warrant a follow-up report?</p> <p>In line with GVP Module VI. Follow-up information, the sender should report follow-up information on an expedited basis if significant new medical information has been received or where new administrative information is available that could impact on the case management, e.g. new case identifiers have become known or additional documents which may be relevant for the medical assessment of the case have become available to the sender.</p> <p>If the master case with new information added would not normally be reportable e.g. if it is now downgraded to non-serious, this should still be reported</p> <p>If yes, continue with step 9</p> <p>If no, end process.</p>
9.	<p>Send (Master) report to EDI partner</p> <p>Send the latest version of the case, or, if applicable, the master case, to the relevant EDI partners.</p> <p>If the original case was sent to an NCA before 22 Nov 2017 and the latest version is to be sent on or after 22 Nov 2017, then you should send it to EudraVigilance and not to the NCA.</p>
	<p>End</p>

VI. Add I.4.3. Sending nullifications

GVP Module VI contains detailed guidance on the sending of nullifications, and should be taken into account when performing this task. Specifically, the following scenario and applicable action are presented, if all the duplicates originate from the same sender:

Table VI. Add I.5. Actions to take when duplicates are identified

Scenario	Action
An individual case has been identified as a duplicate of another individual case previously submitted by the same sender.	One of the individual cases should be nullified. The remaining valid case should be updated with any additional information as relevant to the nullified case. NOTE: In case of duplicate reports where one report needs to be nullified, the update of the remaining case should be performed in the form of a follow-up report. Information on the identification of the nullified case(s) should be provided (ICH-E2B(R2) data field 'A.1.11'/ICH-E2B(R3) data field 'C.1.11').

VI. Add I.4.4. Duplicates received from the same sender organisation

If cases in a duplicate cluster are received from the same sender¹¹, the sender organisation should be notified about the identified duplicates. If the sender organisation agrees that the cases are duplicates, the sender organisation should proceed as indicated in VI.Add I.4., merging the cases and sending a nullification report for the other duplicate case(s) as applicable to the receiver(s).

¹¹ The sender organisation should be distinguished from the primary source (the person who is reporting the facts). For the purpose of this document the sender organisation relates to the applicant, marketing authorisation holder, sponsor or the national competent authority (including regional pharmacovigilance centres).