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CHMP Guideline on detection and management of duplicate individual cases and Individual Case Safety Reports (ICSRs)

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Executive summary

Duplicate cases can pose significant problems for analysing signals arising from pharmacovigilance databases, both artificially inflating and masking signals of disproportionate reporting.

Pharmacovigilance databases should be routinely screened to detect and eliminate duplicate cases. This guideline proposes methods for detecting, confirming and managing duplicate cases suitable for organisations receiving reports of suspected adverse reactions in various formats and from different sources.

1. Introduction

1.1. Background

The European Commission has published detailed guidance[1] on the reporting of suspected (unexpected) serious adverse reactions in compliance with the legal provisions laid down in Regulation (EC) No 726/2004 (and the associated Implementing Regulation[2]), Directive 2001/83/EC as amended (and the associated Implementing Regulation) and Directive 2001/20/EC.

Guidance is also provided for situations where individual cases might be reported by different senders e.g. where a Marketing Authorisation Holder (MAH) is aware that a healthcare professional 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. The MAH should still report the adverse reaction, informing the Competent Authority that the report may be a duplicate of a previous report. In this situation, it is essential for the MAH to provide all the available details including all case identification numbers allocated to the case, in order to aid identification of the duplicate.

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.

Detection and handling of duplicates by national Competent Authorities (NCAs), MAHs and Sponsors of clinical trials (Sponsors) is an important element of good case management. 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, FDA researchers identified 20% of 141 reports as duplicates.[3] Norèn et al.[4] highlighted that since

[1] The Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products, hereafter referred to as GVP Module VI, and Volume 10 of The Rules Governing Medicinal Products in the EU - Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')
[2] Implementing Regulation on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council.
[3] 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
[4] 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

commonly used data-mining procedures may highlight associations with as few as three reports, one or two duplicates may severely affect their utility.

1.2. Objective of this document

The objective of this Guideline is to promote accurate detection and handling of duplicate cases, with the ultimate aim of achieving duplicate-free pharmacovigilance databases. 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) format 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 pharmacovigilance 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 guideline should be adhered to.

2. General aspects of duplicate cases

Regardless of the pharmacovigilance database used for collecting and collating ICSRs, there should always be an appropriate mechanism in place for identifying duplicates. The established causes of 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, if appropriate.

Examples for common causes of duplicate reports are:

- A consumer and health care professional reporting the same event/reaction occurrence;
- Multiple health care professionals treating the same patient reporting the same event/reaction occurrence;
- An event/reaction occurrence being reported by the original reporter to both the MAH and the NCA;
- Literature reporting of the same event/reaction occurrence for generics.

Handling duplicate cases typically involves three steps: (1) searching for and detection of duplicates, (2) confirmation of duplicates and (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 pharmacovigilance databases, 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. The problem of duplicate reports is fairly common in pharmacovigilance databases, although there is certainly a lack of published research, both on the extent of the problem and the methods employed to detect them[5]. Even upon the confirmation that reports are indeed

[5] Norén GN, Bate A, Orre R. A hit-miss model for duplicate detection in the WHO drug safety database. In - KDD '05: Proceedings of the 11th ACM SIGKDD conference on Knowledge Discovery and Data-mining, 2005, 459-468

duplicates it is not always obvious how to proceed: should the duplicates be maintained in the pharmacovigilance database or should one of them perhaps be removed from the data set; if so, which one(s)?

Reviewing pharmacovigilance databases for potential duplicates is also important when evaluating signals e.g. Signals of Disproportionate Reporting (SDR)[6]. Such review may be necessary in addition to routine duplicate and data quality checking. Although pharmacovigilance databases should be screened regularly for potential duplicates, there may be situations when an individual case was reported more than once in the pharmacovigilance database and may have not appeared initially as a potential duplicate.

All stakeholders are reminded about the duplicate handling provisions laid down in the detailed guidance[7] 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 MAHs as part of their pharmacovigilance plan.

2.1. Detection of duplicate cases

According to the detailed guidance[8] pharmacovigilance databases should be reviewed regularly to identify duplicates. However, 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 one's pharmacovigilance database. Therefore, screening for duplicates should be done at the time when a new ICSR arrives in one's pharmacovigilance database i.e. during data entry or during the process of loading ICSRs that have been received electronically. Some pharmacovigilance databases 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) format.

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 databases 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 events/reactions can be suitable to detect similarities. Adding 'country' to this search can be valuable, depending on the dataset. For cases received in E2B(R2) format, screening of the duplicate fields (A.1.11 - Other case identifiers in previous transmissions, A.1.11.1 - Source(s) of the case identifier and A.1.11.2 - Case identifier) should be taken into account as a screening criterion.

In large pharmacovigilance 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.

[6] Guideline on the use of statistical signal detection methods in the EudraVigilance Data Analysis System (Doc. Ref. EMEA/106464/2006), 26 June 2008
[7] GVP Module VI – Management and reporting of adverse reactions to medicinal products
[8] GVP Module VI – Management and reporting of adverse reactions to medicinal products

Other data fields (e.g. reaction end/start date) can be used to make the identification of potential duplicates more likely to be accurate. 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 concerning female patients and cases where the patient's gender is unknown).

Differences in MedDRA coding practices 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 events/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 (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 pharmacovigilance 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, if data fields become mandatory, these might be considered for inclusion in future revisions of a duplicate detection algorithm.

Duplicates may 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.

2.2. Confirmation of duplicate cases

Upon initial identification of potential duplicates, 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 the Implementing Regulation on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council. and the detailed guidance[9] 'How to Prepare Individual Case Safety Reports'. This applies also for cases that are reportable in line with Directive 2001/20/EC.

Judgement will always need to be applied especially for certain types of medicinal products and adverse reactions, such as cases related to widely used medicinal products amongst 'elderly' patients or to vaccines in 'neonates/infants' (e.g. cases in 'neonates' with a reaction (ICH E2B(R2) B.2.i.1.b) of 'injection site reaction' associated with the same vaccine; even if the dates of administration, primary source, medical history and concurrent drug fields match, one can not 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 ICH E2B(R2) section 'Linked Reports' (A.1.12) with the numbers of other cases that are linked by a common element or elements (e.g. the same primary source), but are distinct from one another, is a particularly effective method of enabling confirmation that cases are not

[9] GVP Module VI – Electronic Reporting of Individual Case Safety Reports

duplicates of one another. Conversely, population of the ICH E2B(R2) section 'Report Duplicates' (A.1.11) 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 reporting timelines, it is recommended to enter the potential duplicated case into the pharmacovigilance 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 chapter 2.3.

2.3. Management of duplicate 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 ICH E2B(R2) fields 'Date report was first received from source' (A.1.6) ('Receive Date') and 'Date of receipt of the most recent information for this report' (A.1.7) ('Receipt Date') of the duplicates should not be changed from what they were prior to identification of the duplication, unless new information is received or incorporated into one of the cases.

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 the ICH E2B(R2) guideline and the detailed guidance provided[10]. Regarding the reported adverse events/reactions, one can choose to merge all reported events/reactions as presented in the duplicated cases in the master case. However, if the events/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

[10] GVP Module VI – Electronic exchange of safety information in the EU

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 & 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 certain instances, 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, 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 under dose, and medical judgement is always required in such instances.

If information has been provided 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. For example, if you have a confirmed duplicate pair, but case 1 has no concomitant medication, whereas case 2 has; unless case 1 is the more recent, and clearly states that the patient was not, contrary to previous information, receiving concomitant medication, then the concomitant medication should be included in the master case.

2.3.1. Process of managing duplicates detected during periodic screening

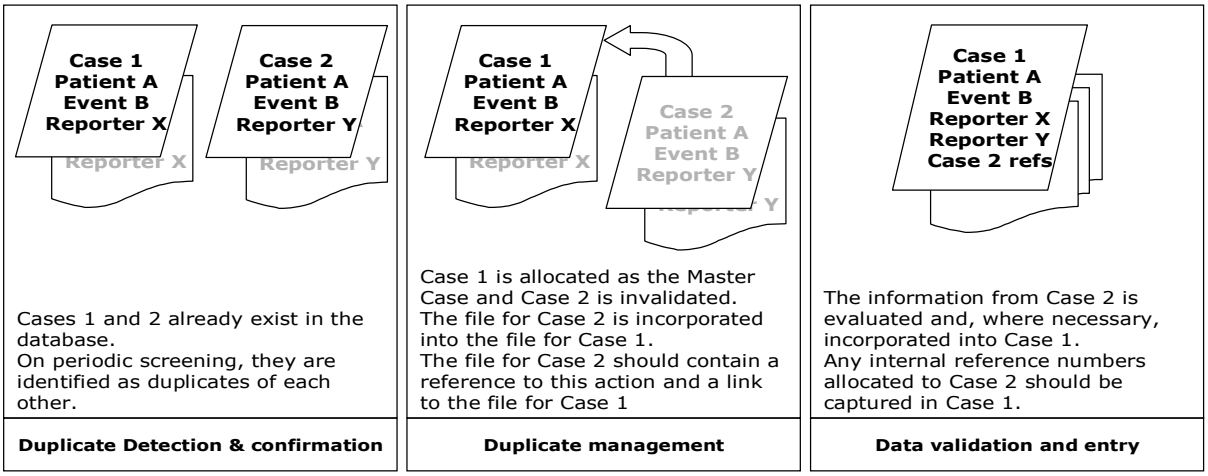
Confirmed duplicates that have been detected after data entry are usually managed through a merging process. By merging cases, usually a 'master case' is created in a pharmacovigilance database, which refers to the case chosen or created to represent the duplicated information. When creating a master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

2.3.1.1. 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 evaluation.

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

Figure 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(R2)-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 ICH E2B(R2) Worldwide unique case identification number (A.1.10.1 or A.1.10.2) 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 ICH E2B(R2) section (A.1.11) 'Other case identifiers in previous transmissions'.

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 the detailed guidance[11]), the master case does not need to be transmitted to external partners (e.g. National Competent Authorities, 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 pharmacovigilance database entries.

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

2.3.1.2. Creation of a master case

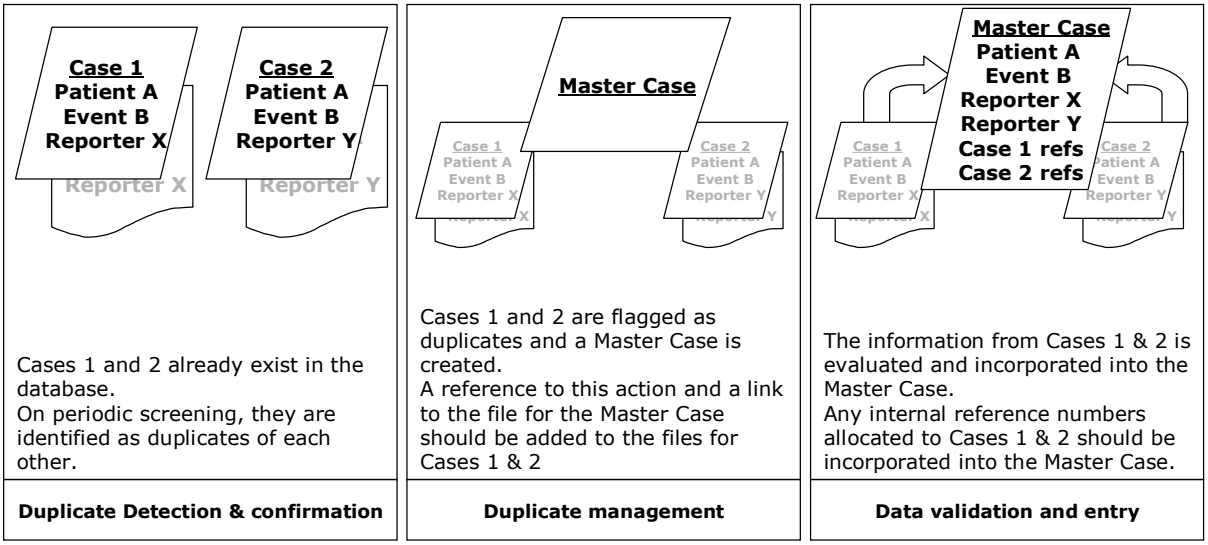
The creation of a master case refers to the procedure where a master case is created with a new Worldwide Unique Case Identifier (ICH E2B(R2) A.1.10) based on all the information contained in the subordinate duplicate cases. All of these subordinates are flagged as duplicates and linked to the

[11] GVP Module VI – Electronic reporting of Individual Case Safety Reports

master case and remain valid for the purposes of receiving follow-up information; only the master case, will be used for pharmacovigilance purposes such as signal detection and evaluation.

If there is no significant new information related to the case (see the detailed guidance[12]), the master case does not need to be transmitted to external partners (e.g. National Competent Authorities, European Medicines Agency). Figure 2 provides a pictorial representation of the creation of a master case.

Figure 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. NCAs, European Medicines Agency), which mainly receive individual cases electronically in ICH E2B(R2)-format from multiple Electronic Data Interchange (EDI) partners as it allows maintenance and traceability of all ICSRs as received originally from the Sender.

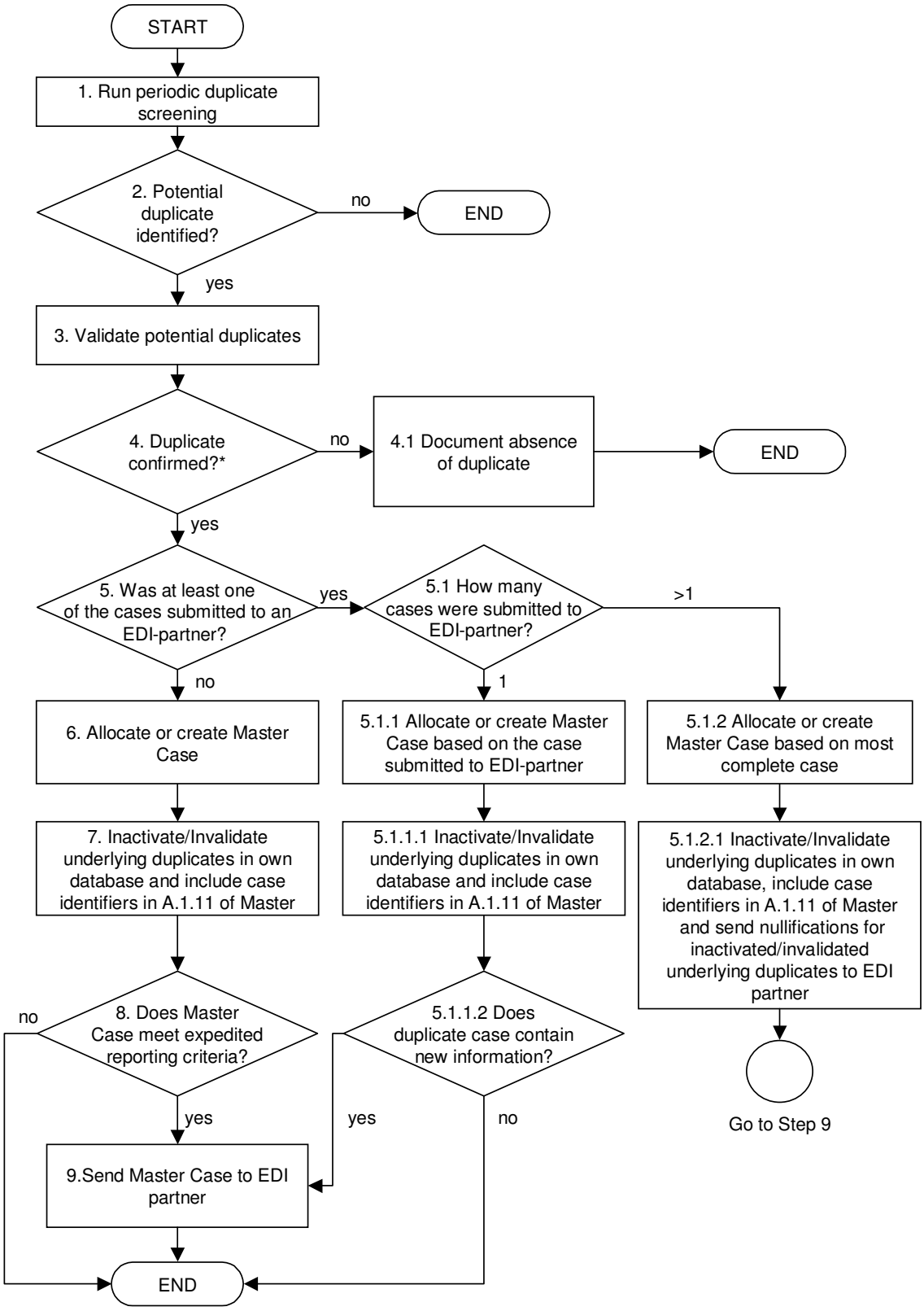
2.3.1.3. Process description for allocation or creation of a master case

A detailed description of the process flow for the allocation or creation of a master case based on duplicates existing in a pharmacovigilance database is presented in Flowchart 1.

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 Flowchart 2. 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 pharmacovigilance database.

[12] GVP Module VI – Electronic reporting of Individual Case Safety Reports

Flowchart 1 Process of 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

Step	Action
1.	Run periodic duplicate screening. Periodically search the pharmacovigilance database for potential duplicates. In line with the detailed guidance[13], "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. If receipt of cases is not a daily occurrence, then the pharmacovigilance database should be reviewed whenever cases have been received and processed.
2.	Potential duplicate identified? If no, end process If yes, continue with Step 3
3.	Validate potential duplicates. Manually verify whether the automatically identified potential duplicates are actual duplicates.
4.	Duplicate confirmed? Is the case a duplicate of a case that already exists in the pharmacovigilance database? 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. If it is not possible to be certain that cases are duplicates of one another, continue as though they are not. If no, continue with Step 4.1 If yes, continue with Step 5
4.1	Document absence of duplicate. 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. End process
5.	Was at least one of the cases submitted to an EDI-partner? Were any of the most recent versions of the cases in the duplicate cluster previously submitted to an EDI partner? If yes continue with step 5.1 If no, continue with step 6.

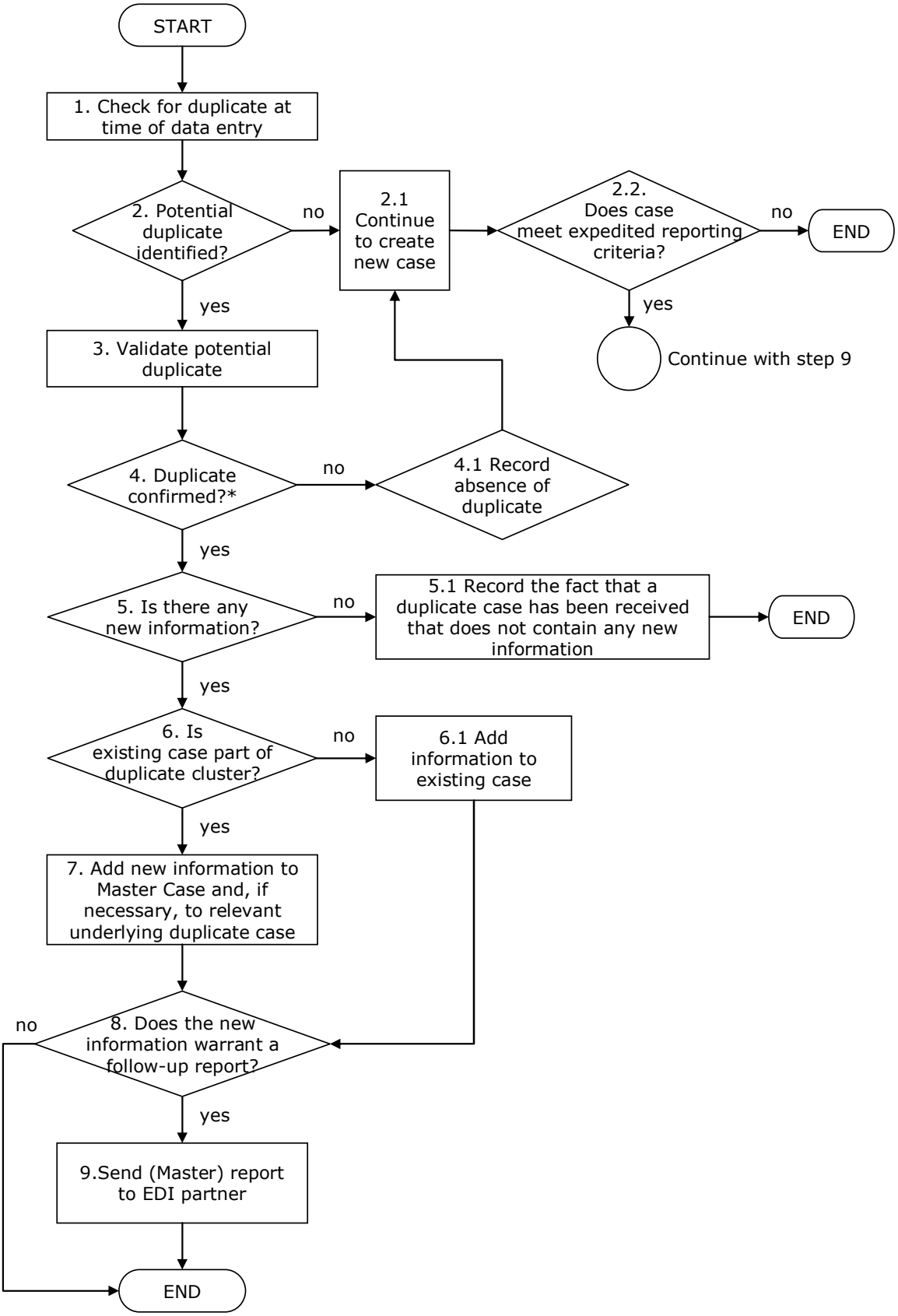
[13] GVP Module VI – Electronic reporting of Individual Case Safety Reports

Step	Action
5.1	How many cases were submitted to EDI-partner? How many of the cases in the duplicate cluster were submitted to an EDI partner? If only one of the cases was submitted, then base the master case on that one. If more than one case was submitted, then base the master case on one of those which was submitted. When allocating a case, the worldwide case safety ID (ICH E2B(R2) A.1.10.1 or A.1.10.2) of the master case should be that of one of the submitted cases. If only one case was submitted, continue with step 5.1.1 If more than one case was submitted, continue with step 5.1.2
5.1.1	Allocate or create master case based on the case submitted to EDI-partner. Depending on the method of duplicate management in the pharmacovigilance database, create or allocate a master case based on the case already submitted to an EDI partner. The Worldwide Case Safety ID (ICH E2B(R2) A.1.10) of the case already submitted to an EDI partner should be retained, if possible.
5.1.1.1	Inactivate/Invalidate the underlying duplicates in own database and include case identifiers in A.1.11 of Master. All underlying duplicates in the pharmacovigilance database should be inactivated, invalidated or otherwise marked as part of a duplicate cluster. Case identifiers from the underlying duplicates should be included in section ICH E2B(R2) A.1.11 of the master case. Go to Step 5.1.1.2.
5.1.1.2	Does duplicate case contain significant new information? Do(es) the duplicate case(s) contain any significant new information as described in the detailed guidance[14]? If yes, go to step 9. If no, end process.
5.1.2	Allocate or create master case based on most complete case submitted to EDI-partner. Depending on the method of duplicate management in the pharmacovigilance database, create or allocate a master case based on the most-complete case already submitted to an EDI partner.
5.1.2.1	Inactivate/Invalidate the underlying duplicates in own database, include case identifiers in A.1.11 of Master and send nullifications for inactivated underlying duplicates to EDI partner. 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 section ICH E2B(R2) A.1.11 of the master case.

[14] GVP Module VI – Electronic reporting of Individual Case Safety Reports

Step	Action
	For the underlying duplicates that were created in your pharmacovigilance database, and have already been transmitted to an EDI partner, nullification reports should be transmitted to the same EDI partner(s). Since at least two 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 partner. Therefore, the master case should be transmitted. Go to Step 9.
6.	Allocate or create master case based on most complete case. Depending on the method of duplicate management applied in the pharmacovigilance database, create or allocate a master case based on the most-complete case.
7.	Inactivate/Invalidate the underlying duplicates in own database and include case identifiers in A.1.11 of Master. All underlying duplicates in the pharmacovigilance database should be inactivated, invalidated or otherwise marked as part of a duplicate cluster. Case identifiers from the underlying duplicates should be included in section ICH E2B(R2) A.1.11 of the master case.
8.	Does Master meet expedited reporting criteria? Does the master case, now meet expedited reporting criteria or warrant transmission to an EDI partner? If no, end process If yes, continue with step 9.
9.	Send Master report to EDI partner. Send the master case to the relevant EDI partners. 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. If the cases merged under a master case were transmitted to the receiving pharmacovigilance 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.
	End

Flowchart 2 Process of 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 Flowchart 2 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 A.1.11, but in another relevant field in one's pharmacovigilance database.

Step	Action
1.	Check for duplicate at time of data entry. During data entry, search your pharmacovigilance database for potential duplicates.
2.	Potential duplicate identified? If no, continue with Step 2.1 If yes, continue with Step 3
2.1	Continue to create new case
2.2	Does case meet expedited reporting criteria? If no, end process. If yes, continue with Step 9
3.	Validate potential duplicate. Manually verify whether the automatically identified potential duplicates are actual duplicates
4.	Duplicate confirmed? Is the case a duplicate of a case that already exists in your pharmacovigilance database? This decision is only valid at this point in time and should 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. If you cannot be certain that cases are duplicates of one another, the process should be continued as though they are not. If no, continue with Step 4.1 If yes, continue with Step 5
4.1	Record absence of duplicate. 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. This step may not be relevant depending on the pharmacovigilance database used and the volume of data processed by the organisation. Go to Step 2.1
5.	Is there any new information?

Step	Action
	Do(es) the duplicate(s) contain any new information that you do not currently hold? If no, continue with step 5.1 If yes, continue with step 6.
5.1	Record the fact that a duplicate case has been received that does not contain any new information. This information should be captured in the duplicates section (ICH E2B(R2) A.1.11) and also the case narrative (ICH E2B(R2) B.5.1) of the existing case. If the date that the most recent information for the duplicate case was received is different to that of the master case, this should be recorded in the case, but it should not be recorded in the ICH E2B(R2) field A.1.7b 'Date of receipt of the most recent information for this report' End process
6.	Is existing case part of duplicate cluster? Is the existing case already part of a duplicate cluster? If no, continue with step 6.1 If yes, continue with step 7.
6.1	Add information to existing case. Add the new information to the existing case as follow-up information. Continue with Step 8.
7.	Add new information to master case and, if necessary, to relevant underlying duplicate case. Add the new information to the master case and, if necessary, also add it to the relevant underlying duplicate case.
8.	Does the new information warrant a follow-up report? In line with the detailed guidance[15], 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. If the previous version of the master case was transmitted to an EDI partner, but with the new information added it would not normally be reportable, e.g. if it is now downgraded to non-serious, this should still be reported. If yes, continue with step 9 If no, end process.

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Step	Action
9.	Send (Master) report to EDI partner. Send the latest version of the case, or, if applicable, the master case, to the relevant EDI partners.
	End process

2.3.2. Duplicates repeatedly received from the same sender organisation

If cases in a duplicate cluster are being repeatedly received from the same sender, 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 Section 2.3, merging the cases and sending a nullification report for the other duplicate case(s) as applicable to the receiver(s).

2.3.3. Sending nullifications

The detailed guidance on the sending of nullifications[16] should be taken into account when performing this task. Specifically, the action related to the following scenario should be followed:

Scenario	**Action**
An individual case has been identified as a duplicate of another individual case previously submitted.	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. The update of the remaining case should be performed in form of a follow-up report. The duplicate number fields in this report ICH E2B(R2) A.1.11.1 'Source(s) of the case identifier (e.g. name of the company, name of regulatory agency)' and ICH E2B(R2) A.1.11.2 'Case identifier(s)' should be updated with the case identification numbers of the nullified case.

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Definitions

ADR	Adverse Drug Reaction
Duplicate Cluster	Two or more cases which have been identified as potential duplicates of each other
EDI	Electronic Data Interchange. Electronic transfer, from computer to computer, of commercial and administrative data using an agreed standard to structure an EDI message. EDI is based on the use of structured and coded messages, the main characteristic of which is their ability to be processed by computers and transmitted automatically and without ambiguity. This makes EDI specific in comparison with other data exchange such as electronic mail.
EDI-partner	An organisation exchanging EDI Messages in the area of pharmacovigilance in the pre- or post-authorisation phase with another organisation. For the purpose of this guideline, EDI partners in the pre- and post-authorisation phase in pharmacovigilance are as follows: NCAs in the EEA MAHs in the EEA Applicants Sponsors of interventional clinical trials and non-interventional studies in the EEA EMA
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EV	EudraVigilance
EV EWG	EudraVigilance Expert Working Group
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
E2B	An ICH guideline on clinical safety data management: data elements for transmission of individual case safety reports
MAH	Marketing Authorisation Holder
Master case	A case based on two or more duplicate cases. The master case is the one which should be used for all pharmacovigilance activities.
MedDRA	Medical Dictionary for Regulatory Activities
NCA	A National Competent Authority. A regulatory authority within the EEA responsible for: Granting the authorisation to conduct a clinical trial in at least one Centre

	located within the Community, The granting of marketing authorisations for medicinal products, and The supervision of marketing of such products in accordance with the relevant laws and regulations established under Community law.
Nullification	A nullification message is an EDI message informing the receiver organisation that a case should be nullified (inactivated) in their database
Sender	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).