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Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs)

Draft

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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. The current reporting rules guarantee duplicate reporting.

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 pharmacovigilance data in various different formats.

1. Introduction

1.1. Background

Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use[1] and Volume 10 of The Rules Governing Medicinal Products in the EU[2] provide detailed guidance on the reporting of suspected (unexpected) serious adverse reactions in compliance with the legal provisions laid dawn in Regulation (EC) No 726/2004, Directive 2001/83/EC as amended and Directive 2001/20/EC.

Guidance is also provided for situations where individual cases might be reported by different senders e.g. where a MAH is aware that a healthcare professional has reported an adverse reaction to one of the medicinal products, for which he holds a marketing authorisation, to the Competent Authority of a Member State. Volume 9A states that 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.

Based on the current reporting rules and reporting practices, duplication of individual cases can occur. 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), Marketing Authorisation Holders (MAHs) and Sponsors of clinical trials (Sponsors) is an important element of good case management. The presence of duplicates in any pharmacovigilance system 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 commonly used data-mining procedures may highlight associations with as few as three reports, one or two duplicates may severely affect their utility.

[1] Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use, website http://ec.europa.eu
[2] Volume 10 of The Rules Governing Medicinal Products in the EU, website http://ec.europa.eu
[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

The problem of duplicated reporting of cases based on the current legal reporting rules was identified by the European Commission in their Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance", released for public consultation in December 2007. Although it is expected that the proposed provisions for simplified reporting rules in the new EU pharmaceutical legislation will significantly reduce the number of duplicates, they can never be completely excluded. As an initial step to investigate which procedures exists for handling potential duplicates, the EudraVigilance Expert Working Group (EV EWG) has distributed a questionnaire on the various aspects of duplicate detection and management to stakeholders from NCAs, MAHs as well as Clinical Trial Sponsors. Based on the feedback received, the EV EWG has prepared this Guideline on Duplicate Detection and Management of Individual Cases and Individual Case Safety Reports (ICSRs) (hereafter referred as Guideline), which should provide NCAs, MAHs and 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.

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 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) 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 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 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, 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.

[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

Handling duplicate reports typically involves three steps: (1) searching/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 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[5]. 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)[6]**.** 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 Volume 9A of the *'Rules Governing Medicinal Products in the European Union: Pharmacovigilance for medicinal products for human use*' 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 Detailed Description of their Pharmacovigilance System (DPPS).

2.1. Detection of duplicate cases

According to Volume 9A, 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 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) 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 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 events/reactions can already be suitable to

[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

[6] Guideline on the use of statistical signal detection methods in the EudraVigilance Data Analysis System (Doc. Ref. EMEA/106464/2006), 26 June 2008

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) may offer a quick start.

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 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 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 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 HLGT (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 also that 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 duplicates of each other.

2.2. Confirmation of duplicate 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 Volume 9A, part III chapter 5.1 'How to Prepare Individual Case Safety Reports'. This applies also for cases that are reportable in line with Directive 2001/20/EC.

In Volume 9A, Part II, Chapter 1.3.3, it is stated that the NCA "should make every effort to ensure that case reports contain sufficient information to identify such duplicates … and should liaise with relevant

MAHs to facilitate identification of possible duplicate cases." This principle should apply to all stakeholders in the context of electronic reporting of ICSRs.

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 event of 'injection site reaction', 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).

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 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) field 'Date report was first received from source' (A.1.6) ('Receive Date') and the 'Date of receipt of the most recent information for this report' (A.1.7) ('Receipt Date') 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 the ICH E2B(R2) guideline and the guidance provided in part III of Volume 9A. Regarding the 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 these and other decisions which are based on whether the extra specificity is clinically important. If there is conflicting information, e.g. regarding drug dosing whereby one report stated that a patient received 200 mg daily and the other report stated that the patient received 400 mg daily, it is not considered appropriate to reflect the conflicting information twice in the structured fields of the Master Case as this would impede calculation of cumulative doses. Instead an average can be stated with clear reference in the case narrative that there is conflicting information obtained from different sources.

2.3.1. Process of managing duplicates detected during periodic screening

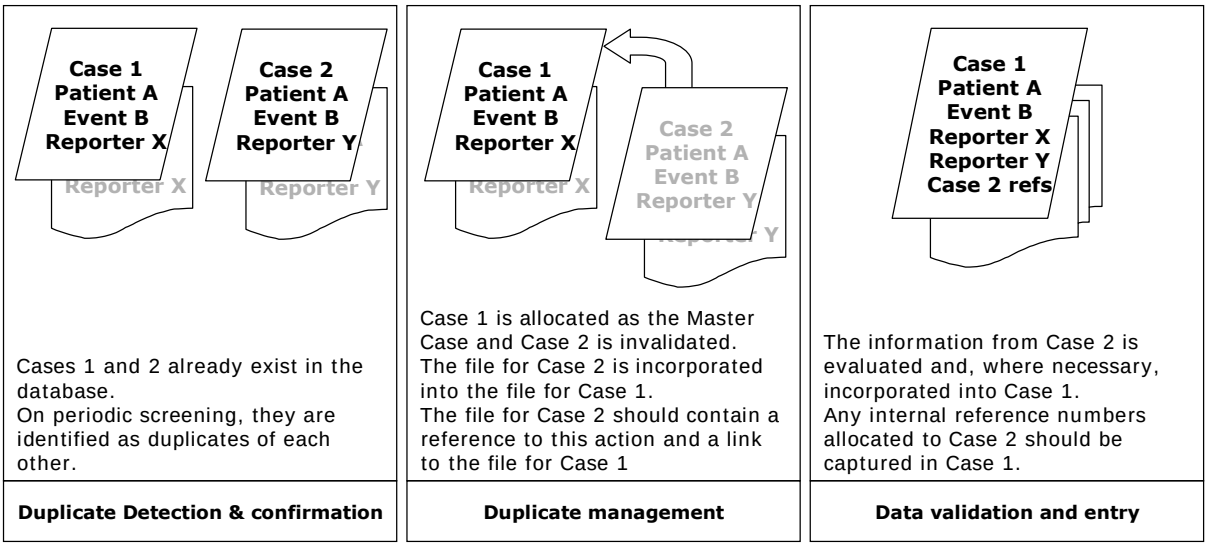
Confirmed duplicates that have been detected after data entry are usually managed through a merging process. By merging cases, usually a ‘Master Case’ is created in a database, which refers to the case chosen or created to represent the duplicated information. When creating a Master Case it is important 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 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 Volume 9A Part III, Chapter 5.3), the Master Case does not need to be transmitted to external partners (e.g. National Competent Authorities, EMA).

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

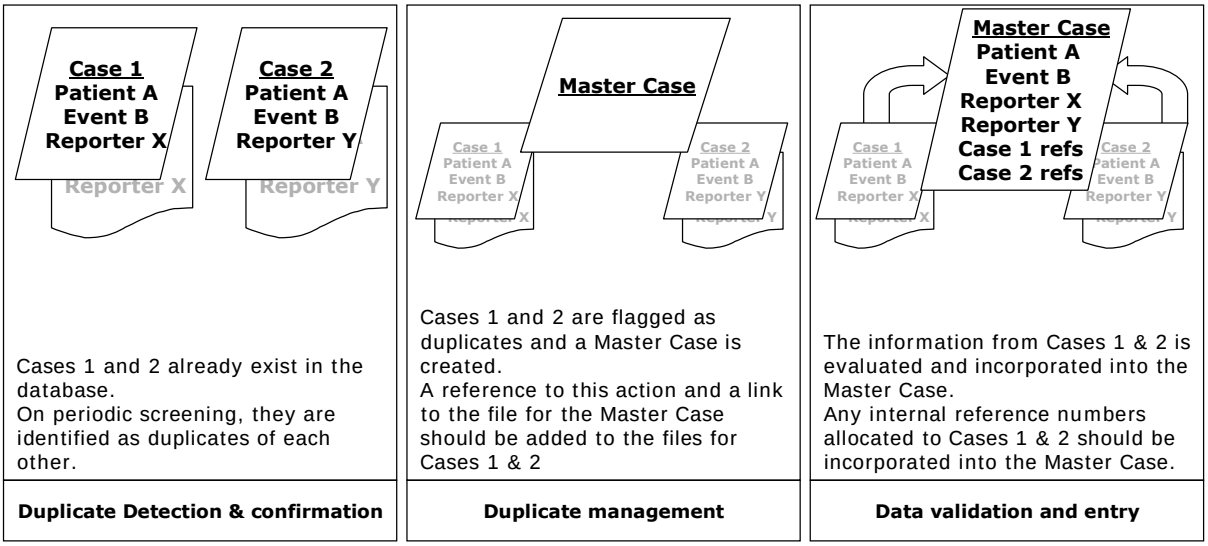
If follow-up information is received for any of the duplicated cases, the Master Case should be updated accordingly.

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 (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 Volume 9A Part III, Chapter 5.3), 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:

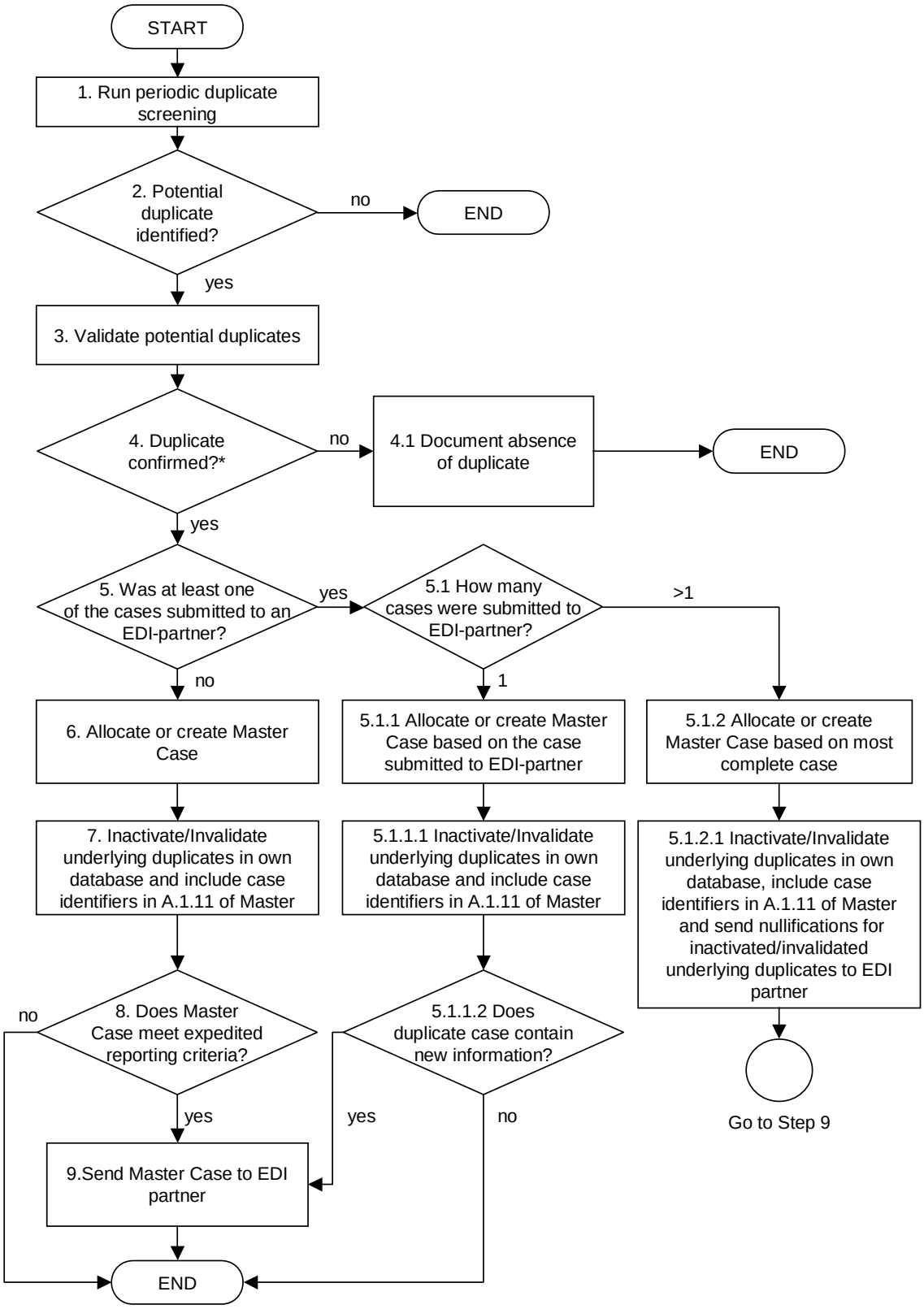
- Organisations (e.g. NCAs, European Medicines Agency), which mainly receive individual cases electronically in ICH E2B(R2)-format from multiple EDI partners as it allows maintenance and traceability of all ICSRs as received originally from the Sender.

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 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 database.

Flowchart 1 Process of Allocating or Creating a ‘Master Case’ of duplicates existing in a database



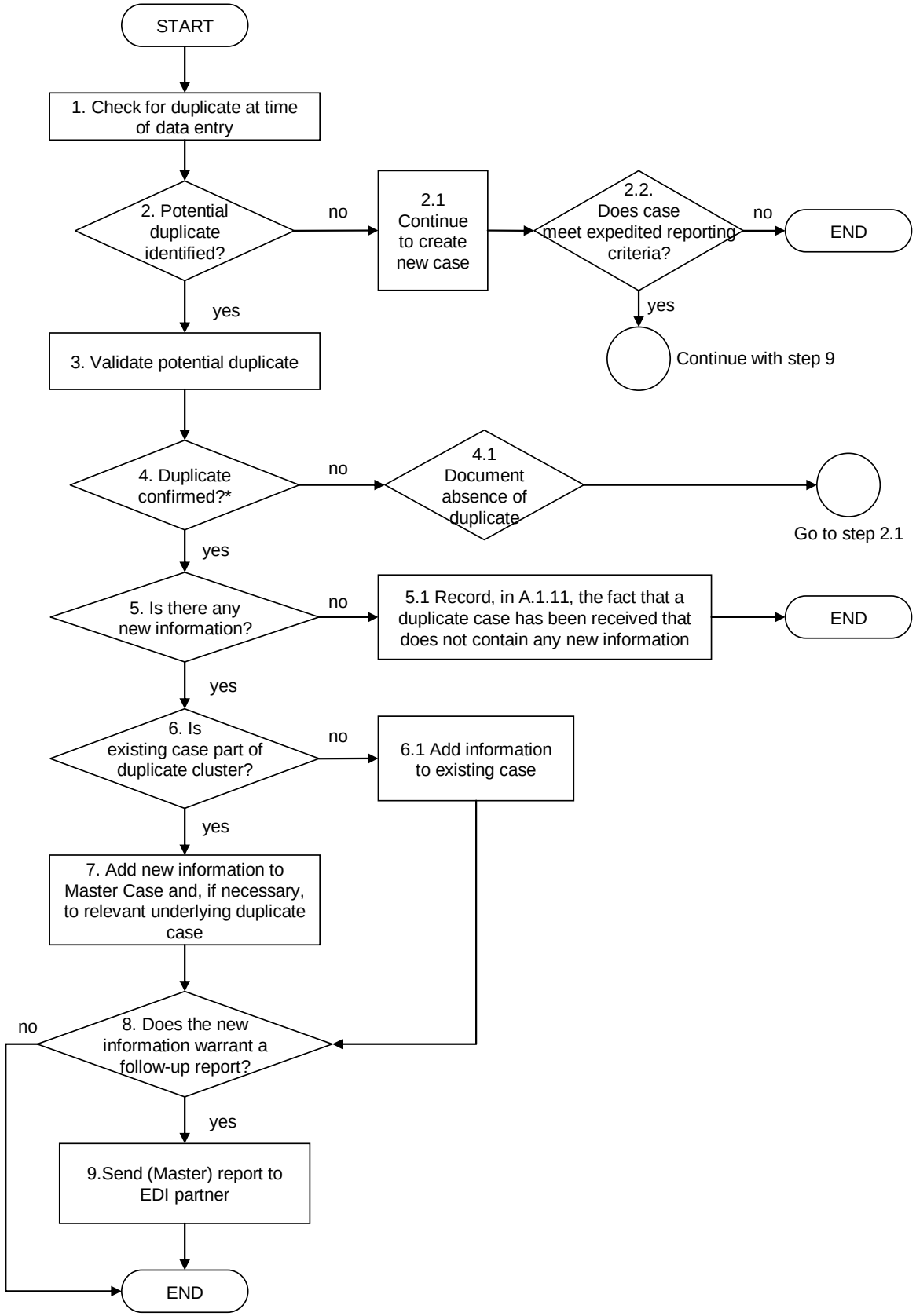
* assessment is valid only at this point in time and can change upon receipt of new information. Receipt of new information should trigger a new check for duplicates

Step	Action
1.	Run periodic duplicate screening Periodically search the database for potential duplicates. In line with Volume 9A, Part II, Chapter 1.3.3, “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 occurence, then the 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 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. Go to Step 2.1
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.
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?

Step	Action
	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. When allocating a case, the worldwide case safety ID (A.1.10.1 or A.1.10.2) of the Master Case should be that of one of the submitted cases. If only 1 case was submitted, continue with step 5.1.1 If more than 1 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 system, create or allocate a Master case based on the case already submitted to an EDI partner. The Worldwide Case Safety ID (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 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 A.1.11 of the Master case. Go to Step 9.
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 Volume 9A, Part III, Chapter 5.3? 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 system, 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 A.1.11 of the Master case. 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). 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 partner. Therefore, the Master Case should be transmitted.

Step	Action
	Go to Step 9.
6.	Allocate or create Master Case based on most complete case Depending on the method of duplicate management in the system, 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 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 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.
	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

Step	Action
1.	Check for duplicate at time of data entry During data entry, search your 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 10
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 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 you cannot be certain that cases are duplicates of one another, you should 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. Go to Step 2.1
5.	Is there any new information? 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)

Step	Action
	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 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 Volume 9A, Part III, chapter 5.3, 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 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 If yes, continue with step 11. If no, end process.
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

2.3.2. Sending nullifications

Volume 9A, Part III, Chapter 6 "Nullification of Individual Cases" 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:

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(M) A.1.11.2 'Case identifier(s)' should be updated with the case identification numbers of the nullified case.

2.3.3. Duplicates repeatedly received from the same sender organisation

If cases in a duplicate cluster are being repeatedly received from the same sender[7], 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 for the other duplicate case(s) as applicable to the receiver(s).

[7] 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).

Definitions

ADR	Adverse Drug Reaction
EDI	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 EMEA
EMA	European Medicines Agency
EU	European Union
EV	EudraVigilance
EV EWG	EudraVigilance Expert Working Group
ICH	International Conference on Harmonisation
E2B	A topic of the ICH
MAH	A Marketing Authorisation Holder.
Master Case	A case based on 2 or more duplicate cases. The Master Case is the one which should be used for all pharmacovigilance activities.
MedDRA	Medical Dictionary for Regulatory Affairs
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).