EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Inspections and Human Medicines Pharmacovigilance Division

Detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency

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1. Introduction and legal basis

Scientific and medical literature is an important source of information on suspected adverse reaction case reports (also referred to as individual case safety reports (ICSRs)). Currently, for active substances included in more than one medicinal product for human use, literature cases are reported in adverse reaction case reports in a duplicative way by marketing authorisation holders (MAHs) in the European Economic Area (EEA), which is based on their obligation to monitor scientific and medical literature as outlined in the Good Pharmacovigilance Practices (GVP) guideline, Module VI 'Management and reporting of adverse reactions to medicinal products'.

To enhance the efficiency of reporting and to provide a simplification for pharmaceutical industry, Article 27 of Regulation (EC) No 726/2004[1] sets out the following:

1. The Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish a list of active substances being monitored and the medical literature subject to this monitoring.
2. The Agency shall enter into the EudraVigilance database relevant information from the selected medical literature.
3. The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database.

In accordance with Article 107, paragraph 3 of Directive 2001/83/EC[2], for medicinal products containing the active substances referred to in the list of publications monitored by the European Medicines Agency (EMA) pursuant to Article 27 of Regulation (EC) No 726/2004, MAHs shall not be required to report to the EudraVigilance database the suspected adverse reactions recorded in the listed medical literature. *However, MAHs shall monitor all other medical literature and report any suspected adverse reactions.*

Article 28 of Regulation 726/2004 states that the obligations of MAHs and of Member States laid down in Articles 107 and 107a of Directive 2001/83/EC shall apply to the recording and reporting of suspected adverse reactions for medicinal products for human use authorised in accordance with this Regulation.

For the purpose of the literature-monitoring service to be provided by the Agency in line with Article 27 of Regulation (EC) No 726/2004, the structures and processes as outlined in GVP Module VI apply accordingly.

The Agency has decided to outsource the monitoring of scientific and medical literature and the entry of relevant information into EudraVigilance (hereafter referred to as MLM) to a service provider.

In summary, this detailed guide describes the technical and procedural aspects of the literature-monitoring service to be provided by the Agency in line with the requirements set out in Article 27 of Regulation (EC) No 726/2004 and GVP Module VI.

[1] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Consolidated version: 05/06/2013).
[2] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version: 16/11/2012)

2. Monitoring of selected medical literature for reports of suspected adverse reactions

2.1. Active substances that the Agency is monitoring

The Agency defines a range of active substances including herbal active substances for the purpose of the literature-monitoring service. These substances are selected on the basis of medicinal product information submitted in line with the provisions set out in Article 57(2), second subparagraph of Regulation (EC) No 726/2004[3]. More specifically, active substances contained in medicinal products for which a high number of marketing authorisations were granted to various MAHs in the EEA are selected.

They are grouped as follows:

i. Substances by active moiety including e.g. salts, esters as well as combinations (hereafter referred to as “substance groups”).

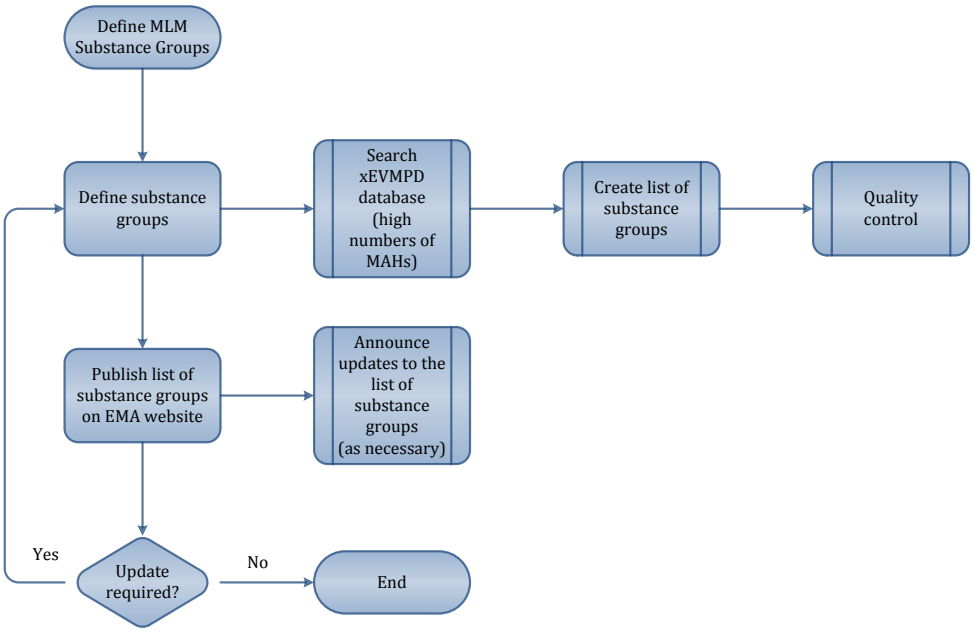
ii. Herbal substances by genus including combinations (hereafter referred to as “herbal substance groups”).

The total number of all substance groups included in the literature-monitoring service is based on the Agency’s allocated budget.

The lists of substance and herbal substance groups subject to the monitoring activities by the Agency are published at a dedicated area of the Agency’s website “MLM Substance and Herbal Substance Groups”.

A summary of the process of defining the active substances that the Agency is monitoring is provided in Figure 1.

Figure 1. Process of defining active substances that the Agency is monitoring



[3] Data submission for authorised medicines and the Extended EudraVigilance Medicinal Product Dictionary (xEVMPD) http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000336.jsp&mid=WC0b01ac058079126c

2.2. Scientific and medical literature that the Agency is monitoring

In accordance with Article 27 of Regulation (EC) No 726/2004, the Agency's monitoring service focuses on selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. The medical literature has been designated in line with the provisions set out in GVP Module VI[4] and based on the use of literature reference databases as follows:

- Large, comprehensive and widely used, daily updated and indexed biomedical reference database covering literature from EEA and non-EEA countries;
- Reference database covering a large spectrum of drug therapy and pharmaceutical information thus providing a worldwide, comprehensive bibliographic coverage of pharmaceutical, medical and health related literature including herbals;
- Reference database focusing on complimentary medicine and alternative treatments with mainly European coverage.

Details on these literature reference databases and their journal coverage are published at a dedicated area of the EMA website “MLM Description of the Journal/Reference databases”.

In accordance with Article 107, paragraph 3 of Directive 2001/83/EC, MAHs shall continue to monitor all other medical literature not listed as being monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004 and report any suspected adverse reactions.

2.3. Search of scientific and medical literature that the Agency is monitoring

GVP Module VI[5] describes the principles for database searches. For the substance groups outlined in chapter 2.1. the following applies:

- A daily search of the biomedical reference database as described in chapter 2.2. Daily refers to calendar days with the exception of weekends (Saturday and Sunday). Bank holidays are considered as calendar days.
- A monthly search of the two reference databases focusing on drug therapy and pharmaceutical information as well as complimentary medicine and alternative treatments as referred to in chapter 2.2. Monthly refers to updates of the database as issued by the database provider every calendar month.

The Agency maintains the right to change the required timelines if considered necessary to perform its pharmacovigilance functions.

The search strategies applied are customised for each substance group based on key strings, which are published at a dedicated area of the Agency’s website “MLM Search Strategies”. The search strategies are to be applied to the entire dataset of indexed journals contained in the aforementioned reference databases. Generally, no other search restrictions apply (e.g. language or sub-headings referring to safety) to achieve the widest possible search coverage.

The following main principles are being applied:

[4] GVP Module VI, Appendix 2.2 Where to look
[5] GVP Module VI, Appendix 2.3 Database Searches

- Substance Groups [INN name] or [Synonym]
  - A key string is defined for each substance group and is constituted of multiple components, separated by an 'OR' operator. The first component will be the INN name. The other components will be alternative names (variants) for the substances based on the Extended EudraVigilance Medicinal Product Dictionary (xEVMPD) or other reference sources.
- Herbal Substance Group [Herbal substance name] or [Common Name] or [core description of Latin name] or [Synonym]
  - A key string for each herbal substance group is constituted of four components separated by an 'OR' operator. The first component is the herbal substance name, which corresponds to the name of the herbal substance as referred to in the xEVMPD. The second component is the Common Name. The third component is the core description of the Latin name of the herbal (e.g. genus and species). The forth component will be synonyms.

Search strings are updated and maintained where necessary to improve search precision. This can relate to alignments of substance variants related to the substance groups referred to in chapter 2.1. updates applicable to the thesauri of the reference databases or other modifications required e.g. as a result from stakeholder feedback. Updates will be reflected in the "MLM Search Strategies" as applicable.

The search results for the reference databases and the applied search strategies are to be reproducible and tracked. Documented quality controls are put in place to ensure timeliness, accuracy and completeness of the literature search process.

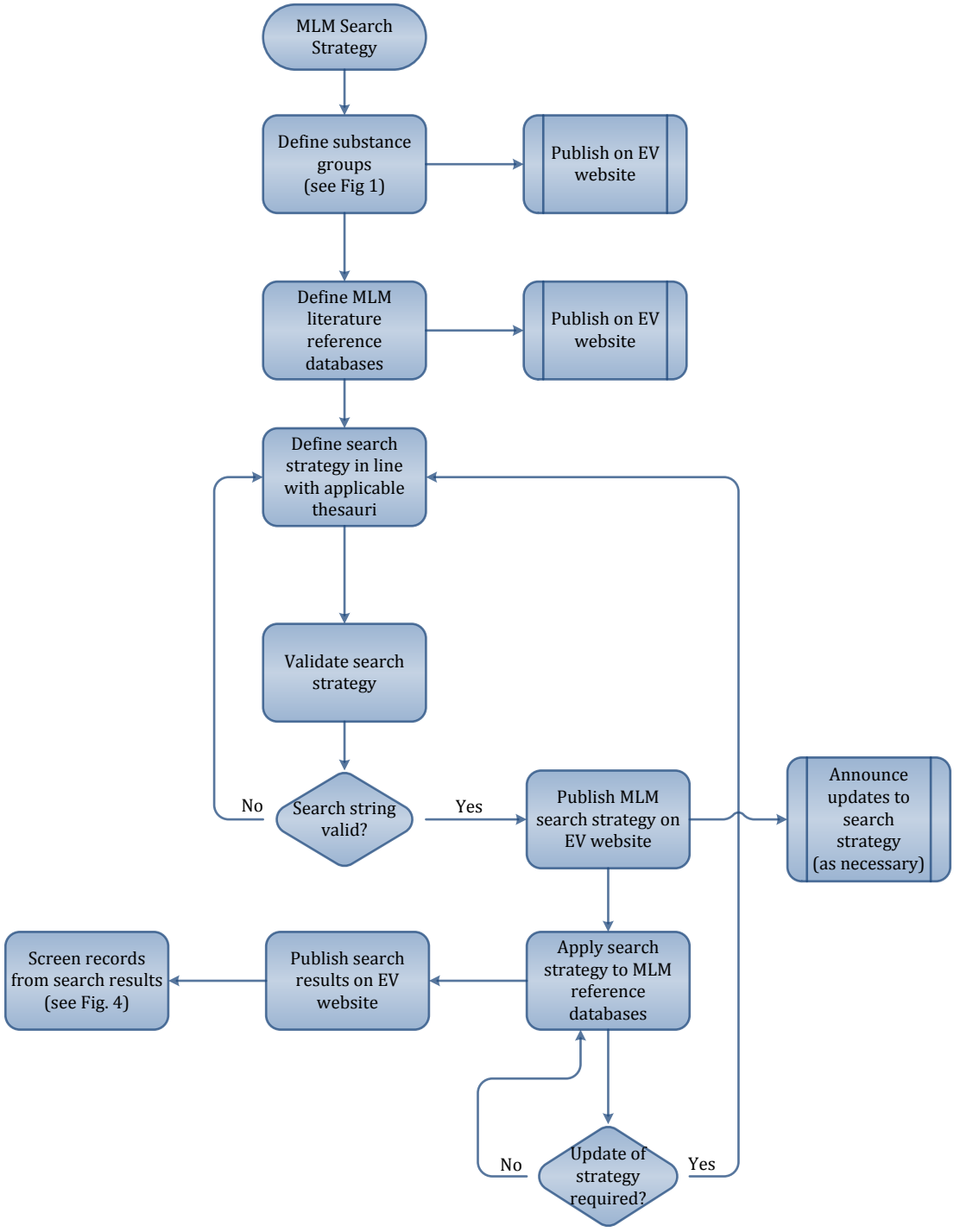
The search results are published at the dedicated area of the EudraVigilance website "MLM Search Results" at the next calendar day following execution of the search. As a minimum, the search results contain the following parameters:

- The name of each substance group.
- The name of the reference database(s).
- The date and time when the search was performed.
- The title of the record, the name of the author(s), the journal title incl. a Document Object Identifier (DOI) or where not available the database reference number for the record[6]. The information is provided in Vancouver style[7] as follows: *Author. Title of article. Title of Journal [Medium]. Date of publication [Date cited]; Volume [Issue]: Page numbers. DOI.*
  - The country of the primary author.

A summary of the process to define and maintain the search strategies and publishing search results is provided in Figure 2. Detailed Standard Operating Procedures (SOPs) and Work Instructions (WINs) are published on the Agency's website.

[6] Note: The Document Object Identifier (DOI) is not unique to an individual case safety report, which is characterised by the world-wide unique case identifier. Where a literature article refers to several individual cases, the same DOI is referenced in these cases.
[7] Vancouver style reference:
http://www.lib.unimelb.edu.au/recite/citations/Vancouver/ref444-elecSourceArticleWithDOI.html?style=4&type=2&detail=4

Figure 2. Process of defining and maintaining search strategies and publishing search results



2.4. Screening, review and assessment of scientific and medical literature and recording of activities

The review and initial assessment of each record resulting from the literature search as outlined in chapter 2.3. is performed within one calendar day[8] following the conduct of the search.

[8] Bank holidays are considered as calendar days.

In accordance with GVP Module VI, the purpose of the screening, review and assessment process is to identify valid Individual Case Safety Reports (ICSRs) related to:

- suspected adverse reactions originating from spontaneous reports and solicited reports in humans;
- special situations such as use of a medicinal product during pregnancy or breastfeeding[9], use of a medicinal product in a paediatric or elderly population[10], reports of off-label use, misuse, abuse, overdose, medication errors and occupational exposure with suspected adverse reactions[11];
- lack of therapeutic efficacy[12];
- suspected adverse reactions related to quality defects or falsified medicinal products[13];
- suspected transmission via a medicinal product of an infectious agent[14].

This refers to suspected serious adverse reactions occurring in the EEA and in third countries and suspected non-serious adverse reactions occurring in the EEA.

Based on the principles and reporting requirements outlined in GVP Module VI, inclusion/exclusion criteria are applied to facilitate the screening process. The criteria are published on a dedicated area of the Agency's website "MLM inclusion/exclusion criteria"[15]. The inclusion/exclusion criteria are regularly reviewed and updated as necessary.

A summary of the process of defining these criteria is provided in Figure 3. Detailed SOPs and WINs are published on the Agency's website.

The search results obtained in line with the process described in chapter 2.3. are exported to a library management tool, where an initial review of the records based on title, citations, key words and abstract (or article if available at this stage) is performed. Records, which do not qualify for ICSR reporting, are archived in an exclusion group with the exclusion criteria recorded.

Records, which could qualify for ICSR reporting, are moved to an inclusion group, where records are further screened for possible duplication. The duplicate check is performed since several reference databases are applied to ensure widest possible journal coverage.

Following completion of the duplication check, the records are further categorised as those that may refer to potential ICSRs and those that refer to confirmed reports based on the criteria for valid ICSRs as outlined in GVP Module VI[16].

The outcome of the screening results is published on a dedicated area of the EudraVigilance website on a daily basis "MLM Search Results" including at least the following parameters:

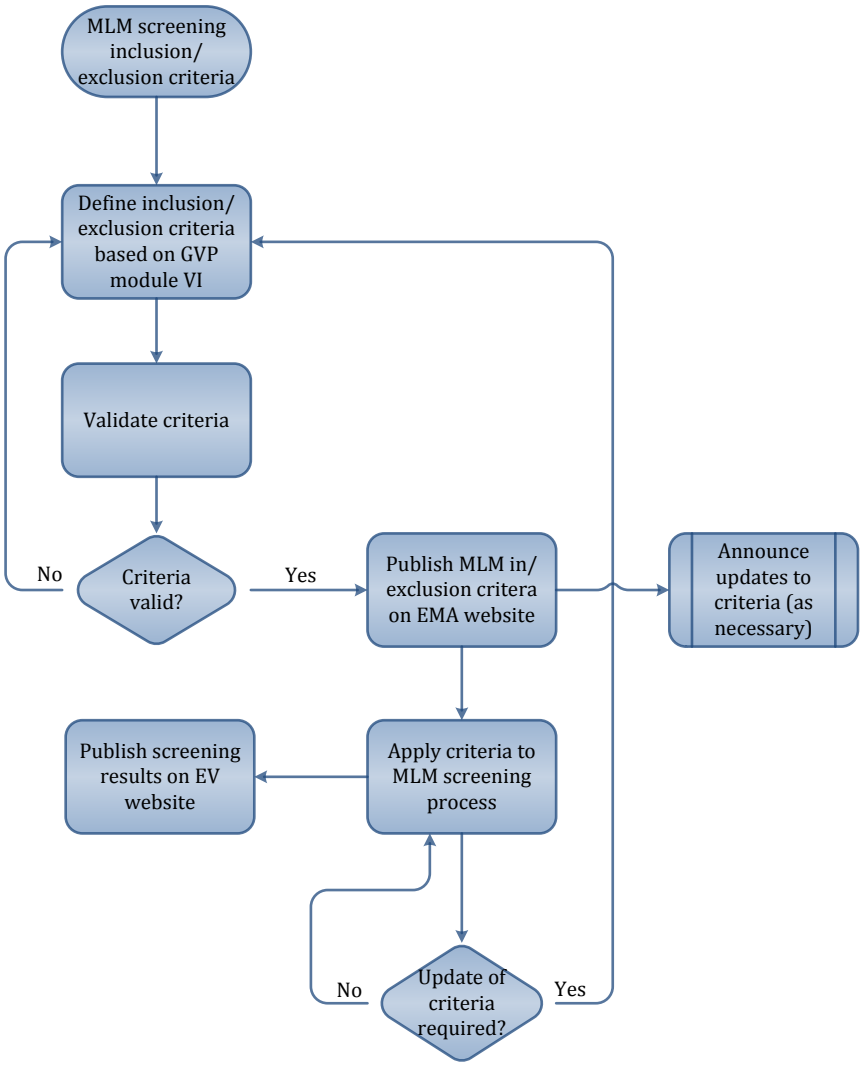
- The name of each substance group.
- The name of the reference database(s).
- The date and time when searches where performed.
- The title of the record, the name of the author(s), the journal title (Vancouver Style) incl. a Document Object Identifier (DOI) or where not available the database reference number for the

[9] GVP Module VI.B.6.1. Use of a medicinal product during pregnancy or breastfeeding
[10] GVP Module VI.B.6.2. Use of a medicinal product in a paediatric or elderly population
[11] GVP Module VI.B.6.3. Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure
[12] GVP Module VI.B.6.4 Lack of therapeutic efficacy
[13] GVP Module VI.C.2.2.4. Suspected adverse reactions related to quality defect or falsified medicinal products
[14] GVP Module VI.C.2.2.5. Suspected transmission via a medicinal product of an infectious agent
[15] Monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency: Inclusion and exclusion criteria for processing of Individual Case Safety Reports (EMA/119265/2015)
[16] GVP Module VI.B.2. Validation of reports

record. The information is provided in Vancouver style as follows: *Author. Title of article. Title of Journal [Medium]. Date of publication [Date cited]; Volume (Issue): Page numbers. DOI*.

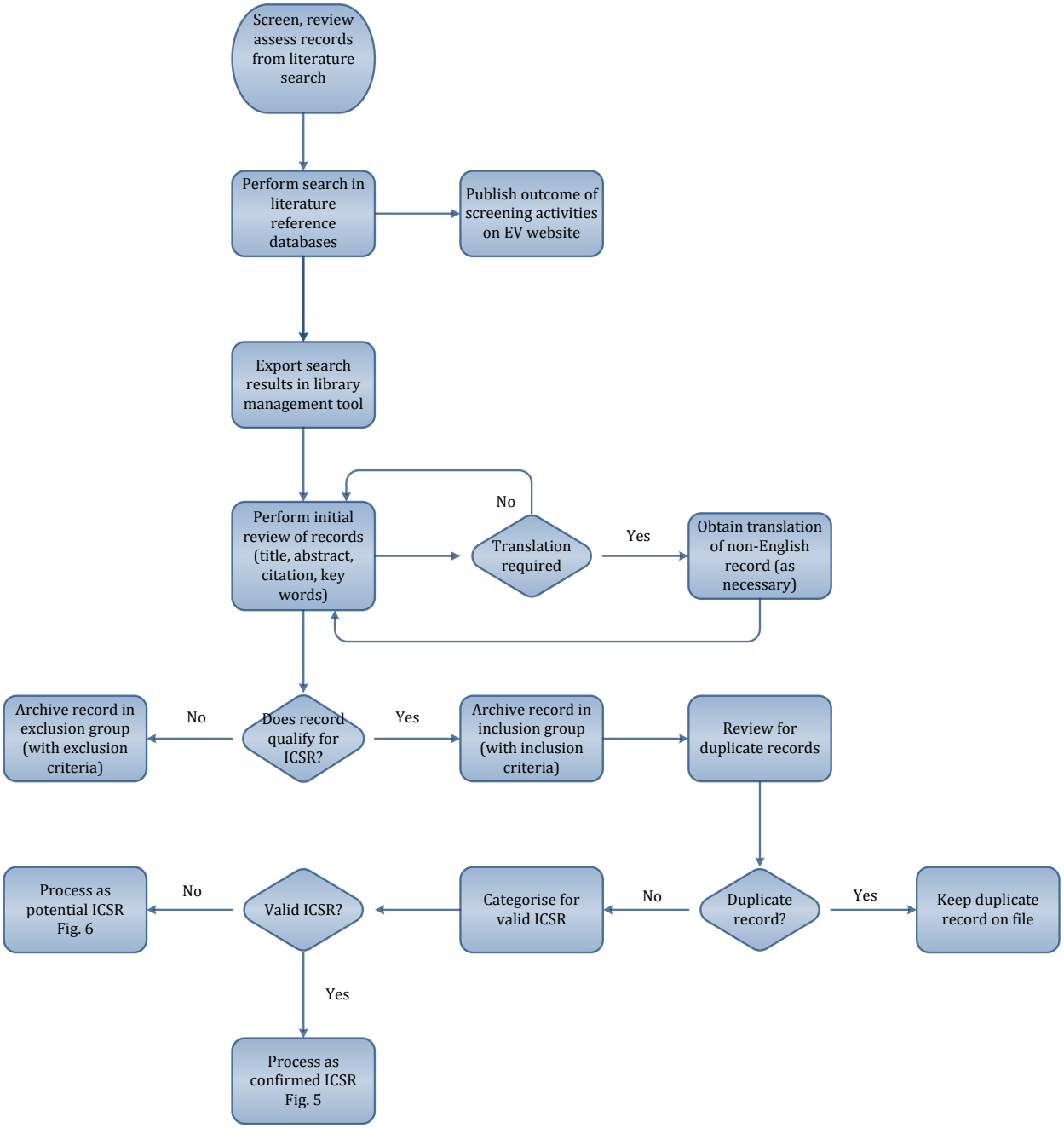
- The country of the primary author.
- The date when the record was screened.
- The criteria upon which the record was excluded or included for further case processing and creation of ICSRs in EudraVigilance and reporting to concerned NCA(s).
- A flag if the record refers to confirmed or potential ICSRs.
- A flag if the records refer to serious and/or non-serious adverse reactions.
- The primary source country.
- The date when full text article (and translation where applicable) is requested.

Figure 3. Inclusion/exclusion criteria for record screening



Documented quality controls are in place to ensure timeliness, accuracy and completeness of the literature screening, review and assessment process.

Figure 4. Screening, review and assessment of search records



3. Processing of ICSRs

3.1. Processing of confirmed ICSRs

For records of confirmed ICSRs, which have been identified as part of the screening process as outlined in chapter 2.4. , the full text article (and where necessary, an English translation) is obtained. This is where the full text article is not immediately accessible within the reference databases outlined in chapter 2.2. Following review of the full text article, the number of valid ICSRs referred to in the article is determined including seriousness of the suspected adverse reactions.

Prior to the ICSR creation, a duplicate check is performed in EudraVigilance. This duplicate check focuses primarily on identifying ICSRs that might originate from the same article. Where one or more duplicates are identified, the world-wide unique case identifier is recorded (in the ICSR "Other case identifiers in previous transmissions"). A further duplicate check is conducted once the ICSRs are processed in EudraVigilance with the aim to identify duplicates originating from the literature screening and other sources than the literature.

ICSRs are created in English, in compliance with EU personal data protection legislation[17] and copyright law (no text or images can be "copied" and "pasted" from articles to the ICSRs). The provisions set out in GVP Module VI[18] and in Articles 27, 28 and 29 of the Commission Implementing Regulation (EU) No 520/2012 are also applied. A literature reference in Vancouver Style together with a DOI is recorded as follows: *Author. Title of article. Title of Journal [Medium]. Date of publication [Date cited]; Volume(Issue): Page numbers. DOI.*

The information provided in the article is structured with the applicable ICSR format as outlined in Article 26 of the Commission Implementing Regulation (EU) No 520/2012. A case narrative is prepared for all individual cases summarising all relevant information required for the medical assessment of the case. For non-serious adverse reactions, no specific case narrative is prepared.

No copies of relevant abstracts, full text articles or other journal records of scientific and medical literature are made available taking into account that related ICSRs are well documented. However, where considered necessary and taking into account copyright restrictions, the Agency, national competent authorities (NCAs) in EEA Member States, the European Commission and MAHs should obtain their own copy of the relevant records. The same applies to translations, where applicable.

Causality assessment and suspected relatedness of each medicinal product to the adverse reaction(s) are performed in accordance with the provisions of GVP Module VI[19].

ICSRs[20] are created within the following timelines:

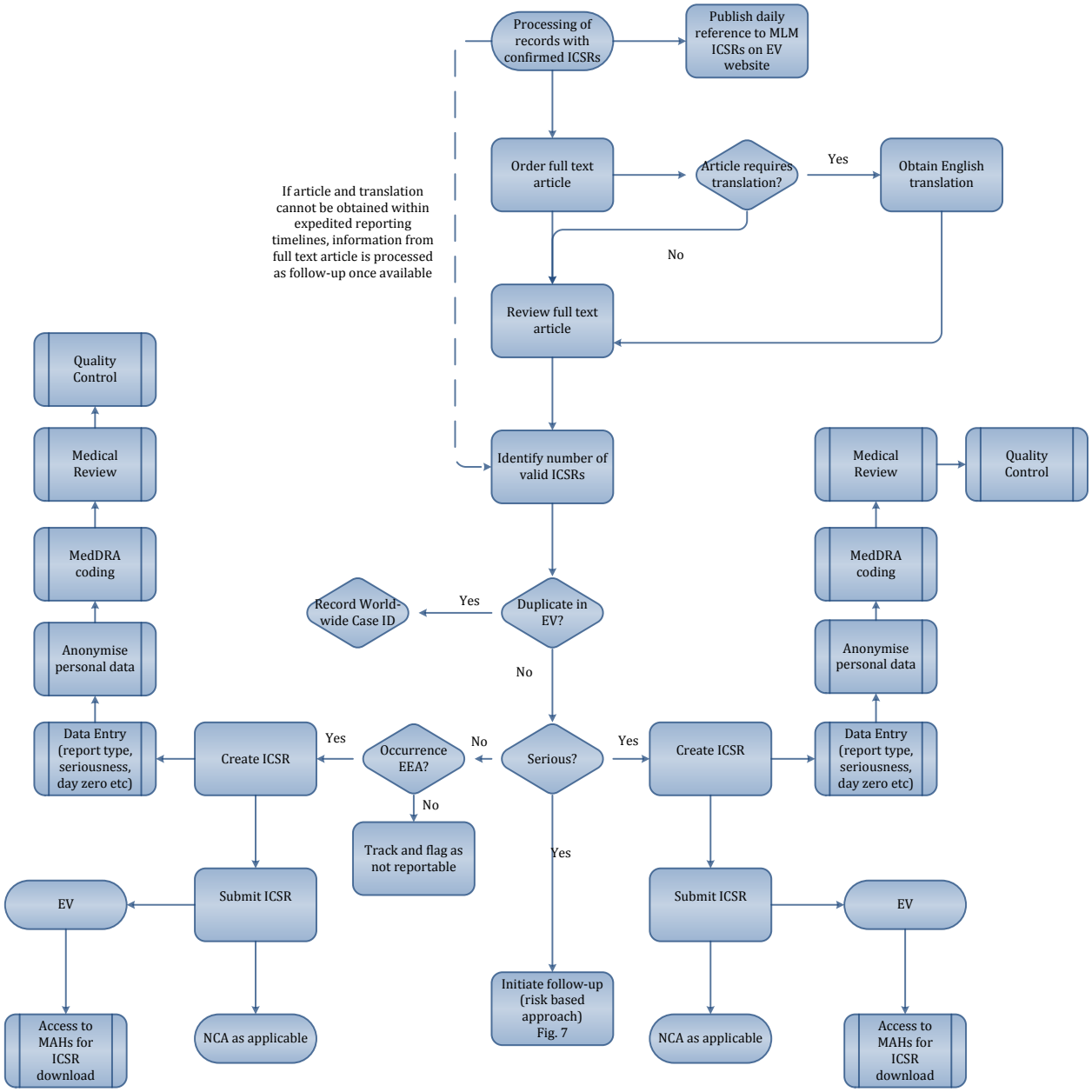
- Suspected serious adverse reactions originating from the EEA or in third countries immediately and no later than seven calendar days from day zero.
- Non-serious adverse reactions originating from the EEA within 21 calendar days from day zero.

[17] Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data.
[18] GVP Module VI.B.2. Validation of reports, GVP Module VI.B.7 Reporting of ICSRs
[19] GVP Module VI.C.6.2.2.4 Case narrative, causality assessment and comments
[20] This refers to reporting requirements as outlined in chapter 2.4.

The principles set out in GVP Module VI[21] apply i.e. day zero refers to the date on which the Agency's service provider becomes aware of a record containing the minimum information for a valid ICSR to be reportable as part of the activities carried out in accordance with Article 27 of Regulation (EC) No 726/2004.

In instances, where the full text article (and translation where applicable) cannot be obtained within a timeframe that would allow for compliance with the reporting timelines as outlined above, the ICSRs are processed based on the minimum information available in the initial record. New information resulting from the full text article is processed as follow-up (see chapter 3.3.).

Figure 5. Processing of confirmed ICSRs



[21] GVP Module VI Appendix 2.7 Day zero

A summary of the screening, review and assessment process is provided in Figure 5. Detailed SOPs and WINs are published on the Agency's website.

The ICSRs related to serious and non-serious adverse reactions are submitted within one calendar day to the concerned NCA in accordance with the reporting requirements of ICSRs as outlined in GVP Module VI[22].

MAHs can access and download the ICSRs from EudraVigilance or a dedicated area of the EudraVigilance website in line with the applicable formats and standards as outlined in Article 25 and 26 of the Commission Implementing Regulation (EC) No 520/2010. A list of ICSRs entered in EudraVigilance is published daily at a dedicated area of the EudraVigilance website "MLM ICSRs" including the following parameters:

- The name of each substance group.
- The name of the reference database(s).
- The date and time when searches were performed.
- The title of the record/article, the name of the author(s), the journal title (Vancouver Style) incl. a Document Object Identifier (DOI) or where not available the database reference number for the record. The information is provided in Vancouver style as follows: Author. Title of article. Title of Journal [Medium]. Date of publication [Date cited]; Volume (Issue): Page numbers. DOI.
  - The country of the primary author.
  - The date when the record was screened.
  - The criteria upon which the record was included for further case processing and creation of ICSRs in EudraVigilance and reporting to concerned NCA(s).
  - A flag if the record refers to confirmed/potential ICSRs.
  - A flag if the record refers to serious and/or non-serious adverse reactions.
  - The primary source country.
  - The date when full text article (and translation where applicable) is requested.
  - The date when full text article (and translation where applicable) is received.
  - The name of medicinal products/substances (suspect, interacting).*
  - The world-wide unique case identifier for each valid ICSR.
  - The date when the initial ICSR was created and transmitted to EudraVigilance and concerned NCA(s).
  - The follow-up status (follow-up to be initiated Yes/No).

Documented quality controls are in place to ensure timeliness, accuracy and completeness of the processing of confirmed ICSRs.

* Note: For ICSRs which refer to suspect or interacting medicinal products/substances other than the substance groups subject to the monitoring by the Agency, MAHs should not report those ICSRs

[22] GVP Module VI.B.8 Reporting modalities; GVP Module VI.C Operation of the EU Network; GVP Module VI, Appendix 3 Modalities for reporting and Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period (17 October 2013, EMA/321386/2012 Rev.8 or later if applicable)

separately to the concerned NCA(s) in the EEA or the Agency as applicable to avoid duplication of reports.

3.2. Processing of potential ICSRs

For records of potential ICSRs, which are identified as part of the screening process as outlined in chapter 2.4. , the full text article (and where necessary, an English translation) is obtained and reviewed in line with the inclusion/exclusion criteria outlined in chapter 2.4.

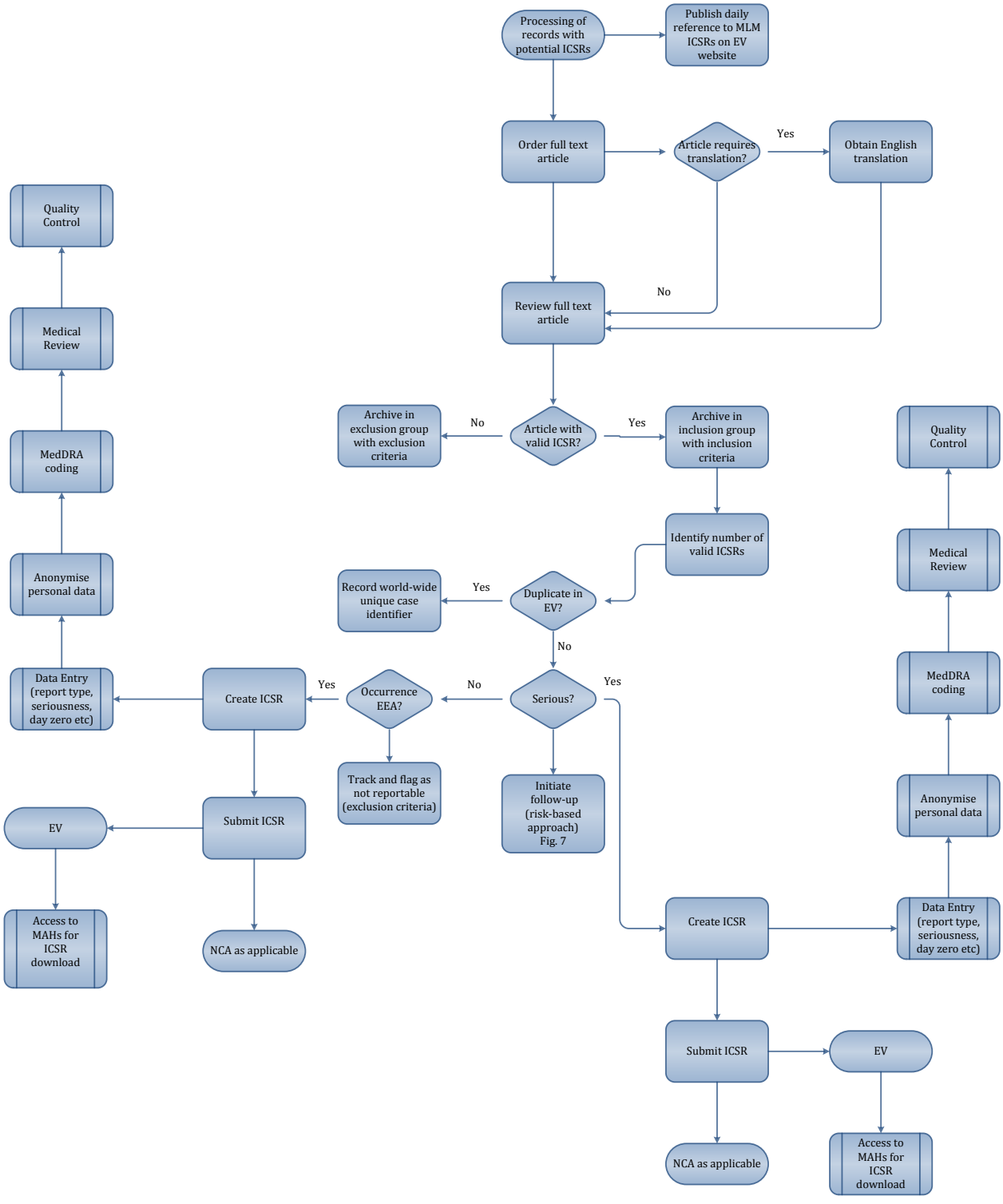
Articles which do not qualify for a valid ICSR are archived in an exclusion group with the exclusion criteria recorded. Articles which refer to one or more valid ICSRs are archived in the inclusion group with the inclusion criteria recorded. The outcome of the screening of the full text article and the processing of potential ICSRs is recorded in the file “MLM ICSR” (see chapter 3.1.).

Valid ICSRs are processed as outlined in chapter 3.1.

A summary of the processing of potential ICSRs is provided in Figure 6. Detailed SOPs and WINs are published on the Agency’s website.

Documented quality controls are in place to ensure timeliness, accuracy and completeness of the processing of potential ICSRs.

Figure 6. Processing of potential ICSRs



3.3. Follow-up of individual cases

A process is put in place by the Agency that ensures that individual case reports are followed-up with the publication author(s) as necessary to obtain supplementary detailed information, which is important for the scientific evaluation of the cases in line with the requirements set out in GVP Module VI. This is in addition to any effort to collect missing minimum information as outlined in GVP Module VI and in chapter 3.2[23].

In principle, one attempt to follow-up with the primary author is made for suspected serious adverse reactions based on a risk-based approach. This refers to individual cases, where the outcome is not known, where pre-defined clinical information is missing as regards important medical events or for both and for individual cases where not all of the minimum reporting criteria are available for a valid ICSR. The MedDRA Important Medical Events (IME) list is published by the Agency at the EudraVigilance website[24].

Any new information is presented and reported in the follow-up ICSR in accordance with GVP Module VI. Personal data are anonymised in order to ensure full compliance with the requirements of the EU data protection legislation.

Any attempt to obtain follow-up information is documented and a check for potential duplicates in EudraVigilance is performed in the context of processing of any new-follow-up information.

Where follow-up is pursued, the status is recorded in the file “MLM ICSRs”, which is published daily at a dedicated area of the EudraVigilance website with the following additional parameters besides those listed under chapter 3.1. :

- The date when the follow-up was initiated.
- The date by which a response is requested.
- A flag, if a response is received (no response, response with new information, response with no additional information).
- The date when follow-up information is received.
- The date when the follow-up ICSR was created and transmitted to EudraVigilance and concerned NCA(s).

ICSRs are created within seven calendar days following receipt of new information related to suspected serious adverse reactions. Day zero refers to the date of receipt of any new follow-up information by the Agency’s service provider.

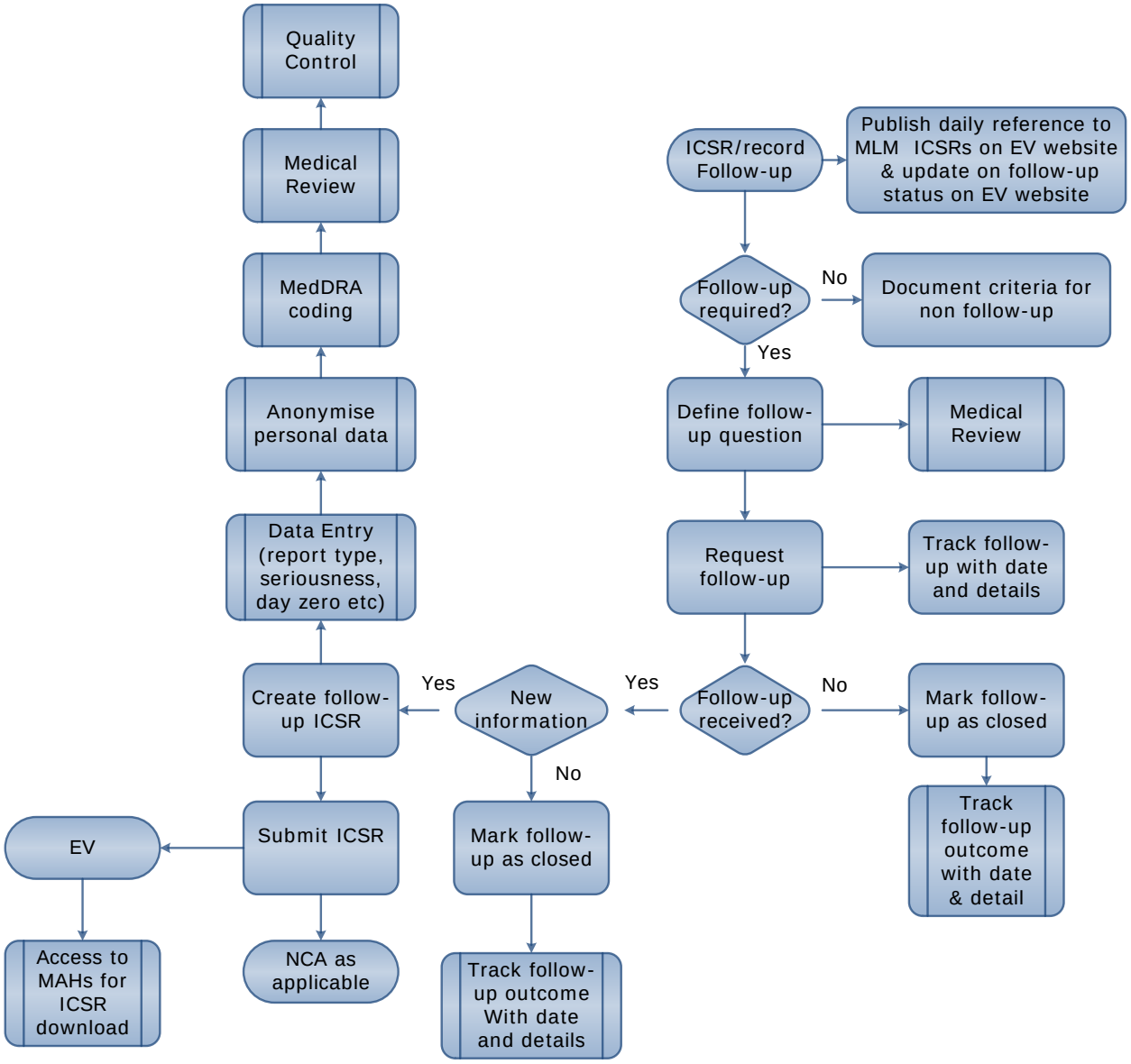
In instances, where a NCA/MAH obtains new information outside the follow-up process operated by the Agency e.g. in the context of the validation of a signal, the NCA/MAH should send a follow-up report in accordance with the reporting requirements of ICSRs as outlined in GVP Module VI[25].

A summary of the follow-up process is provided in Figure 7. Detailed SOPs and WINs are published on the Agency’s website.

[23] Based on missing information identified as part of the screening process outlined in chapter 2.4 and the inclusion/exclusion criteria published at the Agency’s website.
[24] Important Medical Events (IME) list published at the EudraVigilance.ema.europa.eu
[25] GVP Module VI.B.8 Reporting modalities; GVP Module VI.C Operation of the EU Network; VI, Appendix 3 Modalities for reporting and Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period (17 October 2013, EMA/321386/2012 Rev.8 or later if applicable)

Documented quality controls are in place to ensure timeliness, accuracy and completeness of the follow-up process.

Figure 7. Process of follow-up



4. Quality management

Well-defined and regularly audited quality management practices are put in place to ensure that the service provider operates to consistently high levels of quality, efficiency and cost-effectiveness. The business processes are based on Standard Operating Procedures (SOPs) and Work Instructions (WINs) prepared and maintained by the service provider, which are subject to approval and publication by the Agency[26]. Processes have to be in compliance with the requirements of ISO 9001:2001. Records have to be maintained in accordance with the provisions of ISO 15489.

Measures are put in place to facilitate performance monitoring, the assessment whether performance meets the Agency's stakeholders' needs and that allow taking appropriate action such as understanding and extending features of good performance and correcting areas of underperformance. Those measures are further defined as part of a Service Level Agreement between the Agency and the service provider.

The principles for literature monitoring and adverse reaction reporting as outlined in Regulation (EC) No 726/2004, Directive 2001/83/EC, the Commission Implementing Regulation (EU) No 520/2012 and the GVP Module VI apply accordingly.

Records of literature searches including the results of the review of the articles returned from searches as well as the status of the ICSR processing and ICSR follow-up are maintained in accordance with the requirements described in Article 16 of the Commission Implementing Regulation (EU) No 520/2012[27].

Surveys are conducted at six monthly intervals of MAHs and NCAs in EEA Member States to aid the identification of potential areas of improvement and to enhance performance if required.

The Agency also initiates two yearly audits of the service provider's internal quality management and control systems and of the services provided to assess their effectiveness with a view to bringing about continuous improvement. The audits are to be performed by an independent auditor appointed by the Agency. The first audit of the literature screening process will be conducted within three months following the successful launch of the literature monitoring service.

5. Interaction with stakeholders

A service desk is operated to assist in dealing with enquiries from MAHs and NCAs in EEA Member States. The working language of the service desk is English, the working hours are those of the business hours of the Agency[28]. The contact details of the service desk are published at a dedicated area of the EMA website.

[26] Procedures:http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000338.jsp
[27] Implementing Regulation (EU) No 520/2012 of 19 June 2012 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.
[28] Agency business hours and holidays: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000247.jsp&mid=WC0b01ac05800293ff