Medical Literature Monitoring Service Contractor Work Instruction (MLM WIN-03)

Title: WIN on Processing and submitting ICSRs in EVWEB		
Applies to: Staff members in EMA and its contractors		
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1. Changes since last revision

WIN formatted as per the agency's current template.

LMTT replaced with LiEMA throughout the document.

Complete WIN updated as per the new technology system.

Formatting changed to first display each EVWEB section followed by its respective code in EVWEB throughout the document.

Definitions added/updated for EVWEB sections (as appropriate) throughout this document.

WIN corrected grammatically.

Under section 5.1,

Step 2: Information added to access and import XML generated from LiEMA.

Step 6 (Safety report): Step 6a. merged in Step 6, format for Safety Report ID has been updated, additional information to enter First received date and Last received date has been added, format for Case identification number updated and options for First Sender added.

Step 7 (Patient): Options available for patient sex added.

Step 8 (Drug): Step 10 (Drug reaction) merged under Step 8, Additional fields visible updated, options available for action taken added, Information for Dose Unit, Dosage time interval unit, Batch Lot number, Dose form text and Dose form added, Information for Route of administration and Drug Indications updated.

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Step 9 (Reactions): Step 9a. merged under 9, Process to navigate to reaction section and to add more reaction added, Information for Seriousness criteria at reaction level added, Information for Reaction text native language, Reaction (MedDRA) and Outcome updated.

Step 11 renumbered as 10 (Patient Medical History): Process to navigate to medical history section added, Information for Medical History (MedDRA) added, Information for Continuing updated.

Step 12 renumbered as 11 (Test): Information for Quantity operator, Test result value and Test result unit added.

Step 13 renumbered as 12 (Study Information): Process to navigate to studies section added.

Step 14 renumbered as 13 (Case Summary)

Step 15 renumbered as 14 (Reporter Information): Information for Reporter qualification and Province state updated.

Step 16 renumbered as 15 (Validation and XML Export)

Step 17 renumbered as 16 (Medical Review)

Step 18 renumbered as 17 (Pre-submission check for the follow-up case)

Step 19 renumbered as 18 (Submit ICSRs)

Step 20 renumbered as 19 (Acknowledgements): Process to retrieve message acknowledgements updated and Step 21 merged in Step 19

2. Records

Electronic copy of this WIN will be stored in Document Management System (DMS).

No paper copies are archived.

3. Scope

The aim of this WIN is to outline the process for Processing and submitting ICSRs in EVWEB.

4. Definitions

Term	**Definition**
DocID	DocID is the unique ID generated by LiEMA for each literature reference(s) in the tracking tool.
EMA	European Medicines Agency
EudraVigilance	The European data-processing network and management system, which has been developed according to internationally agreed standards and which allows the EMA to manage the electronic data exchange of Individual Case Safety Reports (ICSRs) and to support the EU pharmacovigilance activities at Community level.
EV	EudraVigilance

Term	Definition
EVWEB	EudraVigilance Database Management System provides interactive tools to allow for a 'manual' safety and acknowledgement message as well as medicinal product report generation and administration by a user via a web interface, called EVWEB.
FTA	Full Text Article
Individual Case Safety Report (ICSR)	An ICSR is an electronic report, which provides the most complete information related to an individual case at a certain point of time. An individual case is the information provided 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.
LiEMA	LiEMA is a reference management system that provides literature safety surveillance and reference management capabilities.
MedDRA	Medical Dictionary for Regulatory Activities
MLM	Medical Literature Monitoring
XML	eXtensible Markup Language

5. Instructions

General principles

All valid MLM ICSRs will be transmitted to EudraVigilance (EV) using the EVWEB application.

ICSRs and any follow-up received will be transmitted by 7 calendar days for serious ICSRs, and 21 calendar days non-serious ICSRs.

5.1. Processing of ICSRs

Step	Action
1. Login to EVWEB	Login to EVWEB by accessing URL https://eudravigilance-human.ema.europa.eu/#/ and select the account associated with EVWEB as per Multi-Factor Authentication (MFA) implemented by EMA. Enter the password associated with the account and click 'Sign in'. Approve the push notification received on your mobile phone through Microsoft Authenticator App. Once approved, EVWEB page will open up. Select the organisation 'MLMSERVICE – EMA MLM SERVICE' from the drop-down menu. After organisation is selected, click 'Submit'.

Step	Action
2. Main Menu	Select 'Create and Send ICSRs'. Click 'New' to create a new ICSR from scratch or click or click 'Import XML' to upload the XML generated from LiEMA into EVWEB. The Import window will open allowing you to navigate to, and select, the saved XML. If you are importing an XML, go to the relevant case in LiEMA and click 'Export XML' and save the exported XML in computer, then navigate to where you saved it and select it via the EVWEB Import window.
3. Tree Menu	Expand the tree menu by clicking the arrow next to the safety report identifier in the tree view to reveal the other sections of the ICSR. Headers highlighted in Red require completion before an ICSR can be transmitted or validated.
4. Batch Number and Batch Identifier	Enter the 'Batch number' and 'Batch receiver identifier'. **Batch number (N.1.2):** The Batch number must contain the MLM case number followed by the version number of the case. This should be unique for every ICSR. An initial case version number would be 00. A follow up case version number would be the subsequent number, e.g. 01, 02, 03. **Batch Sender Identifier (N.1.3) and Message sender identifier (N.2.r.2):** These both are automatically populated with 'EMA MLMSERVICE (MLMSERVICE)' after logging into EVWEB. **Message receiver identifier (N.2.r.3):** This should be populated with EudraVigilance-(EVHUMAN) after selecting it from the drop-down menu.
5. General notes before commencing data entry	The main section of the screen is where data entry takes place. Mandatory data fields are indicated on the right-hand side until the field is completed.  = Mandatory All entered values must have corresponding units, if provided in the article or by the reporter. Where a data field has been entered incorrectly, the text can be replaced by clicking on the field in question and then deleting the incorrect data. To remove 'rows' of data, select the row and click 'Remove sign' on the right side of the row.

Step	Action
	Rows of information can be duplicated in EVWEB where the information is largely the same and subsequently edited as appropriate. Where duplication of cases is required, use 'Copy' sign to create multiple cases that are related (i.e. originated from the same article) but appropriate individual data needs to be entered subsequently.  = Copy  = Remove
6. Safety report	Click '<safety report>' in the tree menu. 'Safety report' screen will be displayed. **Safety report identifier (C.1.1):** Copy and paste from the generated case ID. The Safety report ID should display as per convention 'Country Code-MLMSERVICE-YYYYMMDD-Doc ID-Drug ID-Number of cases'. After entering Safety report identifier, the value "<safety report>" in the tree menu will be replaced with the Safety report identifier. **Creation Date (C.1.2):** This field gets auto populated and is different for each ICSR. **Report Type (C.1.3):** Select the report type from the drop-down menu options, as appropriate. Select from the from the drop-down list. **First received date (C.1.4):** The date of receipt of the initial report (Day zero) will be date when all four criteria for a valid ICSR are met i.e., reporter, patient, suspect drug, reaction). This date will remain same in follow-up reports. **Last received date (C.1.5):** For initial reports, Last Received Date is same as 'First Received Date' (C.1.4). For follow-up reports, Last Received Date will be the date of latest follow-up received. Enter 'First received date' and 'Last received date' by clicking calendar icon. Click year displayed, then select the month (as appropriate) and select the required date. Date will be populated in the field. **Note:** By clicking 'Now', today's date will be populated. Clicking on year, month page will be displayed. **Additional document (C.1.6.1):** Select 'No' from the drop-down menu option. **Fulfil local criteria (C.1.7):** Auto selected as 'Yes' by default. Do not change this.

Step	Action
	Other case Identifier (C.1.9.1): Select 'Yes' or 'No' as appropriate. **Case identification number (C.1.8.1):** This data field contains an identifier for the ICSR that is unique. The value should be a concatenation of 6 segments separated by a dash/hyphen: 'Country Code-MLMSERVICE-YYYYMMDD-Doc ID-Drug ID-Number of cases'. Enter 'Case identification number' by copying and pasting generated case ID. For cases created by the MLM Service, 'Case identification number' is same as 'Safety report identifier (C.1.1)'. **First Sender (C.1.8.2):** This data field corresponds to the organization that assigned the worldwide case ID. Select 'Regulator' or 'Other' as appropriate. For cases created by the MLM Service, 'First sender' is always 'Other'. Expand the tree menu by clicking the arrow next to the safety report identifier in the tree view to reveal the other sections of the ICSR which are as mentioned below- **Linked report (C.1.10.r):** This data field captures 'Case identification number' of another ICSR that needs to be evaluated together with this ICSR. If there are multiple cases from the same literature article, 'Case identification number' for all other cases should be entered here. **Literature Reference(s)(C.4.r.1):** This data field corresponds to literature reference in Vancouver style Click '+' to add literature reference and enter literature reference (along with DOI; if available) after retrieving from LiEMA. **Note:** In the tree view, '0' indicates that there is no literature reference element in the safety report.
7. Patient	Navigate to tree view area and select 'Patient' and patient page will be displayed. Next to 'Patient' tab, the below mentioned icons will be visible:  (Add Death Section) - To add information related to patient's death i.e. death date, was autopsy performed and cause of death.  (Add Parent) - To add information related to parent-child report i.e. parent identification, birth date, age, last menstrual period, body weight, height, sex, past drug and medical history.

Step	Action
	Enter the patient details, as provided. For several fields in patient tab, you have the option to choose either of the below mentioned Null Flavor- • Masked • Unknown • Asked but unknown • Not asked Masked – This nullflavor to be used when privacy protection requires not to communicate particular information. Remember this nullflavor SHOULD NOT BE used on patient age and patient sex fields. **Initial (D.1):** This data field corresponds to the patient initials. It is important that this data field is populated; if known, to identify duplicates. It should only be populated when it is in conformance with national confidentiality laws and requirements. If it's the first version of the case and all information comes from the literature article, then patient initials can be entered. If it's a follow-up version of the case and patient initials are received from the author, then it SHOULD NOT BE entered. **Birth Date (D.2.1):** This data field corresponds to the patient's date of birth. **Note:** If this information is known by the sender but cannot be provided to the receiver due to national confidentiality laws, the null flavor 'Masked' should be selected. If it's first version of the case and all information comes from the literature article, then patient's date of birth can be entered. If it's a follow-up version of the case and patient's date of birth is received from the author, then it SHOULD NOT BE entered. **Onset age (D.2.2a):** This data field corresponds to the patient age at time of onset of reaction. **Onset age unit (D.2.2b):** This data field should be used to select the appropriate unit corresponding to the onset age (D.2.2a) from the drop-down menu options. **Weight (D.3):** This data field corresponds to the patient's weight (in kg).

Step	Action
	Height (D.4): This data field corresponds to the patient's height (in cm). **Note:** Units for patient's weight and height are not displayed and must be expressed in kilograms and centimetres respectively, as per E2B (R3) specifications. **Patient sex (D.5):** This data field corresponds to the patient's gender. Select patient sex as 'Male' or 'Female', as appropriate.
8. Drug	Navigate to tree view area, select 'Patient' section and expand patient section by clicking the arrows to the left of the section/subsection headers. Drug section will be displayed as a sub-section. **Note:** One drug section will already be visible to the user as it is a part of the 4 minimum elements of an ICH valid ICSR and hence, a safety report must contain at least one drug. To add more than one drug, click '+'. **Drug Name (G.k.2.2):** This data field corresponds to the name of the medicinal product as reported. Enter the name of the medicinal product as stated by the primary reporter. **Characterisation (G.k.1):** This data field corresponds to the characterisation of the drug role. Select the appropriate characterisation (drug role) as reported by the primary reporter by clicking on the drop-down menu options: • Suspect • Concomitant • Interacting • Drug Not Administered Select the drug role characterization as 'Suspect'. Scroll down the active area to see all the drug fields available on the drug page like cumulative dose and dose unit, gestation period and unit, action taken etc. **Note:** For some of the drug fields, click on the drop-down arrow to choose the appropriate option available. For example, click drop down arrow in action and select the action taken from the options mentioned below- • Drug withdrawn • Dose reduced • Dose increased

Step	Action
	• Dose not changed • Unknown • Not applicable **Active Substances (G.k.2.3.r.1):** This data field corresponds to the name of the active substance in the medicinal product. Click '+' present to the right of 'Active Substances' to create a new active substance within the drug section. Select '<*active substance*>' and enter the active substance in 'Substance name'. While entering the active substance, the system will provide a list of active substance to choose from and the user should select the most appropriate active substance. **Note:** To code MLM monitored active substances, please refer the most updated version of the 'Medical literature monitoring: active-substance and herbal-substance groups' list. **Dosages (G.k.4.r):** This data field corresponds to drug dosage and other associated relevant information. Click '+' present to the right of 'Dosages' to create a new drug dosage. **a) Dose (G.k.4.r.1a) and Dose Unit (G.k.4.r.1b):** This refers to the amount of dose administered to the patient. While entering the Dose unit, the system will provide a list of dose unit to choose from and the user should select the most appropriate dose unit. **b) Number of units in interval (G.k.4.r.2):** This refers to the time interval between each administered dose. **c) Dosage time interval unit (G.k.4.r.3):** This refers to the unit for the dosing time interval. This can be selected using the options available in the drop-down menu. Example: Hours, Days, Weeks Months, Years etc. **d) Start date (G.k.4.r.4):** This refers to the date and time when drug was administered. **e) End date (G.k.4.r.5):** This refers to the date and time when drug was last administered. **f) Batch Lot number (G.k.4.r.7):** For all suspect or interacting drugs, the Batch number is mandatory. Batch Lot number is rarely provided, hence; select the appropriate nullFlavor. **Note:** Unless explicitly asked from the author as a part of the follow-up, select 'Unknown'. **g) Dose form text (G.k.4.r.9.1):** This refers to free text description of the pharmaceutical dose form.

Step	Action
	h) Dose form (G.k.4.r.9.2b): This refers to pharmaceutical dose form. Both G.k.4.r.9.1 and G.k.4.r.9.2b can be entered but either of the two, should always be populated. While entering the dose form, the system will provide a list of dose form to choose from and the user should select the most appropriate dose form as per the priority order i.e. PDF>BDF>PFT. **Note:** CMTs should not be used. • PDF-Pharmaceutical Dose Form • PFT-Patient-Friendly Term • CDF-Combined Dose/Dosage Forms • BDF-Basic Dosage Form • CMT-Combined Mixed Terms If dose form does not match with any of the options available in Dose form, enter the reported term in 'Dose form text' and select 'Unknown (BDF)' in Dose form. If no information provided about the dose form in the source document, select the Nullflavor 'Unknown' in Dose form text and keep Dose form as blank. **i) Route of administration (G.k.4.r.10.2b):** This refers to route through which drug was administered**.** Select the appropriate route of administration from the available drop-down menu options. **Note:** If Route of Administration (G.k.4.r.10.2b) is not available, the data field 'Route of administration text (G.k.4.r.10.1)' should be used to enter the free text description of the route of administration. NullFlavor should never be used if route of administration is not provided. **Drug Additionals (G.k.10.r):** This data field corresponds to the additional information pertinent to the drug i.e. additional characteristics of the drug that is not covered in the sections above. **Drug Indications (G.k.7.r.1):** This data field corresponds to the drug indication as reported by the primary source. **Note**: To capture MedDRA LLT code for the drug indication, 'select a meddra item' from the available options in 'Indication(MedDRA) (G.k.7.r.2b)'

Step	Action
	To code more than one indication, use Copy symbol. **Drug Reactions (G.k.9.i):** This data field refers to the degree of suspected relatedness of the drug with a suspect role to each reaction(s) in Section E. **Note:** In spontaneous reports, for the purpose of reporting, there should be implied causality for each of the drug reaction. Navigate to tree view area, select drug for which drug reaction needs to be added. Expand drug section by clicking the arrows to the left of the section/subsection headers. <drug> section will be displayed as a sub-section. Click '+' to add a Drug Reaction. **a) Reaction (G.k.9.i.1):** This refers to the reaction(s) in Section E.I. which is being assessed. Select the reaction from the drop down. **b) Interval first time (G.k.9.i.3.1a):** This refers to time interval between beginning of suspect drug administration and start of reaction. **c) Interval last time (G.k.9.i.3.2a):** This refers to time interval between last dose of suspect drug administration and start of reaction. **d) Reaction recur readmin (G.k.9.i.4):** This refers to rechallenge information i.e., did reaction recur on re-administration. This data field indicates both, if the patient was re-challenged with the drug and if the outcome is known. Select the appropriate option from the drop-down menu options to complete the rechallenge information. **Note:** If no rechallenge was performed, select 'no-n/a (no re-challenge was done recurrence is not applicable)' from the drop-down options.
9. Reactions	Navigate to tree view area, select 'Reactions' section and expand reactions section by clicking the arrows to the left of the section/subsection headers. <reaction> section will be displayed as a sub-section. **Note:** One reaction section will already be visible to the user as it is a part of the 4 minimum elements of an ICH valid ICSR and hence, a safety report must contain at least one reaction. To add more than one reaction, click '+'. **Reaction text native language (E.i.1.1a):** This data field corresponds to the reaction reported by the primary source in native language. Enter the reaction as reported in the source and select 'Native language (E.i.1.1b)' as English.

Step	Action
	Reaction (MedDRA) (E.i.1.2b): This data field captures the MedDRA LLT most closely corresponding to the reaction as reported by the primary source. There is a default search mode selected as 'Begins". Enter MedDRA LLT and select the most appropriate from the available options. To change default search mode, select the options from the drop-down list menu. **Note:** In an exceptional circumstance, when a MedDRA term cannot be found, use clinical judgment to complete this data field with the best MedDRA approximation (Refer to MedDRA Term Selection: Points to Consider). **Seriousness criteria at reaction level (E.i.3.2):** Select the most appropriate seriousness criteria (E.i.3.2a - E.i.3.2f) from the available options. **Note:** Any reaction(s) for which MedDRA LLT corresponds to a MedDRA PT available on the latest version of the IME list, select 'Other medically important' criteria as 'Yes'. **Outcome (E.i.7):** This data field captures latest outcome of the reaction. Select the most appropriate outcome from the available drop-down menu options.
10. Patient Medical History	Navigate to tree view area, expand patient section by clicking the arrows to the left of the section/subsection headers. 'Patient Medical Histories' will be displayed as a sub-section. Click '+' to add a patient medical history. **Medical History (MedDRA) (D.7.1.r.1a and D.7.1.r.1b):** This refers to the relevant medical history and concurrent conditions (not including reaction). **Family history (D.7.1.r.6):** Select the check box if the medical condition captured in D.7.1.r is reported to be present in a family member(s). **Continuing (D.7.1.r.3):** Select the appropriate radio button based on the current clinical status of the medical condition (captured in D.7.1.r.1b) at the time of the report. • **Yes:** Medical condition is still ongoing • **No:** Medical condition is not ongoing **Note:** Select Nullflavor as 'Unknown' if clinical Status of medical condition is not provided.

Step	Action
11. Test	Navigate to tree view area, expand patient section by clicking the arrows to the left of the section/subsection headers. 'Tests' will be displayed as a sub-section. Click '+' to add a test. **Test name (F.r.2.1):** This refers to tests and procedures performed to diagnose or confirm the reaction. Enter the test reported by the primary source. **Test Name MedDRA (F.r.2.2a and F.r.2.2b):** This data field captures the MedDRA LLT most closely corresponding to the test name (F.r.2.1). **Test result code (F.r.3.1):** Select the most appropriate code from the available drop-down menu options- Positive Negative Borderline Inconclusive **Quantity operator:** This data field is used when test result value is provided as a number and test result value and unit is known. **Test result value (F.r.3.2) and Test result unit (F.r.3.3):** This data field is used to capture the value and unit of the test result respectively. **Result unstructured data (F.r.3.4):** This data field is used to enter any test value or result that cannot be entered into the structured fields mentioned above.
12. Study Information	Navigate to tree view area, click '+' sign and expand 'Studies' to add study information under <study>. **Study Identification:** **Study Name (C.5.2):** This data field should be populated with the study name as registered in the jurisdiction where the ICSR/SUSAR is reported. In practice, enter the study name as provided in the article or follow-up, if applicable. If the study name is not specified in the article, enter study name as 'NOT SPECIFIED' for other studies. **Sponsor Study Number (C.5.3):** This data field should be completed only if the study number has been provided in the article or through follow-up.

Step	Action
	Study Type where Reaction(s)/Event(s) were observed (C.5.4): This field captures the type of study associated with ICSR/SUSAR being reported.
13. Case Summary	**Case Summary (H.1):** This section must be populated with case narrative including clinical course, therapeutic measures, outcome, and additional relevant information. This includes description of the case, including the words or short phrases used by the reporter.
14. Reporter Information	Navigate to tree view area, click arrow next to 'Reporters' to open the list of reporters and <reporter> will be displayed as a sub section. **Note:** One reporter will already be visible to the user as it is a part of the 4 minimum elements of an ICH valid ICSR and hence, a safety report must contain at least one reporter. **Given Name (C.2.r.1.2) and Family Name (C.2.r.1.3):** This data field is used to enter the first or correspondence author's given name and family name in the respective fields. **Reporter qualification (C.2.r.2):** This data field is used to populate the qualification of the primary source by selecting the appropriate qualification from the available drop-down menu options. **Country (C.2.r.3):** This is as per reporter's country code ISO 3166-1 (alpha 2) and is used to enter the country of the primary source. **Province state (C.2.r.2.5):** For Spanish and Italian cases, after selecting country Spain or Italy (as needed), this data field will be displayed. This data field is used to enter reporter's state or province. **Primary Source for Regulatory Purposes (C.2.r.5):** This data field is used to identify which primary source to be used for regulatory purposes. Select the check box next to 'Primary Source for Regulatory Purposes'. **Note:** Reporter qualification, Country, Province state (when applicable) and Primary Source for Regulatory Purposes are mandatory fields. Furthermore, if there are multiple authors, it should always be checked for correspondence author. All other fields in Reporter section can be populated based on the information from the FTA/Abstract.
15. Validation and XML Export	Click 'Validate' to validate XML. **Note:** 'Validate & Send' should not be used as it is used to transmit the case in EVWEB.

Step	Action
	While validating, if there are any error(s) in ICSR, a message on the screen will provide detailed information of the errors and all errors should be rectified before validating the case again. Click on 'Export XML' to save a copy of the ICSR. Once your file is ready for export, the message 'Download File. Your file is ready' is displayed. Click 'Download'. A dialogue box will open that will allow you to save the file in the document management system.
16. Medical Review	Medical reviewer reviews and accesses the XML against the source information (literature or follow-up information) saved in document management system and requests updates to the case, if necessary. Medical reviewer will update the relevant sections in LiEMA and once medical review is complete, select 'Decision' as 'MR Complete' in LiEMA and click 'Submit'.
17. Pre-submission check for the follow-up case	Pre submission check for the cases where the patient identifying details are included in the follow-up cases: Every case report must be checked in EVWEB and MLM_Extract-R3 tool (MLM crucial field check) for any of the below mentioned patient identifying details before submission into EudraVigilance. If a case report has more than one version, the earlier version must also be checked for the below identifiable information (other than the original article as it has been published and is in the public domain). Patient detail: 1) Patients name/Initial 2) Medical record number 3) Specialist record number 4) Hospital record number 5) Investigation number 6) Birth date This process specifically applies to case reports where the follow-up version has been created post receipt of additional information from the author. If any of the above patient identification details were added into the case report, they must be removed immediately before transmitting the ICSR in the EudraVigilance. If a case report with above mentioned patient's identification details gets transmitted inadvertently, then Project Lead/Project Manager must be informed immediately. If identifiable information is identified, then the below escalation process must be followed:

Step	Action
	Project Lead/Project Manager must bring this to the notice of EMA Program Manager immediately with the local report number and details of the fields with the patient identification details. MLM team must nullify the ICSR immediately while ensuring that the patient's identifiers are removed from the nullified ICSR. MLM team then must instigate corrective measures as per the internal policy IT-03 after informing EMA.
18. Submit ICSRs	To send the reports in EVWEB, click 'Create and send ICSRs' tab, then 'Import XML'. Browse and upload XML of the ICSR. Once the XML is uploaded, amend the XML, if required. **Batch Sender Identifier (N.1.3):** This data field refers to the origin of the ICSR reports (creator of ICH ICSR batch file), e.g. company name or regulatory authority. If you are correctly logged in as an MLM Service user, then it should state 'EMA MLMSERVICE (MLMSERVICE)' **Batch Receiver Identifier (N.1.4):** This data field refers to the intended destination of the ICSR batch file. If you are correctly logged in as an MLM Service user, then ICSR must be sent to 'EudraVigilance (EVHUMAN)'. Prior to transmitting the ICSR, click 'Validate'. If the validation step does not report any error, then the ICSR is ready to be transmitted to EudraVigilance. Click on 'Validate & Send'. Take a screenshot (showing the intended recipients) and save it in the document management system.
19. Acknowledgements	The acknowledgements must be checked once all the ICSRs have been transmitted in EudraVigilance. If EudraVigilance is down, check for acknowledgements on the next business day. While reconciling daily submissions, first search for ICSRs with errors. Count should be = 0. Then, search for 'Correct' ICSR. If n ICSRs = n ICSRs from LiEMA, stop. If n ICSRs < n ICSRs from LiEMA, check reports with warnings. Verify that the combined totals are correct and for ICSR 'with warnings' check the ACK to identify the warning. Check whether the ICSR requires immediate changes or if the changes can be done in the future.

Step	Action
	To retrieve message acknowledgements in EVWEB, navigate 'ICSRs' tab, click on '+More Criteria'. Under '+More Criteria' select 'sender Identifier' as 'MLM Service' and select 'Transmission Date' as appropriate. Run the search to retrieve the ICSR(s). Click on "Safety report ack" to see the ACK(s) retrieved for each ICSR(s). **Note:** An acknowledgment is received from each message recipient (for all ICSRs transmitted since 22/11/2017, the only receiver will be EVHUMAN). Review each acknowledgment and save it in document management system for each ICSR. Access LiEMA and update that acknowledgement received date. If Application Acknowledgment Error/Application Acknowledgment Reject has been received, revert to the ICSR to ascertain the root cause. Correct the ICSR and resubmit. If the reason for Application Acknowledgment Error/Application Acknowledgment Reject is not apparent, immediately escalate to the EMA MLM coordinators for resolution.

6. Reference documents

Not Applicable

7. Annexes

7.1. Annex 1: Spanish INE codes

Spanish Codes.xls

7.2. Annex 2: Case Narrative Template

"This case was detected in the medical literature by the EMA MLM Service from (insert article reference in Vancouver style) on (insert date of search or receipt of FTA if appropriate).

This spontaneous case was reported in the medical literature by a <physician> from <enter Country> and concerns a <enter age/ gender if available> patient who experienced a (serious) adverse reaction of <enter reaction terms> associated with <enter suspect active substance(s)>

Enter the narrative as per the flow of the FTA or Abstract. It should be grammatically correct and the text should be in past tense.

<If follow-up or FTA has been requested> Follow-up has been requested.