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

Processing and submitting ICSRs in EVWEB

Preamble

This WIN governs the activities of contractors working for the European Medicines Agency providing the Medical Literature Monitoring service. The WIN was created by the contractors and approved by the Agency.

1. Changes since last revision

New WIN.

2. Records

Not applicable.

3. Definitions

Term	Definition
DMTT	Literature Monitoring Tracking Tool – a subset of the Data Management Tracking Tool used by the contractor and the EMA to record & monitor work on EV data
EEA	European Economic Area
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 EMEA to manage the electronic data exchange of Individual Case Safety Reports (ICSRs) and to support the EU pharmacovigilance activities at Community level.
EV	EudraVigilance
FTA	Full text article

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Term	Definition
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.
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Affairs
MLM	Medical Literature Monitoring
NCA	National Competent Authority

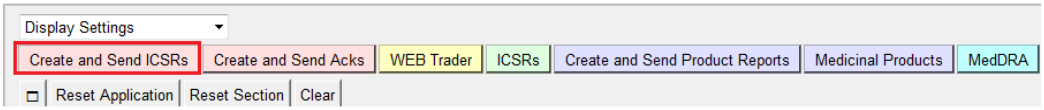
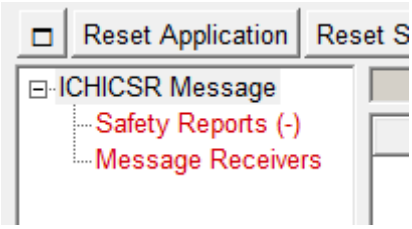
4. Instructions

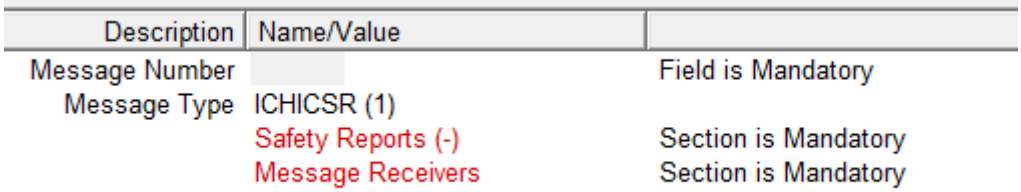
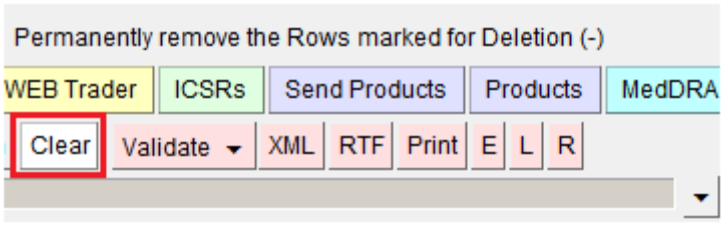
General principles

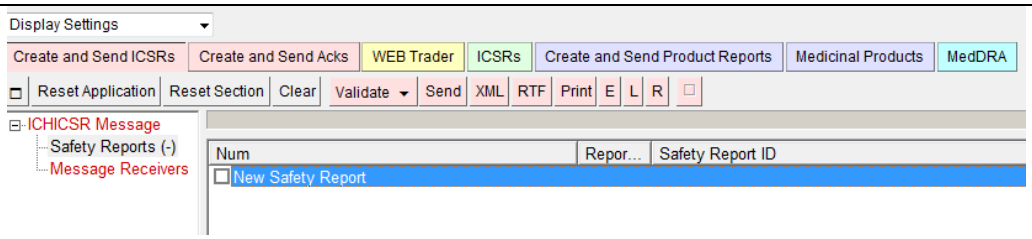
All valid MLM ICSRs will be submitted in EudraVigilance using the EVWEB application.

ICSRs and any follow-up received will be submitted by day 7 for serious ICSRs, and by day 21 day for non-serious ICSRs.

4.1. Processing of ICSRs

Step	Action
1. Login	Log into EVWEB by going to URL: https://eudravigilance.ema.europa.eu/X/?6 & enter username & password when prompted
2. Main menu	To create and send an ICSR, select 'Create and Send ICSR' 
3. Tree menu	On the left hand side of the screen is a tree menu. Headers highlighted in Red require completion before an ICSR can be transmitted or validated 
4. General notes before commencing data	The main section of the screen is where data entry occurs. Click on the data field and then press 'enter' in order to type in the highlighted field.

entry	 Mandatory data elements are indicated on the right hand side until the field is completed. A description of the field is shown at the bottom of the screen when the user selects a data element. 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, pressing 'enter', and then deleting the incorrect data. To remove 'rows' of data, mark it as (-), and then selecting 'Clear' from the menu options;  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, the duplicate function can be used to create multiple cases that are related (i.e. originate from the same article) with appropriate individual data subsequently entered.
5. Safety report	Click on safety report in Tree menu  Select the 'New safety reports' in active area



5a.

Complete all mandatory A.1 Data elements as applicable

Description	Name/Value	
Report Version		
Safety Report ID		Field is Mandatory
Primary Source Country		Field is Mandatory
Occurrence Country		
Date		Field is Mandatory
Report Type		Field is Mandatory
Serious ?		
Results in death ?		
Life Threatening ?		
Caused/Prolonged Hospitalization ?		
Disabling / Incapacitating ?		
Congenital Anomaly ?		
Other medically important condition ?		
Receive Date		Field is Mandatory
Receipt Date		Field is Mandatory
Additional Documents ?		
Document List		
Fulfill Expedited Criteria ?		
Case Type		Field is Mandatory
Case Number		Field is Mandatory
Duplicate		
Report Nullification		
Nullification Reason		
Medically Confirmed ?		

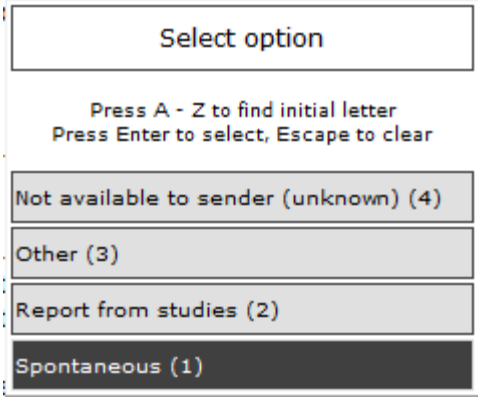
Note:

Report version: Enter ‘00’ for initial cases.

A.1.0.1 Safety Report ID – Copy and pasted from the generated case ID in DMTT.

A.1.3b Transmission date – This should be left blank in initial data entry as it is to be completed with the date the case is transmitted in EVWEB. A full precision date should be used (i.e., day, month, year).

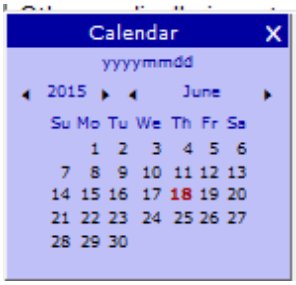
A.1.4 Report Type – Select the appropriate option from the drop down:



A.1.6b Receive date – The date of receipt of the initial report (i.e. day zero where four minimum criteria for a valid ICSR – reporter, patient, product, reaction). This date will remain the same in follow-up reports.

Receive Date Field is Mandatory

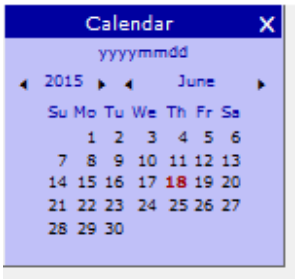
Enter and select the date:



A.1.7b Receipt date – For initial reports it is the same date as 'Receive date' (**A.1.6b**). For follow-up reports it is the date of latest follow-up received date

Receipt Date Field is Mandatory

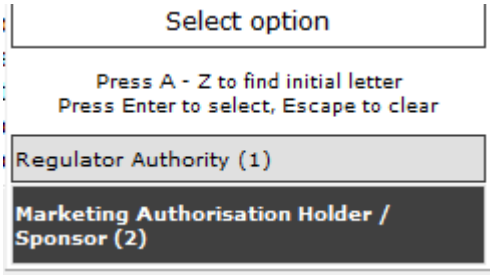
Eneter and select the date:



Case type: Enter and select the MAH.

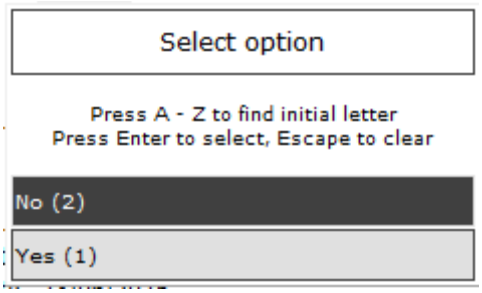
Case Type Field is Mandatory

Select Marketing Authorisation Holder / Sponsor form drop down:

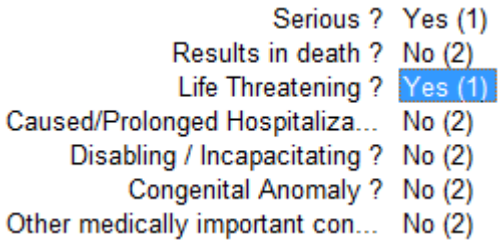


A.1.10.2 Case number – should be the same as entered in '**A.1.0.1** Safety report Id' and should be copied and pasted.

A.1.5.1 Serious – Select 'Yes' if case is serious and 'No' if case is non-serious from drop down.

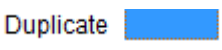


A.1.5.2 Seriousness criteria – At least one of the data elements should be populated with the value 'yes' for each serious ICSR. Leave all reasons that are not populated blank.

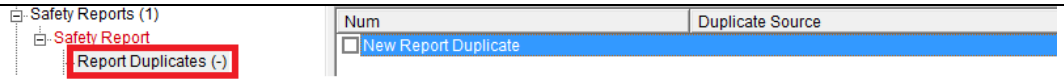


A.1.11 Duplicate

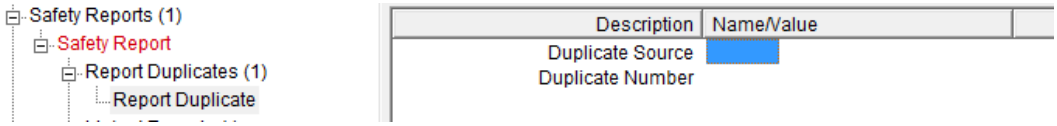
Enter 'Yes', in case of Duplicate report information is present.



Select the 'Report Duplicates' (A.1.11) section in tree menu and Select 'New Report Duplicate' in active area



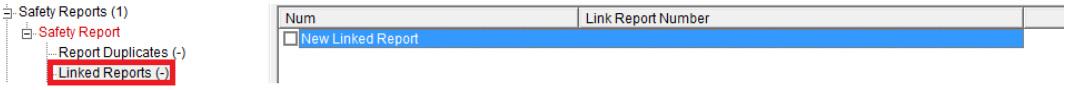
Enter the related information in respective sections Duplicte socurce (A.1.11.1) and Duplicate number information (A.1.11.2)



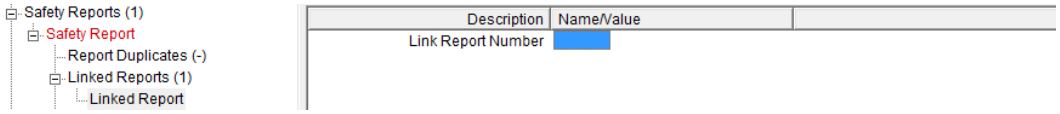
A.1.12 Linked report

Where multiple ICSRs are identified from the same literature article, all ICSRs should be cross referenced in accordance with GVP Module VI, Table VI.3. If there are more than three ICSRs associated with one article, then only the first case should be cross-referenced to all other ICSRs, and all ICSRs should only be referenced to the first case.

Select the 'linked reports' (A.1.12) section in tree menu and select the 'new linked report' in active area.

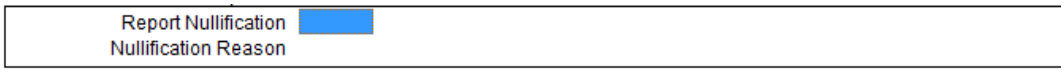


Enter the linked report number in ICH E2B format.



A.1.13 Report Nullification

Enter 'Yes' in Report nullification (A.1.13) section and 'reason for nullify' in Nullification reason (A.1.13.1) section in accordance with GVP Module VI Appendix V Table VI.12, in case nullification is required.

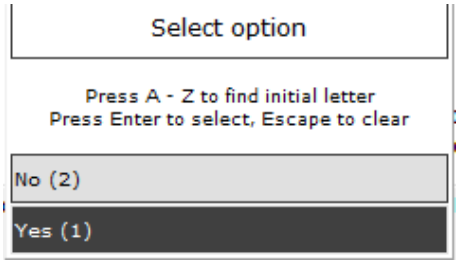
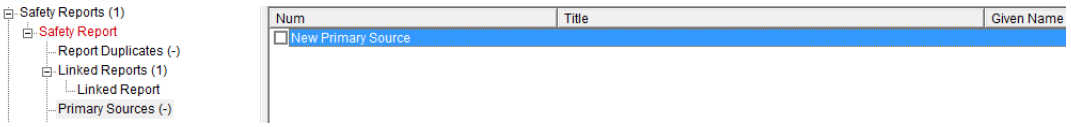


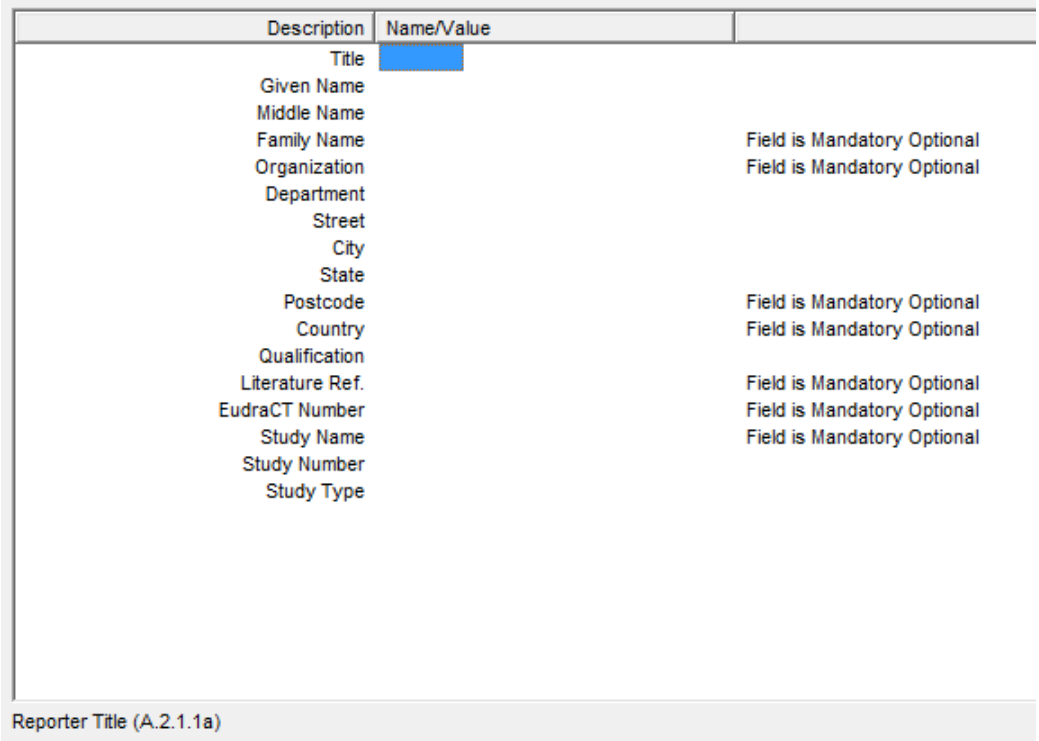
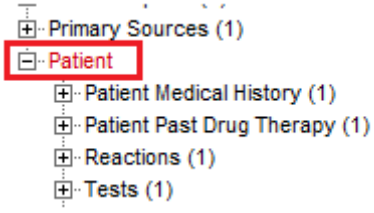
NOTE: Nullification is final and cannot be reversed. If required, request confirmation from EMA MLM co-ordinators.

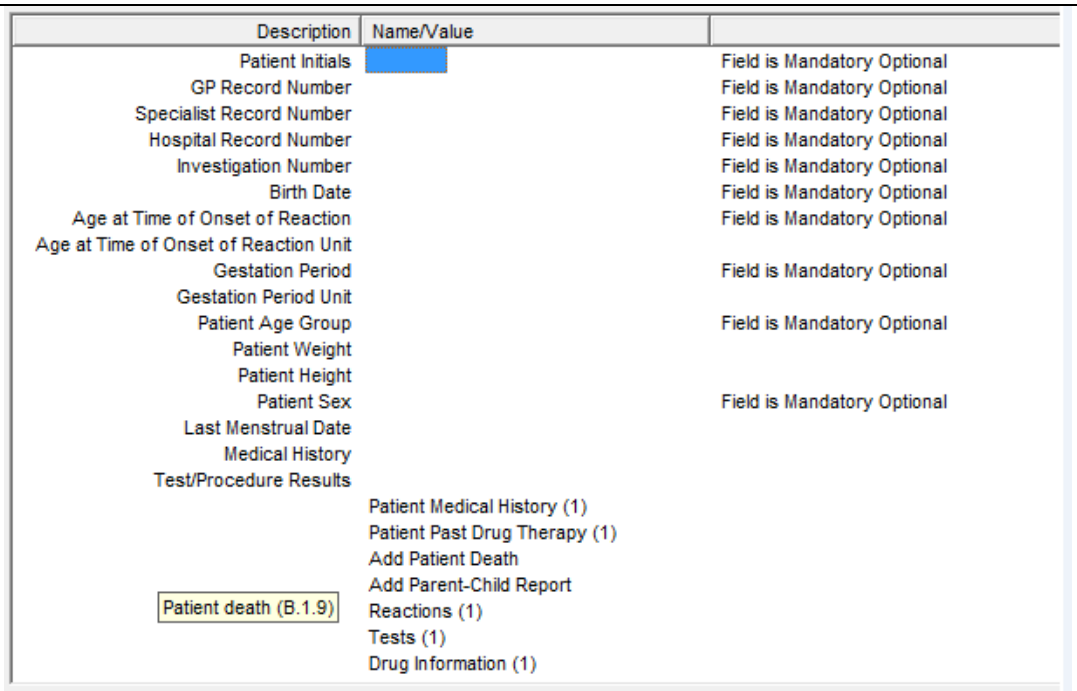
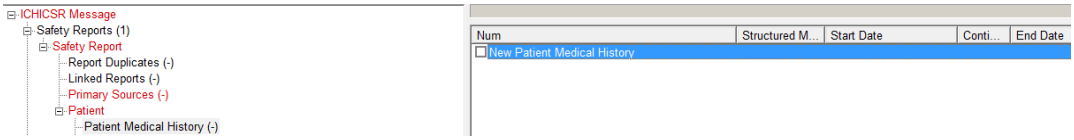
A.1.14 Medically Confirmed

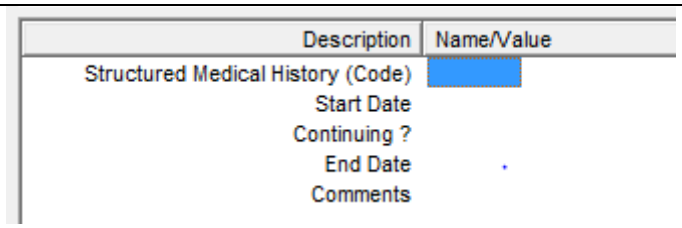
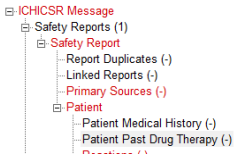
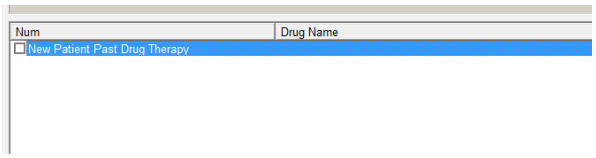
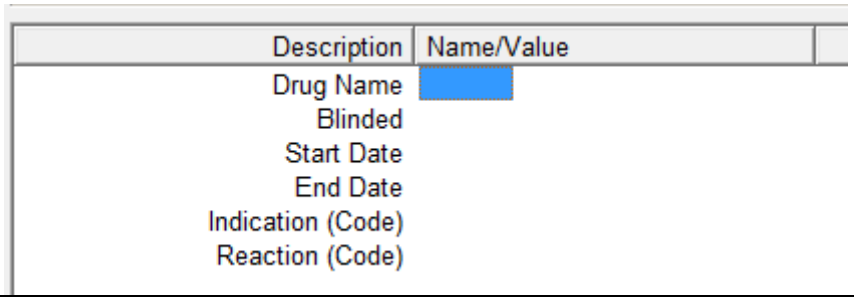
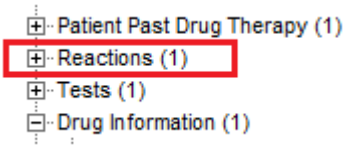
Should only be populated if the initial report was reported by a non-healthcare professional. The following conventions apply;

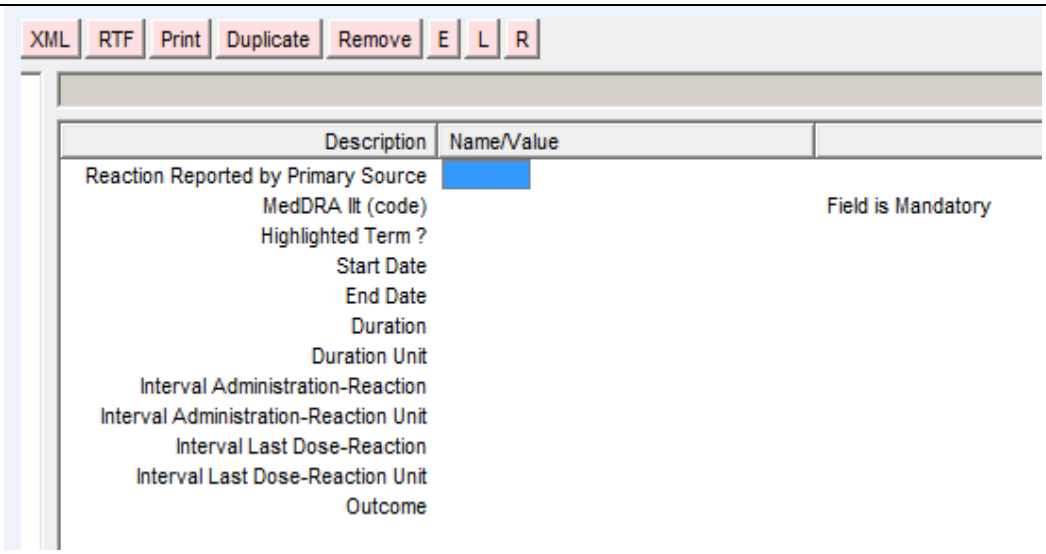
- Assume literature is from a healthcare provider based on journal title (normally assume physician unless e.g. Journal of Pharmacy).
- Leave 'blank', if the initial case reporter is Physician / OHCP / Pharmacist.
- Leave 'blank', if the initial case reporter is Physician / OHCP / Pharmacist and the follow up reported from Physician / OHCP / Pharmacist.
- Enter 'No', if the initial case reporter is Consumer / Lawyer / Non-HCP.
- Enter 'Yes', if Initial reporter is Consumer / Lawyer / Non-HCP and follow-up received from Physician / OHCP / Pharmacist and confirm that the event is

	related to Suspect drug. 
6. Primary source	Select “Primary Source” (A.2.1) section from the tree area  Select the ‘New Primary Source’ in active area. 

	Complete all mandatory A.2 Data elements as applicable  **A.2.1.4** Qualification - to be included for all primary sources entered (at least 1 of the data fields required) **Note:** Cases originating from Spain require reporter state and postcode (seeAnnex 1). **A.2.2** Literature Ref. – copy and paste in Vancouver style from DMTT. Enter only the lead author.
7. Sender	Leave this blank.
8. Patient	Select “Patient” from the tree-view menu 
8a.	Complete all mandatory B.1 Data elements as applicable

	 **At least a the definite existence of a patient would be required to enter in this section.** **B.1.1** Patient Initials – if unknown or not provided leave BLANK, except for when the need is to differentiate ICSRs where multiple ICSRs are retrieved from the same article (i.e. PT1, PT2, PT3 etc.) When performing follow-up, if the initals are provided enter 'PRIVACY', **B.1.2.3** Patient Age Group – Where patient age is known, this field does not require completion.
9. Medical history	Select 'Patient Medical History' from the tree-view menu 
9a.	Enter the all the information in related fields, if reported in article. Use lookup for MedDRA LLT to code the term. For information that does not code in MedDRA, use free text field

	
10. Past drug therapy	Select 'Past drug therapy' (B.1.8) from the tree-view menu.   Enter the all the information in related fields, if reported in article. Use lookup for MedDRA LLT to code the terms under Indication and reaction fields. Use free text field for information that does not code in MedDRA or for example can be attribute to a class of drugs instead of individual active substances 
11. Reaction	Select "Reaction" from the tree menu 
11a.	Complete all mandatory "B.2" Data elements as applicable



B.2 Reaction reported by primary source – enter term as reported if not exact MedDRA term match.

B.2.i.1.b MedDRA llt (code) - Use lookup for MedDRA LLT to code the term.

Only enter the reactions reported in full accordance with the latest MedDRA term selection points to consider document.

Typical symptoms associated with the reactions should only be entered in the narrative summary and not coded. Atypical symptoms can be coded if deemed necessary by the physician.

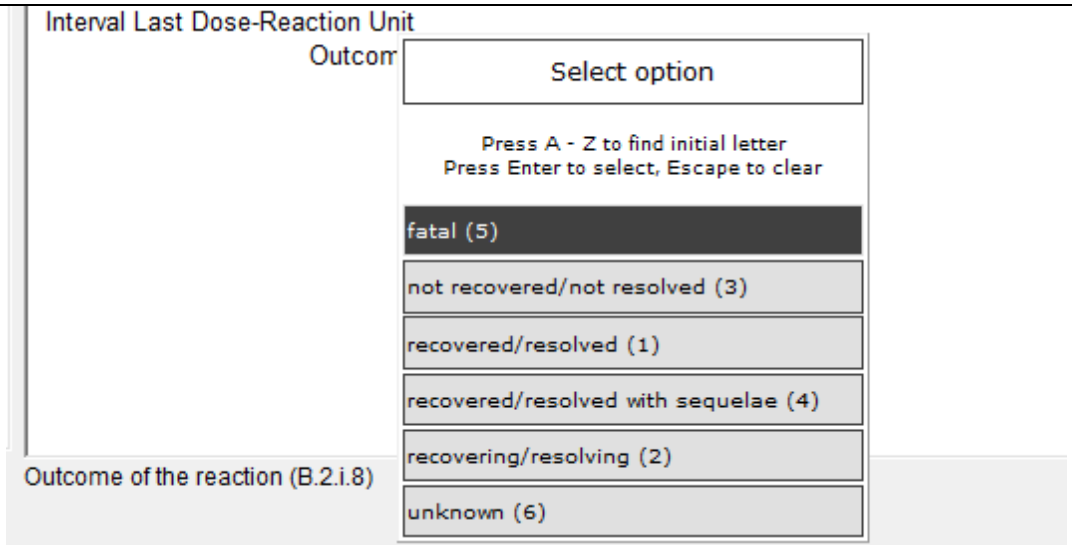
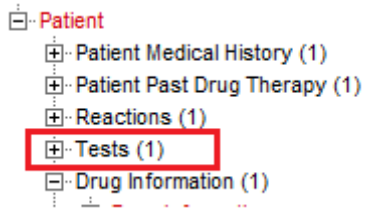
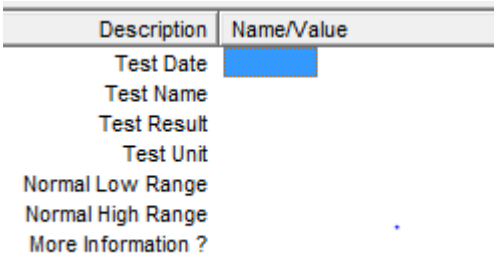
If only a series of reactions is listed which is indicative of a diagnosis, do not enter the presumed diagnosis and code all reactions.

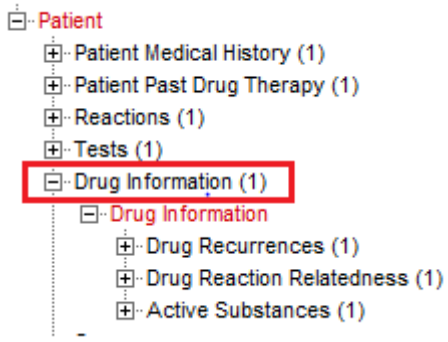
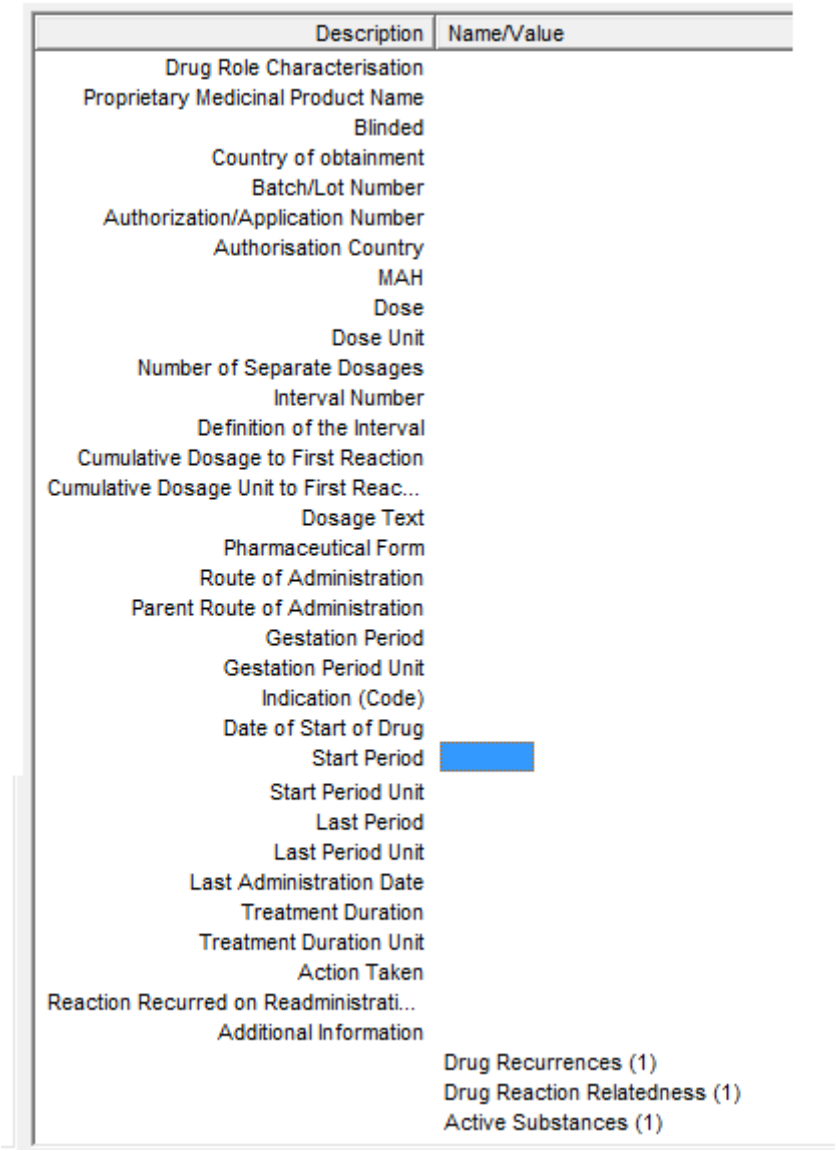
If the symptoms are related to diagnosis, only enter the diagnosis in reaction section (B.2.i.1.b) and code it in MedDRA.

If only symptoms are provided in article, enter all the symptoms in reaction section (B.2.i.1.b) and code it with MedDRA.

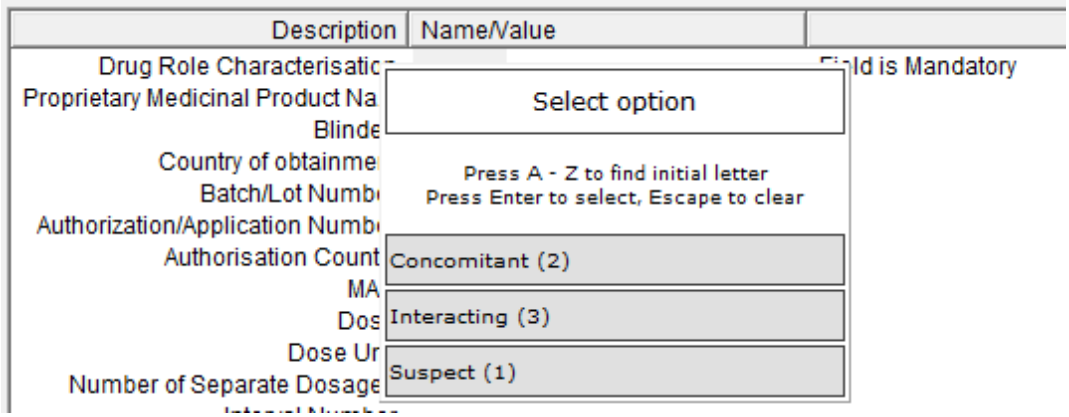
Outcome (B.2.i.8):

Select ‘outcome’ from drop down menu:

	 Where death is <u>unrelated</u> to the reported reaction, ensure the following data fields are in agreement **B.1.9** Patient death section should be completed. **B.2.i.8** Outcome – Fatal is NOT selected **A.1.5.2** (Seriousness = yes) Results in Death? – Select 'no'
12. Structured test	Select "Test" (B.3) from the tree-view menu  Enter the all the information in related fields, if reported in article. Use lookup for MedDRA LLT to code the terms under Indication and reaction fields.  Where necessary, use the duplicate functionality for test results repeated several times, ensuring the date and test results are changed appropriately. Use free text field for test information that does not code in MedDRA
13. Drug Information	Select "Drug Information" from the tree menu

<table>
<tr><td></td><td> 
</td></tr>
<tr><td>13a.</td><td>Complete all mandatory “B.4” Data elements as applicable
 

B.4.k.1 Drug role characterisation – Select from drop down menu, at least one drug should be characterised as (1) Suspect or (2) concomitant (3) or Interacting from drop down.</td></tr>
</table>



B.4.k.2.1 Proprietary medicinal product name field- Enter the proprietary medicinal product “brand” name if known.

B.4.k.2.2 Active substances (Subfolder of main tree) – Enter substance name in this mandatory field for every medicinal substance.

B.4.k.5 Structured Dosage Information: Enter the dosage information in related fields (e.g., 2 mg three times a day for five days)

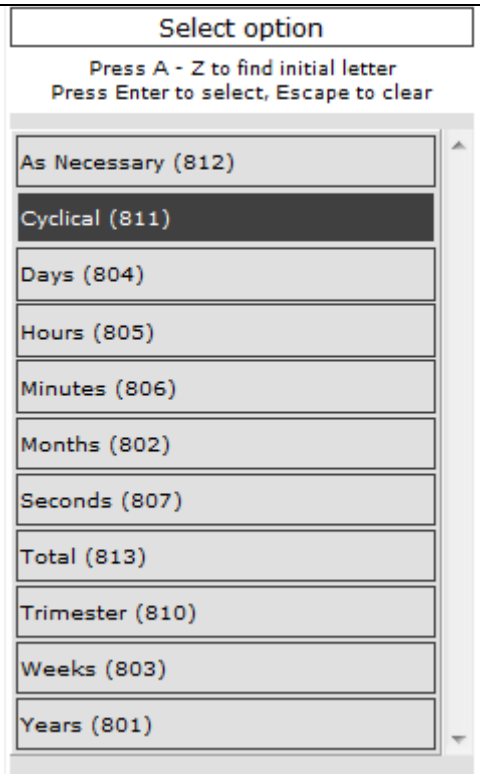
B.4.k.5.1 dose (number) 2

B.4.k.5.2 dose (unit) mg

B.4.k.5.3 number of separate dosages 3

B.4.k.5.4 number of units in the interval 1

B.4.k.5.5 definition of the interval unit day. Select the option from drop down.



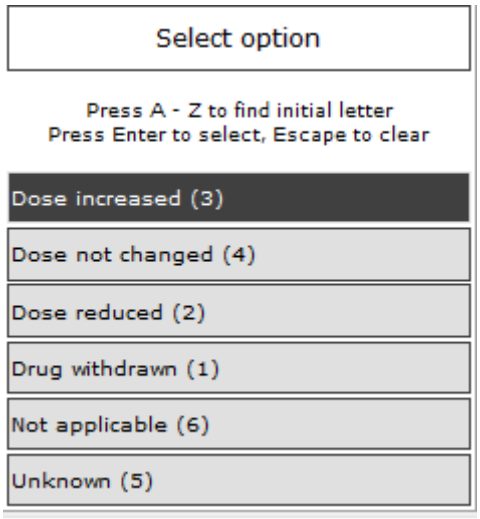
B.4.k.7 Pharmaceutical Form – Where entered, this should conform to latest version of the European Pharmacopoeia Dosage Forms List.

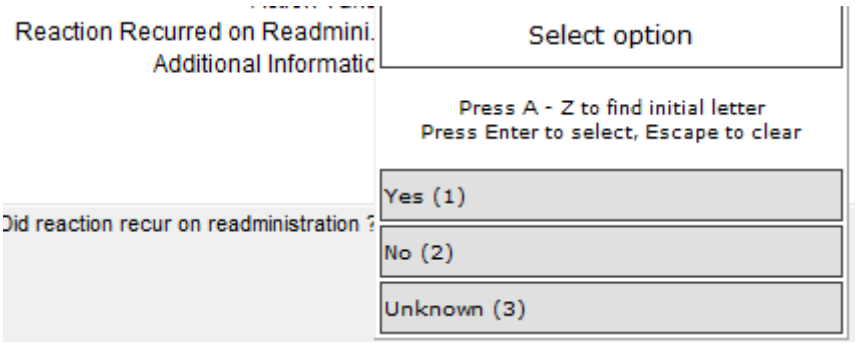
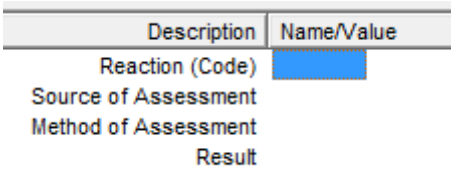
B.4.k.12b Date of start of drug – Where multiple date ranges exist, enter dates most significant to the date of the earliest reaction that is being reported.

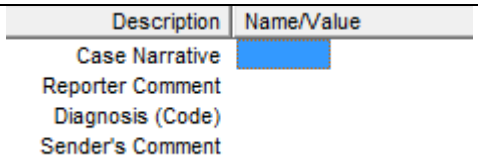
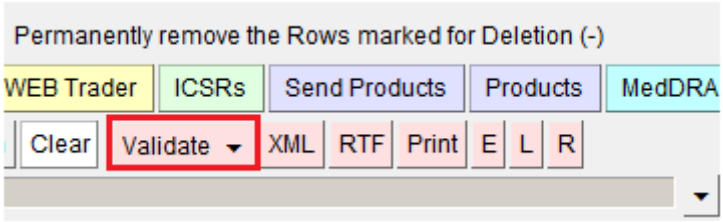
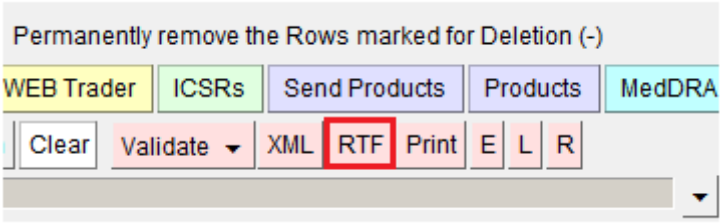
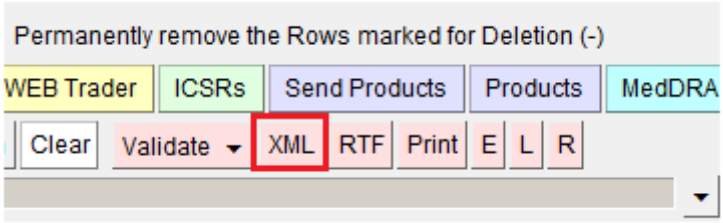
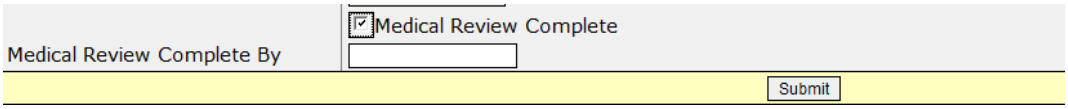
B.4.k.14b Last administration date – Where multiple date ranges exist, enter date corresponding to the final administration date.

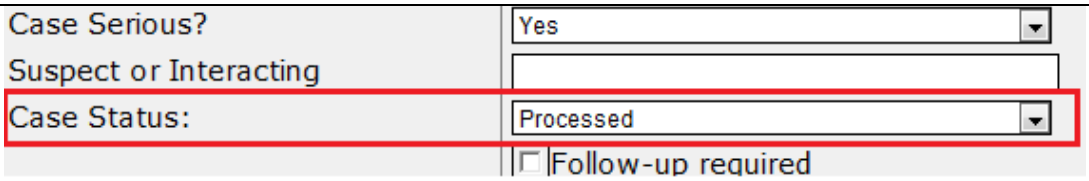
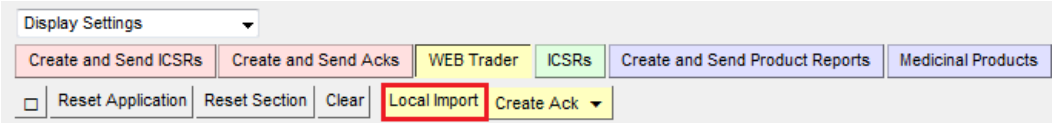
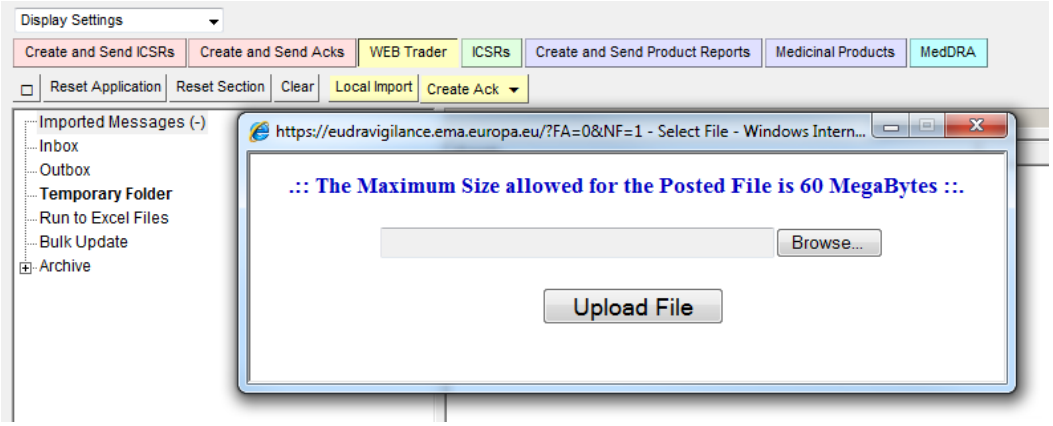
B.4.k.16 Action taken – Action taken with suspect drug as a result of the reaction.

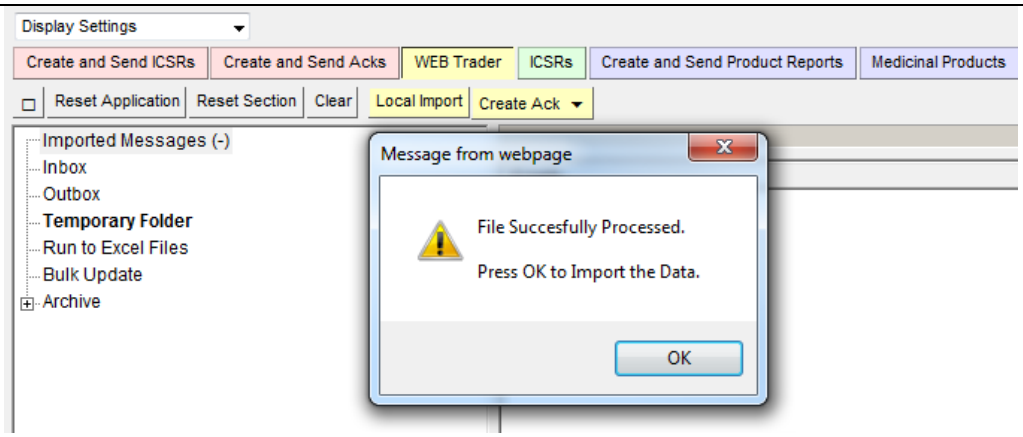
Select the suitable option from drop down.



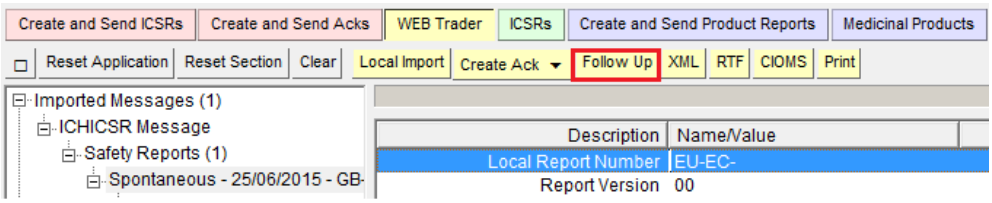
	"Not applicable" should be used in circumstances such as if the patient died or the treatment had been completed prior to reaction/event. **B.4.k.17.1** Reaction recurred on re-administration? = Drug re-challenge Select the option from drop down.  Unknown indicates that a re-challenge was done but it is not known if the event recurred. This segment should not be completed if it is unknown whether a re-challenge was done. **B.4.k.18** Drug reaction relatedness – In most cases, you would not need to enter drug-reaction relatedness. If you do, enter records for the reporter, for each reported reaction taking into account the following criteria for relatedness assessments. • For spontaneous cases with assumed causality, there is no need to provide a drug-reaction relatedness, except where specifically stated by the author(s) in the literature article • For cases where not all reactions are related to all drugs (e.g. 2 drugs, 2 reactions, drug 1 associated with both, drug 2 only associated with the 1st reaction), provide all relevant relatedness sections as stated by the author(s) in the literature article • For cases from non-interventional studies: always provide relatedness (even if not provided by the primary author)  **B.4.k.18.4** Result – For all MLM Initial cases, the minimum is 'possible'
14. Summary	Select 'Summary' from the tree-view menu

	 **B.5.1** Case narrative – Copy and paste MLM ICSR narrative into this section. Character limit is 20,000. Use the Annex 2, as a template and complete in MS Word, including performing spell check, before copying and pasting. Avoid entering special characters
15. Validate	Select 'Validate' to ensure that the entered data fields meet the validation criteria within the EVWEB tool.  Select 'ISCR' from the drop-down menu. If an error is identified, correct the issue in the appropriate data entry screens.
16. Generate RTF	Create the RTF file and save accordingly on the Shared Drive. 
17. Generate XML	Create the XML file and save accordingly on the SharePoint site. 
18. Medical Review	The Physician accesses the RTF and reviews against the source information saved in DMTT (literature or follow-up information), and requests updates to the case as necessary. Confirm medical review in the DMTT by ticking the medical review box and enter initials.  Once medical review is complete in DMTT. Update case status to 'processed' and submit in DMTT.

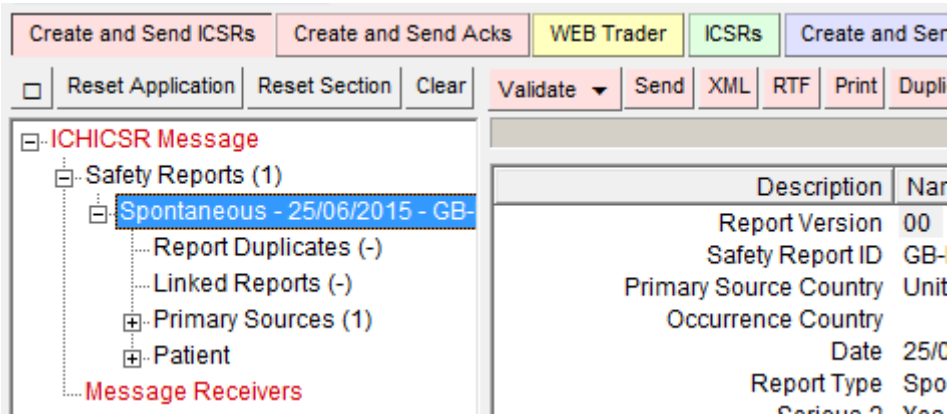
	
19. Message No.	The “Message Number” is a unique tracking number assigned to the ICSR message by the report generating database, or where manual, the responsible MLM analyst, prior to submission of an ICSR. For manually assigned message numbers, the following format is followed: Format = DMTT ID (version number in brackets) **Note**. No two ICSRs (or versions of an ICSR) should have the same message number.
20. Submit ICSRs	To send the reports in EVWEB, select WEB trader > local import (xml)> browse and load XML for ICSR.   



Once the Xml is uploaded in web trader, select the follow-up.

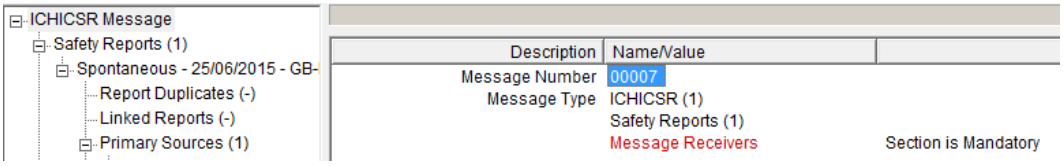


ICSR would shift in to create and sent ICSRs Section to amend if require.



The Message number (M.1.4) would be the number as allocated by DMTT and Message type (M.1.1) would be ICHICSR for all literature case.

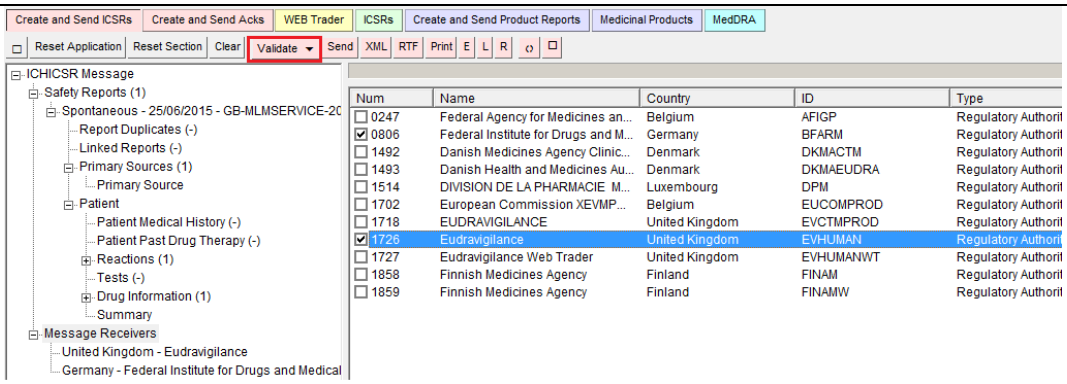
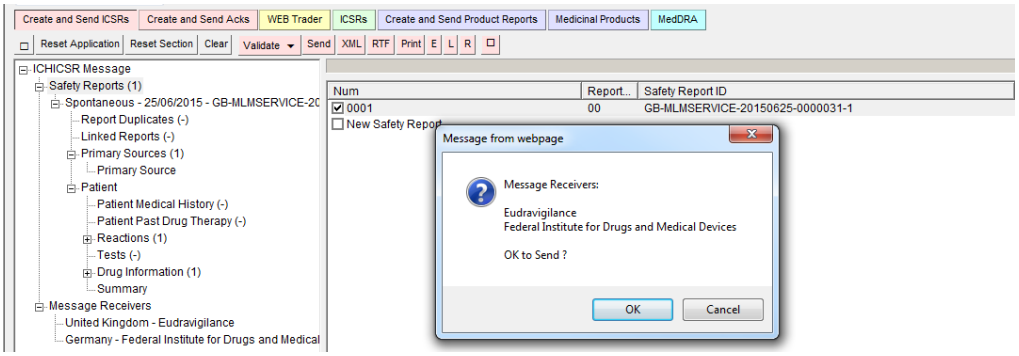
Ensure the transmission date is entered.

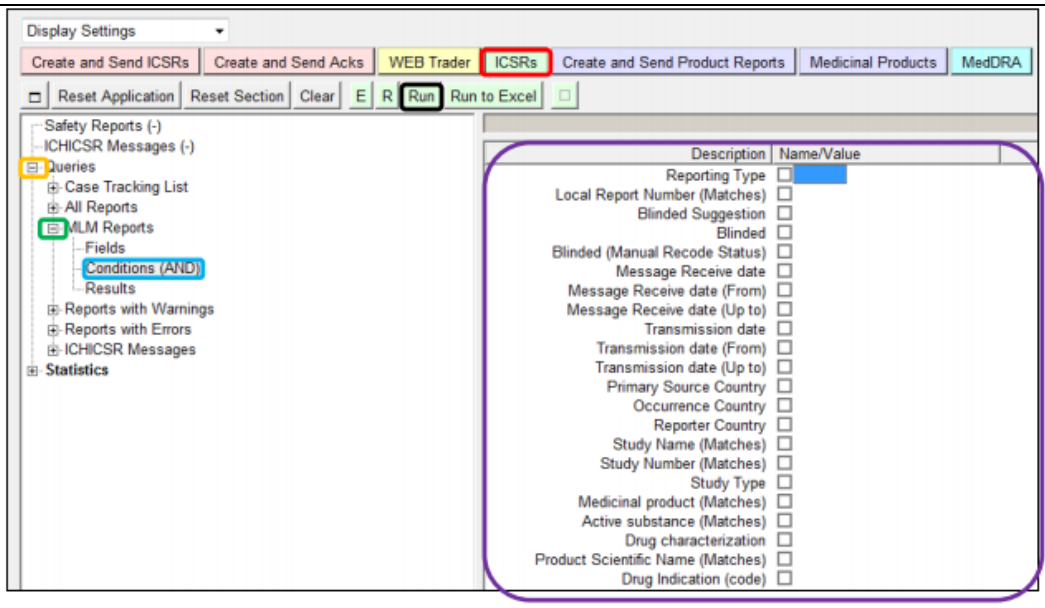
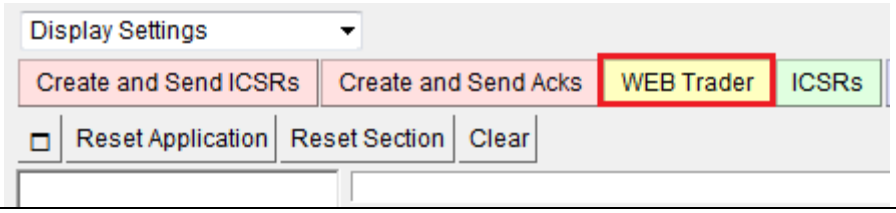


Select the Message Receivers> Message Receivers> Regulatory Authority.

Select all relevant NCAs (EV plus NCA where necessary) to which the case has to be sent and validate.

Prior to sending the case, select Validate and select ICHICSR. If the validation step does not report any error, the case is ready to be submitted to the selected NCAs.

	 Save a copy of the XML in the case folder on the shared drive and select send. A pop-up opens with the NCAs that have been selected. Click OK and a webpage dialog box opens. Click OK and a summary of the case as well as the authorities the case was sent to appear.  Save a text copy of the screen that appears showing the intended recipients in share drive.
21. Acknowledgements in WEB Trader	The acknowledgements should be checked every business day for cases submitted. Access the DMTT and run query for ICSR submission for case submitted, ack not received. To retrieve message acknowledgements in EVWEB, navigate to the menu and select 'ICSRs' Navigate to 'Queries' and click on '+' Click on '+' on MLM Reports and click on Conditions and select the appropriate filter Case Safety Report (matches)

	 Run the search to retrieve the case and load. Click Safety Report ack to see the ack(s) retrieved for this case. 
21c.	An acknowledgment is received for each message recipient (EV and relevant NCAs). Review each acknowledgment and save on the Share drive in each case file. Access DMTT and update that acknowledgement received. If a 02 Ack is received, revert back to the ICSR to ascertain the root cause. Correct the case and resubmit. If the reason for 02 is not apparent, escalate to the EMA MLM coordinators for resolution immediately.

Annex 1: Spanish INE codes.

Copia de Tabla_CCAA_codigo.

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)>

The patient’s medical and drug history included <xx>. (Delete if not known / reported)

On <insert DD MMM YYYY/ or an unknown date>, the patient began treatment with <active substance> (batch number and expiration date, if available) at a dose of <XX / frequency> for <indication>.

On (insert date DDMMMYYYY or unknown), the patient experienced <Preferred terms>. This reaction was considered serious due to <insert qualifying criteria>

The patient received treatment with [all available details of treatment (delete if not stated)

The outcome of the adverse events was <recovered/not recovered/ recovering/ unknown>

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

Annex 3: Reporting Matrix, EEA NCA requiring cases sent directly to NCAs

NCAs list.pdf