EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Handling of requests for ADR-related EudraVigilance data		
Status: PUBLIC		Document no.: SOP/H/3326
Lead author	Approver	Effective date: 07-DEC-18
Names: Agnieszka Szmigiel, Daniel Becker	Name: Peter Arlett	Review date: 07-DEC-21
Signature: ON FILE	Signature: ON FILE	Supersedes: SOP/H/3326 (25-SEP-12)
Date: 07-DEC-18	Date: 07-DEC-18	TrackWise record no.: 5490

1. Purpose

This document describes the process followed by the Inspection and Human Pharmacovigilance department (P-PE) and the Information Management division (I) when a request for EudraVigilance data, i.e. information about a suspected adverse reaction associated with a medicinal product and/or a substance contained in EudraVigilance, is received from within the EU regulatory network, e.g. the European Medicines Agency, the European Commission, the Committee for Medicinal Products for Human Use (CHMP), the Pharmacovigilance Risk Assessment Committee (PRAC) and the National Competent Authorities (NCAs).

This procedure also applies to respective external requests, taking into account the levels of access for specific stakeholder groups as outlined in the EudraVigilance Access Policy. Marketing authorisation holders access EudraVigilance through their own access, in line with this policy.

In the spirit of transparency, all reasonable efforts to provide the requester with the desired EV data shall be made. The necessity of timely and valid provision of safety data received in EudraVigilance sets the basis for a standardised approach as described in this document.

2. Scope

This SOP applies to staff of the E-Division, P-Division, S-Division, International Affairs (AF-IA), Documents Access and Publication (DED-DAP) and Data Standardisation and Analytics (I-BD-DSA).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

3. Responsibilities

It is the responsibility of each Head of Department (HoD) to ensure that this procedure is adhered to within his/her department. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of section "9. Procedure."

4. Changes since last revision

Major revision

5. Documents needed for this SOP

- Tracking of queries received and output provided as well as the rota for leaders and validators are based on an Excel spreadsheet tracking table (*Tracking of EV requests.xls*) saved under the following location in DREAM: Cabinets/03. Pharmacovigilance/PhV – human/3.2 Eudravigilance requests
- Templates for responses (according to the query type) are saved under the following location in DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM/Templates and guidance documents/Standard cover letters for responses to requests for EV data

6. Related documents

- SOP/H/3289 – Data analysis of EudraVigilance (DREAM: Cabinets/06. Corporate governance/06.2 Integrated Management System/2. IMS Manual/2. Corporate controlled documents/4. SOPs and WINs/*3000 - 3999 H (Human)/3289 SOP - Data analysis of EudraVigilance)
- European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use (EudraVigilance Access Policy) (Doc. Ref.: EMA/759287/2009 Revision 3*, https://www.ema.europa.eu/documents/other/european-medicines-agency-policy-access-eudravigilance-data-medicinal-products-human-use-revision-3_en.pdf)
- Guide on access to unpublished documents (https://www.ema.europa.eu/documents/other/guide-access-unpublished-documents_en.pdf)
- The European Medicines Agency Code of Good Administrative Behaviour (https://www.ema.europa.eu/documents/other/european-medicines-agency-code-good-administrative-behaviour_en.pdf)
- The European Medicines Agency Code of Conduct (https://www.ema.europa.eu/documents/other/european-medicines-agency-code-conduct_en.pdf)
- Common guidelines on practical arrangements for the sharing of scientific data between the scientific committees and panels of European agencies and the scientific committees of the commission (version revised by DG SANCO following a consultation of the commission legal service). Brussels, 10.11.2008. (http://ec.europa.eu/health/ph_risk/documents/cons_draftguidelines_confidentiality_081110_final.pdf)
- Rules for the implementation of Regulation (EC) No 1049/2001 on access to EMEA documents (Doc. Ref. EMEA/MB/203359/2006 Rev 1 Adopted, https://www.ema.europa.eu/documents/other/rules-implementation-regulation-ec-no-1049/2001-access-emea-documents_en.pdf)

- SOP/EMA/0019 - Handling of Requests for Information (http://www.ema.europa.eu/docs/en_GB/document_library/Standard_Operating_Procedure_-_SOP/2009/09/WC500002659.pdf)
- European Medicines Agency policy on access to documents (Doc. Ref. EMA/729522/2016, https://www.ema.europa.eu/documents/other/policy-43-european-medicines-agency-policy-access-documents_en.pdf)
- Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32001R1049)
- Working arrangement between the European Medicines Agency (EMA) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (Doc. Ref. EMA/248916/2010 (Rev.1); DREAM: Cabinets/09. Relationship management and communication/09.1 Stakeholder liaison/02 European organisations/2. EU Agencies & Joint Undertakings/4. EMCDDA/1. EMA-EMCDDA MoU & Governance/Working Arrangement)
- Records management policy (https://www.ema.europa.eu/documents/other/policy-26-records-management_en.pdf)
- Dispatch channels for RFIs (Doc. Ref. ID EMA/212834/2014; DREAM: Cabinets/09. Relationship management and communication/09.7 ATD, RFI & CDP/Requests for information/02 Reports and work reference documents)
- JIRA keywords for assignment to the EV data provision assistant and the Access to Eudravigilance data dashboard (Doc. Ref. ID EMA/747592/2015; DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM/Templates and guidance documents/Eudravigilance access request standards other than templates)
- SOP/H/3293 -– Management of general external pharmacovigilance-related queries assigned to the Pharmacovigilance Dashboard in JIRA (https://www.ema.europa.eu/documents/sop/standard-operating-procedure-management-general-external-pharmacovigilance-related-queries-assigned_en.pdf)

7. Definitions

Adrreports.eu portal (http://www.adrreports.eu/): This website was launched by the European Medicines Agency in 2012 to provide public access to reports of suspected side effects (also known as suspected adverse drug reactions) submitted electronically to EV.

AskEMA and JIRA: The AskEMA management tool (JIRA) is used to record, manage and track all requests for information or document received via the web form (https://www.ema.europa.eu/send-question-european-medicines-agency). Each request is allocated a unique reference number, and the start date (the date when the query is received) and deadline are recorded and tracked.

Core business EudraVigilance data requests should be responded to within 2 months (unless agreed otherwise), in line with the Code of Good Administrative Behaviour. They include:

- Requests from academia
- Requests from Medicines Regulatory Authorities in third countries
- Requests for a patient's own ICSR data. This should be answered within 30 calendar days.

Electronic Reaction Monitoring Report (eRMR): Report extracted from EudraVigilance which provides an overview of the ICSRs transmitted to EV over a defined period of time. The eRMR contains information on adverse drug reactions grouped according to the MedDRA hierarchy, per active substance(s)/medicinal product(s) and allow filters and thresholds to be applied on several fields as appropriate. Contents of the eRMR are further detailed in WIN/H/3406 - Screening Electronic Reaction Monitoring Reports for new Signals.

EudraVigilance (EV) - the European data-processing network and management system as established in accordance with Regulation (EC) No 726/2004 and Directive 2001/83/EC. It allows the Agency to manage the electronic data exchange of Individual Case Safety Reports (ICSRs) and to support the EU pharmacovigilance and risk management activities at EEA level.

EudraVigilance Datawarehouse and Analysis System (EVDAS) – the EudraVigilance Datawarehouse and Analysis System has been designed to allow users to analyse safety data collected in EudraVigilance in view of allowing better-informed decisions about the safety profile of medicinal products. It provides a range of analytical tools: from measuring reporting compliance for regulatory purposes, to pharmacovigilance analyses (such as signal detection tools).

EudraVigilance web-reporting application (EVWEB): The EudraVigilance web application (EVWEB) is the interface to the EudraVigilance database management system (EDBMS) and allows registered users to create, send and view ICSRs, safety and acknowledgement messages. EVWEB also enables users to perform queries.

EV data provider(s) – the EV data provision leader and – if nominated – the EV data provision validator.

EV data provision assisstant - staff member of P-PE-SIM responsible for the tracking of the requests for data analysis, i.e. receipt and supporting allocation of data requests, ensuring correct archiving of all query-related documents, creating a DREAM folder for each query, communicating with external requesters and in JIRA, providing data for reports and presentations.

EV data provision coordinator(s) – staff member(s) of P-PE-SIM responsible for coordination of EV data provision, e.g. allocation of resources, supervision of and advice to the EV data provision assistant, coordination of responses as well as advising requesters and EV data providers. The EV data provision coordinator ensures that all documents required to proceed with academic or third country regulators' requests for EV data are submitted and archived in line with the provisions of the EV access policy and P-PE-SIM policy. If the EV data provision leader is from I-BD-DSA the EV data provision coordinator validates the data as much as feasible, drafts and – for internal queries – sends out the response, keeps the EV data provision coordinator and the EV data provision assisstant informed, is responsible for the procedure, answers any follow-up question by the requester and archives the EV data provision leader's files.

EV data provision leader – staff member of P-PE-SIM (occasionaly of I-BD-DSA) responsible for planning and execution of EV data extraction, obtaining validation (if applicabe), keeping the EV data provision coordinator and the EV data provision assisstant informed, collaborating with the I-BD-DSA analysts, drafting and – for internal queries – sending out the response and archiving relevant documents and information. The responsibilities of the EV data provision leader also includes answering any follow-up question by the requester. Requests involving a potential signal are assigned to the requested product's SML if possible.

EV data provision validator – staff member of P-PE-SIM responsible for validating the EV query and the extracted EV data of the EV data provision leader, i.e. scrutinising the product/substance selection, the need for recoding, the MedDRA selection and any additional query criteria. The EV data provision validator also repeats the EVDAS query, emails to the leader the validation outcome and reviews the

response. The EV data provision validator archives his/her files. Of note, an EV data provision validator is only required for external EV queries.

I-BD-DSA Analysts– staff members of the Data Standardisation and Analytics service involved in the provision of redacted line listings when responding to the external requests and in answering complex queries which cannot be answered with the existing EVDAS queries. This is done in collaboration with the P-PE-SIM service.

MedDRA - the Medical Dictionary for Regulatory Activities - is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g. medical devices and vaccines). Coding these data to a standard set of MedDRA terms allows health authorities and the biopharmaceutical industry to more readily exchange and analyse data related to the safe use of medical products.

- SOC – System Organ Class - Highest level of the terminology, and distinguished by anatomical or physiological system, aetiology, or purpose
- HLGT – High Level Group Term - Subordinate to SOC, superordinate descriptor for one or more HLTs
- HLT – High Level Term - Subordinate to HLGT, superordinate descriptor for one or more PTs
- PT – Preferred Term - Represents a single medical concept
- LLT – Lowest Level term - Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym (Note: All PTs have an identical LLT).
- SMQs – Standardised MedDRA Queries - are groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory, and other physiologic test data etc., related to the medical condition or area of interest.

Request for access to documents - any external written request for access to any unpublished business document produced or received and held by the Agency which is not core business. These requests shall be handled in accordance with the Rules for the implementation of Regulation (EC) No 1049/2001 on access to EMA documents. Request for specific Individual Case Safety Reports (ICSRs) from EV are considered as access to documents when the requested document(s) are not available on www.adrreports.eu and the request is not core business. These documents will be provided as a redacted excel line listing of the types of reports defined in the EV access policy and containing the data fields for the stakeholder group II: Healthcare Professionals and the Public as referred to in Annex B of the EV Access Policy within 15 EMA business days. The period can, in exceptional circumstances, be extended to 30 EMA business days (or instead the query can be answered in batches if feasible). These documents are made available to DED-DAP so they can send it to the requester, using the respective standard.

Request for access to information - external request requiring an answer from the Agency and not falling within the scope of access to documents or core business. Any EV document or output which is available on, and therefore considered as published on www.adrreports.eu is to be processed as a request for information (or core business), even if it concerns case details or line listings which the EMA retrieves for the requester, as they are included there. External requests for numbers/statistics of ICSRs received in EV for a particular medicinal product/adverse drug reaction or a group of medicinal products are considered as requests for information or core business (depending on the requester).

Request for ADR-related EV data – a request for ADR-related data (e.g. a drug-event pair) contained in EV received from a party that can be provided with it in accordance with the EudraVigilance Access Policy, Code of Conduct, Memorandum of Understanding or guidelines as listed in section 6 of this SOP or a request falling under the scope of request for information/access to documents. An ADR-related request for EV data can also be related to an active substance, substance combination or more than one medicinal product, and to any level of MedDRA. It will typically contain:

- Drug(s) and adverse reaction(s) of interest
- Output criteria (number of cases, number of fatal cases, cases over time, paediatric cases, case line listing, geographical distribution etc.)

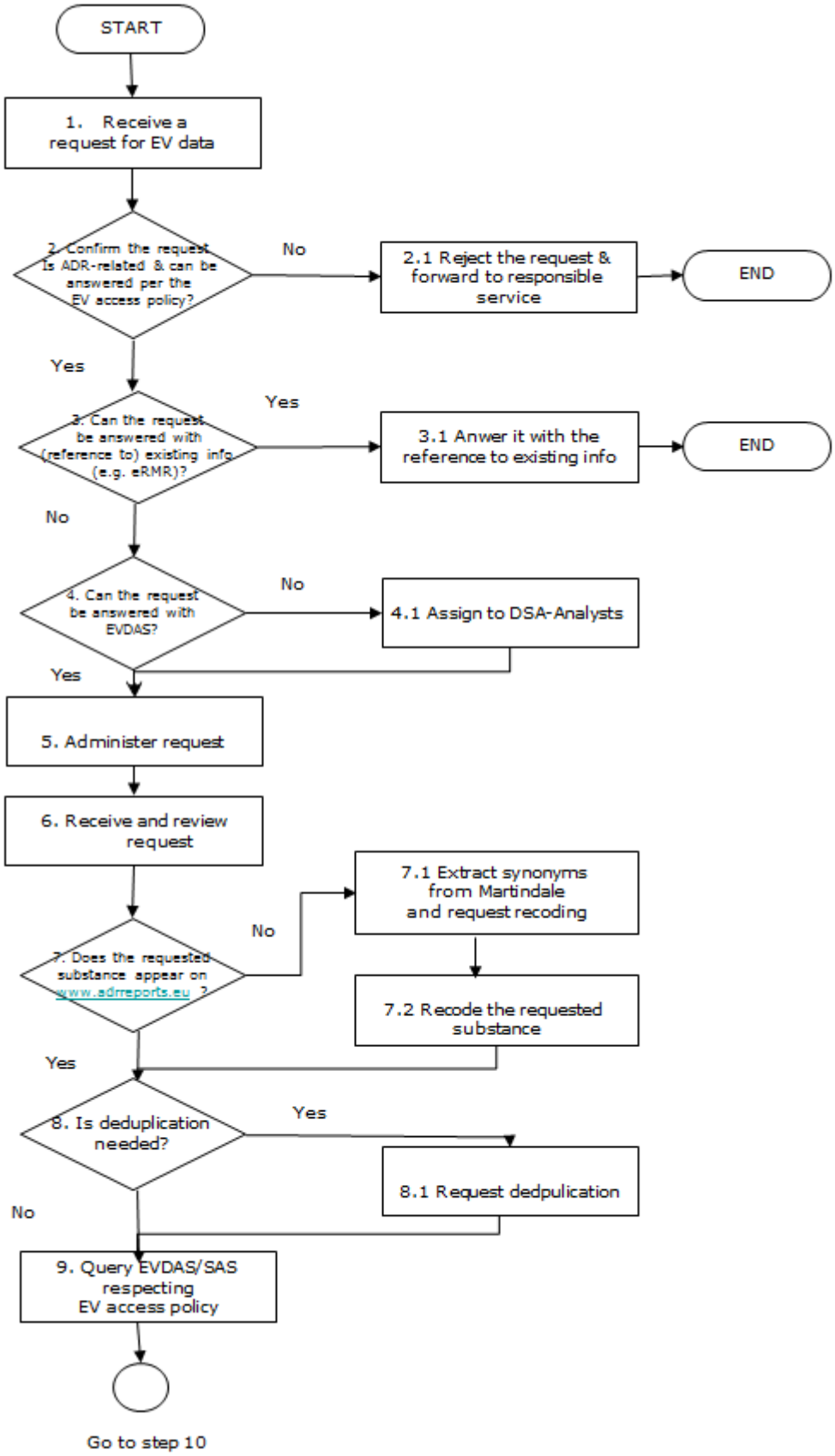
Any request meeting these criteria will be considered a request for ADR-related EV data. Requests for EV data analysis are covered by SOP/H/3289. Also excluded are requests for EV data related to a signal procedure, which are dealt with by the assigned SML.

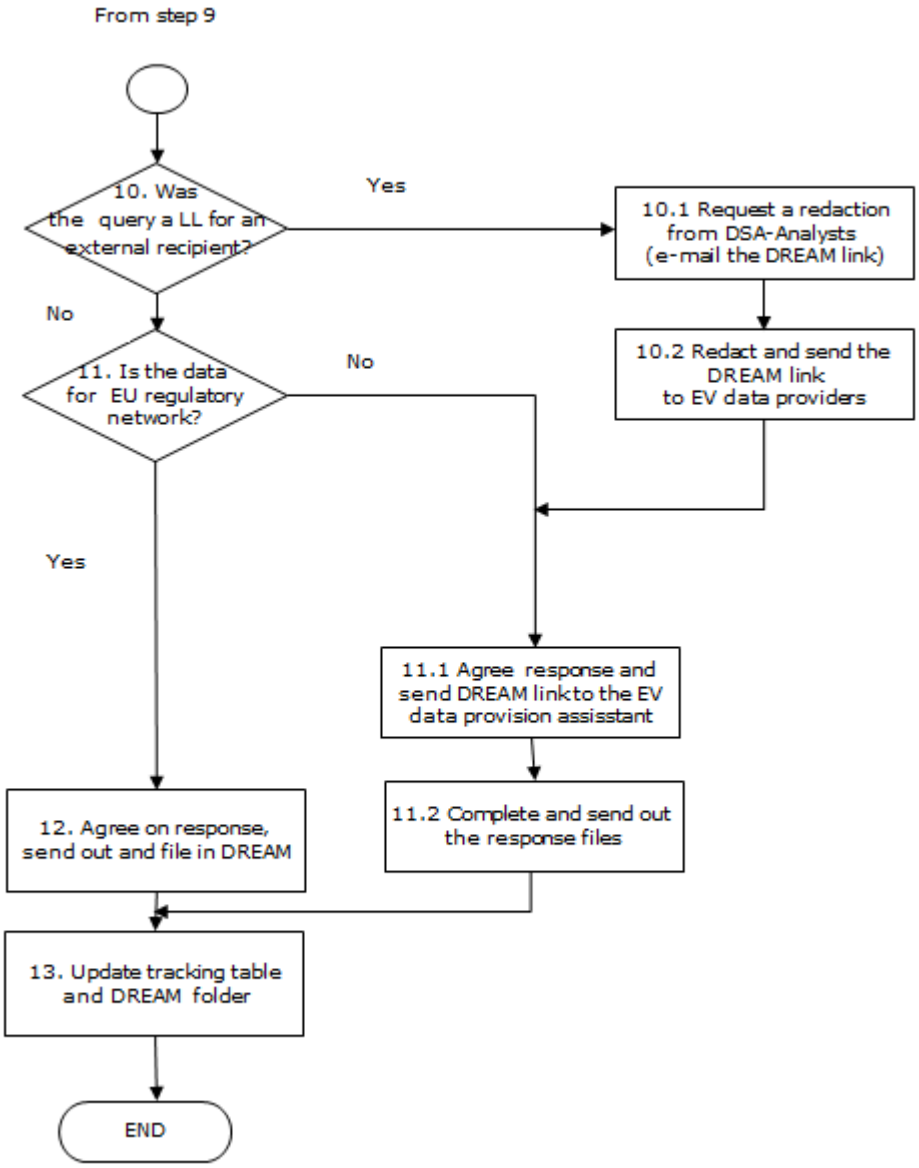
Example of a request for ADR-related EV data: "Please provide data from EV for the PT anaphylactic reaction with SUBSTANCE. Focus on data for centrally authorised products – PRODUCT1 and PRODUCT2, received since 30 June 2008 (last follow-up). Desired output: number of cases and line listing."

SAS (previously "Statistical Analysis System") - A software suite developed by SAS Institute for advanced analytics, multivariate analyses, business intelligence, data management, and predictive analytics.

Signal Management Lead (SML) – staff member of P-PE-SIM responsible for EV monitoring, detection and validation of signals for allocated active substances contained in Centrally Authorised Products. The allocation is retrievable in SIAMED under product resourcess as signal detection.

8. Process map(s)/ flow chart(s)




From step 9
10. Was the query a LL for an external recipient?
Yes
10.1 Request a redaction from DSA-Analysts (e-mail the DREAM link)
10.2 Redact and send the DREAM link to EV data providers
No
11. Is the data for EU regulatory network?
No
Yes
11.1 Agree response and send DREAM linkto the EV data provision assisstant
11.2 Complete and send out the response files
12. Agree on response, send out and file in DREAM
13. Update tracking table and DREAM folder
END

9. Procedure

Step	Action	Responsibility
1	All requests for ADR-related EV data (not for analysis) received by the Agency (via askEMA, Medical and Health Information, Press Office, Quality Defects, EPLs etc.) should be forwarded to the EV data provision coordinator(s) and EV data provision assistant. Their names can be obtained from sma-assistants@ema.europa.eu.	All relavant EMA staff
2	Confirm the request is for ADR-related EV data which can be provided according to the EV access policy. Of note: EV requests within signal procedures or as part of colleagues' research or reporting projects as well as EV data analysis are not covered by this SOP. If it is not an ADR-related EV data request which can be provided according to the EV access policy, inform EV data provision assistant and continue with step 2.1. Otherwise, continue with step 3.	EV data provision coordinator
2.1	Reject request or forward it to the responsible service (e.g. EV registration). END of procedure.	EV data provision assistant
3	Can the request be answered with (a reference to) existing information, e.g. in www.adrreports.eu, in EVWEB or in an eRMR, or is it generally unclear or incomplete? If yes, continue with step 3.1. Otherwise, continue with step 4.	EV data provision coordinator
3.1	Answer the request with (a reference to) existing information or – if generally unclear or incomplete - advice. END of procedure	EV data provision coordinator and assistant
4	Can the request be answered with EVDAS? If yes, inform the EV data provision assistant and continue with step 5. Otherwise go to step 4.1.	EV data provision coordinator
4.1	Inform the EV data provision assistant that the EV data provision leader will be I-BD-DSA-Analysts@ema.europa.eu.	EV data provision coordinator
5	Allocate a SIM reference number to the request according to the sequence recorded in the *Tracking of EV requests.xls* (as per section 5 of this SOP). The reference numbers are 8 digits containing the year, month and a 2 digits sequential number (e.g. 20120301). For AskEMA queries to be responded with EV data, the unique JIRA tracking number of the main task should be recorded in addition to the SIM number. For queries to be responded via JIRA the AskEMA number should be used for all relevant correspondence.	EV data provision assisstant

Step	Action	Responsibility
	Determine an initial deadline according to the type of the request. The deadline is provided in requests handled by AF-IA and the S-Division and in EU regulatory network requests. The standard deadline to answer requests for EV documents received directly from DED-DAP is 15 EMA business days; whereas the deadline to answer requests for EV information received via DED-DAP is 2 months. Requests for own data should be answered within 30 calendar days. Other core business requests should be answered within 2 months. Allocate the EV data provision leader and – if applicable – validator according to the rota. However, request for own ICSR data are assigned to the EV data provision coordinators. If informed by the EV data provision coordinator that I-BD-DSA-Analysts is the EV data provision leader (see step 4 above), allocate accordingly and assign the EV data provision coordinator as validator. If the request involves a potential signal assign the requested product's SML as EV data provision leader. Suspensions from the rota can be granted by the Head of P-PE-SIM. Create/record a DREAM folder (as per section 10 of this SOP) where all documents will be stored. Save the request and all communication regarding it there. For external requests draft the response as per the template(s) and store it in above mentioned DREAM folder. Complete the file *Tracking of EV requests.xls* with all available information. Send the request to the leader and validator (if allocated), using the assignment email standards agreed with the EV data provision coordinator(s).	
6	Receive a request for ADR-related EV data via email from the EV data provision assistant. Inform him/her immediately if the deadline will likely not be met and in this case of the earliest likely response date. If needed clarify the request with the requester (e.g. if deadline is missing), either via or copying the EV data provision assistant. If a requested clarification is not received within one month close the query and inform the requester accordingly. END of procedure. If there is no EV data provision validator consult the EV data provision coordinator(s) if needed.	EV data provider(s)
7	Do(es) the requested product(s)/substance(s) appear (at least as substance) on www.adrreports.eu? If yes, continue with step 8. Otherwise, continue with step 7.1.	EV data provider(s)
7.1	Extract a list of product names/synonyms for the requested product(s)/substance(s) from "Martindale: The Complete Drug Reference" and email it to I-BD-DSA-Analysts@ema.europa.eu with a request for recoding and a deadline.	EV data provider(s)

Step	Action	Responsibility
7.2	Recode the requested substance(s)/product(s) within the requested deadline and inform the EV data provider(s) when done.	I-BD-DSA analysts
8	Is deduplication needed and the number of cases (probably) significant? Of note, deduplication is needed for PRAC requests and if explicitly requested for internal queries. Consult the EV data provision coordinator(s) if needed. If yes, continue with step 8.1. Otherwise, continue with step 9.	EV data provider(s)
8.1	Request deduplication from I-BD-DSA-Analysts@ema.europa.eu with a deadline (standard deduplication takes 1 to 2 weeks).	EV data provider(s)
8.2	Deduplicate the requested substance(s)/product(s) within the requested deadline and inform the EV data provider(s) when done.	I-BD-DSA analysts
9	Query EVDAS/SAS based on the request, any clarification(s) and the EV access policy, Figure 2 and table 10, specifically: • For requests from the EU regulatory network (level 3), all data elements for all ICSRs can be provided, from both the post-marketing and clinical trials modules of EV (EVPM and EVCTM, respectively), and all EV report types; • For requests for information/access to document(s) from Healthcare professionals (HCPs) and the public (level 1), only spontaneous post-marketing (EVPM) reports should be selected; • For requests for an extended ICSR data set from academia (level 2A), all post-marketing (EVPM) report types (i.e. spontaneous, report from studies, other and not available to sender (unknown)) can be included. For other requests by academia, access is the same as for HCPs and the public. • For requests from medicines regulatory authorities in third countries (level 2C), all post-marketing (EVPM) report types (i.e. spontaneous, report from studies, other and not available to sender (unknown)) from the EEA can be included. • For requests for own ICSR data download the E2B version and manually redact the output as appropriate. Select a historic cut-off date according to the daily DWH audit emails so that the data is valid. If deduplication is needed (see above) and the number of cases is insignificant manually deduplicate them. Save the results with EVDAS filter details and relevant correspondence in the above mentioned DREAM folder. If there is an EV data provision validator he/she validates in addition the results of the EV data provision leader, emails the EV data provision	EV data provider(s)

Step	Action	Responsibility
	leader the validation outcome and stores it in above mentioned DREAM folder. If there is no EV data provision validator the EV data provision leader consults the EV data provision coordinator(s) on any of the above aspects if needed.	
10	Was the query “line listing” of the “EV access policy queries” in EVDAS used (for a redacted line listing), i.e. for a recipient outside the EU regulatory network? If yes, continue with step 10.1. Otherwise, continue with step 11.	EV data providers
10.1	Email the DREAM link of the result(s) to I-BD-DSA-Analysts@ema.europa.eu with a request for (a) redacted line listing(s) according to the access level (1, 2A or 2C) and a deadline.	EV data providers
10.2	Produce the requested line listing(s) within the requested deadline and email its/their DREAM link(s) to the EV data providers. Continue with step 11.1.	I-BD-DSA analysts
11	Is the data for the EU regulatory network? If yes, continue with step 12. Otherwise, continue with step 11.1.	EV data provider(s)
11.1	Complete response file(s) and send the DREAM link(s) to it/them and to any associated data file(s) to the EV data provision assistant. Store all files and relevant communication in above mentioned DREAM folder.	EV data providers
11.2	Ensure the note sheet is included in any external line listing mailing and update its DREAM number and date. Add EMA’s cover sheet to attached Excel-files. Omit the properties from Excel-files. Send response to the requester/transmitter. Forward/copy the response to the Pharmacovigilance Dashboard Coordinator. Continue with step 13.	EV data provision assistant
12	Email the response to the requester, copy the EV data provision assistant and store all files and relevant communication in above mentioned DREAM folder.	EV data provider
13	Update above mentioned tracking table and ensure all files and relevant communication have been stored in above mentioned DREAM folder.	EV data provision assistant

Step	Action	Responsibility
	END of procedure	

10. Records

Tracking of queries received and output provided as well as the rota for leaders and validators are based on an Excel spreadsheet tracking table (*Tracking of EV requests.xls*) saved under the following location in DREAM:

Cabinets/03. Pharmacovigilance/PhV – human/3.2 EudraVigilance requests

All other files produced as part of this procedure including emails are considered records according to the Agency's Records management policy.

They – other than access to document files - are stored under the following location in DREAM:

Cabinets/03. Pharmacovigilance/PhV – human/3.2 Eudravigilance requests /[receipt year]

Access to document files are stored in the DREAM folder assigned by DED-DAP.