EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Data analysis of EudraVigilance		
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1. Purpose

This document describes the process followed by the Pharmacovigilance and Epidemiology Department (P-PE) and the Information Management division (I) to perform data analysis of EudraVigilance aimed at providing transparent, reproducible, research-grade analyses to inform decision-making.

This procedure shares common aspects with the procedure for “Handling of requests for product-related EudraVigilance data” (SOP/H/3326) but is distinct from it as it concerns Eudravigilance data analysis rather than Eudravigilance data provision.

Requests may stem from the Pharmacovigilance Risk Assessment Committee’s (PRAC) chair, PRAC rapporteurs and lead Member state (MS), the European Commission (EC) or its agencies, National competent authorities (NCA) and other Regulatory authorities.

Requests can also be proposed by P-PE Department or come from other Departments or Services at the European Medicines Agency.

2. Scope

This SOP applies to staff of the Pharmacovigilance and Epidemiology Department (P-PE) and Data Standardisation and Analytics Service (I-BD-DSA).

3. Responsibilities

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

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4. Changes since last revision

Major revision.

5. Documents needed for this SOP

WIN/H/3290 - Design of an analysis of EudraVigilance data

EMA/243244/2016 - EudraVigilance Data Analysis System

6. Related documents

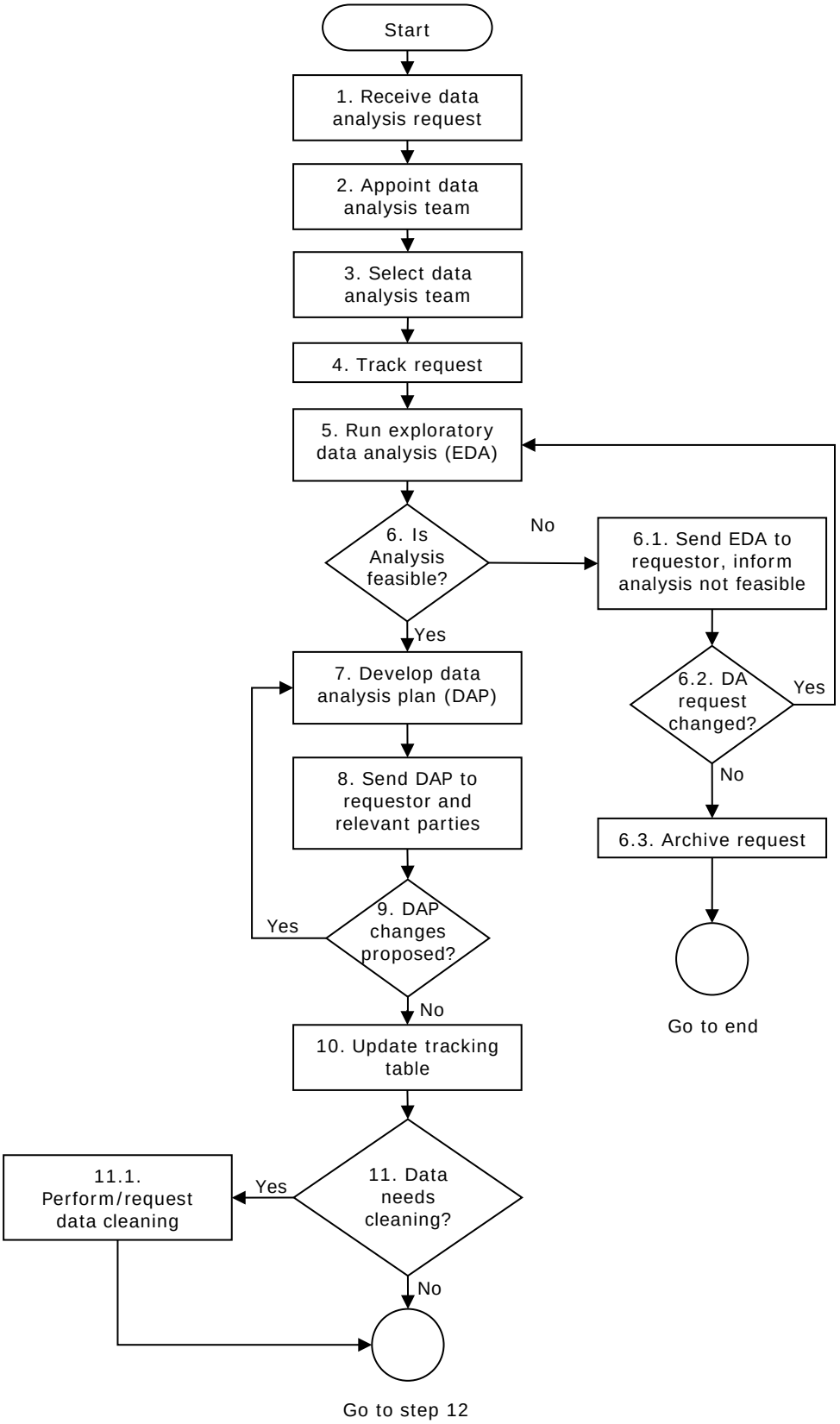
- EMA/759287/2009 Revision 3 - European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use (EudraVigilance Access Policy)
- EMA/385894/2012 Revision 1 - The EMA Code of Conduct
- EMA/264257/2013 – Code of good administrative behaviour and dealing with public requests for information
- SOP/EMA/3386 - Handling of external requests for access to information from patients, healthcare professionals, academia and the general public
- EMA/7295522/2016 – European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use)
- 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
- EMA/688937/2012 - Working arrangement between the European Medicines Agency (EMA) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)
- Records management policy:
- EMA/849944/2016 Screening for adverse reactions in EudraVigilance

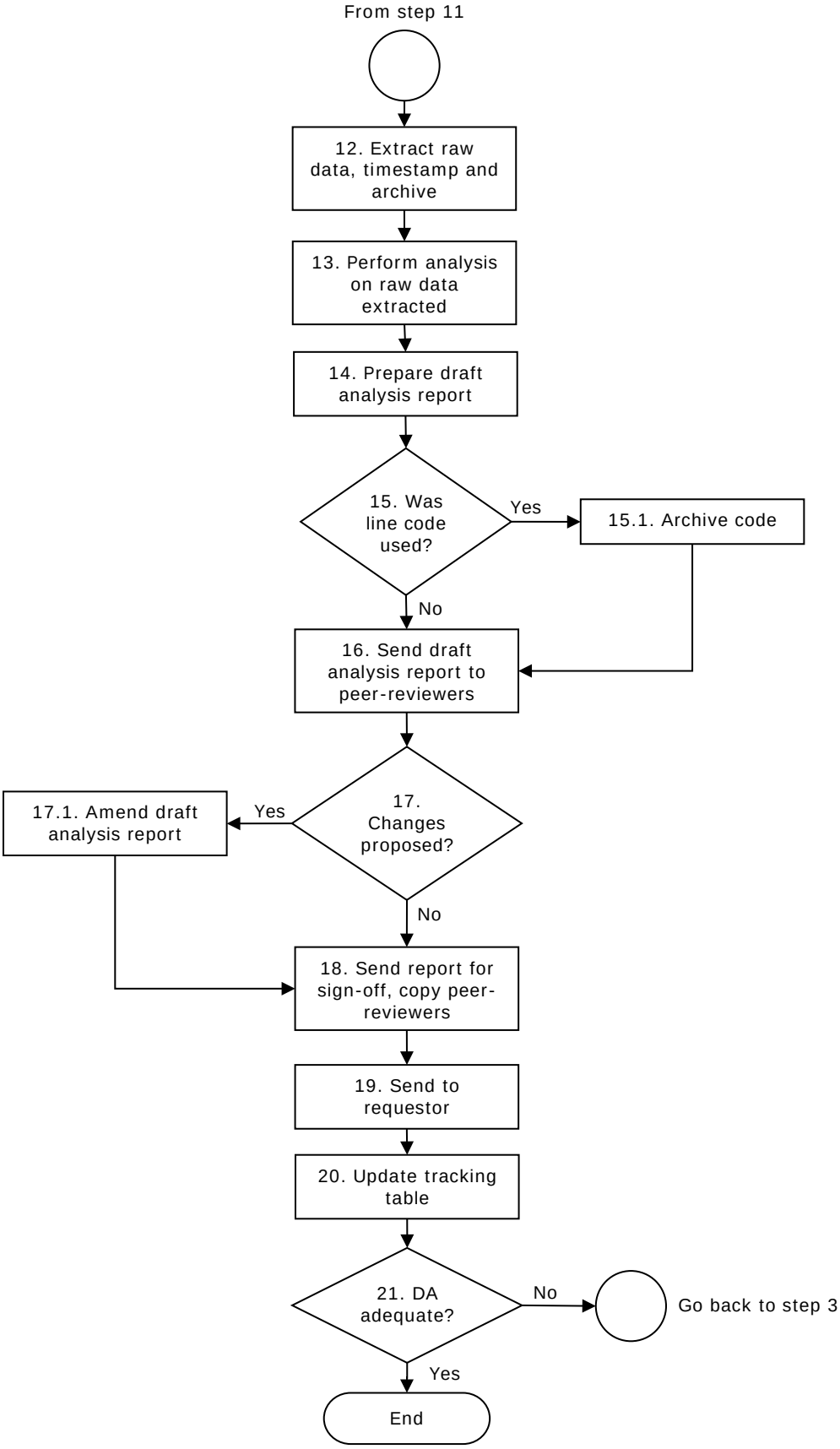
7. Definitions

Term	Definition
Data analysis	Data analysis is the process of developing answers to questions through the examination and interpretation of data.
Data analysis lead (DAL)	Person responsible for the conduct of the analysis and nominated either by P-PE-SIM Head of service (HoS) or P-PE HoD.
Data analysis plan (DAP)	Document prepared at the start of the analysis, described in the WIN/H/3290, that details the technical and statistical methods proposed by the Data Analysis team. Where there is an ongoing procedure, this document is shared with the Rapporteurs or lead member states as applicable, to collect their input.
Data analysis team	The data analysis team is responsible for conducting the data analysis and consists of primarily of Data Analysis Lead, which may be supported by additional data analysis resources from P-PE, I-BD-DSA, or different department, as needed, namely: • Signal management lead (SML) for product (if DAL is not the SML) • Data scientists, (Pharmaco)epidemiologists and Statisticians • Methodology experts
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 Community level.
Individual Case Safety Report (ICSR)	This 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
Peer-reviewers	Person or persons responsible for peer-reviewing the analysis with a view to ensure its scientific robustness and overall quality. Peer-reviewers are selected based on domain (e.g. immunology, bacteriology, etc.) or technical knowledge (e.g. statistics, methodology, etc.). The person responsible for sign-off should be a peer-reviewer by default.
Exploratory data analysis	The act of collecting information on the quality and extent of data available for a specific safety concern. This could include, for

Term	Definition
	instance, case report count, counts stratified by a specific variable, count of case reports with a specific variable (e.g. a test result), etc.
R	Statistical software for data analyses. R is a programming language and software environment for statistical computing and graphics. http://www.r-project.org/
Relevant parties to an analysis	The relevant parties are the persons that should be informed or consulted during the analysis. These include at a minimum the requestor, peer-reviewers and P-PE-SIM HoS. Other relevant parties may include procedure leads, regulatory advice experts, external or internal experts involved in the analysis, and any other staff or manager that has been involved by the procedure lead.
SAS	SAS (Statistical Analysis System) is an integrated system of software products provided by SAS Institute Inc. that enables the programmer to perform: data entry, retrieval, management, and mining, report writing and graphics, statistical analysis, business planning, forecasting, and decision support, operations research and project management, quality improvement, applications development, data warehousing (extract, transform, load), platform independent and remote computing.
Sign-off	The formal act of discharging the analysis report. Sign-off is performed by the P-PE HoD, or in its absence P-PE-SIM HoS or a staff member nominated by them.

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




From step 11
12. Extract raw data, timestamp and archive
13. Perform analysis on raw data extracted
14. Prepare draft analysis report
15. Was line code used?
Yes
15.1. Archive code
No
16. Send draft analysis report to peer-reviewers
17. Changes proposed?
Yes
17.1. Amend draft analysis report
No
18. Send report for sign-off, copy peer-reviewers
19. Send to requestor
20. Update tracking table
21. DA adequate?
No
Go back to step 3
Yes
End

9. Procedure

Step	Action	Responsibility
1.	Receive a request for analysis of EudraVigilance data	P-PE-SIM HoS
2.	Appoint data analysis lead The data analysis team is composed, at a minimum, of a data analysis lead (DAL). The data analysis lead can be either the signal management lead for the substance(s), if the substance(s) include a centrally authorised product, or an analyst or epidemiologist with domain knowledge on the methodologies required to conduct the analysis.	P-PE-SIM HoS
3.	Select data analysis team Depending on the type of request, the team may require additional resources such as epidemiologists, statisticians, methodologists, etc. The type of resources needed might not be evident at early stages of the analysis.	Data analysis lead
4.	Track the request Track the request in the tracking table for EV requests	P-PE-SIM assistant
5.	Run an Exploratory Data Analysis (EDA) Run an exploratory data analysis to 1) ensure that there is information available in EV to allow for the type of analysis requested and 2) prepare the draft data analysis plan. Save the EDA in the folder assigned for EV request tracking.	Data analysis lead
6.	Is the analysis feasible? The results of the EDA may indicate that the analysis is not feasible (e.g. if insufficient data is available or if the purpose of the analysis is to understand a safety aspect which is heavily confounded or biased in the cases in EV). If the analysis is feasible go to step 6 If the analysis is not feasible go to step 5.1	Data analysis lead
6.1	Inform requestor that the analysis is not feasible Send EDA results to requestor and relevant parties and inform that the analysis is not feasible under the original request. If appropriate, discuss with the requestor possible changes to the analysis to address identified issues (e.g. extend MedDRA[1] terms, change the nature of the analysis from inferential to descriptive, etc.)	Data analysis lead

[1] Medical Dictionary for Regulatory Activities

Step	Action	Responsibility
6.2	Is revised data analysis requested? If yes, go back to step 4. If no, go to step 5.3	Data analysis lead
6.3.	Track request If the requestor does not propose a change to the data analysis, the request is tracked, relevant parties are informed (procedure lead, peer-reviewers and HoD and HoS).	Data analysis lead
7.	Develop Data Analysis Plan (DAP) Develop Data Analysis Plan according to WIN/H/3290 and save it in a new folder created in Cabinets/13. Programmes and Projects/zz. Closed projects 2004-2014/EudraVigilance - NEW STRUCTURE/Pharmacovigilance/Data Analysis/DWH Analysis/Product Analysis/<corresponding year> Title the folder as follows: [Product name(s), substance or class] – [concern] – [Procedure (if one exists)] - YYYYMM – [procedure nbr. (if a referral)]. E.g. “Quinolones – QT prolongation – Signal - 201801”.	Data analysis team
8.	Send DAP to requestor and relevant parties Send the DAP to the requestor and relevant parties for comments by an agreed deadline.	Data analysis lead
9.	Does the DAP require amendments? If yes, go back to step 6 If no, go to step 9	Data analysis lead
10.	Update tracking table	P-PE-SIM assistant
11.	Does the data need cleaning? While there is a baseline data cleaning (de-duplication) and data recoding in EV, it may be necessary to perform additional data cleaning on the data. If data cleaning is needed, go to step 10.1. If not, go to step 11.	Data analysis team
11.1	Perform or request data cleaning The deadline for data cleaning should be agreed in writing with I-BD-DSA and tracked in the data analysis plan. If the analysis requested involves individual case review, those cases reviewed individually should be de-duplicated by the data analysis team.	

Step	Action	Responsibility
12.	Extract raw data, timestamp and archive The raw data should be extracted, timestamped and archived in the data analysis folder, to ensure traceability. File formats should be XLS or other non-proprietary or open-source formats (e.g. CSV), to ensure ease of use and reproducibility.	Data analysis team member from P-PE-SIM or I-BD-DSA
13.	Perform the analysis The analysis should be performed on the raw extracted data. If a literature search needs to be conducted, if possible, it should be done prior to running the analysis, as it may impact the interpretation of the results. E.g. The geographical distribution of interstitial lung disease can be explained by safety concerns that happened in Japan, which a literature review can explain better than solely relying on the information in case reports. Where statistical programming languages are used (such as R or SAS), the code should be literate (i.e. the analyst should include notes for each code steps explaining what the code does).	Data analysis team
14.	Prepare the draft analysis report	Data analysis team
15.	Was a statistical programing language used? If yes, go to step 15.1 If no, go to step 16	Data analysis lead
15.1	Archive code	Data analysis lead
16.	Circulate draft analysis report to peer-reviewers Circulate draft analysis report to peer-reviewers, copying P-PE HoD and P-PE-SIM HoS for comments by an agreed deadline. The peer-review process is a quality review stage to ensure best possible scientific quality of the report. This stage involves final proofreading and content comments. The person responsible for the sign-off should be requested to comment at this stage.	Data analysis lead
17.	Changes to draft report proposed? If yes, go to step 17.1 If no, go to step 18	Data analysis team
17.1	Amend report	Data analysis

Step	Action	Responsibility
	Data analysis team prepares an amended report based on the comments from peer-reviewers. Peer-reviewers may need to be consulted in the process.	team
18.	Send updated report for sign-off Send updated report to person responsible for sign-off, copy peer-reviewers.	Data analysis lead
19.	Send final report to requestor and relevant parties Copy P-PE-SIM assistant. If the request includes sending data sets, these should be sent using the highest security setting in EudraLink, to ensure highest data privacy standards. Archive the report in the folder referred to in 10. Records.	Data analysis lead
20.	Update tracking table	P-PE-SIM assistant
21.	Data analysis considered adequate? Did the requestor consider that the report was adequate, i.e. addressed the question, selected correct data, used sound methodology and does not require corrections? If yes, go to end If no, go back to step 3	Data analysis lead

10. Records

Copies of all requests, exploratory data analysis, data analysis plan, raw data, draft and final reports, the code used to perform the analysis should be stored electronically in the Agency's file system, DREAM; the locations of the correct places to store the electronic copies are given below.

The following directory and relevant subdirectory should be used:

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

The EudraVigilance queries tracking table is located under the following folder:
Cabinets/03. Pharmacovigilance/PhV – human/3.2 Eudravigilance requests