EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Signal management		
Status: PUBLIC		Document no.: SOP/H/3065
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Signature: ON FILE	Signature: ON FILE	Supersedes: SOP/H/3065 (07-MAR-13)
Date: 06-DEC-18	Date: 06-DEC-18	TrackWise record no.: 4273

1. Purpose

To describe the process by which identification and management of safety signals for active substances contained in Centrally Authorised medicinal Products (CAPs) for human use is conducted periodically based on electronic Reaction Monitoring Reports (eRMRs) generated from the EudraVigilance (EV) database, as well as other sources of information such as the scientific literature. The SOP also provides guidance on the handling by the Agency of signals validated and confirmed by national competent authorities for nationally authorised products (NAPs). It also applies to confirmed signals originating from marketing authorisation holder (MAHs). The purpose of this SOP is to ensure that these activities, from signal detection to provision of support to the Pharmacovigilance Risk Assessment Committee (PRAC) in its initial analysis, prioritisation and evaluation of signals, are handled in an efficient and consistent way. This SOP applies to standard signal management as well as specific situations such as a pandemic, however for such situations adapted processes and shorter timelines may apply.

2. Scope

This SOP applies to the Signal and Incident Management Service of the Pharmacovigilance and Epidemiology Department (P-PE-SIM).

3. Responsibilities

It is the responsibility of the Heads of Department and Service to ensure that this procedure is adhered to within their own Department/Service. The responsibility for the execution of each step of this procedure is identified in the right-hand column of 9. Procedure.

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4. Changes since last revision

This SOP has been updated to reflect organisational changes within the Agency, revision 1 of GVP Module IX, the support provided by the Agency in relation to signals for nationally authorised products, as well as various improvements to the process since the last revision.

5. Documents needed for this SOP

Best practice guidance on using PRAC plenary time efficiently and effectively (PRAC/EMA/242096/2018)

EPITT User Guide (EMA/240784/2012)

EudraVigilance Data Analysis System (EVDAS) User manual (EMA/243244/2016)

Signal assessment report template
https://www.ema.europa.eu/documents/template-form/signal-assessment-report-template_en.doc

Signal assessment timetables
https://www.ema.europa.eu/documents/other/timetable-safety-signal-assessment-responses-request-supplementary-information-rsi_en.pdf

Screening for adverse reactions in EudraVigilance
https://www.ema.europa.eu/documents/other/screening-adverse-reactions-eudravigilance_en.pdf

SOP/H/3382 - Handling of safety information from non-EEA regulatory authorities

SOP/H/3441 - Tracking and handling in SIAMED of SDA post-authorisation measures for centrally authorised products

User Manual of the electronic Reaction Monitoring Report (eRMR) for National Competent Authorities and EMA (EMA/746442/2017)

WIN/H/3268 - Maintenance of the Signal Detection tracking table

WIN/H/3287 – Validation of signals from the review of individual cases

WIN/H/3406 - Screening Electronic Reaction Monitoring Reports for new Signals

Supportive service guidance documents and templates:

- CAP + NAP signal process workflow (DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM /Templates and guidances / PRAC communication templates and instructions)
- Cover e-mail to PRAC Rapporteur when sending signal for confirmation (DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM /Templates and guidances)
- Guidance on activities performed by Signal Leads while supporting the PRAC (DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM /Templates and guidances)
- PRAC support workflow – Email templates (DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM /Templates and guidances / PRAC communication templates and instructions)
- PRAC support workflow guidance (DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM /Templates and guidances / PRAC communication templates and instructions)

- Publication of PRAC signal documents (DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM /Templates and guidances / PRAC communication templates and instructions)
- Signal AR redaction guideline (DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM /Templates and guidances / PRAC communication templates and instructions)
- Signal description template (DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM /Templates and guidances)
- Templates of communication to MAHs regarding signals (DREAM: Cabinets/14. Working areas/14.03 P-Division/03. P-PE Activities/P-PE-SIM /Templates and guidances)

6. Related documents

Commission Implementing Regulation (EU) No 520/2012

Directive 2001/83/EC

Guideline on good pharmacovigilance practices (GVP) – Module IX – Signal management
https://www.ema.europa.eu/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions
https://www.ema.europa.eu/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Questions & answers on signal management
https://www.ema.europa.eu/documents/other/questions-answers-signal-management_en.pdf

Practical aspects of signal detection in pharmacovigilance. Report of CIOMS Working Group VIII

Regulation (EC) No 726/2004

WIN/H/3364 – Training for signal management leads

7. Definitions

Adverse reaction: According to Directive 2001/83/EC an adverse reaction is a response to a medicinal product which is noxious and unintended.

Centrally Authorised Product (CAP): A medicinal product with a single marketing authorisation issued by the European Commission and valid across the European Union.

DREAM (Documents Records Electronic Archive Management): electronic document management system of the EMA.

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.

EMA Product Lead (EPL): EMA staff member responsible for clinical and regulatory science input for a given CAP from initial marketing authorisation and through post-authorisation.

EPITT: European Pharmacovigilance Issues Tracking Tool. A database developed by the EMA to promote the rapid communication of pharmacovigilance and risk management issues between the EMA, all National Competent Authorities (NCAs) of the European Economic Area (EEA), the Committee for Medicinal Products for Human use (CHMP), the Pharmacovigilance Risk Assessment Committee (PRAC), the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human [CMD(h)] and (Co-) Rapporteurs.

EudraVigilance (EV): the European data processing network and management system, which has been developed according to internationally agreed standards and allows the EMA to manage the electronic data exchange of Individual Case Safety Reports (ICSRs) and to support the pharmacovigilance activities at Community level.

EudraVigilance data analysis system (EVDAS): component of EudraVigilance supporting EU pharmacovigilance safety monitoring activities with a main focus on signal detection and evaluation of ICSRs. EVDAS outputs in relation to pharmacovigilance include eRMRs, line listings of individual cases of suspected adverse reactions and ICSR forms.

H-SD: EMA functional mailbox for signal management

Individual Case Safety Report (ICSR) form: output from EudraVigilance providing in a human readable format those ICH-E2B(R3)[1,2] data elements that are needed to assess individual case safety reports.

Lead Member State for signal management: The Member State responsible for monitoring the EudraVigilance database for an active substance or combination of active substances contained in medicinal products authorised in more than one Member State through the national, mutual recognition or decentralised procedures. The lead Member State shall validate and confirm signals on behalf of the other Member States. If the active substance is authorised in only one Member State, that Member State automatically assumes the responsibilities of the Lead Member State.

MedDRA: Medical Dictionary for Regulatory Activities.

MMD (Managing Meeting Document): system linked to DREAM and intending to support the management of documents connected to EMA meetings.

NAP: nationally authorised medicinal product, including mutual recognition and decentralised procedures

Peer-reviewers: signal management leads designated to review the conclusions for closed or monitored signals. Two peer-reviewers are appointed every SVM week on a rota basis.

Periodic Safety Update Report (PSUR): Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase. PSURs are defined in Module VII of the GVP.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

Pharmacovigilance Risk Assessment Committee (PRAC): Committee at the European Medicines Agency responsible for assessing and monitoring safety issues related to medicines for human use.

[1] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) http://www.ich.org/
[2] See ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide

PRAC rapporteur: Rapporteur appointed by the PRAC in the context of the centralised procedure. Within the EU signal management process, the PRAC rapporteur is responsible for the confirmation of signals concerning CAPs.

Risk Management Plan (RMP): Detailed description of a product's risk management system. RMPs are defined in Module V of the GVP.

SIAMED: EMA's product information and application tracking system

Signal: Information that arises from one or multiple sources (including observation and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. In the context of signal detection in EV, only signals related to adverse reactions are considered.

A potential signal is considered urgent if it may warrant expedited signal validation due to its potential important impact on public health impact and/or on the benefit-risk profile of the medicinal product.

Signal confirmation: In the context of the EU signal management process (see GVP IX), process of deciding whether or not a validated signal shall be transmitted to the PRAC for initial analysis and prioritisation.

Signal detection tracking table: document where signals raised by SVT members are tracked with their validation outcomes. See WIN/H/3268 - Maintenance of the Signal Detection tracking table.

Signal management lead (SML): P-PE member responsible for signal management activities related to assigned medicinal products.

Signal tracking table: document where validated signals entered in EPITT (for both CAPs and NAPs) are tracked from the confirmation step throughout PRAC evaluation.

Signal validation: Process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis. General guidance on signal validation can be found in GVP IX, with more detailed instructions in WIN/H/3287 - Validation of signals from the review of individual cases.

Signal validation meeting (SVM): Meeting of the SVT at which identified signals for substances included in CAPs are discussed. SVMs take place three times a month. In addition, a meeting dedicated to general scientific issues relevant to signal detection, or to organisational matters (ORGAM) is organised once a month.

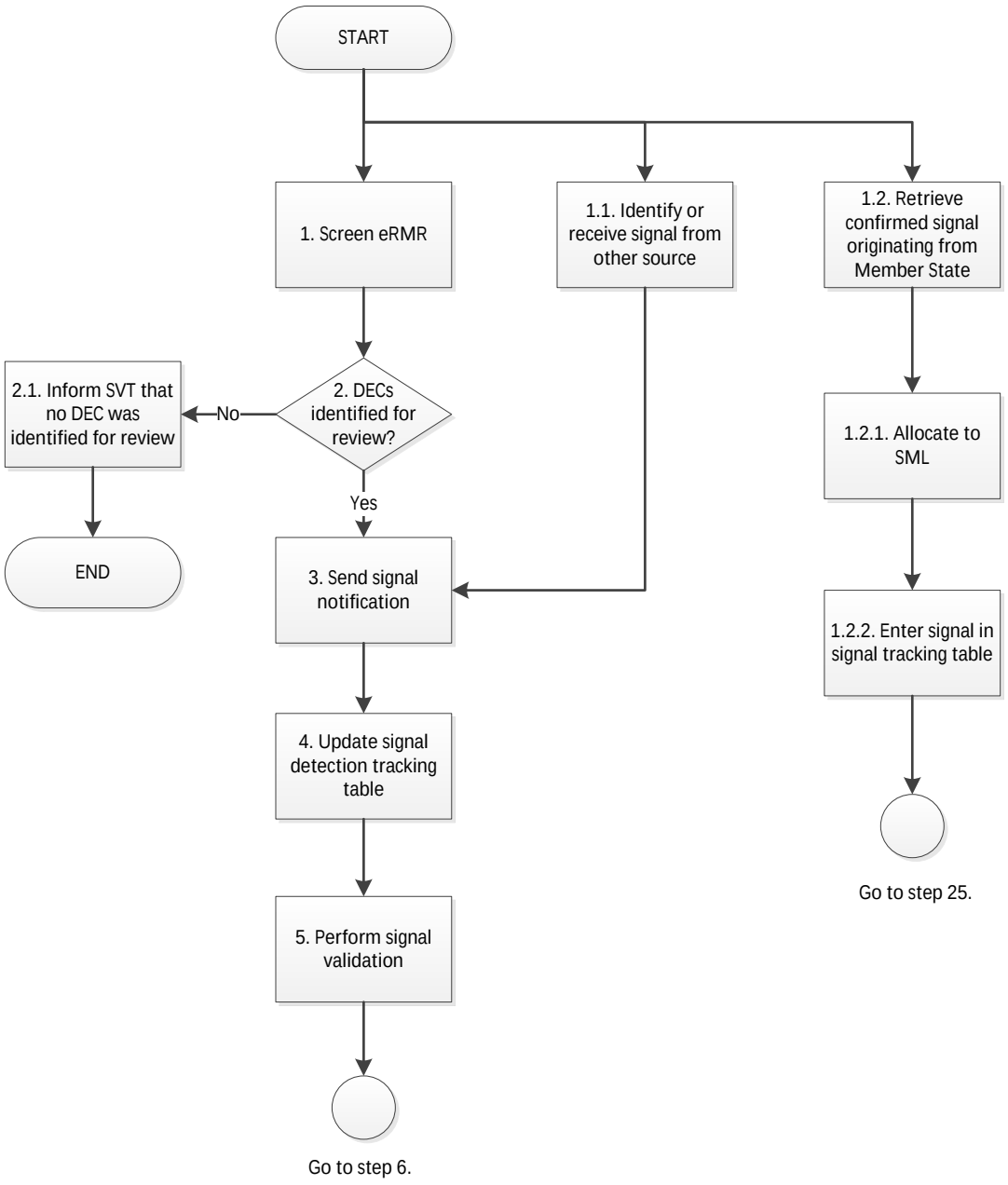
The chairperson of the SVM is the Service Head for Signal and Incident Management (P-PE-SIM), or, if absent, a SML nominated by the P-PE-SIM Service Head.

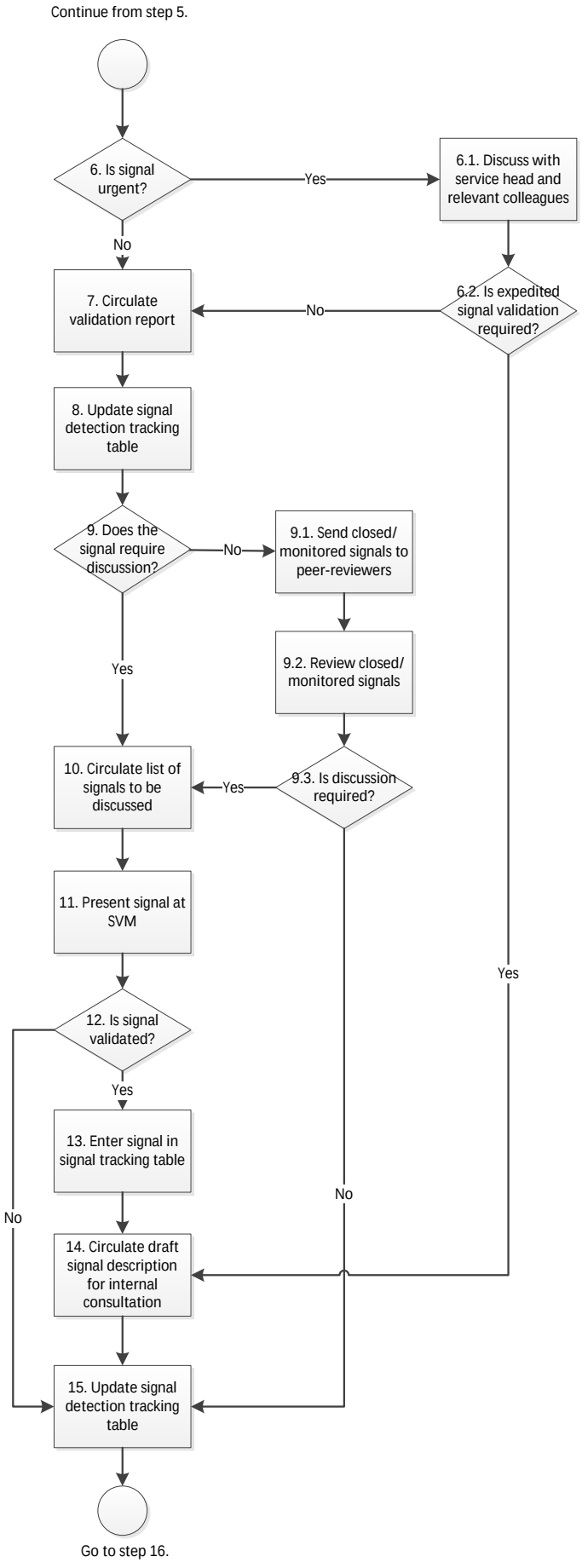
SVMs are organised by P-PE-SIM assistants and usually take place on Thursday. Changes to the schedule of SVM (cancellation, change of date or time, ad hoc meeting as necessary) may be proposed by any SVT member and should be approved by the Chairperson and the P-PE-SIM assistant. All SMLs should attend each meeting. In case a SML cannot attend a meeting, he/she should inform the P-PE-SIM assistant, preferably before 12:00 noon on the day of the meeting, stating the reason for their absence.

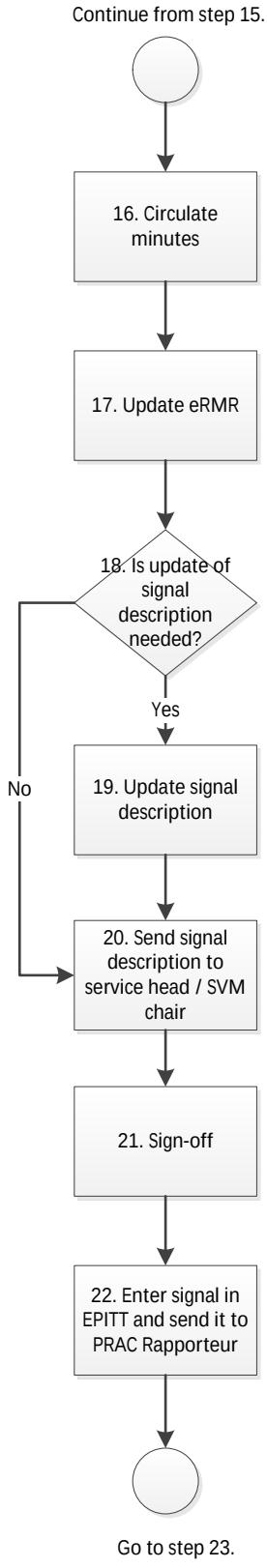
Signal validation team (SVT): EMA team responsible for the detection and management of new safety signals associated with the use of substances included in CAPs. The SVT includes:

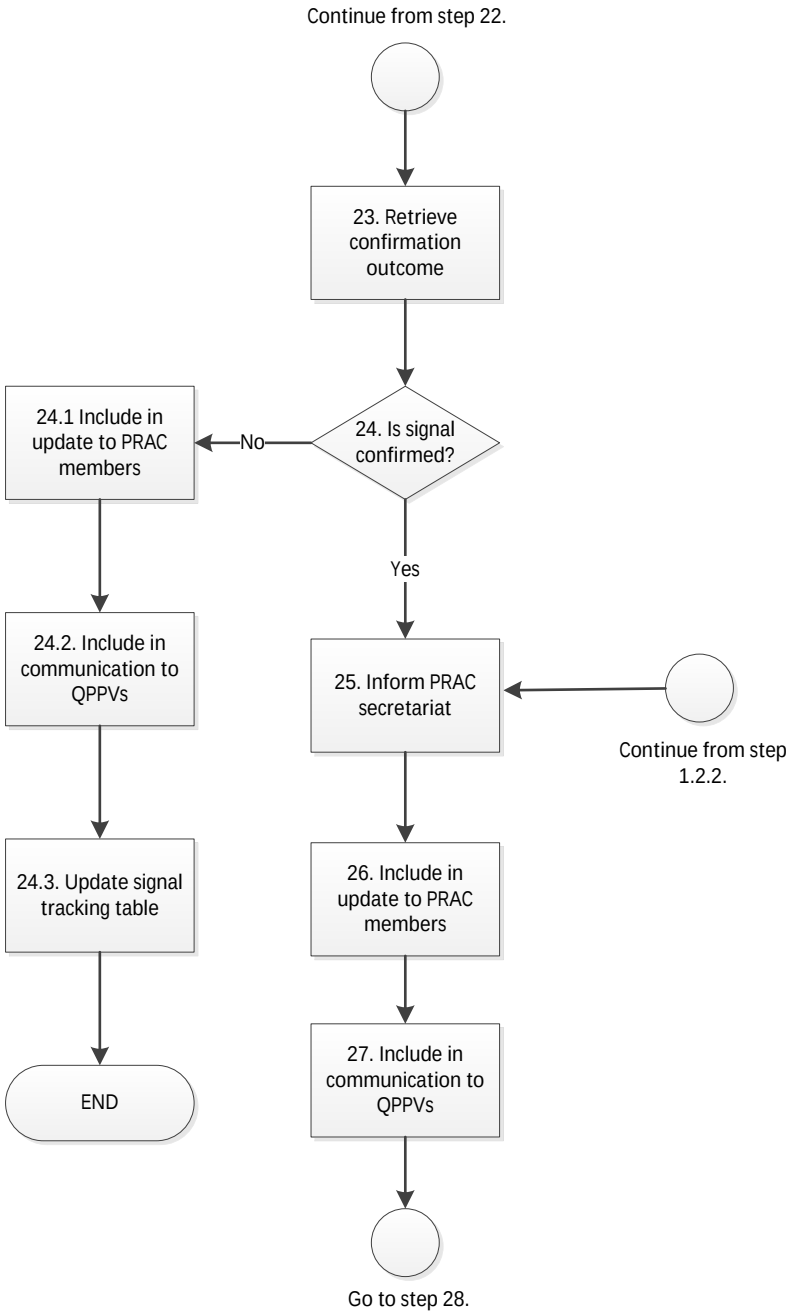
- members of the P-PE-SIM service,
- other members of the P-PE department nominated by the Head of Department,
- other EMA staff member(s) as necessary.

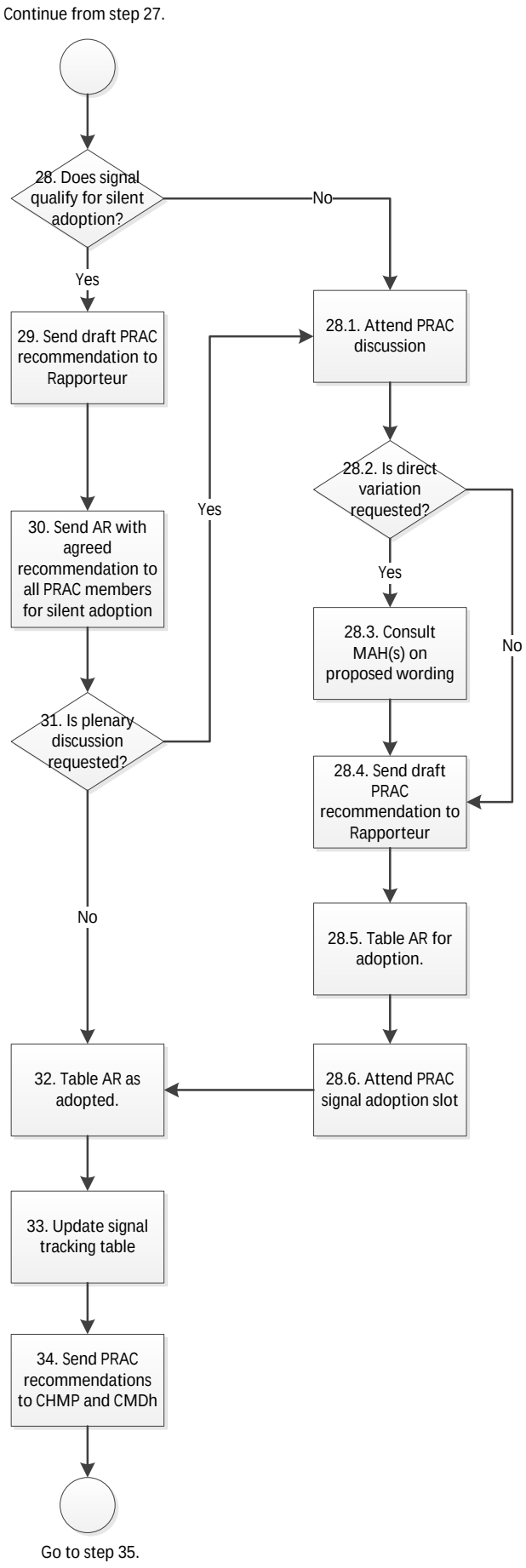
8. Process map(s)/ flow chart(s)

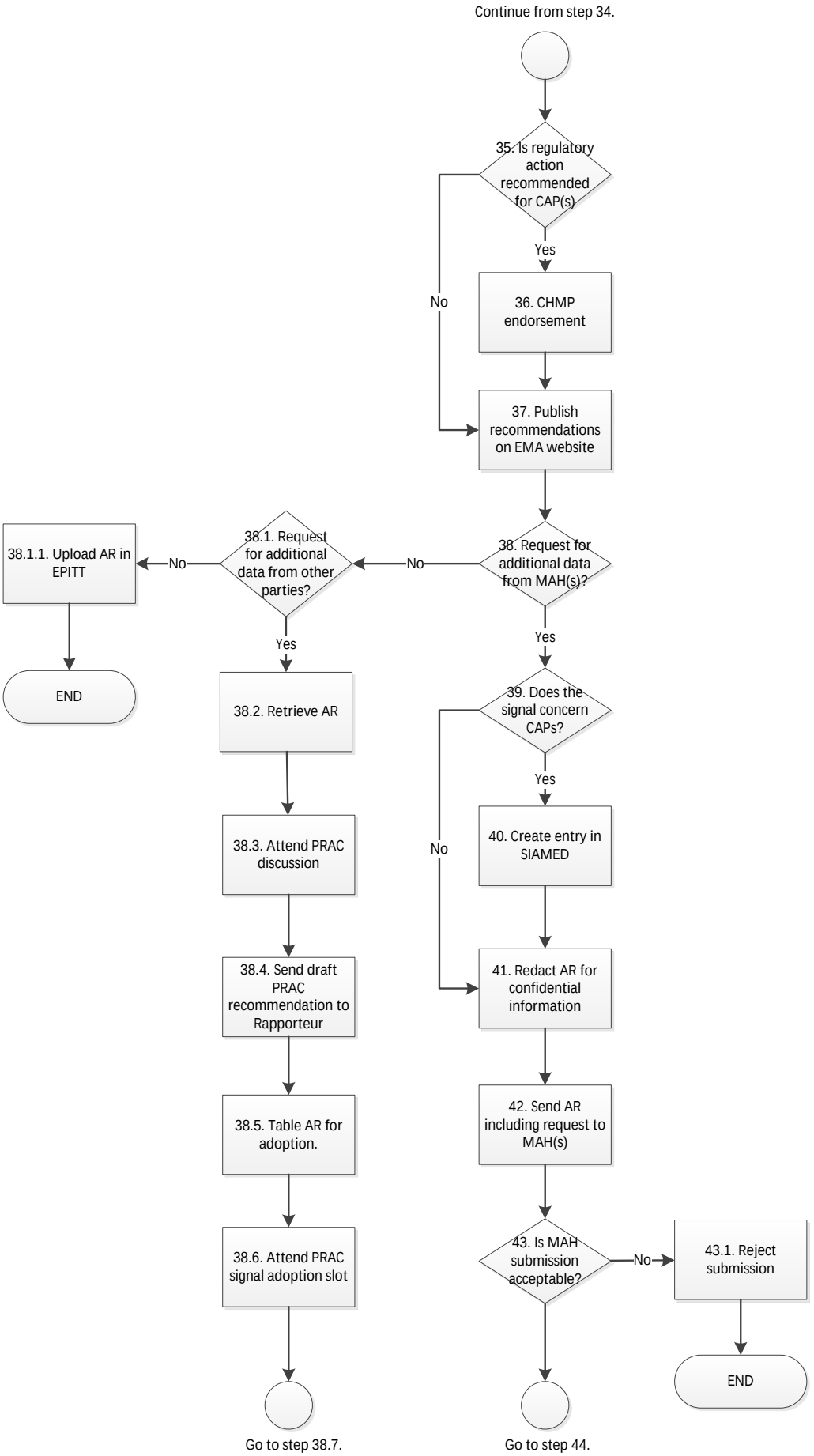


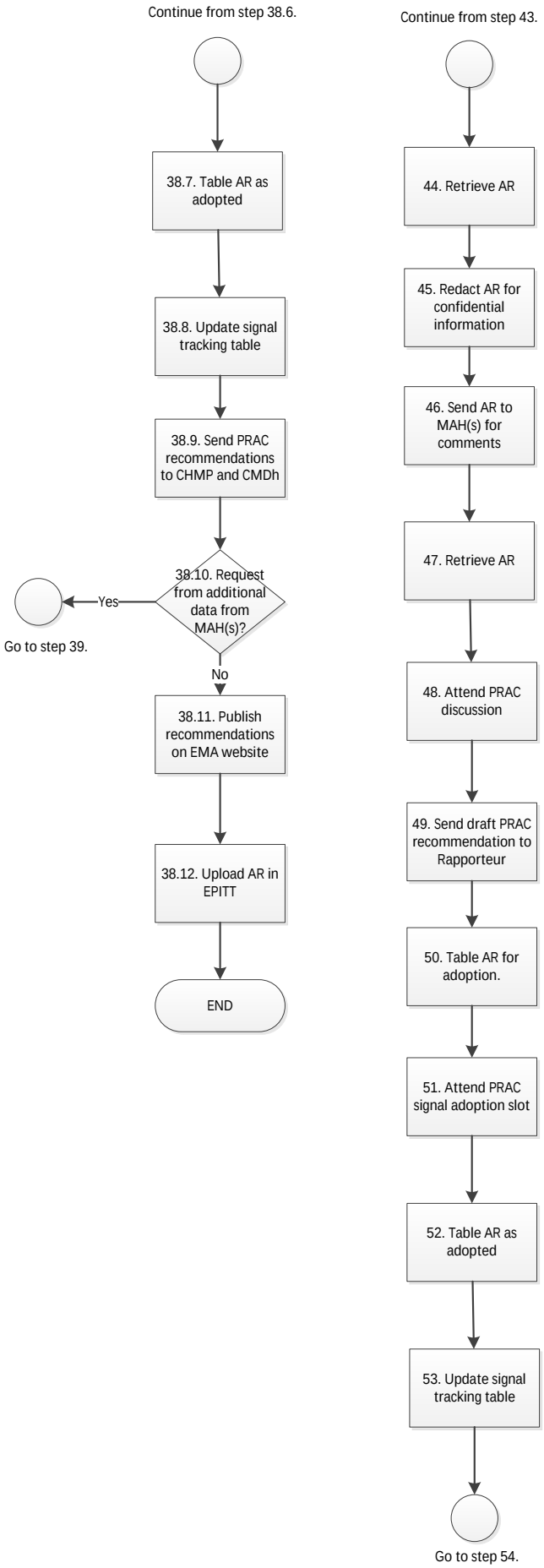

Continue from step 5.
6. Is signal urgent?
Yes
6.1. Discuss with service head and relevant colleagues
No
7. Circulate validation report
No
6.2. Is expedited signal validation required?
8. Update signal detection tracking table
9. Does the signal require discussion?
No
9.1. Send closed/ monitored signals to peer-reviewers
Yes
9.2. Review closed/ monitored signals
10. Circulate list of signals to be discussed
Yes
9.3. Is discussion required?
11. Present signal at SVM
Yes
12. Is signal validated?
Yes
13. Enter signal in signal tracking table
No
No
14. Circulate draft signal description for internal consultation
15. Update signal detection tracking table
Go to step 16.

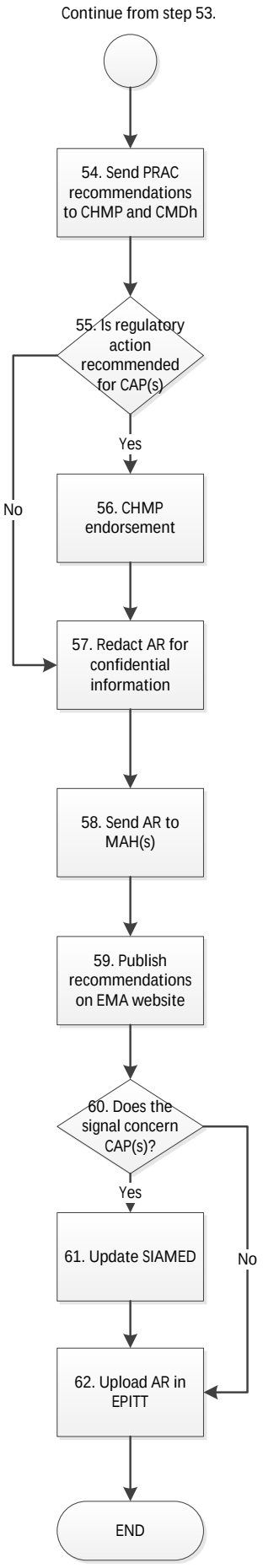

Continue from step 15.
16. Circulate minutes
17. Update eRMR
18. Is update of signal description needed?
Yes
No
19. Update signal description
20. Send signal description to service head / SVM chair
21. Sign-off
22. Enter signal in EPITT and send it to PRAC Rapporteur
Go to step 23.


Continue from step 22.
23. Retrieve confirmation outcome
24. Is signal confirmed?
No
24.1 Include in update to PRAC members
Yes
24.2. Include in communication to QPPVs
24.3. Update signal tracking table
END
25. Inform PRAC secretariat
Continue from step 1.2.2.
26. Include in update to PRAC members
27. Include in communication to QPPVs
Go to step 28.


Continue from step 27.
28. Does signal qualify for silent adoption?
No
Yes
29. Send draft PRAC recommendation to Rapporteur
28.1. Attend PRAC discussion
28.2. Is direct variation requested?
Yes
No
30. Send AR with agreed recommendation to all PRAC members for silent adoption
Yes
28.3. Consult MAH(s) on proposed wording
31. Is plenary discussion requested?
28.4. Send draft PRAC recommendation to Rapporteur
No
28.5. Table AR for adoption.
32. Table AR as adopted.
28.6. Attend PRAC signal adoption slot
33. Update signal tracking table
34. Send PRAC recommendations to CHMP and CMDh
Go to step 35.


Continue from step 34.
35. Is regulatory action recommended for CAP(s)
Yes
No
36. CHMP endorsement
37. Publish recommendations on EMA website
38. Request for additional data from MAH(s)?
No
Yes
38.1. Request for additional data from other parties?
No
38.1.1. Upload AR in EPITT
END
Yes
38.2. Retrieve AR
38.3. Attend PRAC discussion
38.4. Send draft PRAC recommendation to Rapporteur
38.5. Table AR for adoption.
38.6. Attend PRAC signal adoption slot
Go to step 38.7.
39. Does the signal concern CAPs?
Yes
No
40. Create entry in SIAMED
41. Redact AR for confidential information
42. Send AR including request to MAH(s)
43. Is MAH submission acceptable?
No
43.1. Reject submission
END
Go to step 44.


Continue from step 38.6.
38.7. Table AR as adopted
38.8. Update signal tracking table
38.9. Send PRAC recommendations to CHMP and CMDh
38.10. Request from additional data from MAH(s)?
Yes
Go to step 39.
No
38.11. Publish recommendations on EMA website
38.12. Upload AR in EPITT
END
Continue from step 43.
44. Retrieve AR
45. Redact AR for confidential information
46. Send AR to MAH(s) for comments
47. Retrieve AR
48. Attend PRAC discussion
49. Send draft PRAC recommendation to Rapporteur
50. Table AR for adoption.
51. Attend PRAC signal adoption slot
52. Table AR as adopted
53. Update signal tracking table
Go to step 54.


Continue from step 53.
54. Send PRAC recommendations to CHMP and CMDh
55. Is regulatory action recommended for CAP(s)
Yes
No
56. CHMP endorsement
57. Redact AR for confidential information
58. Send AR to MAH(s)
59. Publish recommendations on EMA website
60. Does the signal concern CAP(s)?
Yes
No
61. Update SIAMED
62. Upload AR in EPITT
END

9. Procedure

Step	Action	Responsibility
	SIGNAL DETECTION AND VALIDATION	
1.	Screen electronic Reaction Monitoring Report. *As described in WIN/H/3406 - Screening Electronic Reaction Monitoring Reports for new Signals*. Go to step 2.	SML
1.1.	Identify or receive potential signal from sources other than EudraVigilance (e.g. literature, other regulatory authority, emerging safety issue etc.) Go to step 3. *Note: Handling of safety information from non-EEA regulatory authorities is described in SOP/H/3382.*	SML
1.2.	Retrieve signal validated and confirmed by Member State for NAP(s) or CAP(s) from the H-SD / PRAC mailbox. Go to step 1.2.1.	Assistant
1.2.1.	Assign SML for the signal.	Service head
1.2.2.	Enter signal in signal tracking table. Go to step 25.	Assistant
2.	Is any drug-event combination (DEC) identified for further review? If yes, go to step 3. If not, go to step 2.1.	SML
2.1	Send an e-mail to the H-SD mailbox stating that no DEC was identified for further review for the reporting period. End of procedure.	SML
3.	Send signal notification Send the list of signals to be opened to the H-SD mailbox. *The notification of signals arising from the review of eRMRs is described in WIN/H/3406 - Screening Electronic Reaction Monitoring Reports for new Signals.*	SML
4.	Update signal detection tracking table *As described in WIN/H/3268 - Maintenance of the Signal Detection tracking table.*	Assistant
5.	Perform signal validation Review ICSR forms or Line Listings and other sources of	SML

Step	Action	Responsibility
	information, as relevant. *As described in WIN/H/3287 - Validation of signals from the review of individual cases* *Retrieval of line listings and ICSR forms is described in the EVDAS User manual*	
6.	Is the signal thought to be urgent? If yes, go to step 6.1. If not, go to step 7.	SML
6.1.	Discuss signal with service head and relevant colleagues as applicable (e.g. EPL, regulatory affairs)	SML
6.2.	Is expedited signal validation required? Expedited validation should be considered if the signal cannot wait until the next SVM. If expedited validation is warranted, a draft signal description should be circulated, go to step 14. If the signal can be handled with standard timelines, go to step 7.	SML / service head
7.	Circulate signal validation report *As described in WIN/H/3287 – Validation of signals from the review of individual cases*	SML
8.	Receive signal validation report and update signal detection tracking table *As described in WIN/H/3268 - Maintenance of the Signal Detection tracking table.*	Assistant
9.	Does the signal require discussion? If the SML concludes that the signal should be validated and/or discussed at SVM, go to step 10. If the SML concludes that the signal should be closed or monitored, go to step 9.1. Closed signals require no further immediate action. For monitored signals, new cases reported to EudraVigilance should be reviewed at a frequency determined by the SML. *See WIN/H/3406 - Screening Electronic Reaction Monitoring Reports for new Signals for the handling of monitored signals when screening Reaction Monitoring Reports.*	SML
9.1.	Send proposed closed/monitored signals to peer-reviewers Send extract of signal detection tracking table with signals to be closed or monitored according to the SMLs to the designated peer-	Assistant

Step	Action	Responsibility
	reviewers, cc H-SD mailbox. *As described in WIN/H/3268 - Maintenance of the Signal Detection tracking table.*	
9.2.	Review proposed closed/monitored signals. The two designated peer-reviewers review the conclusions for closed and monitored signals and send comments, if applicable, to individual SMLs, cc P-PE-SIM assistant and service head.	Peer-reviewers
9.3.	Is a discussion at SVM required? If comments raised during the peer-review warrant discussion at SVM, inform P-PE-SIM assistant and go to step 10. If not, go to step 15.	SML / peer-reviewers
10.	Send list of signals to be discussed at SVM (meeting agenda). Prior to each SVM, the assistant sends an extract of the signal detection tracking table with the signals to be discussed, including those for which validation is proposed by the SML, together with any presentation to the H-SD mailbox.	Assistant
11.	Present signal during SVM The SML presents the information supporting the signal (e.g. EV data, scientific literature, PSURs, RMP, regulatory procedures…) together with proposed action(s). *As described in WIN/H/3287 – Validation of signal from the review of individual cases.*	SML
12.	Is the signal validated? Based on the information presented by the SML, SVT members discuss and agree on whether or not the signal is validated. If yes, go to step 13. If not, go to step 15. *Note: the SVT may also wish to see additional information before making a decision and, if not already done, may request a more formal and comprehensive presentation of the signal at the following SVM, in which case steps 10 to 12 should be repeated.*	SVT members
13.	Enter signal in signal tracking table.	Assistant
14.	Circulate draft signal description for internal consultation A draft signal description is sent to H-SD and the EMA Product Lead (EPL), copying the product shared mailbox(es), for comments. The consultation period is in principle 2 working days, but may be shortened in case of urgent signals. No response means agreement	SML

Step	Action	Responsibility
	with the signal description. *Note: a Word template replicating the EPITT signal description is available for draft signal descriptions (see Section 5).*	
15.	Update signal detection tracking table *As described in WIN/H/3268 - Maintenance of the Signal Detection tracking table.*	Assistant
16.	Send minutes to H-SD mailbox *As described in WIN/H/3268 - Maintenance of the Signal Detection tracking table.*	Assistant
17.	Update electronic Reaction Monitoring Report Update the eRMR with the agreed action and conclusion for each raised signal. *Follow WIN/H/3406 - Screening Electronic Reaction Monitoring Reports for new Signals*	SML
18.	Consider comments received from SVT members and EPL, as applicable. If an update of the signal description is required, go to step 19. If no update is needed, go to step 20.	SML
19.	Update signal description taking into account comments received.	SML
20.	Send signal description to service head, or in their absence, to staff member who chaired the SVM, copying the assistant. *Note: If controversial or numerous comments were made during the consultation, the SML may be requested to provide an overview of those, together with a brief explanation/justification of how they have been addressed or not, as applicable.*	SML
21.	Written sign-off by email within one working day provided by service head or designated alternate, e.g. SML in charge of chairing relevant SVM. For urgent signals, a shorter timeframe may apply.	Service head / SVM chair
22.	Send signal description to PRAC rapporteur(s) The SML enters the final signal description in EPITT and sends it by e-mail to the PRAC rapporteur(s), copying: - all PRAC members (using the PRAC functional mailbox: 'All Human Pharmacovigilance'), - H-SD, - the EPL, - the product shared mailbox(es).	SML

Step	Action	Responsibility
	Follow EPITT User Guide. *A template for cover e-mails when sending signal descriptions to PRAC rapporteurs is available (see section 5).* *Note: if the signal is urgent, this should be clearly identified in the subject of the e-mail.*	
	SIGNAL CONFIRMATION	
23.	Monitor H-SD / PRAC mailbox and/or check EPITT, to retrieve the outcome of the confirmation.	Assistant
24.	Is the signal confirmed? The PRAC rapporteur confirms or not the signal in EPITT within 30 days. For confirmed signals, the rapporteur / Lead Member State circulates a signal confirmation assessment report (AR) and specifies whether or not the signal qualifies for silent adoption. For non-confirmed signals, a justification should be included in EPITT and circulated to all PRAC members. If the signal is confirmed, go to step 25. If the signal is not confirmed, go to step 24.1.	PRAC rapporteur / Lead Member State
24.1.	Include in list of signals extracted from EPITT circulated to PRAC members prior to each PRAC meeting.	Assistant
24.2.	Include in list of non-confirmed signals circulated to all Qualified Persons responsible for Pharmacovigilance (QPPVs) prior to each PRAC meeting	Assistant
24.3.	Update signal tracking table. End of procedure.	Assistant
25.	Inform PRAC secretariat. The assistant liaises with the PRAC secretariat so that the confirmed signal can be added to the PRAC agenda.	Assistant
26.	Include in list of signals extracted from EPITT circulated to PRAC members prior to each PRAC meeting.	Assistant
27.	Include in advance notification to QPPVs regarding signals on PRAC agenda.	Assistant
	SIGNAL ANALYSIS AND PRIORITISATION	
28.	Does the signal qualify for silent adoption? Criteria for silent adoption are outlined in the *'Best practice guidance on using PRAC plenary time efficiently and effectively'.*	SML

Step	Action	Responsibility
	If the signal qualifies for silent adoption, go to step 29. If not, go to step 28.1.	
28.1.	Attend discussion on signal at PRAC plenary meeting.	SML
28.2.	Is a direct variation proposed? In rare occurrences where PRAC recommends a variation without first requesting data from the MAH(s), the MAH(s) should be consulted on the proposed wording in an expedited manner; go to step to step 28.3. If not, go to step 28.4.	SML
28.3.	Send the proposed wording to the MAH(s). MAH comments should be provided as soon as possible to allow for finalisation of the PRAC recommendation during the meeting.	SML
28.4.	Send draft PRAC recommendation to PRAC rapporteur / (Lead) Member State. *Guidance on PRAC recommendations is provided in 'Guidance on activities performed by Signal Leads while supporting the PRAC'.*	SML
28.5.	Update assessment report if needed based on feedback from rapporteur / (Lead) Member State and table it in MMD for adoption.	SML / assistant
28.6.	Attend PRAC plenary adoption slot for recommendations on signals and update recommendation if needed. Go to step 32.	Service head / SML
29.	Prepare and send draft PRAC recommendation to PRAC rapporteur / (Lead) Member State The SML drafts the PRAC recommendation based on the proposal outlined in the assessment report and sends it to the rapporteur / (Lead) Member State for agreement. If required, the SML also confirms with the rapporteur / (Lead) Member State that silent adoption is appropriate. *Guidance on PRAC recommendations, including on the selection of MAH(s) to be involved in procedure, is provided in 'Guidance on activities performed by Signal Leads while supporting the PRAC'. Timetables for signal assessment are published on the EMA website.*	SML
30.	Send assessment report with agreed PRAC recommendation to all PRAC members for silent adoption. For signals related to NAPs, the proposed rapporteur for the signal (usually the Member State that confirmed the signal) should also be agreed at this stage.	SML

Step	Action	Responsibility
	The deadline for comments is usually the Friday preceding the PRAC plenary meeting. In the absence of comments, the recommendation is considered agreed.	
31.	Is plenary discussion requested by PRAC member(s)? If a PRAC member considers that plenary discussion is required, go to step 28.1. If not, go to step 32.	PRAC member
32.	Table assessment report with PRAC recommendation (updated as appropriate) in MMD as adopted.	SML / assistant
33.	Update signal tracking table.	Assistant
34.	Send PRAC recommendations on signals to CHMP and CMDh members.	Assistant
35.	Is regulatory action recommended for CAP(s)? For CAPs, requests for regulatory actions such as variations should be formally endorsed by the CHMP, go to step 36. If not, go to step 37.	Assistant
36.	The CHMP formally endorses the PRAC recommendation. The signal is included on the agenda for the next CHMP meeting and the recommendation is agreed via silent adoption.	CHMP / CHMP secretariat
37.	Publish PRAC recommendations on EMA website. *The process for the publication of signal recommendations, including translation of product information updates, is described in the 'Guidance on signal documents for publication'.*	Assistant
38.	Are additional data requested from MAH(s) as part of the PRAC recommendation? If yes, go to step 39. If not, go to step 38.1.	SML
38.1.	Are additional data requested from other parties? If the PRAC recommendation includes questions addressed to e.g. EMA, study authors etc., go to step 38.2. If not, go to step 38.1.1.	SML
38.1.1.	Upload AR in EPITT The signal procedure is considered closed when the signal is to be further handled in another procedure (e.g. PSUR) or if routine pharmacovigilance is considered sufficient. End of procedure.	Assistant

Step	Action	Responsibility
	SIGNAL ASSESSMENT	
38.2.	Receives Rapporteur's preliminary and updated assessment reports on additional data or retrieve them from H-SD / PRAC mailbox.	SML
38.3.	Attend discussion on signal at PRAC plenary meeting.	SML
38.4.	Prepare and send draft PRAC recommendation to rapporteur.	SML
38.5.	Update assessment report if needed based on feedback from rapporteur and table it in MMD for adoption.	SML
38.6.	Attend PRAC plenary adoption slot for recommendations on signals and update recommendation if needed.	Service Head / SML
38.7.	Table assessment report with PRAC recommendation (updated as appropriate) in MMD as adopted.	SML / assistant
38.8.	Update signal tracking table.	Assistant
38.9.	Send PRAC recommendations on signals to CHMP and CMDh members.	Assistant
38.10.	Are additional data requested from MAH(s) as part of the PRAC recommendation? If yes, go to step 39. If not, go to step 38.11.	SML
38.11.	Publish PRAC recommendations on EMA website.	Assistant
38.12.	Upload AR in EPITT The signal procedure is considered closed when the signal is to be further handled in another procedure (e.g. PSUR) or if routine pharmacovigilance is considered sufficient. End of procedure.	Assistant
39.	Are CAPs involved in the signal? If yes, go to step 40. If not, go to step 41.	Assistant
40.	Create an entry for the signal in SIAMED. *As described in SOP/H/3441 - Tracking and handling in SIAMED of SDA post-authorisation measures for centrally authorised products.*	Assistant
41.	Redact assessment report for confidential information. *As described in the 'Signal AR redaction guideline'.*	SML / assistant
42.	Send redacted assessment report, including PRAC request for additional data to MAH(s).	Assistant
43.	Is MAH submission acceptable?	SML / assistant

Step	Action	Responsibility
	The assistant informs the SML that the MAH responses have been received and should be checked. MAH submissions containing revised annexes (dossier section 1.3.1.) should in principle be rejected and resubmitted as variations. If the submission is acceptable, go to step 44. If not, go to step 43.1. *See SOP/H/3441 - Tracking and handling in SIAMED of SDA post-authorisation measures for centrally authorised products.*	
43.1.	Send rejection letter. *As described in SOP/H/3441 - Tracking and handling in SIAMED of SDA post-authorisation measures for centrally authorised products.*	Assistant
44.	Receive rapporteur's preliminary assessment report on additional data or retrieve it from the H-SD / PRAC mailbox.	SML / assistant
45.	Redact assessment report for confidential information. As described in the 'Signal AR redaction guideline'.	SML / assistant
46.	Send the redacted assessment report to MAH(s), stating the deadline for comments.	Assistant
47.	Receive rapporteur's updated assessment report or retrieve it from the H-SD / PRAC mailbox.	SML
48.	Attend discussion on signal at PRAC plenary meeting.	SML
49.	Prepare and send draft PRAC recommendation to rapporteur.	SML
50.	Update assessment report if needed based on feedback from rapporteur and table it in MMD for adoption.	SML
51.	Attend PRAC plenary adoption slot for recommendations on signals and update recommendation if needed.	Service Head / SML
52.	Table assessment report with PRAC recommendation (updated as appropriate) in MMD as adopted.	SML / assistant
53.	Update signal tracking table.	Assistant
54.	Send PRAC recommendations on signals to CHMP and CMDh members.	Assistant
55.	Is regulatory action recommended for CAP(s)? If yes, go to step 56. If not, go to step 57.	Assistant
56.	Formal endorsement of PRAC recommendation. The signal is included on the agenda for the next CHMP meeting and the recommendation is agreed via silent adoption.	CHMP / CHMP secretariat

Step	Action	Responsibility
57.	Redact assessment report for confidential information.	SML / assistant
58.	Send redacted assessment report to MAH(s).	Assistant
59.	Publish PRAC recommendations on EMA website.	Assistant
60.	Are CAPs involved in the signal? If yes, go to step 61. If not, go to step 62.	Assistant
61.	Update signal entry in SIAMED *As described in SOP/H/3441 - Tracking and handling in SIAMED of SDA post-authorisation measures for centrally authorised products.*	Assistant
62.	Upload assessment report in EPITT End of procedure.	Assistant

10. Records

- The Signal Detection Tracking Table called 'SDMDB-IM_RM 2.xls' is saved in DREAM: Cabinets/03. Pharmacovigilance/PhV - Human/3.3 Signal detection activities/01 Signal detection tracking tools/IM RM CAP list.
- The signal tracking table is saved in DREAM: Cabinets/03. Pharmacovigilance/PhV - Human/3.3 Signal detection activities/01 Signal detection tracking tools/IM RM CAP list.
- Signal Notifications are stored in electronic format in the mailbox Public Folders/All Public Folders/Chrono In/EMAILS/H-SD
- Signal Validation Reports are stored in:
  - the mailbox Public Folders/All Public Folders/Chrono In/EMAILS/H-SD
  - DREAM: Cabinets/ 03. Pharmacovigilance/PhV - Human/3.3 Signal detection activities/03 Signal validation meeting/Intensively_Routinely Monitored Products/[Year]/[Month]/[Day]
- Signal descriptions of validated signals, justifications for non-confirmation and PRAC assessment reports are stored in EPITT (fmp://fmapps3.eudra.org/EPITT.fmp12)
- Relevant documents on validated signals (e.g. further analyses, presentation, signal description…) are archived in DREAM in the product folder in a dedicated subfolder (example: Cabinets/01. Evaluation of Medicine/H-C/A-C/Abilify-000471/09 PHV/Signal Detection/[Signal X]).
- Relevant communications on validated signals concerning CAPs are stored in the product mailboxes.
- Electronic Reaction Monitoring Reports are named "IM or RM_[Name of SML]" and saved in DREAM: Cabinets/03. Pharmacovigilance/PhV - Human/3.3 Signal detection activities/01 Signal detection tracking tools/IM RM CAP list/eRMRs (IM or RM) since [date]