SAFETY REPORTING AND ASSESSMENT

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Disclaimer

The Implementing Regulation for safety is not finalised

The IT database for safety reports and assessment is not finalised

Therefore the data presented in this presentation is in draft and may be updated before the go-live date

Low interventional trials

Article 41 - Two possible risk adaptations to safety reporting:

- selective recording and reporting of adverse events (AEs),

- adaptations to immediate reporting from the investigator to the sponsor, for certain serious adverse events (SAEs)

May be considered for:

- IMPs that are used according to the conditions of the marketing authorisation

- IMPs that are marketed, but used differently to the conditions of the marketing authorisation

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_04_25_risk_proportionate_approaches_in_ct.pdf

ASRs
Annual Safety Reports
Article 43

ASR - What stays the same?

ASR usually per IMP, occasionally per CT (clinical trial)

Definition of SAEs and serious adverse reactions (SARs)

Most of the content of the ASR

Development Safety Update Report (DSUR) format as per ICH E2F

Frequency of submission (annually) and Data Lock Point (DLP)

Development International Birth Date (DIBD), alignment with International Birth Date (IBD) if authorised IMP

ASR – What is new?

Co-ordinated, workshared assessment:

- ASR per IMP/active substance - Assessment led by saMS (safety assessing Member State)
- ASR is submitted per clinical trial (CT) – Reference Member State (RMS) takes on the role of saMS

Assessment report

Minor updates to Cumulative Summary Tabulations of Serious Adverse Events – Section 7

New sections of ASR: Region Specific Information – Section 16

Single submission of ASR to CTIS - No direct reporting to NCAs or ethics committees

Safety data for Auxiliary medicinal products can be included in section 7.2 of the ASR (Line Listings of SARs), separate ASR not needed

ASR Draft procedure

	ASR procedure – all via CTIS
Submission	Sponsor submits ASR
Assessment	Initial assessment by saMS
	saMS shares draft assessment report with RMS/MSC
	RMS/MSC raises considerations on draft assessment report, if any
	saMS consolidates considerations
Request for further information (RFI)	If no RFI, → end of procedure
	If RFI, saMS sends RFI to sponsor
Responses	Sponsor submits responses
	saMS assesses responses and shares updated draft assessment report with RMS/MSC
	RMS/MSC raises considerations, if any
End of Procedure	Final assessment report shared with RMS/MSC
	Sponsor notified of conclusion of assessment
	Recommended actions proposed by saMS, if applicable

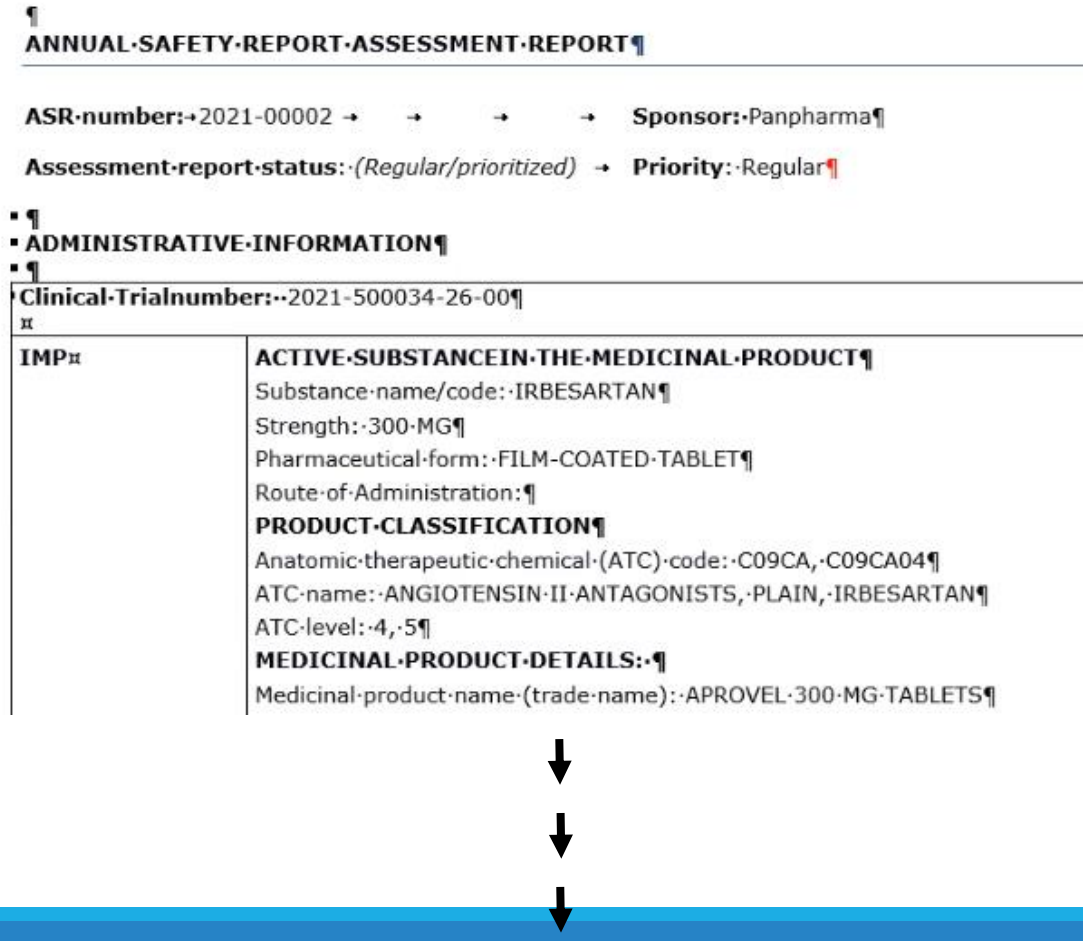
Assessment report

Digital report built into CTIS

Template to be downloaded for each case

Administrative information will be autopopulated

Based on word document used as part of pilot run by CZ



ANNUAL·SAFETY·REPORT·ASSESSMENT·REPORT

ASR·number:·2021-00002 → → → → **Sponsor:**·Panpharma

Assessment·report·status:·*(Regular/prioritized)* → **Priority:**·Regular

ADMINISTRATIVE·INFORMATION

Clinical·Trialnumber:··2021-500034-26-00

IMP	**ACTIVE·SUBSTANCEIN·THE·MEDICINAL·PRODUCT** Substance·name/code:·IRBESARTAN Strength:·300·MG Pharmaceutical·form:·FILM-COATED·TABLET Route·of·Administration: **PRODUCT·CLASSIFICATION** Anatomic·therapeutic·chemical·(ATC)·code:·C09CA,·C09CA04 ATC·name:·ANGIOTENSIN·II·ANTAGONISTS,·PLAIN,·IRBESARTAN ATC·level:·4,·5 **MEDICINAL·PRODUCT·DETAILS:**· Medicinal·product·name·(trade·name):·APROVEL·300·MG·TABLETS

Assessment report

Summary/conclusion section for Member States

4. Summary/Conclusions for MEMBER STATE				
4.1 Any safety issue to be aware of and/or to follow up by RMS/MSC	Yes	☐	No	☐
Be aware of / follow up ☐ specific safety issue (new or ongoing) ☐ extra monitoring required ☐ RSI issue trigger ☐ studies halted/suspended due to safety ☐ prioritise next ASR assessment ☐ other	Yes	☐	No	☐
If any yes, please specify which sections of this report includes details, or brief description:				
4.2. Are there any action required to follow up and/or to take by MSC:	Yes	☐	No	☐
Requested action to sponsor **to follow up** ☐ Protocol ☐ RSI during IB update ☐ IB ☐ ICF ☐ ASR content ☐ Other	Yes	☐	No	☐
Corrective measure ☐ If requests not fulfilled by sponsor in time set ☐ Request changes **now/immediately** ☐ Suspend ☐ Revoke ☐ Other	Yes	☐	No	☐
Specify recommended actions that should be taken:				

Cumulative Summary Tabulations of Serious Adverse Events – Section 7

Absolute numbers of patients that have been treated as per the column headings should be included in the text body of the ASR or preferably within the table itself

Patient treatment years may also be included

See Q7.40 of European Commission Q+A for more details

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

Cumulative Summary Tabulation of Serious Adverse Events (SAEs)

System Organ Class	Total up to 31-Dec-09			
Preferred Term	[Study drug]	Blinded	Active comparator	Placebo
	n=100	n=1	n=98	n=15
Investigations	**18**	**4**	**7**	**2**
Alanine aminotransferase increased	9	2	4	1
Aspartate aminotransferase increased	9	2	3	1
Nervous System Disorder	**2**	**2**	**4**	**7**
Syncope	2	2	4	7

Region-Specific Information – Section 16

- Cumulative summary tabulation of SARs
- List of subjects who died during the reporting period
- List of subjects who dropped out of clinical trials in association with an AE during the reporting period

Already in most global ASRs as other agencies require these sections

= Now also an EU/EEA requirement

Region-Specific Information – Section 16

A high level overview of the safety review process including but not limited to:

- how often data is reviewed and by whom
- what type of data source/format is reviewed
- what potential action may arise as a result of the surveillance process
- the criteria used for determining the addition or deletion of expected terms to the RSI

See Q7.42 of European Commission Q+A for more details

Region-Specific Information – Section 16

See Q7.42 of European Commission Q+A for more details

The outcome of the safety signal review process during the ASR reporting period should be outlined.

- Potential new safety signals that were identified should be listed
- Preferred format: PBRER table
- It may not always be possible or appropriate, in which case a justification for not including this information should be provided instead (eg not enough patients treated with IMP, authorised IMP used in line with SmPC etc)

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
Anaemia	04 March 2015	Ongoing	NA	Single serious case	The signal consisted of a single report of….	Individual case analysis; Review of relevant scientific literature. Reassessment of preclinical and clinical development safety data.	Review at the next Safety Review Team meeting

SUSARs
Suspected, **U**nexpected, **S**erious **A**dverse **R**eactions
Article 42

SUSARs – What stays the same?

Content of SUSAR reports (ICSR, ICH E2B)

Timelines for submission of SUSAR reports:

- 7 days for fatal and life-threatening SUSARs
- 15 days for other SUSARs

Reference Safety Information (RSI) used to determine expectedness

Reports submitted to and stored in EudraVigilance (EVCTM)

Member State Concerned (MSC) may choose to perform national assessments of SUSARs which occur in their territory

SUSARs – What is new?

Co-ordinated, workshared assessment:

- Per active substance - assessment led by saMS (safety assessing Member State)

Assessment includes all SUSARs in EudraVigilance (EU SUSARs and third country SUSARs)

No direct reporting to ethics committees and NCAs (reported to EudraVigilance only, re-routing available if necessary)

Safety profile changes sent to investigators, not individual SUSARs

Draft SUSAR procedures for saMS

Procedure 1: SUSAR Screen

- SUSAR screening of EudraVigilance
- Routine, regular work – weekly screen
- *Brief* documentation of assessment of each SUSAR should be recorded
- For active substance with high number of SUSARs may need to prioritise
- *In discussion with EMA to modify/develop EudraVigilance tools to support screen*

If no signal detected →

- End of assessment until the next weekly SUSAR screen

Majority of cases

Procedure 2: Signal assessment

If potential signal detected →

- 'Ad hoc' assessment case initiated by saMS

Minority of cases

SUSAR procedure – Signal assessment

Procedure 2: Signal assessment

<u>If potential signal detected</u> →

- Similar workflow and steps as for ASRs, but faster timelines
  - All RMS/MSC are informed and have the chance to comment/raise queries
  - Request for further information (RFI), if necessary
  - Assessment report written by saMS
  - Recommended actions proposed by saMS, if applicable

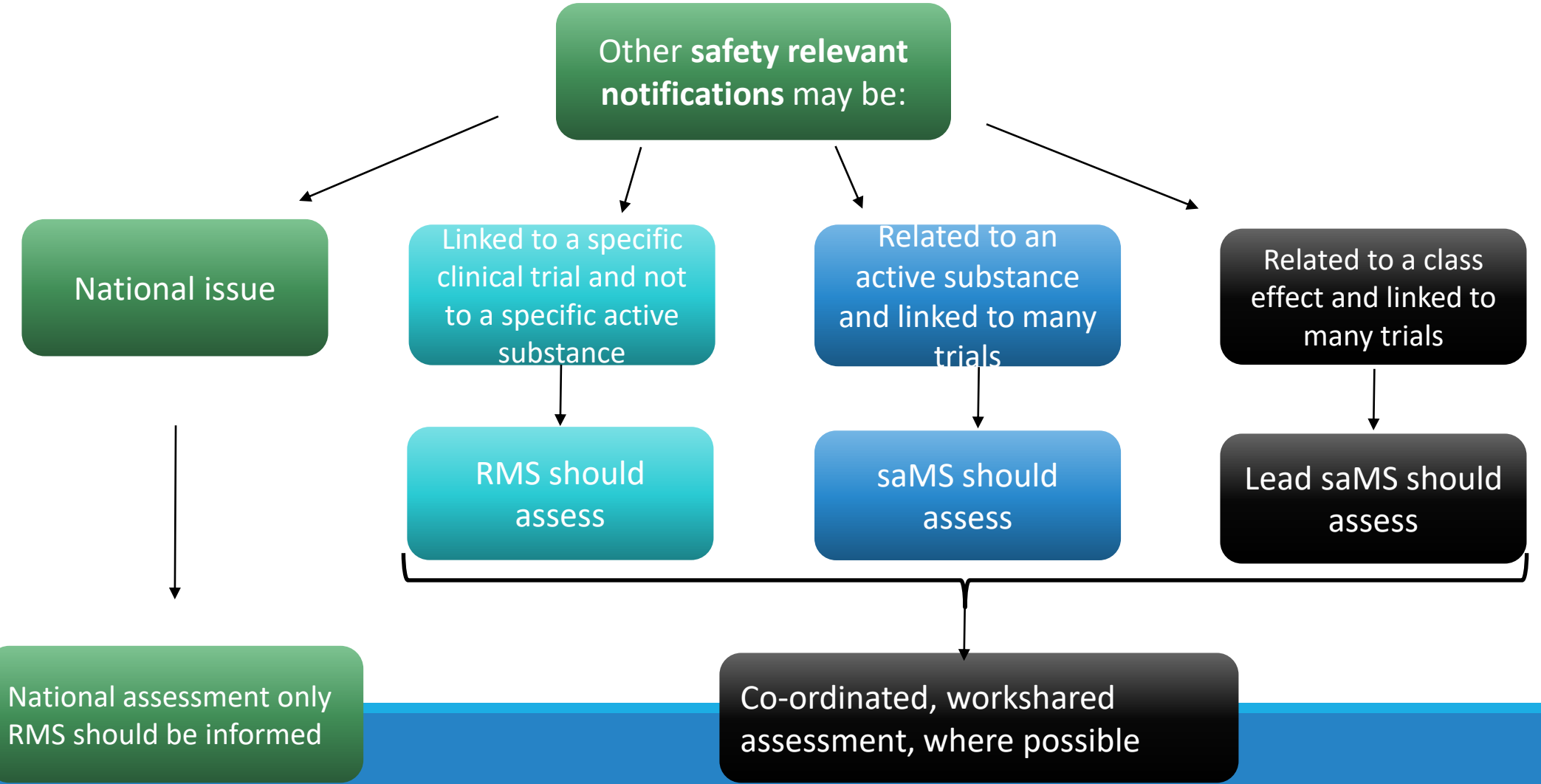
Other safety notifications and information

Other safety notifications and information

Other safety reports may include:

Type of notification/information	Article #
Temporary halt or early termination by the sponsor for reasons of subject safety	Article 38
Other reporting obligations relevant for subject safety • eg change in benefit risk	Article 53
Urgent safety measures (USM)	Article 54
Any other source of safety information • includes safety information that does fall under remit of Articles 38,42,43,53,54 • eg may come through CTFG via other committees [EMA, PRAC, CHMP, IRN etc]	None

Other safety notifications and information – General concepts



Draft procedures for other safety notifications and information

Procedure 1: Critical

- All MSC take **immediate action**
- Information on an issue will be shared
- **No time** for coordinated, workshared assessment initially
- Cooperation may be possible **after** initial action

Procedure 2: Regular

- Co-ordinated, workshared assessment
- Case created in CTIS
- All MSC are informed and have the chance to comment/raise queries

Lead saMS

Lead saMS

Where there are multiple active substances involved in a safety signal:

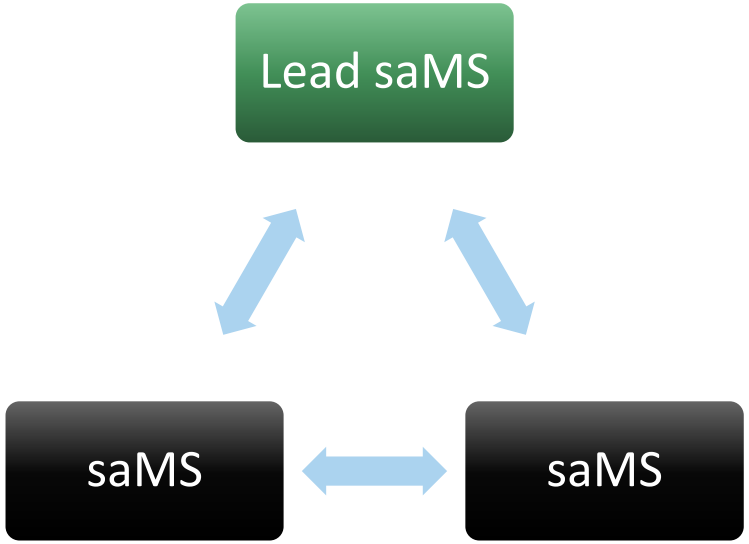
- One saMS takes the lead and co-ordinates exchanges with other relevant saMS

- Each relevant saMS still responsible for assessment of their active substance

- Rely on volunteer for lead saMS

Example: Drug class effect

Rare occasion



Corrective Measures

Corrective Measures – Art 77

saMS (or lead saMS) may propose recommended actions in relation to an active substance(s) following the assessment of:

- SUSARs
- ASR
- Other safety notifications or information

As per best practice guide:

- Relevant RMS to check and decide for impact on their specific trial
- If all MSC agree: RMS can implement corrective measures on behalf of all MSC eg RMS requests substantial modification
- If any MSC disagree: each MSC takes action themselves

However overall responsibility for a CT remains with individual MSC

Overview – Lead for workshared safety assessments

Type of safety information	National issue only	Linked to a specific clinical trial	Single active substance	Multiple active substances
ASR	-	RMS takes on the role of saMS	saMS	-
SUSAR	-	-	saMS	-
Temporary halt/ early termination	MSC	RMS	saMS	Lead saMS
Other reporting obligations	MSC	RMS	saMS	Lead saMS
Urgent safety measures	MSC	RMS	saMS	Lead saMS
Any other safety info (not covered above)	MSC	RMS	saMS	Lead saMS

THANKS

Clinical Trial Facilitation
and Coordination Group
CTFG