Vaccine Safety Investigation Group – Work Instruction

Pharmacovigilance and Special Access Branch
Signal Investigation Unit

Purpose

The Vaccine Safety Investigation Group (VSIG) is a time-limited working group which will be convened when specific criteria for an Adverse Event Following Immunisation (AEFI) or vaccine safety signal are met. The purpose of the VSIG is to provide independent specialist immunisation (and other relevant) expertise to assist the TGA and OHP to investigate and manage AEFI and vaccine safety signals of concern.

Role

Activities of the VSIG include (but are not limited to) the following:

- Causality assessment;
- Root cause analysis;
- Multi-case investigation;
- Development of communication material and risk communication messages including advice for clinicians;
- Advice on programmatic action;
- Advice on risk minimisation through regulatory action.

VSIG Membership

Members of the time-limited VSIG can include representatives from the following:

- Therapeutic Goods Administration, Department of Health, Australian Government
- Office of Health Protection, Department of Health, Australian Government
- The Jurisdictional Immunisation Co-ordinator for the jurisdiction(s) in which the AEFI occurred, and other representatives from the jurisdiction(s) (as required)
- The Chair of the Advisory Committee on Vaccines (ACV) (as required)
- ACV members (as required)
- Australian Technical Advisory Group on Immunisation (ATAGI) members (as required)
- National Centre for Immunisation Research and Surveillance members (as required)
- External clinical experts (as required)

ACV, NCIRS and ATAGI members will provide independent advice and will not represent their respective committee or group when participating in causality assessments.

Criteria to Convene the VSIG

The 'WHO Global manual on surveillance of adverse events following immunization' recommends that investigations that require the services of national-level experts need to be prioritised.[1] Consequently, the VSIG will be convened when the following criteria are met:

1) When an **AEFI of concern** or a **safety signal of concern** is identified by the TGA or OHP; AND
2) The TGA and OHP agree that the AEFI or signal:
    a. Has the potential to change the favourable benefit-risk balance of the vaccine in a National or State Immunisation program OR
    b. Could threaten public confidence in vaccine safety; AND
3) The case(s) is/are considered **eligible** for assessment and/or investigation.

An **AEFI of concern** is a single serious AEFI that is unexpected and without an obvious non-vaccine cause**.** A serious AEFI is an event that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered serious.[1] An AEFI is considered 'unexpected' if it is not listed in the Product Information document for the vaccine or is listed but causality has not been established.

For the purpose of convening the VSIG, a **safety signal of concern** would include the following:

- Serious AEFIs above an expected rate or level of severity; or
- A cluster of AEFIs which are serious or could be due to administration or quality issues. A cluster is considered to be two or more cases of the same or similar events related in time, geography, and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/provider, health facility, and/or a vial of vaccine or a batch of vaccines.[1]

For a case to be **eligible**, the following minimum criteria need to be met:[2]

- The name of the vaccine is available;
- Confirmation that the vaccine was administered before the event;
- A valid diagnosis for the reported AEFI. This can be an unfavourable or unintended sign, an abnormal laboratory finding, a symptom or a disease. For example, an AEFI report of "death" without any information on the preceding cause(s) would be considered ineligible pending further information.
- There is adequate information available to investigate/assess the case(s) e.g. pathology reports, radiological reports, post-mortem results (if applicable).

Once a jurisdiction becomes aware of an AEFI or safety signal of concern, it is expected that the jurisdiction will escalate the issue to the TGA in an expedited manner.

If an AEFI meets all of the above criteria except for criterion 3, it is important that attempts be made to collect further information so that the case can be assessed and/or investigated

at a later date. The Adverse Event Management System (AEMS) Co-ordinator should alert the Senior Medical Officer(s) within the SIU when further information is submitted to the TGA for these cases.

Outside of these criteria, the VSIG can be convened at any time at the discretion of the OHP and TGA, for example, in the instance that an AEFI or signal does not meet the above-mentioned criteria but has the potential to threaten public confidence in vaccine safety.

The TGA process for responding to AEFI and vaccine safety signals is outlined in the flowchart in Appendix 1. Pathways and timeframes for the escalation of AEFIs meeting certain criteria are outlined in Table 2 (Appendix 2). AEFIs or safety signals of concern may be brought initially to the attention of senior staff within the Department of Health. These AEFIs or safety signals of concern should be communicated to the Senior Signal Investigation Unit (SIU) Medical Officer (MO) on the same business day.

Process to convene the time-limited VSIG

- Following consensus between the OHP and the TGA to convene the VSIG, the Chair of the Advisory Committee on Vaccines (ACV) will be contacted by the relevant TGA or OHP representative.
- The ACV Chair will be provided with initial information about the AEFI report(s) (verbal or written) and the anticipated activities required of the VSIG.
- The ACV Chair may choose to be the VSIG Chair or may nominate an alternative Chair within the VSIG membership who is not a representative from the Department of Health.
- The VSIG Chair will recruit relevant experts to the VSIG based on the expertise required to respond to the AEFI or safety signal of concern.
- In situations where the VSIG needs to be convened in an emergent manner, there should be the capacity for the group to be convened within 1 business day following a request to the VSIG Chair.

VSIG Meetings

- Meetings will be chaired by the VSIG Chair (see above).
- To ensure independence and transparency, conflicts of interest and competing interests will be declared at the beginning of the meeting to enable the working group to consider whether a conflict of interest exists with the vaccine Sponsor(s), manufacturer(s), or distributor(s).
- The TGA will provide secretariat support for VSIG meetings. Secretariat support will include:
    - Liaising with the relevant jurisdiction(s) or sponsor(s) to obtain further information from the clinician(s) and/or patient(s) as required;
    - If relevant, liaising with international regulator(s) for further information;
    - Collating relevant information about the case(s) or safety signal and providing this to members of the VSIG ahead of any meetings;

- Providing a clinical summary document which outlines the key clinical features of the AEFI(s) that need to be considered by the group (template available at D18-10878774). If possible, before being provided to the group, the summary document will be reviewed and finalised by the VSIG chair;
- Providing relevant protocols, procedures or templates;
- Providing an agenda for the meeting which outlines the activities that the VSIG is required to undertake (not applicable to causality assessments);
- For causality assessments, prepopulating the causality assessment template (D18-10927314) with relevant information;
- Arranging the facilities for meetings whether they be face-to-face meetings, teleconferences or videoconferences; and
- Taking meeting minutes (except for causality assessments where a close-out document will be prepared by the TGA in the place of minutes – see 'Causality Assessments').

Causality Assessments

A causality assessment involves the systematic review of data about an AEFI case in order to determine the likelihood of a causal association between the vaccine(s) received and the event(s).[2] Causality assessments are one activity that the VSIG may perform. Causality assessment may be a stand-alone activity carried out by the VSIG for a single serious AEFI or it may be part of a broader and more comprehensive response, e.g. for a cluster of serious AEFIs.

The following should be adhered to when carrying out a causality assessment:

- A causality assessment will be carried out for each vaccine-event (valid diagnosis) pair relevant to the case(s).
- The summary document of salient clinical features will be read through at the beginning of the meeting by the meeting Chair to ensure all participants are across the pertinent clinical information.
- TGA representatives will provide a supportive secretariat role during causality assessments. For independence and transparency, TGA and OHP representatives and the jurisdictional representative(s) will not be involved in assessments of causality. The Chair and experts (herein referred to as 'the panel') will make decisions on causality.
- The causality assessment will be guided by the World Health Organization (WHO) 'Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification, (Second edition)'[2]. A causality assessment template is available at D18-10927314.
- The valid diagnosis should meet a standard case definition. If available, the Brighton Collaboration case definition is preferred however if one does not exist, a case definition can be adopted from the medical literature or national guidelines or developed. The case definition will be determined through consensus among the panel members.

- During the meeting, the participants should consider whether any programmatic or regulatory action is required based on the outcome of the causality assessment. If programmatic or regulatory actions are discussed, these will be captured in a meeting record which will be prepared by the TGA representative(s) and emailed to participants. Table 1 provides potential actions for consideration based on the causality conclusion.
- Following the meeting, the Chair will finalise the completed causality assessment report following review by the panel.
- The TGA will circulate the completed causality assessment report to the VSIG members and the relevant jurisdiction. The jurisdiction can forward the assessment to other relevant stakeholders (e.g. the Coroner for AEFIs with a fatal outcome)].
- The TGA will prepare a cover letter (template available at D18-11259693) addressed to the treating clinician that acknowledges any uncertainty associated with the causality assessment and the role of the causality assessment for individual cases. The Chair will sign the cover letter. The TGA will send a copy of the report and cover letter to the treating clinician.
- The Chair will provide an opportunity for the treating clinician to discuss the outcome of the causality assessment with the panel. The assessment and cover letter are intended to be shared by the treating clinician with the patient and/or family ideally after a discussion between the panel and the treating clinician (if required).
- Following the completion of the causality assessment, the TGA will:
    - Review the coding of the Individual Case Safety Report (ICSR) in AEMS and whether the causality categorisation initially assigned to the case when it was received by the TGA, is still appropriate. This will be considered on a case-by-case basis, giving consideration to the specific circumstances surrounding the case and will be decided by the SIU vaccine team. Referral to the SIU team meeting may be required in some circumstances. If the causality category differs from the causality conclusion of the panel, the case narrative of the ICSR will be updated to reflect this.
    - Prepare a close-out record in the form of a note for file (see template available at D18-10878801) which documents the outcome of the causality assessment, any regulatory or programmatic actions arising, and the outcome of any communications with the treating clinician and patient or patient's family.
    - Report the outcome of the causality assessment and actions arising back to the ACV and JIC through a VSIG standing agenda item at the following ACV meeting and the monthly TGA-OHP JIC teleconference respectively.

Table 1: Actions for consideration based on the causality conclusion (adapted to the Australian context from pps 81-82 of the WHO Global Manual on Surveillance of adverse events following immunization[1]).

Causality Conclusion	Action(s) for consideration
A. Consistent causal association to immunisation	
A1. Vaccine product-related reaction	• Managed on a case-by-case basis through programmatic and/or regulatory action.
A2. Vaccine quality defect-related reaction	• If related to a particular lot or batch, the distribution of the lot or batch must be ascertained. • Specific instructions must be provided on the utilisation or non-utilisation of the lot or batch. • The event should be communicated to the Sponsor and manufacturer. • WHO should be contacted through the organisation's local country office or the WHO Uppsala Monitoring Centre and the information communicated to ensure that other countries using the vaccine are alerted.
A3. Immunisation error-related reaction	• Further education (e.g. risk communication), training and capacity-building may be required to avoid recurrences of such events.
A4. Immunisation anxiety-related reaction	• Depending on the solitary or clustered nature of the event, there are separate approaches for prevention, diagnosis, and management including communications, training and capacity-building to avoid recurrences of such events.
B. Indeterminate	
B1. Consistent temporal relationship but insufficient evidence for causality	• Maintain the AEFI report in AEMS as it may help to identify a signal in the future. • Consider adding to the TGA's Intensive Drug Monitoring Program (IDMP)
B2. Conflicting trends of consistency and inconsistency with causality	• During the assessment, the panel members should clarify what additional information would be helpful to finalise the assessment. The TGA should seek this information from the treating clinician(s) and/or patient through the relevant jurisdiction. If applicable, consideration should be given to seeking expertise from national or international resources to finalise the assessment. If the event is likely to affect the immunisation program significantly, consideration should be given to approaching the Global Advisory Committee on Vaccine Safety (GACVS) through the WHO. • Reclassify to a more definitive category if additional information becomes available.
C. Inconsistent causal association to immunisation (coincidental)	
C. Coincidental	• Provision of information and confirmation to the patient and their relatives, through the patient's treating clinician.

Multi-case investigation (for a cluster or serious AEFIs above an expected rate or severity)

- There are two types of safety signals of concern which could warrant a multi-case investigation:
    1. **Serious AEFIs occurring above an expected frequency or severity.** The objective of the investigation is to determine whether there is a real increase in reaction rates/severity, identify the likely cause of the increase and decide whether any programmatic or regulatory action is required.
    2. **A cluster of cases.** The objective of the investigation is to assess the likely cause of the cluster and determine whether any programmatic or regulatory action is required. Clusters can be caused by immunisation error, immunisation anxiety, a vaccine quality problem, a new unrecognised vaccine product reaction, or a coincidental event.
- A standard case definition will be used for the event of interest in a multi-case investigation. Adoption of a Brighton Collaboration case definition is preferred, however if one is not available, case definitions can be adopted from standard medical literature, national guidelines or developed by the VSIG clinical experts. The case definition for a cluster investigation may include details of the related circumstances. The case definition will be determined through consensus among the VSIG working group members.
- Cases will be characterised and presented in a line list with salient information on time, person (past medical history, date(s) of vaccination and event onset, concomitant vaccinations and medications, investigation findings, outcome), place (e.g. geographic location of health care provider), antigens and type of event. This will be provided to committee members by the TGA.
- Cluster investigations may require the collection and collation of data on vaccine batch number, storage and handling of vaccines, immunisation practices and relevant health care workers' practices. If the cluster is location-specific, data may need to be collected on other people in the region, and any potentially coincident factors in the community or region. Data collection would usually be carried out by the relevant jurisdiction(s).
- Verification that the cases meet the established case definition will be undertaken by two independent working group experts.
- The working group may carry out causality assessments on the individual cases depending on the circumstances of the signal.
- For a signal due to serious AEFIs occurring above an expected frequency or severity, the reporting rate of the event will be estimated using the best available denominator data.
- To assess the strength of the signal, the reporting rate of the event should be compared with the known background rate in the Australian population (or comparable international populations) and expected rates[a] or historical reporting

[a] Based on the product information document for the vaccine and/or the WHO vaccine reaction rates information sheets (http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/).

trends. Depending on the signal, the best available denominator data may be 'number of doses administered', extracted from the Australian Immunisation Register (AIR).

- Other technical support, such as for an epidemiological analysis, may be required and would be organised by the Department of Health.
- Laboratory testing of the vaccine may occasionally be required and will be requested on the basis of a clear suspicion following the development of a working hypothesis and not as routine practice. The TGA will organise laboratory testing by emailing a request to the Director of the Immunobiology Section (for all vaccines except influenza vaccines) or for influenza vaccines to the Director of the Biomedicines and Influenza Vaccines Section, with a copy to the Heads of the Pharmacovigilance and Special Access Branch and Laboratories Branch. If appropriate, the TGA may request the Sponsor to carry out laboratory testing.
- The TGA will report the outcome of the multi-case investigation and actions arising back to the ACV and JIC through a VSIG standing agenda item for the following ACV meeting and TGA-OHP JIC teleconference respectively.

Communication with Stakeholders

The outcome of VSIG investigations and causality assessments will be promptly and clearly communicated to ACV members and jurisdictional stakeholders through the following processes:

- There will be a standing 'VSIG Investigation(s)' agenda item at ACV meetings and TGA-OHP JIC teleconferences to report the outcome of VSIG investigations, including causality assessments.
- The standing agenda item will provide ACV committee and JIC members with a high-level update on the outcome of any VSIG investigation(s) including whether any programmatic or regulatory action is being undertaken.
- For investigations that the TGA and OHP are proposing to close, the relevant documentation will be provided to ACV and formal agreement will be sought to close the investigation. Formal agreement of ACV does not apply to causality assessments.

Jurisdictional stakeholders and non-TGA committees such as ATAGI and the National Immunisation Committee (NIC) will be kept informed of the progress of investigations as appropriate.

In some circumstances, communication with health professionals and the wider community may be required (e.g. for reassurance or to communicate programmatic changes or regulatory action).

Review of Working Instruction

This work instruction will be reviewed following its implementation for a vaccine safety signal of concern or after 12 months of implementation, whichever comes first.

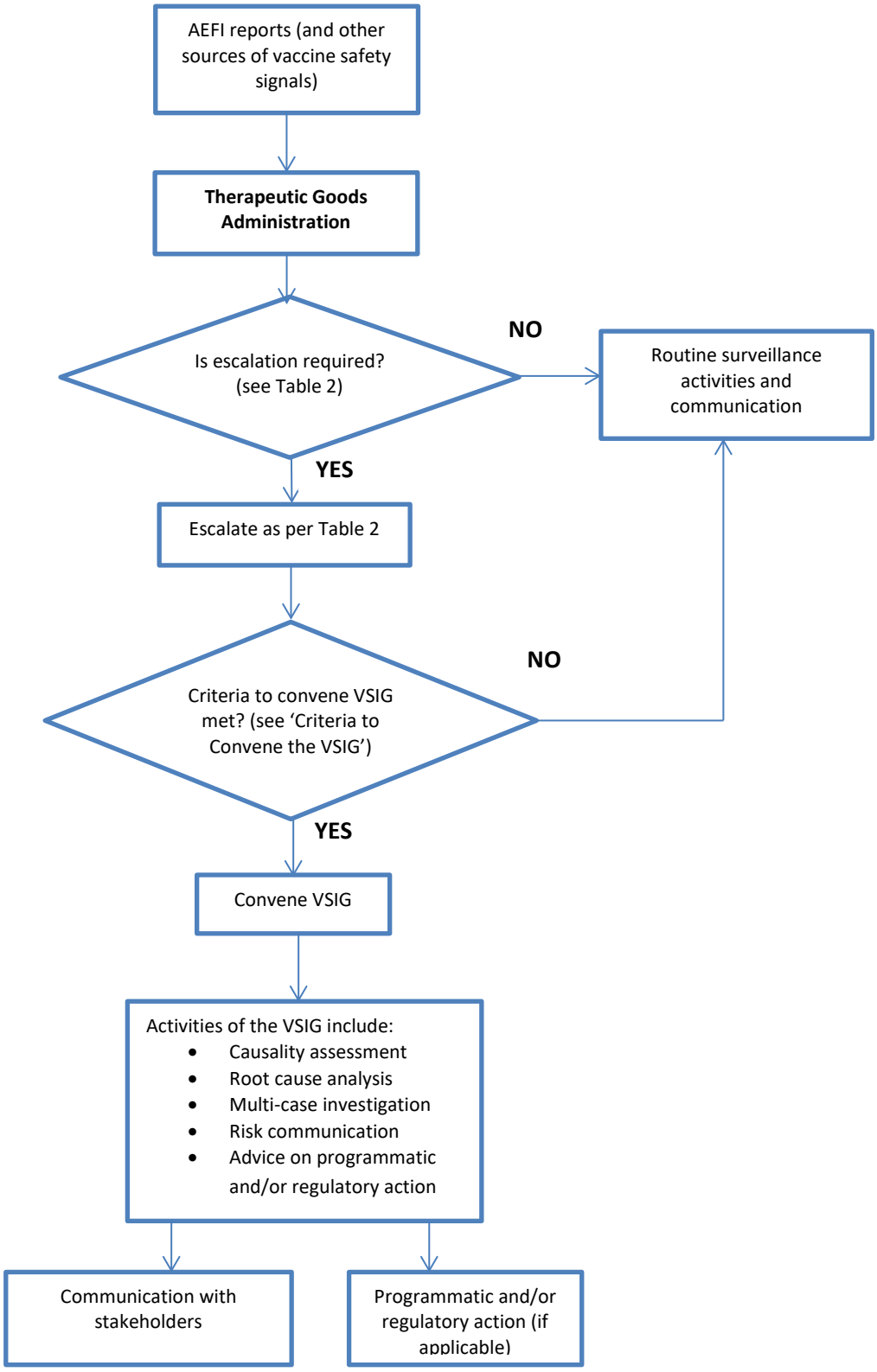
Related Documents

- AEFI Clinical Summary Template – D18-10878774
- AEFI Causality Assessment Template – D18-10927314
- Causality Assessment Close-out Summary Template – D18-10878801
- Causality Assessment Panel Cover Letter - D18-11259693

References

1. Global manual on surveillance of adverse events following immunisation. Geneva: World Health Organization; 2014 (revised March 2016).
2. Causality assessment of an adverse event following immunization (AEF): user manual for the revised WHO classification (Second edition). Geneva: World Health Organization; 2018. License: CC BY-NC-SA 3.0 IGO.

Appendix 1: Flowchart demonstrating the TGA process for responding to AEFIs and vaccine safety signals



Appendix 2

Table 2: Escalation timeframes and pathways for AEFIs meeting certain criteria

Escalation Pathway		Escalation Timeframe	
Person responsible for escalating	**Person escalated to**	**AEFI resulting in death**	**AEFI(s) which are serious unexpected, associated with a cluster, or for which specific surveillance is being undertaken**
Adverse Event Management System (AEMS) Coordinator[b]	Senior Signal Investigation Unit (SIU) Medical Officer (MO)	**Immediately** in person and by email	By email within **2 business days** of TGA receipt of report
AEMS Coordinator[c]	Jurisdictional Public Health Unit Immunisation Coordinator	By phone and email within **1 business day** of TGA receipt of report	By email within **2 business days** of TGA receipt of report
Senior SIU MO reviews the AEFI and follows the reporting pathway if the AEFI constitutes a safety signal[d] and the report contains adequate information[e]			
Senior SIU MO	SIU Director	**Immediately** in person and by email	By email within **2 business days** of TGA receipt of report
Senior SIU MO	Immunisation Branch Assistant Secretary	By email within **1 business day** of TGA receipt of report	As required, these may be sent as individual reports or collated.

[b] The AEMS Coordinator will also request further information from the reporter if required.
[c] If reported directly to the TGA (i.e. not through a jurisdictional public health unit).
[d] Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action.
[e] This includes the name of the vaccine, confirmation that the vaccine was administered before the event, a valid diagnosis has been reported, and there is adequate information to assess the case further e.g. past medical history, medications history, pathology results etc.

Escalation Pathway		Escalation Timeframe	
SIU Director/ Senior SIU MO	Pharmacovigilance and Special Access Branch (PSAB) Assistant Secretary	By email or in person within **1 business day** of TGA receipt of report	As required, depending on assessment by senior MO[f].
SIU Director/PSAB Assistant Secretary	TGA Executive • Medicines Regulation First Assistant Secretary • TGA Chief Medical Advisor	By email (simultaneously with PSAB Assistant Secretary) within **1 business day** of TGA receipt of report.	If required.
TGA Chief Medical Advisor	Deputy Secretary	By email within **1 business day** of TGA receipt of report (at the discretion of the CMA).	At the discretion of the CMA.
TGA Chief Medical Advisor	Commonwealth Chief Medical Officer	By email within **1 business day** of TGA receipt of report (at the discretion of the CMA).	At the discretion of the CMA.

[f] If the signal has the potential to change the favourable risk-benefit balance of the vaccine in a National or State Immunisation program OR could threaten public confidence in vaccine safety the AEFI will be escalated to the PSAB AS

Version history

Version	Description of change	Author	Effective date
1.0	Original publication	s22 [redacted]	7 January 2019

Authorisation

Name	Position	Date
s22 [redacted]	s22 [redacted]	7 January 2019