Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

COVID-19 vaccine pharmacovigilance: review of signal detection methods

Background

The current vaccine pharmacovigilance system used in the Signal Investigation Unit (SIU) employs a number of different methods for the surveillance of adverse events following immunisation (AEFI) and vaccine safety signal detection. In preparation for COVID-19 vaccines becoming available in Australia, the current signal detection methods used by the SIU have been reviewed to identify where they can be strengthened, and options for additional statistical data analysis methods to enhance the current system have been explored.

Aims

To strengthen the current safety signal surveillance methods and consider inclusion of additional statistical methods to facilitate the rapid detection of safety signals related to COVID-19 vaccines, allowing for timely assessment and investigation.

Objectives

1. Strengthening of current vaccine signal detection methods to increase any of the following:
    - Sensitivity to detect Adverse events of special interest and serious adverse events related to COVID-19 vaccines
    - sensitivity to detect unexpected AEFIs related to COVID-19 vaccine (where unexpected could be previously unidentified, unexpected severity or unexpected frequency)
    - positive predictive value (reducing no. of false positive signals and optimising efficient use of resources)
    - timeliness in detecting adverse events to allow for signal confirm and action or signal refutation and reassurance in vaccine safety
2. Review and consider alternate data mining algorithms (DMAs) that may be beneficial in addition to current safety signal detection methods
3. Develop and establish methods for the use of data from the Australian Immunisation Register (AIR) to calculate the reporting rates of COVID-19 AEFIs and compare observed with expected rates for signal detection and/or signal investigation
4. Consider the use of subgroup analysis in the detection and assessment of COVID-19 vaccine safety signals

DRAFT

5. Incorporate any improvements or new methods to wider vaccine and prescription medicine pharmacovigilance activities

DRAFT

Document overview

Section 1: Current system description

Section 2: Observed versus expected analyses

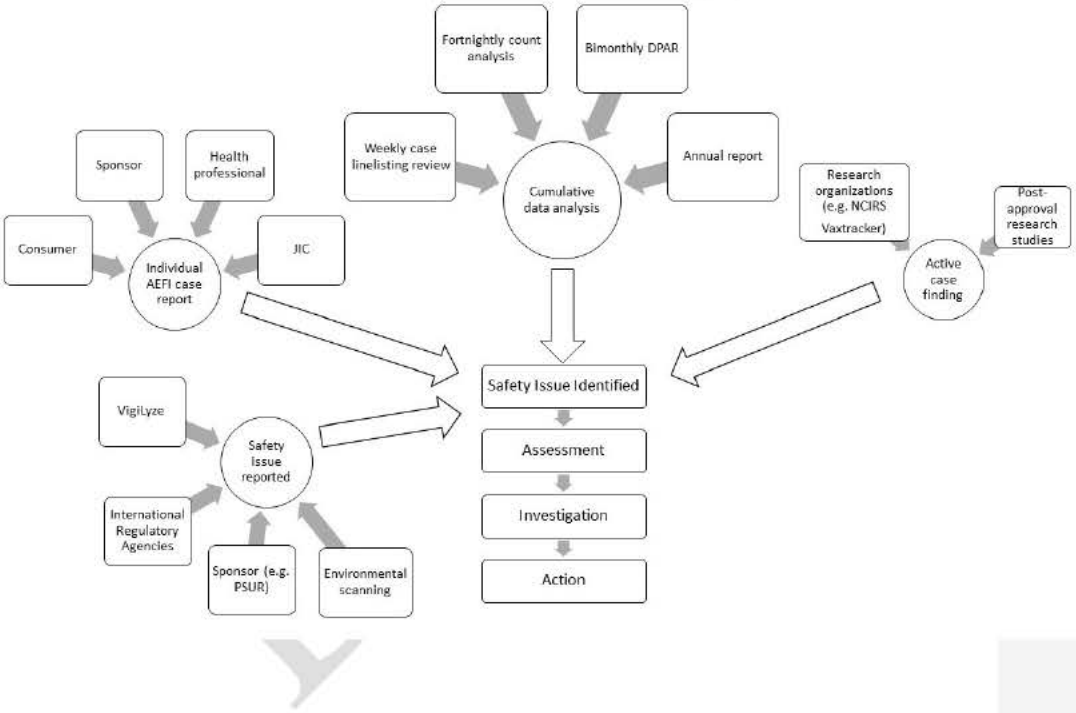
Section 3: Disproportionality assessment

DRAFT

Section 1: Current System description

There are three main components to the current vaccine safety pharmacovigilance system; spontaneous reporting of individual AEFI cases (e.g. by consumers, sponsors, health professionals), analysis of cumulative AEFI reports to detect safety signals, and active surveillance programs run by external agencies (e.g. Vaxtracker, SmartVax). Figure 1, below, summarises the main sources of information leading identification of vaccine safety issues.

Figure 1: Simplified overview of SIU vaccine pharmacovigilance system



Spontaneous reporting System (SRS)

Individual adverse event case reports

Reports of Adverse Events Following Immunisation (AEFI) are notified to SIU in several ways, such as notification from:

- Sponsors
- Consumers
- Health Professionals
- NPS Medicine line

AEFIs are coded using MedDRA Preferred Terms (PTs) and entered onto the Adverse Events Management System (AEMS) by the Adverse Event and Medicine Defect Section (AEMDS). Vaccines are coded using the Anatomical Therapeutic Chemical (ATC) code for the generic medicine name (begins with J07). Medically significant AEFI (serious AEFI and AESI) are escalated to the SIU team to assess and investigate as necessary. Additional AESI related to COVID-19 vaccines will be monitored based on safety information from the vaccine clinical trials and guidance from the Brighton Collaboration.

Serious AEFI

- Result in death
- Life-threatening
- In-patient hospitalisation/prolonged hospitalisation
- Result in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Requires intervention to prevent one of the above

Adverse events of special interest (AESI)

- Anaphylaxis
- Seizures/convulsions/fits
- Hypotonic-Hyporesponsive episodes
- Extensive limb swelling
- Serum Sickness
- Neurological conditions:
  - Acute disseminated encephalomyelitis
  - Bell's palsy
  - Encephalitis
  - Encephalopathy
  - Gullian-Barre Syndrome
  - Multiple sclerosis
  - Neuritis
  - Optic neuritis
  - Paralysis
  - Transverse myelitis

DRAFT

Additional AESI related to COVID-19 vaccine (not already included in serious AEFI or AESI)

- Thrombocytopenia
- Vasculitides
- Aseptic meningitis encephalitis/ encephalitis (live viral vaccines)
- Arthritis (r-VSV platform)
- Myocarditis (MVA platform)
- Vaccine-associated enhanced disease (VAED)
- Paediatric inflammatory multisystem syndrome temporally associated with SARS CoV-2 (PIMS-TS)
- Acute respiratory distress syndrome (ARDS)
- Acute cardiac injury
- Coagulation disorder
- Acute kidney injury
- Liver injury
- Anosmia, ageusia
- Chilblain-like lesions
- Single organ cutaneous vasculitis
- Erythema multiforme
- Thrombosis with thrombocytopenia Syndrome

■ General for all vaccines

■ Risk with specific COVID-19 vaccine platforms

■ Theoretical risk with COVID-19 vaccines (AESI has been seen with other vaccines or concern based on immuopathogenisis or viral replication during wild type disease)

Adverse Events of Special Interest (AESI) related to COVID-19 vaccines

Pharmacovigilance preparedness for new and emerging adverse events following immunisation (AEFI) will be integral to building our understanding of COVID-19 vaccine safety. A list of adverse events of special interest (AESI) will aid timely and effective signal detection, coding and escalation of potential safety issues for investigation and regulatory action.

The SIU has reviewed the Priority List of Adverse Events of Special Interest: COVID-19 published by the Brighton Collaboration in conjunction with the Safety Platform for Emergency vACcines group (SPEAC) [1]. Inclusion of potential AESI for COVID-19 vaccines is based on experience with existing vaccines, those associated with vaccine platform and anticipated AESI related to vaccine associated enhanced disease and/or the disease itself (COVID-19 infection). The AESI list will be subject to ongoing TGA review as new data arises from sources such as pre-market clinical trials, risk management evaluation and investigation of post-market case reports.

Published case definitions by the Brighton Collaboration will inform and guide development of SIU processes for consistent and accurate MedDRA coding of post-

DRAFT

market AEFI reports. Case definitions published for selected COVID-19 AESI will assist the prioritisation and escalation of significant cases for rapid regulatory action and communication. In turn, this will enhance data collection by the TGA from initial AEFI reporting pathways and follow-up for additional information related to COVID-19 vaccines.

Further methods for investigating individual AESI cases include liaison with local state and territory jurisdictions, as well as sharing information and collaboration with international regulators on COVID-19 vaccine safety signals. The SIU will also strengthen existing processes for establishing a standing Vaccine Signal Investigation Group (VSIG) to be called upon for expert advice on new and emerging COVID-19 vaccine safety issues.

DRAFT

Advantages

- Easy identification of significant adverse events allowing for timely response
- Best method to rapidly identify and serious adverse events

Disadvantages

- Not all adverse events reported (under-reporting)
- Increased public awareness/media coverage may lead to over-reporting
- Based on individual case reports so unable to detect trends
- Information reported is of variable quality and not consistent between jurisdictions (no standardised format)
- Additional information may need to be sought for case report assessment and investigation
- Potential duplication of reports from different sources
- Information from some reporting sources require manual entry of information into AEMS

Improvements for consideration

- Enhanced passive surveillance: actions to minimise under-reporting
  - Develop a communication strategy for immunisation providers and AEFI reporters providing information about anticipated COVID-19 vaccine AEs and increase awareness about reporting (noting this will require collaboration and coordination with other stakeholders)
  - Consideration of novel reporting formats – use of social media, dedicated COVID-19 reporting hotline

    - Consider the use of data from electronic medical records and administrative healthcare databases to detect AEFIs that might be missed by spontaneous reporting methods
        - Potential for automated extraction of data (search terms related to AEFI) from clinical information systems to detect potential safety signals
        - Set-up would require significant time, resources and expertise. Consider possible scoping project to establish feasibility, resource requirements, access to data and assessment of additional benefits (particularly) sensitivity achieved through incorporation of this type of data.
- Improve AEFI reporting data quality
    - Standardisation of AEFI case reporting across jurisdictions (standard form/data fields)
    - Modification of reporting forms to collect or request additional data will needed to assess AEFI related to COVID-19 vaccines (e.g. VAEDS).
- Reduce manual data entry
    - Establishing standardised reporting formats so AEFI report data can be directly imported into AEMS (move towards Electronic Data Interchange (EDI), online reporting)
- Establish active surveillance program/methods
    - Collaboration with research organisations and providers to review active surveillance programs and consider establishment of sentinel reporting sites

Other vaccine safety signal identification sources

Weekly Environmental scanning

Vaccine safety issues are also identified through post-approval research, either through the sponsor (ongoing clinical trials and monitoring) or research organisations. On a weekly basis a SIU staff member reviews updates from medical regulatory bodies and scientific literature to identify any new safety issues from these sources.

SIU vaccine team staff have also implemented a regular media watch update, providing a regular email update related to COVID-19 vaccine news in the media.

Commented [s22]: Was this replaced or does it need to be reinstated

Improvements for consideration

- Consider more formalised/systematic approach to rumour surveillance/media watch in order to identify any public concerns about vaccine/possible safety issues from media sources early. These report may be difficult to investigate but will provide situational awareness about public concerns with vaccine

DRAFT

safety and could potentially flag larger safety issues early which can then be further investigated through more formal methods.

Sponsors and regulatory bodies

Sponsors are also required to update the TGA with periodic safety update reports and any safety signals that they have identified through their own surveillance programs and risk management plans. The TGA, and SIU are also working closely with the International Coalition of Medicines Regulatory Authorities (ICMRA) so that international safety information will be shared between different regulatory bodies and signals identified overseas will also be reviewed for their potential impact in the Australian context.

References

1. Law B, Sturkenboom M. D2.3 Priority list of adverse events of special interest: COVID-19. Safety Platform for Emergency vACcines; May 25 2020.

DRAFT

Quantitative analysis of cumulative data from the Adverse Events Management System

Data from all AEFI case reports are stored in the AEMS. Whilst the individual case safety reports focus on serious AEFIs and AESI, the aim of quantitative analysis of cumulative AEFI reports is to detect new (unrecognised) adverse events, clustering of an AEFI (in time or place), or a higher frequency of an AEFI than expected. This may include higher rates of febrile or allergic type reactions related to a particular vaccine, which could indicate stronger reactogenicity and potential for more serious AEFIs to occur.

Current cumulative data analysis reports:

- weekly case linelisting review
- fortnightly aggregate analyses of case reports using absolute case counts
- bimonthly disproportionality analysis report (DPAR)
- annual report

Weekly Case Linelisting Review

With respect to COVID-19 vaccines the sheer number of reports has meant that his process is no longer feasible, however coding checks remain for Adverse events in evaluation or vaccine related high priority investigations (VRHPI). It is imperative that due to the inability to cross check all coding that any AEFI investigation does and expanded term or case narrative search.

A linelist of all AEFI cases reported for the week is generated from the AEMS database via Qlik. For quality assurance, this list is reviewed and crosschecked with a list of all AEFI cases escalated to the SIU team to ensure all serious AEFIs or AESI have been escalated and assessed. The list is also reviewed to check for any interesting cases, provide a data quality check of coding and as a reference at the Jurisdictional Immunisation Coordinators meetings.

The list of AEFI cases escalated to the SIU is stored on an excel spreadsheet that is manually generated by one of the SIU staff members. Depending on the number of serious AEFIS or AESIs reported, entering all case report details into this spreadsheet a time consuming process.

Advantages	Disadvantages

DRAFT

- Quality assurance for data coding and escalated AEFIs
- Safety net to ensure no significant reactions are missed
- Reference for JIC meetings

- List of escalated AEFI cases is manually entered
- Duplication of data that is already stored in CRM/AEMS
- Not best suited to identify trends over time
- Requires experienced pharmacist to review cases to check coding and identify 'unusal' AEFI-vaccine reports for further review

Improvements for consideration

- Investigate the possibility of an automated report generated from AEMS/QLIK listing all AEFIs that meet escalation criteria which could be used for case escalation
- Review other coding data quality processes to make sure systematic checks are in place noting the director of the Adverse Events Management DS undertakes a fortnightly quality control check.
- Consider quality control checks for new AEFI coding relating to COVID-19 vaccines

Fortnightly aggregate analyses of case reports using absolute case counts

With respect to COVID-19 vaccines the sheer number of reports has meant that his process is no longer a viable analysis tool. It remains of value for non-covid reports

On a fortnightly basis, a staff member from SIU generates a report from Qlik that provides the absolute year-to-date case numbers for AESI, which is then compared with the year-to-date numbers for the previous year. If the absolute number of cases appears to be higher in the current year-to-date, further investigation in undertaken.

Advantages

- Comparing year-to-date data takes into account seasonal fluctuations in vaccine administration (e.g. influenza)
- Relatively simple and quick check to flag potential increases in frequency of certain AESI

Disadvantages

- No denominator data is used, so there is no context provided in terms of the relative increase of AESI compared with previous year, which in turn can generate false positive flags for investigation

DRAFT

- Anecdotally does not appear to have detected issues that were not already detected through one of the other surveillance methods
- May be of limited benefit for initial COVID-19 vaccine surveillance as the vaccines will be new with no previous year comparator data available. Would need to consider weekly/fortnightly comparisons instead.

Improvements for consideration

- As stated in the disadvantages above, fortnightly comparisons of absolute year-to-date numbers for AESI related to COVID-19 vaccines will not be appropriate initially as there will be no previous year data. Recommend looking at comparing weekly trend in absolute numbers with the cumulative numbers to-date. Weekly review could be adjusted to be less frequent (e.g. fortnightly) depending on number of reports received.
- Review of which AESI relevant to COVID-19 vaccines as per the list of AESI determined by the Brighton Collaboration as discussed above. Consider the removal of AESI that are not relevant to COVID-19 vaccines such as HHE, as the vaccine will not be used in children initially.
- Consider the addition of additional serious AEFI to the weekly absolute case count review (e.g. anaphylaxis)

Weekly AESI review

Weekly AEDI review

Formatted: Font: (Default) Arial, 14 pt, Bold

Formatted: Font: (Default) Arial, 14 pt, Bold

Formatted: Normal, Indent: Left: 0.63 cm, No bullets or numbering

DRAFT

Section 2: Observed versus expected rates using Australian Immunisation Register (AIR) data and expected rates

Background

The Australian Immunisation Register (AIR) is a national register which records vaccines given under the National Immunisation Program, school programs and those given privately. The TGA ~~is currently in negotiation with the AIR data custodians~~has ~~for~~ access to de-identified data on immunisation numbers and related demographic information. As reporting of COVID-19 vaccine administration to the AIR is likely to be made mandatory, the SIU anticipate that this data will provide a denominator value in the calculation of observed rates of adverse events. Utilisation of expected rates will allow 'observed versus expected' analyses.

The AIR utilises vaccine distribution data to calculate reporting rates, which will be an important indicator of the reliability of the AIR data for use in AEFI rate calculations.

Structured observed versus expected analyses can be used prospectively for signal detection, or in a less structured way to inform broader assessment of causality following signal detection. There are different expected rates that can be used, including background historical incidence rates, rates of the AESI with other vaccines and rates of the AESI with the same vaccine in other countries/ locations. For more common adverse events that have already been observed in clinical trials, clinical trial data and product information documents may be a source of expected rates. As always, consideration of the appropriate comparator is required such as whether vaccinated individuals are different to the overall population (when using population incidence rates as the expected), or whether the population that receives one vaccine is sufficiently similar to the population that received another vaccine (when using rates of the AESI with other vaccines as the expected). The appropriate use of risk windows for different AESIs and the limitations of the data sources are also important.

Background historical rates of selected disease events may also have an important role in risk communication ahead of, or during the implementation of the COVID vaccine program. Knowledge of the expected number of cases of these selected disease events in the absence of new vaccine(s) could be used to separate legitimate safety concerns from coincidental health events.

Methods

The TGA is conducting a focussed literature review of observed versus expected vaccine safety analyses (concentrating on analyses using spontaneous reporting data for the observed counts). In addition, TGA is consulting with other regulators through the ICMRA COVID-19 Vaccine Pharmacovigilance Network and stakeholders regarding the use of statistical methods involved in observed versus

DRAFT

expected analyses. Similar to the signal detection algorithm work above, the TGA is considering factors such as sensitivity, timeliness, false positives, ease of implementation and interpretability, and required resources and expertise.

Initial literature findings

a) Observed versus expected analyses for signal detection

Background historical incidence rates

Prior to the H1N1 influenza vaccine program, researchers identified background rates of selected disease events, using published literature, disease registries, and hospital admission databases. These rates at selected sites were used to calculate rates of events likely to occur within one day, one week and six weeks after receipt of a hypothetical dose of a vaccine by multiplying the number of hypothetically vaccinated people by the background rates and the risk window. Although these rates were published, the authors encouraged the development of local databanks of background rates that represent as far as possible the age, sex, ethnic and geographical characteristics of the population being vaccinated [1]. The importance of using age specific background rates to avoid confounding by age is emphasised [4].

Regulators such as the MHRA, as they did during the implementation of other new vaccine programs, are planning to conduct near-real time observed versus expected analyses, to supplement their passive surveillance systems during the COVID-19 vaccine program. For the H1N1 influenza vaccine program, the MHRA used age-stratified background incidence rates (irrespective of vaccination) from their General Practice Research Database (GPRD), to determine how many AESIs would be expected due to chance in vaccinees. Using exposure (or vaccination data), they compared the observed rate (reports submitted via the Yellow Card passive surveillance scheme) with the expected. Adjustment for under-reporting and use of the maximised sequential probability ratio test (max SPRT) allowed real-time evaluation of the likelihood of excess reporting and weekly assessments of their analyses were published [2]. For the HPV vaccine, a similar enhanced pharmacovigilance system was established for anticipated adverse events [3].

Observed versus expected analyses can also be conducted using hospital presentations/ admissions of the health condition of interest as the observed count rather than spontaneous reporting data, alleviating the issue of underreporting associated with passive surveillance. Presentations/ admissions of the health conditions of interest are monitored each week from the commencement of the vaccine program and compared to historical data from the same clinical setting. This is also referred to as an ecological, rapid cycle or before-after analysis. NZ authorities used this analysis as one component of their surveillance program for a new meningococcal B vaccine [5].

Comparator vaccine expected rate

For some AESIs that are less likely to lead to hospitalization, such as thrombocytopenia, it may be difficult to determine background historical incidence rates. In such instances, rates of the AE following other immunization(s) might be

used as the expected rate, giving a rate per dose of vaccine [4,5]. Another example of using the rate of an AESI with comparator vaccine as the expected rate is the MHRA's implementation of enhanced surveillance to determine whether the seasonal influenza vaccine was associated with an increased risk of febrile convulsions, as was observed in Australian in 2010. The MHRA calculated background rates of febrile convulsions after influenza vaccines from 2000-09 and 2009-10 with data from the GPRD. Using these rates and data on the number of children immunised across the UK, they calculated an expected number of cases of febrile convulsions within 72 hours of immunisation every week. Comparing this to the number of Yellow Card reporting, they did not detect any indication of excess reporting [8]. Historical comparator vaccine data is sometimes referred to as historical control data, and an alternative is to use concurrent matched controls [4].

Expected rate from self-controlled risk interval analyses

Using self-controlled data for the expected rate adjusts for known and unknown time-invariant confounders [15].

b) Observed versus expected analyses for signal strengthening

Two analyses from Australia demonstrate the use of comparator vaccine rates, used retrospectively rather than as prospective signal detection. The first examined adverse events following HPV vaccination using 11 years of national spontaneous reporting data, and compared the reporting rate of syncope and anaphylaxis in Australia with that reported to the FDA in the Unites States with the same vaccine [9]. In Victoria, the spontaneous reporting rate for syncope with the HPV vaccine was compared to the reporting rate in the United States for the same vaccine. The reporting rate for syncopal seizures was also compared to that seen in Australia with a measles catch-up vaccination campaign, although the comparison was cautious given the younger age group who receive the measles vaccine [10].

For more common AESIs that are detected in pre-market clinical trials, but which a concern regarding increased frequency of the AESI arises, the observed rate using AEMS and AIR data can be compared to the rate of the AESI from the pre-market clinical trial. For the COVID vaccine(s), clinical trials will be ongoing after initial registration, due to the likely provisional approval that they might be given. Therefore, ongoing clinical trial data and data from post authorisation safety studies may be used as the expected rates. Similarly, rates of AESIs observed overseas with the COVID vaccine may also be useful as a comparison.

Improvements for considerations

1. The TGA should consider the feasibility of undertaking observed versus expected analyses through the establishment of a formal near real time enhanced surveillance system for signal detection, to complement the TGA's existing signal detection methods such as PRR analysis of AEMS data. Barriers to such a system for the TGA include not currently having ready access to national electronic health record or administrative health record databases to establish Australia specific background historical incidence figures. Consideration of the statistical methods, software and expertise is also required, as repeated statistical testing of accumulating data requires special methods, such as the max SPRT method [6, 7].

DRAFT

2. Outside of their use in structured near real time signal detection, expected rates should be used in the assessment of possible vaccine safety concerns generated through other signal detection methods. For this purpose, a reference list of expected rates for the Brighton Collaboration AESIs should be developed in advance. In the first instance, these can be based on published literature. Further consideration should be given to utilising Australian data sources to generate them.

   Deriving comparator vaccine expected rates through AEMS and AIR data is possible, but their use may be limited because of the historical low reporting to AIR for non-childhood vaccines, and the potential for bias in comparing recipients of the COVID vaccine to recipients of other vaccines on the NIP.

3. It is recommended that staff gain familiarity with the use of observed versus expected analyses to aid in the interpretation of signals detected by other regulators using these methods, and for risk communication.

Post market comments

The TGA now has access to hospital admission background rates from NCIRS for many AESI. These rates however should be compared for confidence with the EMA rates when available. If a large inconsistency exists then a sensitivity using both rates should be undertaken.

At all times background rates should be compared on an age stratified basis at a minimum.

For AESI the ability to undertake maximised sequential probability ratio test analysis is possible and has commenced

For AEFI where background rates are not readily available, the dose adjusted Comparator vaccine expected rate should be employed to enable like vaccine comparison for early high level signal detection using Chi square statistic with a 90% confidence interval as described below. Note the use comparison between the COVID-19 vaccines removes a lot of the limitations. This method draws upon the DPAR methodology but adds accuracy by using doses administered and a comparable vaccine.

Definitions and calculations

AEFI frequency = the number of instances of a specified AEFI in the exposed (vaccinated) population over a specified time period

DRAFT

Incidence proportion (cumulative incidence) = incidence expressed as a proportion of the population at risk (noting need to specify time period for context e.g. year 2019)

$$\frac{\text{No. of cases of specific AEFI}}{\text{No.vaccinated with vaccine of interest}}$$

Event rate per 100,000 population per period = Number of reports of specific AEFI divided by the number of exposed (vaccinated) multiplied by 100, 000 (note also need to specify time period for context (e.g. year-to-date 2020))

$$\frac{\text{No. of cases of specific AEFI}}{\text{No.vaccinated with vaccine of interest}} \times 100,000$$

Incidence proportion ratio (Relative risk) = AEFI incidence proportion in the exposed (vaccinated with COVID-19 vaccine) divided by AEFI incidence proportion in the unexposed (comparator vaccine/background population rate).

(a/(a+b))/(c/(c+d))

Statistical comparison of the incidence proportions can be made using the chi square test and calculating the 95% confidence intervals.

Chi square statistic: compares two variables in a contingency table to see if the distributions differ from each other. Tells you how much difference exists between your observed counts vs your expected counts.

$x^2 = \sum \frac{(O-E)^2}{E}$ to 1 degree of freedom

	Reported AEFI of interest (AEMS data)		**TOTAL (denominator data from AIR)**
	Yes	**No**	
COVID-vaccine	A	B	a + b
Comparator	C	D	c + d
TOTAL	a + c	b + d	a + b + c + d

DRAFT

Expected counts are calculated (row total ×column total)/table total (a+b+c+d)

e.g. for a, expected count E = (a+b) × (a+c)/(a+b+c+d)

for b, E = (a+b) × (b+d)/(a+b+c+d)

then use chi square statistic and degrees of freedom to determine p-value.

*noting assumption expected no. for each cell needs to be >5

Excel has an equation function for chi square test.

Can also calculate the standard error and 95% CI for the incidence proportions

Standard error (SE):

$$SE_{(p_1 - p_2)} = \sqrt{\left(\frac{p_1(100-p_1)}{n_1}\right) + \left(\frac{p_2(100-\ _2)}{n_2}\right)}$$

95% Confidence Interval:

95% CI = $(p_1 - p_2) - 1.96 \times SE$ to $(p_1 - p_2) + 1.96 \times SE$

Limitations

- Under-reporting to AIR (however mandatory reporting of COVID-19 vaccines has removed this issue)
  - Reporting likely to be high for childhood vaccinations, but much poorer reporting rates for adults
  - Specific groups may be more prone to underreporting → occupational vaccinations, may not be reported unless done by a private company, aged care residents unlikely to have vaccination status reported
- Potential time lag between vaccinations and reporting
- ~~Can only be used for pre-defined conditions~~

Maximised sequential probability ratio test (MaxSPRT) method

The MaxSPRT was developed in response to direct vaccine safety surveillance needs in the Centers for Disease Control and Prevention (CDC)-sponsored Vaccine Safety Datalink (VSD) and, as such, it is already in practical use [16]

Formatted: Font: (Default) Arial

DRAFT

This method compares the cumulative number of AEs observed to the number expected according to background incidence rate, cumulative doses, risk window and the Poisson-based maximized sequential probability ratio test (MaxSPRT). We define a signal as occurring when the number of AE reports observed after vaccination significantly exceeds the expected, by comparing the log likelihood ratio (LLR) to a threshold, a critical value that is based on the Poisson probability distribution and adjusted for the multiple looks at the data that are inherent with sequential analysis. The threshold value is set to a level designed to keep the cumulative probability of making a type I error below the conventional 5% level over the repeated analyses.

The analysis will take all reported AEs relating to AESIs, regardless of whether the cases are confirmed, because at the signal generation stage, false positives can be tolerated. As soon as the LLR reaches the critical value, the null hypothesis of no association between the AE and vaccine is rejected, the AE signal is generated, and we will stop the formal sequential analysis. Note that because of the randomness of the data, it is possible for the LLR to drop below the threshold again before climbing and staying above. At the time of signal, we will report the observed vs. expected ratio estimate, the total number of doses, observed and expected number of AEs and the LLR.

The signal will be followed up with case reviews to ensure that the reported AEs meet the definition criteria, and with further assessment of causality. Supplementary sequential analyses may be conducted over the confirmed/probable AE cases.

s22 ~~happy to elaborate~~

CUSUM method

The cumulative sum of the data sequence (in most cases, a time-series of data) is used as the statistical variable for detecting significant changes (deviations) from the noise levels22 ~~happy to elaborate~~ This method relies on relatively high frequency data (such as that received through active surveillance).

DRAFT

References

1.Black S, Eskola J, Siegrist CA, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccine. *Lancet 2009*; 374: 2115-2122. [TRIM D20-3568377]

2. Bryan P, Seabroke S, Davies C. H1N1 vaccine safety: real-time surveillance in the UK. *Lancet 2010;* 376: 417-418. [TRIM D20-3669030]

3. Donegan K, Beau-Lejdstrom, King B, et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine 2013*; 31: 4961-4967. [TRIM D20-3669043]

4. Yih WK, Kulldorff M, Fireman BH, et al. Active surveillance for adverse events: the experience of the vaccine safety datalink project. *Pediatrics 2011;* 127; S54. [TRIM D20-3669054]

5. McNicholas A, Galloway Y, Stehr-Green P, et al. *Human Vaccines 2007*; 3: 196-204. [TRIM D20-3593794]

6. Lieu TA, Kulldorf M, Davis RL, et al. Real time vaccine safety surveillance for the early detection of adverse events. *Medical Care 2007*; 45(10): S89-S95. [TRIM D20-3639390]

7. Leite A, Andrews NJ, Thoman SL. Near real-time vaccine safety surveillance using electronic health records –a systematic review of the application of statistical methods. *Pharmacoepidemiology and Drug Safety 2016*; 25: 225-237. [TRIM D20-3669049]

8. Bryan P, Seabroke S. No increased risk of febrile convulsion after seasonal influenza immunisation in the UK. *Lancet 2011;* 377: 904. [TRIM D20-3669036]

9. Phillips A, Hickie M, Totterdell J, et al. Adverse events following HPV vaccinaton: 11 years of surveillance in Australia. *Vaccine 2020*; 38: 6038-6046. [TRIM D20-3677830]

10. Crawford NW, Clothier HJ, Elia S, et al. Syncope and seizures following human papillomavirus vaccination: a retrospective case series. *MJA 2011*; 194: 16-18. [TRIM D20-3677820]

15. Lee GM, Greene SK, Weintraub ES, et al. H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project. *Am J Prev Med 2011*; 41(2): 121-128. [TRIM D20-3669046]

DRAFT

16. Kulldorff M, Davis RL, Kolczak M, Lewis E,et al. A Maximized Sequential Probability Ratio Test for Drug and Vaccine Safety Surveillance, Sequential Analysis, 30: 58–78, 2011 **[TRIM** D21-3002419]

Section 3: Disproportionality Analysis

Any COVID-19 vaccines introduced in Australia will be novel, there is likely to be more than one vaccine approved for use and vaccination is likely to occur on a large scale over a relatively short period. As such, it is essential to make sure pharmacovigilance methods are sensitive to detecting any potential safety signals in a timely manner.

Several different data mining algorithms (DMAs) have been developed as systematic approaches to identify safety signals in large spontaneous reporting databases. [1] Despite variations in their approaches, the overall premise is the same: to identify medicine-adverse event pairings that occur at a disproportional frequency compared with the background dataset.[1] DMAs are used as just one part of a pharmacovigilance surveillance system that can highlight potential vaccine safety issues for further investigation, but are not a tool for determining causal association. They act as a filter to identify potential safety issues for further investigation and are useful for generating hypotheses about potential medicine-AE interactions, but cannot be used to test these hypotheses.[1, 2]

In the initial period following the introduction of a new medicine or vaccine, most serious safety concerns are likely be identified through individual spontaneous adverse event reports or case series. The additional benefit of DMAs to detect long-term, rare or unexpected AEs becomes more applicable over time, with increased use of the vaccine.[1] It is pertinent to note that whilst DMAs can be beneficial in enhancing traditional surveillance methods, they are not a replacement for them and traditional methods can identify adverse events that are missed by DMAs.[3]

Assumptions of disproportionality analyses [1]

- If a drug is causally linked to a specific AE, that AE will be reported at a higher frequency for that drug compared with other drugs not causally associated with the AE
- The reporting rate of AEs for all vaccines is assumed to be an appropriate/valid reference to compare the reports of a specific vaccine-event pair and all other vaccines in the dataset being used as comparators are not associated with the AE of interest (or are expected to occur at the same rate)
- For a specific AE, the extent of reporting (under or over) is expected to be the same amongst all vaccines in the database

DRAFT

Limitations of disproportionality analysis

- Signals are just statistical associations and do not provide any information on causal associations. Any signals must be assessed and further investigated as necessary to determine if it is a true safety signal
- There is no gold standard for determining which threshold(s) should be used to define a signal although some combinations are commonly used or endorsed [1, 4-6]
- Masking can occur if there is a strong association of an AE with another drug/vaccine (if the dataset used for comparison contains a vaccine with high signals for the AEFI of interest). For example, if comparing the rate of GBS in a new COVID vaccine with all other vaccines, the strong association between influenza vaccines and GBS could mask a possible association between COVID-19 vaccine and GBS because the high frequency of this AE in influenza vaccines would mean the reporting frequency will not appear proportionally higher. This limitation can now be limited by comparing only COVID vaccines
- Quality of the data in the database will affect the accuracy of any analysis

Proportional Reporting Ratio

The Vaccines Surveillance Section (VSS) currently uses the proportional reporting ratio (PRR) to interrogate the AEMS database for safety signals and generate a disproportionality analysis report via Qlik on a bimonthly frequency. Only reports with a case decision of accepted (corresponding to WHO causality assessment classification of certain, probable or possible) are included in the report and only spontaneous case reports are included (reports from other reports such as clinical trials are excluded). Only AEFI-vaccine pairs that have been reported in the previous 2 months are shown on the DPAR for review.

The principle of disproportionality analysis is to see if the observed frequency of a specific AEFI-vaccine pair is higher than expected (a signal). This is determined by calculating the PRR. The PRR is used as a screening tool to identify vaccine and adverse event following immunisation (AEFI) pairs reported at an increased frequency compared to the background vaccine dataset. It does so by comparing the ratio of reports of a specific vaccine-AEFI pair of interest with the ratio of reports for the same AEFI caused by all other vaccines in the database.[7] If there is no association between a specific AEFI-vaccine pair, the observed reporting frequency of the AEFI-vaccine pair should be similar to the expected. If the observed number of a specific AEFI-vaccine pairing is higher than expected, it suggests that the observation is not occurring by chance and requires further investigation.

DRAFT

	AEFI of interest	All other AEFIs	TOTAL
Vaccine of interest	a	B	a + b
All other vaccines/ comparator vaccine	c	D	c + d
TOTAL	a + c	b + d	a + b + c + d

PRR = $\frac{a/(a+b)}{c/(c+d)}$ or $\frac{a(c+d)}{c(a+b)}$

Current reporting thresholds

New drugs such as COVID-19 vaccines would fall under the category of the Intensive Drug Monitoring Program, which have lower PRR thresholds for signal investigation.

Signal threshold (IDMP): ≥2 case reports and a PPR ≥2, or any new case of a critical adverse event (as defined in the list available at TRIM link R11/479239).

A 95% confidence interval (CI) is calculated for the PRR.

Advantages

- Useful method to mine large amounts of data and detect potential safety issues that may otherwise go undetected
- All necessary data for analysis contained within AEMS
- Well established, validated method also used by international regulatory bodies
- Useful for detecting new (unexpected) and rare adverse reactions

Disadvantages

- Can only produce a comparative measure (reporting ratio) based on reports, cannot calculate incidence
- Ratio can be largely influenced by small changes for AEs with low report counts
- Ratio influenced by coding errors or duplication of reports
- Detected signals do not necessarily indicate a true signal and still require further investigation (false positives)
- Currently no routine subgroup analysis of different risk groups (e.g. age groups, pregnant women, Aboriginal and Torres Strait Islander peoples)
- Potential masking of signals

DRAFT

- Thresholds used are a subjective decision

Information component [4, 5]

The Information Component is also calculated as part of the DPAR. This is useful as it is the metric used for disproportionality reporting by the WHO VigiLyse, allowing for direct comparisons between signals generated from AEMS with those generated from VigiBase.

The IC uses a logarithmic measure of disproportionality to describe the strength of dependency between a vaccine-AEFI pairing.

$$IC = \log_2\left(\frac{(N_{observed}+0.5)}{N_{expected}+0.5}\right)$$

where $N_{observed}$ = the number of reports of AEFI-vaccine pair of interest

$N_{expected}$ = the number of case reports for the vaccine of interest independent of the AEFI of interest multiplied by the number of reports of the AEFI of interest independent of the vaccine of interest, divided by the total number of reports.

Which can be expressed as follows using the values from the 2x2 table.

$$IC = \text{Log}_2 \frac{a}{\left(\frac{(a+b)(a+c)}{a+b+c+d}\right)} \text{ or } = \text{Log}_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$$

If a drug-AE pair are reported at higher frequency compared with rest of the database, the value of the IC will be positive (the higher the value, the more disproportionate it is to the background database frequency). If there is no dependency between the drug and AE then the IC value will be zero, and if the drug-AE pair occur less frequently than expected the IC value will be negative.

Signal detection threshold

The IC_{025} represents the lower 95% confidence interval value, with a positive value used as the threshold for a value is the used as the threshold for a signal.

IC0.25 = Positive value

Improvements to current DPAR process for consideration

DRAFT

- In order to detect any signals earlier, the frequency of DPAR could be increased to weekly, although the benefits of this frequency will depend on the number and nature (non-serious AEs versus more serious AEs) of reports received each week
- Consider addition of a chi square analysis as another threshold measure to the disproportionality assessment- this is the recommended approach moving forward.
- Consider adjusting the thresholds for PRR, case count and consider use of lower 95% confidence interval >1 as an alternate threshold and test the sensitivity and positive predictive value using different thresholds
- Consider alternate disproportionality methods that may be preferred over PRR (e.g. Bayesian methods)

Other considerations

- Determining what to use as comparator - entire vaccine database or a subset
  - Are there certain vaccines that should be excluded because of potential masking effect (may lead to false negative signal detection)
  - Differences in age groups and AEFI profiles could affect signal detection
  - Discussion with MHRA re: comparison group, they will also be using the entire background database of vaccines, using only a subset could reduce comparison size of background data too much, but do need to consider possible masking that might occur (could do subset analyses in parallel).
- Consideration of groupings of PTs (closely clinically related)
  - IMI PROTECT Good Signal Detection Practices recommendations did not identify any additional benefits from using higher level groupings above PTs, although there did appear to be some benefit in terms of possible earlier signal detection (although minor) when using tighter groups of PTs based on closely (clinically) related terms, which could be run in parallel with PTs.[6]
  - Certain COVID-19 related syndromes will have case definitions
- Subgroup analysis
  Noting that subgroup analysis is of greater benefit in larger databases, and can decrease sensitivity in smaller databases, so should only be done in parallel with crude (whole of dataset) analysis [6], some subgroups analyses could be done based on:
  - Age, sex, Aboriginal and/or Torres Strait Islander status
  - Other subgroups of interest (would require changes to current reporting)
    - Ethnicity
  - Discussion with MHRA re: subgroup analysis. They will not routinely be including subgroup analysis (age, sex etc) in their disproportionality assessments, however may still do some analyses by age groups and

DRAFT

ethnicity, noting the limitations smaller count numbers associated with subgrouping will entail

Alternate disproportionality DMAs

There are several data mining algorithms commonly used for pharmacovigilance, with the most common methods largely divided into frequentist approaches or Bayesian approaches. A focussed review of scientific literature relating to different signal detection algorithms was undertaken to assess if the sensitivity or timeliness of signal detection could be improved by either making changes to the currently used PRR or by employing the use of an alternate signal detection algorithm

Characteristics of other DMAs assessed to determine any additional benefits of implementing them were:

- Sensitivity
- Timeliness
- Precision (PPV)

Other considerations:

- Ease of implementation
- Ease of interpretation
- Resource and maintenance requirements

Frequentist DMAs

ROR

Reporting odds ratio (ROR) is similar to the PRR, in that it aims to identify vaccine-AEFI pairs occurring at a disproportionate frequency, but does so by comparing the odds of reporting a specific vaccine-AEFI pair with the odds of same AEFI caused by all other vaccines in the database.

ROR = ad/bc

As there is not much difference between the ROR and PRR methods, it would be appropriate to continue with using the PRR as the basis for the DPAR, as its use in SIU (and PSAB) is well established and SIU staff are familiar with the principles.

DRAFT

Chi square analysis [7]

The Chi square statistic compares two variables in a contingency table to see if the distributions differ from each other and provides a measure of how much difference exists between the observed counts and the expected counts. In this case, it would provide a measure of how different the distribution of the AEFI of interest in the vaccine of interest group is to the AEFI of interest's distribution in the comparator group (all vaccines or single comparator vaccine). In Evans, Waller and Davis original paper on the PRR, they used a chi-squared test with Yates' correction as a measure of statistical association, using a threshold chi square value of at least 4 (equivalent to p=0.045) in addition to the count and PRR threshold values.[7]

	AEFI of interest	**All other AEFIs**	**TOTAL**
Vaccine of interest	A	b	a + b
All other vaccines/ comparator	C	d	c + d
TOTAL	a + c	b + d	a + b + c + d

$$x^2 = \sum \frac{(|O-E|)^2 - \frac{1}{2}}{E}$$

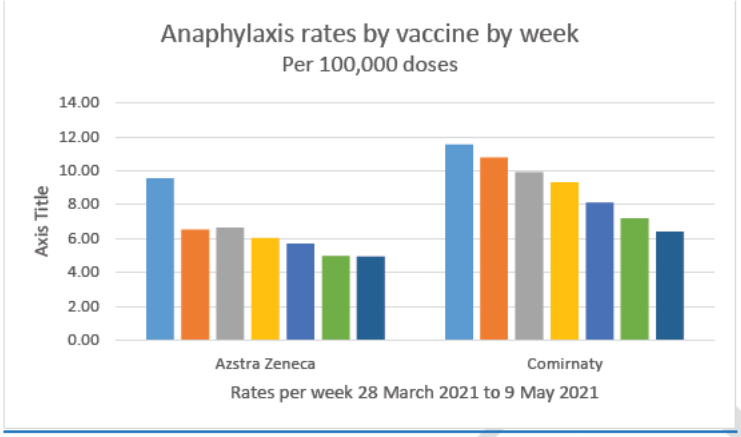
$$x^2 = \left(|ad - bc| - \frac{N}{2}\right)^2 \div (a+b)(a+c)(b+d)$$

The addition of a chi square value would only require a simple calculation and could provide an extra filter to help determine which signals to investigate further.

The proposal to move forward is –

- on a weekly basis compare all reported reactions for COVID-19 Vaccine to all reported reactions of other COVID-19 Vaccines as per the definition above Chi square statistic
- include cases with a Chi square and case report number >= 4
- compare identified signals to those in the PI.
- rates per vaccine in the previous week see figure 1 below.
- the results in DPAR and
- the results in Vigibase.
- Identify new signals for escalation for further evaluation

DRAFT



Bayesian DMAs [8]

Bayesian DMAs are also based on the same disproportionality principles as the frequentist approaches (PRR, ROR) described above, where the aim is to detect vaccine-AEFI pairs occurring at a disproportionate frequency compared with AEFI-vaccine pairings in the rest of the database. Bayesian approaches have been considered beneficial because they deal with the large variance associated with small case report counts often associated with rare events, providing more stable and precise estimates (as described in further detail below).

The multi-item Gamma Poisson Shrinker (MGPS) is a commonly used Bayesian DMA currently used by the MHRA and the FDA. The measure of disproportionality reported for MGPS is the Empirical Bayes Geometric Mean (EBGM).

The MGPS method was first described by DuMouchel for application in the FDA spontaneous reporting database. [8] The statistics behind this method are more complex, but is a simplified summary, the first step in the MPGS method is to calculate the expected reporting rate for every vaccine-AEFI pair in the database. The expected rate ~~is based on the assumption~~assumes that both the vaccine of interest and AEFI of interest are independent of each other and the AEFI of interest should be reported at a fairly consistent rate for all vaccines in the database.

The expected rate = (No. reports of AEFI of interest/ Total no. of AEFIs reported in database) x no. of reports of vaccine of interest.

The actual observed rate of the vaccine-AEFI pair of interest is then divided by the expected (baseline) rate to give a reporting ratio (RR). Another way of interpreting

DRAFT

the RR, is that it is the number of reports of the AEFI-vaccine pair of interest, divided by the proportion of the AEFI of interest out of all AEFIs, multiplied by all reports of the vaccine of interest.

RR = Observed/Expected

Using the 2x2 contingency table, this can also be represented as:

	AEFI of interest	**All other AEFIs**	**TOTAL**
Vaccine of interest	A	b	a + b
All other vaccines	C	d	c + d
TOTAL	a + c	b + d	a + b + c + d

$$RR = \frac{a}{(\frac{a+b}{a+b+c+d})\times(a+C)} = \frac{a(a+b+c+d)}{(a+b)(a+c)}$$

For example, if the AEFI "fever" may be reported 1,000 times out of 10,000 AEFI in the database (rate of 0.1). The MMR vaccine may be reported 5,000 times in the whole database. The expected rate of fever related to MMR would be 0.1 x 5000, or 500 reports of fever associated with MMR. In this example the observed rate of the fever-MMR pair is actually 700.

Therefore the RR= O/E = 700/500 = 1.4

A RR is calculated for every vaccine-AEFI combination in the database. The MPGS method then uses the combined RR information for each vaccine-AEFI pair in the database as a framework to estimate an overall mean O/E value as a baseline and probability distribution around the possible values of the disproportional effects using two probability distributions (Gamma Poisson probability distributions). The pattern across all the AEFI-vaccine combinations is used to construct a prior distribution, which is then combined with Baye's theorem to calculate a weighted adjustment of the individual observed/expected ratio for the AEFI-vaccine pair of interest to get a posterior probability (shrinkage estimate). It is called a "shrinkage" estimate because weighting the posterior distribution based on the baseline estimates from the prior distribution shrinks the estimate towards the null hypothesis (back towards 1), and the effect of this is greater for AEFI-vaccine pairs that have small counts, thus reduces the effect of large variance on the estimate of disproportionality for these pairings.

DRAFT

Threshold

The lower 95% confidence interval limit of the EBGM is used to determine whether a drug-AE pair is occurring at a higher than expected frequency, with an EB05 ≥ 2.0 commonly used as the cut-off for a signal, which is equivalent to the drug-AE pair being reported at least twice as often as it would be there was no association.

Advantages

- Corrects for the high variability associated with small report counts leading to greater precision in signal detection and less false positives
- Package in R (openEBGM) that can be used to implement the Gamma Poisson Shrinker model for data mining*
- EBGM (metric) has commonly used thresholds that make detection of a signal easy to interpret
- Can compare multiple items in a contingency table (not just 2x2), including looking at interactions and potential synergistic effects
- ?better for subgroup analysis

Disadvantages

- Involves more complex underlying theory and statistics
- Requires expertise in use of R (or other alternate statistical packages)
- Reduced sensitivity
- Possibly less timely compared with other methods – differing reports in literature

*This package also computes the PRR for comparison

Comparison of Bayesian vs frequentist approaches

Frequentist and Bayesian approaches generally tend to perform similarly when the number of drug-AE pair reports reach 5 or more.[1] Prior to this threshold, Bayesian thresholds adjust for the large variance seen with small report counts and are considered to be more accurate with lower false positives, but this may come at the expense of sensitivity.[1] As Bayesian methods shrink the estimate towards the null, frequentist approaches may highlight associations earlier. In the context of new vaccines, such as COVID-19 vaccines, earlier detection would be prioritised over accuracy and potentially more false positive signals. Longer term, when there is greater knowledge about these vaccines and their AE profiles the balance between sensitivity and PPV could be re-assessed to determine if greater accuracy and a reduction of false positives would be of greater benefit than increased sensitivity.

DRAFT

Several studies have looked at comparing different methods with varying results. The different findings across various studies supports the findings of IMI Protect and CIOMS, which emphasise no one preferred DMA, and the importance of considering the use of specific DMAs within the context of the database they will be used in, resources available and other pharmacovigilance methods already in place.[1, 6]

Considerations for choice of DMA for interrogating AEMS database:

- Priorities of signal detection
  - In the context of COVID-19 vaccines, sensitivity and timeliness will be prioritised more than accuracy and reducing false positives
- Resources
  - Expertise and understanding of new approaches and associated statistical software required to implement them
  - Access to necessary software
  - Staff training in understanding new approaches and associated metrics
- Existing infrastructure and flexibility of the system to adapt to new DMAs
  - Qlik can integrate with R
- Ability to testing new approaches and make comparisons between approaches
- Time available to implement and test new approaches

Potential options for DMAs to use in DPAR are:

1. Continue using PRR only
2. Use PRR plus chi square analysis
3. Use PRR plus Bayesian algorithm (EGBM)

SIU preferred approach:

A target review of the literature on DMA highlighted that there is currently no gold standard DMA for signal detection, each DMA is associated with its own advantages and disadvantages, and choice of DMA will depend on the database it is being used in and the priorities for signal detection. [1, 4, 6, 7, 9-11] As such, it was decided that the SIU would focus on optimising its use of the PRR method, given it is a well-established method, easy to interpret and the method currently in use.

The PRR method will be optimised by assessing the sensitivity and positive predictive value of different PRR thresholds using data from the AEMS database.

References

DRAFT

1. Council for International Organizations of Medical Sciences, Council for International Organizations of Medical Sciences. Practical aspects of signal detection in pharmacovigilance: report of CIOMS Working Group VIII. Geneva: Council for International Organizations of Medical Sciences. 2010 Sep.
2. Bate A. Bayesian confidence propagation neural network. Drug Saf. 2007;30(7):623-5. doi: 10.2165/00002018-200730070-00011. PMID: 17604417
3. Hauben M. Early postmarketing drug safety surveillance: data mining points to consider. Ann Pharmacother. 2004 Oct;38(10):1625-30. doi: 10.1345/aph.1E023. Epub 2004 Aug 10. PMID: 15304626.
4. Bate, A., Lindquist, M., Edwards, I. R., Olsson, S., Orre, R., Lansner, A., & De Freitas, R. M. (1998). A Bayesian neural network method for adverse drug reaction signal generation. European journal of clinical pharmacology, 54(4), 315-321.
5. Norén, G. N., Hopstadius, J., & Bate, A. (2013). Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. Statistical methods in medical research, 22(1), 57-69.
6. Wisniewski AF, Bate A, Bousquet C, Brueckner A, Candore G, Juhlin K, Macia-Martinez MA, Manlik K, Quarcoo N, Seabroke S, Slattery J, Southworth H, Thakrar B, Tregunno P, Van Holle L, Kayser M, Norén GN. Good Signal Detection Practices: Evidence from IMI PROTECT. Drug Saf. 2016 Jun;39(6):469-90. doi: 10.1007/s40264-016-0405-1. PMID: 26951233; PMCID: PMC4871909.
7. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001 Oct-Nov;10(6):483-6. doi: 10.1002/pds.677. PMID: 11828828
8. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat 1999; 53 (3): 170-90
9. Hauben M. A brief primer on automated signal detection. Annals of Pharmacotherapy. 2003 Jul;37(7-8):1117-23.
10. Hochberg AM, Hauben M, Pearson RK, O'Hara DJ, Reisinger SJ, Goldsmith DI, Gould AL, Madigan D. An evaluation of three signal-detection algorithms using a highly inclusive reference event database. Drug Saf. 2009;32(6):509-25. doi: 10.2165/00002018-200932060-00007. PMID: 19459718.
11. Candore, G., Juhlin, K., Manlik, K. et al. Comparison of Statistical Signal Detection Methods Within and Across Spontaneous Reporting Databases. Drug Saf 38, 577–587 (2015). https://doi.org/10.1007/s40264-015-0289-5

Summary

The strength of the SIU pharmacovigilance system to detect safety signals related to COVID-19 vaccines relies on having robust processes for traditional surveillance in place, with further enhancement possible through the additional use of AIR data, comparison of observed versus expected AEFI rates and the application of statistical data mining algorithms (DMAs).

Based on review of the current pharmacovigilance system, focussed literature reviews and consultation with other regulatory agencies including the MHRA the following actions have been taken to improve COVID-19 vaccine safety signal detection by the SIU.

Traditional surveillance methods:

- Work on communications to remind vaccine providers and consumers to report any suspected AEFIs and how to report
- Actions to make entry of COVID-19 vaccination details onto AIR mandatory
- Update of AEFI reporting forms to improve data quality and ensure important information related to assessment of any COVID-19 vaccines related issues are accurately recorded.
- Continued work on standardised reporting formats so AEFI report data can be directly imported into AEMS (moving towards Electronic Data Interchange (EDI), online reporting)
- Review of active surveillance programs and tailor towards COVID-19 vaccine follow-up with consideration of establishing sentinel surveillance sites in key groups that may be at increased risk of under-reporting of AEFIs such as aged care residents and healthcare workers
- Consideration of establishing a formal method for rumour surveillance in addition to Environmental scanning to identify any potential safety issues or public concerns over the vaccine, through informal sources
- Update AEMS coding to incorporate COVID-19 vaccine-related AEFIs and review coding quality assurance processes
- Update of AESI to include COVID-19 specific AESI and case definitions as determined by the Brighton Collabroation
- Establishment of a standing COVID-19 specific VSIG to assist with causality assessments as part of case report investigations

Observed versus expected rates using Australian Immunisation Register (AIR) data and background population rates:

-

DRAFT

Data mining algorithms:

- Testing of PRR thresholds to determine optimum thresholds
  - Details once determined
- Increased frequency of DPAR to weekly
- Addition of PRR trend analysis

DRAFT

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

Sequential analysis for near real-time surveillance of COVID-19 vaccine safety: analysis plan and methods

19 July, 2021

Nationwide COVID-19 vaccination programmes are currently underway to contain the spread of SARS-COV-2, the virus that causes COVID-19. As pre-approval clinical trials are not powered to detect rare adverse events (AEs), post-approval monitoring is needed to maintain the safety profile of the vaccine products. Since the general population has already been exposed to the products, the early identification of safety problems is critical for a timely response from regulatory and public health agencies to prevent additional exposure. Even if the surveillance detects no safety problems, it is important to do and report this type of surveillance to earn the public trust that the new vaccines are not only effective but also safe, so that people will not avoid taking the vaccines because of safety concerns.

For each COVID-19 vaccine in use, we will conduct sequential analysis as one component of the ongoing continual monitoring of a list of adverse events of special interest (AESIs). Specifically, we will monitor each AESI on a weekly or fortnightly basis, comparing the cumulative number of AEs observed to the number expected according to background incidence rate, cumulative doses, risk window and the Poisson-based maximized sequential probability ratio test (MaxSPRT)[1]. We define a signal as occurring when the number of AE reports observed after vaccination significantly exceeds the expected, by comparing the log likelihood ratio (LLR) to a threshold value that is based on the Poisson probability distribution and adjusted for the multiple looks at the data inherent with sequential analysis. The threshold value is set to a level designed to keep the cumulative probability of making a type I error below the conventional 5% level over the repeated analyses.

The observed vs. expected (OE) analysis take all reported AEs, regardless of whether the cases are confirmed, because at the signal generation stage, false positives can be tolerated. When the LLR reaches the critical value, the null hypothesis of no association between the AE and vaccine is rejected, and the AE signal is generated. The signal is ready for investigation and evaluation, followed up with case reviews and assessment of causality. Supplementary OE analyses are conducted over the refined AE cases incorporating new incoming data wherever warranted.

To start the sequential monitoring, OE analysis for an AESI associated with the use of each vaccine brand is conducted for five different risk windows (see below) using data cumulated through the most recent week in the total population and subgroups of males and females and those aged under and above 50. That is, there are 25 OE analyses for each vaccine brand to start with. If there is no signal for any of the population groups, then there is no sequential analysis for the particular AESI in the first week, with the expectation that if a signal were missed in this first set of analyses, it would be detected in coming weeks. If a signal occurs for any of the population groups, then there is retrospective sequential analysis, starting after the first week of AE reports. This combination of analyses for the most recent week and past weeks is intended to make up for the delays in setting up the analytic infrastructure.

DATA SOURCES

Background incidence rates

Age-sex-specific rates are used when analysing the total populations and age-sex subgroups whenever available. Given the age-dependent vaccine rollout, the age-sex distribution of the source population from which the rates are calculated may differ from that of the vaccinated population. Unless incidence does not vary age or sex, using background rates stratified by age and sex will ensure that any differences between the observed and expected number of events are not due to age or sex structural differences. It will also ensure that the expected number from the total population analysis is equal to the sum of the expected events across the age and sex subgroups.

The background rates are extracted from the website vac4eu.org, a project contracted the European Medicines Agency to estimate the background incidence rates of adverse events of special interest for COVID-19 vaccine monitoring readiness, using [2]a total of 12 participating European healthcare databases. For TGA's continuous monitoring purposes, the primary comparator is the UK_CPRD, consisting of the medical records of general practitioners in about 1700 UK general practices, but with feedback information (e.g. diagnoses) from specialists and hospitals. To guard against the possibility of the comparator not fully capturing inpatient data, background rates based on two additional sources are used: the Danish national DCE_AU database and Spanish-Valencia ES_FISABIO database, both of which include hospital discharges as well as outpatient data.

Rates from each database across the three years 2017, 2018 and 2019 are averaged to stabilize data.

When the rates are not available for a listed AESI, rates from published literature are considered, including the study by Gubernot et al. (Vaccine 2021) for the US population[3]. When the age groups may not match the standard age groups in the signal analysis, some kind of shifting would be used.

Adverse Event Management System (AEMS)

AEMS data are extracted each Tuesday for reports accepted through the preceding Sunday. The following basic data cleaning is performed: removing duplicates based on cases ID and dose sequence, recoding impossible dates and ages, and recoding cases with unknown sex information based on case narratives. Also recoded is time to onset by using vaccination and onset dates. In the OE analysis, median age and modal value of time to onset within each vaccine group are used to recode missing cases, and cases missing for recoded sex are excluded. If a signal occurs, missing time to onset would be randomly imputed to check if the signal is robust.

In the caseline listing output (see below), however, only un-imputed age and time to onset are presented.

Vaccine doses and the Australia Immunisation Register (AIR)

Daily vaccine doses by age, sex, dose sequence and vaccine brand are extracted from the AIR database in the Department of Health Enterprise Data Warehouse each Tuesday for vaccination episodes accepted through the preceding Sunday. Daily dose counts allow for a more precise calculation of population exposure (that is, dose years). For administrated doses that have not lapsed beyond the length of the risk window at the time of analysis, exposure time is calculated as the difference between the Monday of the analysis week and vaccination date. This calculation likely overstates exposure time, but the bias should be minor. Approximation of dose years based on more aggregated dose counts (eg. weekly counts) would have to deal with sudden changes over time in dose administration. Another option is to use data cumulated one risk window before the analysis week, but this is at the expense of not using the most up-to-date data. Also the analysis data would then vary across the different risk windows.

OUTPUT

The OE analysis will produce dose years, number of observed events, number of expected events, OE ratio, LLR and an indicator of whether a signal occurs or not. For completeness and comparison purposes, we will report the 95% confidence interval of the OE ratio. It is likely that the confidence interval is greater than 1 but the LLR statistic suggests no signal. This is because the MaxSPRT threshold value takes into account multiple testing[1].

For each AESI, output tables will be stored in an Excel file including descriptive statistics, results from the most recent week OE analysis, and results from sequential weekly OE analysis if there is a signal in the most recent week analysis. Caseline listing for all cases is also produced, but not uploaded to TRIM to avoid large files. The caseline listing is available upon request.

TERMINOLOGY

Risk window

This is the period during which there is a suspicion or medical plausibility for an increased risk of AE associated with vaccine use[4]. The OE analysis will explore five different risk windows with lengths of 7, 14 21, 28 and 42 days.

Analysis week

In each weekly OE analysis, both the AIR and AEMS data were cumulated through the preceding Sunday. Each week was referred to as the analysis week, and its Monday, the analysis Monday.

REFERENCES

1. Kulldorff M, Davis RL, Kolczak† M, Lewis E, Lieu T, Platt R. A Maximized Sequential Probability Ratio Test for Drug and Vaccine Safety Surveillance. Sequential Analysis 2011;**30**(1):58-78.
2. Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0). Zenodo 2021.
3. Gubernot D, Jazwa A, Niu M, et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine 2021;**39**(28):3666-77.
4. Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiology and drug safety 2016;**25**(2):215-22.

Australian Government
Department of Health
Therapeutic Goods Administration

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

DPAR Comparison 6 months post COVID-19 vaccine rollout

IN CONFIDENCE AND NOT FOR DISTRIBUTION

Pharmacovigilance & Special Access Branch

August 24 2021

TGA Health Safety Regulation

Why and what DPAR?

- DPAR utilises the number of events reported for each vaccine and statistically screens the database for higher than expected vaccine-event combinations signalling a potential vaccine-associated event [1]

- Why
  - DPAR and PRR was introduced **to overcome the lack of denominator**.
  - "The mathematical basis of Proportional Reporting Ratios (PRRs) is straightforward and has been applied in other contexts where there are **difficulties with denominators** (e.g. proportional mortality ratios)." [2]
  - Passive surveillance has recognized limitations: problems with data quality, underreporting, **missing or inadequate denominators**, and the lack of appropriate comparator groups for signal confirmation.[3]

Niu MT, Erwin DE, Braun MM. Data mining in the US Vaccine Adverse Event Reporting System (VAERS): early detection of intussusception and other events after rotavirus vaccination. Vaccine. 2001 Sep 14;19(32):4627-34. doi: 10.1016/s0264-410x(01)00237-7. PMID: 11535310.
Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001 Oct-Nov;10(6):483-6. doi: 10.1002/pds.677. PMID: 11828828
Williamson, T., Lévesque, L., Morkem, R., & Birtwhistle, R. (2014). CPCSSN's role in improving pharmacovigilance. *Canadian family physician Medecin de famille canadien, 60*(7), 678–680.

ACV advice

- DPAR
  - PRR analysis by vaccine trade name rather than generic ingredient;
  - increase frequency of PRR analysis and reporting from bimonthly to weekly;
  - use of a lower threshold of a PRR >1 and case count ≥2 to identify vaccine-event pairs for assessment; D21-2098494
- Data will be able to be analysed by vaccine trade name, batch number, age group, sex and jurisdiction. With both AEMS and AIR data updated overnight, AEFI reporting rate calculation will be possible in near real-time. However, formal analysis will be conducted on a weekly basis to allow for fluctuations in the submission of reports at both the reporter and jurisdictional-level, as well as to ensure adequate time for data cleaning in state and territory databases, AIR, and AEMS.

ACV advice

- The current COVID-19 Vaccine Safety Monitoring Plan in Strategy 2.3 advises that the TGA will conduct enhanced cumulative data reviews for each COVID-19 vaccine to enable rapid analysis of AEFI rates to detect, confirm or disprove emerging COVID-19 safety signals. These methods included
  - Access to Australian Immunisation Register and vaccine distribution data for calculating COVID-19 immunisation rates.
  - **Refined processes and statistical methods for analysing observed COVID-19 AEFI rates for detecting safety signals.**
  - **Enhanced processes to determine if the frequency of particular AEFI are higher than expected.**
  - **Processes for conducting subpopulation analyses to identify and investigate potential safety signals in at-risk populations.**

Normal DPAR

	AEFI of interest	All other AEFIs	TOTAL
Vaccine of interest	a	B	a + b
All other vaccines/ comparator vaccine	c	D	c + d
TOTAL	a + c	b + d	a + b + c + d

$$\text{PRR} = \frac{a/(a+b)}{c/(c+d)} \text{ or } \frac{a(c+d)}{c(a+b)}$$

Comparing vaccine AEFIs



Comparators

- EMA in “Good Signal Detection Practices: Evidence from IMI PROTECT” [4]
  - Consideration should be given to carrying out comparisons of quantitative signal detection methods across spontaneous report databases matching at the drug-event combination level rather than averaging over all drug-event combinations

- Options
  - All adverse reports
  - All vaccine reports
  - Adult vaccine reports
  - Adult gender based vaccine reports
  - Disease specific Vaccines

Wisniewski AF, Bate A, Bousquet C, Brueckner A, Candore G, Juhlin K, Macia-Martinez MA, Manlik K, Quarcoo N, Seabroke S, Slattery J, Southworth H, Thakrar B, Tregunno P, Van Holle L, Kayser M, Norén GN. Good Signal Detection Practices: Evidence from IMI PROTECT. Drug Saf. 2016 Jun;39(6):469-90. doi: 10.1007/s40264-016-0405-1. PMID: 26951233; PMCID: PMC4871909 D20-3621792

Comparing period 22-6-2021 to 22-8-2021

Which is the right DPAR?

Vasculitis over 2 month period

	AEFI of interest	All other AEFIs	TOTAL
Vaccine of interest	10	9,586	9,596
All other vaccines	6	9,589	9,595
TOTAL	16	19,175	19,191

PRR = **1.6**

Comparing AZ to all other vaccines



	AEFI of interest	All other AEFIs	TOTAL
Vaccine of interest	10	9,586	9,596
All other adult vaccines	6	9,180	9,186
TOTAL	16	18,766	18,782

PRR = 1.6

Comparing AZ to all other adult vaccines





6 months since the first dose of Pfiser

- We have an accurate and timely denominator in the form of AIR data
- COVID-19 vaccines make up 46% of all vaccine reports and 71% of all adult vaccine reports. In the last 2 months we have had 257 adult adverse reports for all other vaccines vs 18,525 COVID-19 reports (VAXz 9596 and Pfiser 8929)
- We have statistical system and capability in the form of Stata and R which was not in the SIU team at the time of ACV
- We can now replicate the process for signal detection used in clinical trials to some degree.

Comparing period 22-6-2021 to 22-8-2021

Which is the right DPAR?

Vasculitis over 2 month period

	AEFI of interest	All other AEFIs	TOTAL
Vaccine of interest	10	9,586	9,596
All other non covid vaccines	5	252	257
TOTAL	15	9,838	9,853

PRR = .05

Comparing AZ to all non covid other adult vaccines



	AEFI of interest	All other AEFi	TOTAL
Vaccine of interest	10	9,586	9,596
All other Covid vaccines /Comparator Vaccine	1	8,928	8,929
TOTAL	11	18,514	18,525

PRR = 9.3

Comparing AZ to all Pfiser



Comparing period 22-6-2021 to 22-8-2021

Which is the right DPAR?

Vasculitis over 2 month period

	AEFI of interest	All other AEFIs	TOTAL
Vaccine of interest	10	9,586	9,596
All other non covid vaccines	5	252	257
TOTAL	15	9,838	9,853

PRR = .05

Comparing AZ to all non covid other adult vaccines



	AEFI of interest	All other AEFi	TOTAL
Vaccine of interest	10	9,586	9,596
All other Covid vaccines /Comparator Vaccine	1	8,928	8,929
TOTAL	11	18,514	18,525

PRR = 9.3

Comparing AZ to all Pfiser



Document 3

Rough slide of stuff

- A major limitation of VAERS is the lack of denominator data (number of doses of administered vaccine), an element necessary for calculating reporting rates. Empirical Bayesian data mining, a data analysis method, utilizes the number of events reported for each vaccine and statistically screens the database for higher than expected vaccine-event combinations signaling a potential vaccine-associated event. Niu MT, Erwin DE, Braun MM. Data mining in the US Vaccine Adverse Event Reporting System (VAERS): early detection of intussusception and other events after rotavirus vaccination. Vaccine. 2001 Sep 14;19(32):4627-34. doi: 10.1016/s0264-410x(01)00237-7. PMID: 11535310.
-
- However, passive surveillance also has recognized limitations: problems with data quality, underreporting, missing or inadequate denominators, and the lack of appropriate comparator groups for signal confirmation.
- Williamson, T., Lévesque, L., Morkem, R., & Birtwhistle, R. (2014). CPCSSN's role in improving pharmacovigilance. *Canadian family physician Medecin de famille canadien*, *60*(7), 678–680.
-

D20-3621792

s22 [redacted] Pharmacovigilance and Special Access Branch Medicines Regulation Division UTS Molecule to Market – 15 August 2018 Pharmacovigilance - a regulator's perspective (tga.gov.au) NO denominator



- **ESTIMATION OF THE DENOMINATOR**
- In some countries, the size N and characteristics of the exposed population and its conditions of expo-sure can be precisely derived from health insurance databases. In this case, except for the poor quality of case collection (i.e. under-reporting), SR approaches the cohort design.
- *Example*: 780 000 packages of 20 capsules have been sold in a 1-year period, the used daily dose is 2.1 capsules. This corresponds to the quantity necessary for a cumulative duration of treatment of: (780 000 × 20 2 1 = 2 666 667 days, or 87 719 months. In a more epidemiological parlance, the expo-sure level in the source-population is 87 719 person-months.
- **Pharmacovigilance: Statistical Methods of Evaluating Pharmacovigilance Data**

(Kubota, Koide and Hirai, 2004; van Puijenbroek *et al*., 2002)

Table 21.2. Conditions, advantages and disadvantages of different measures of disproportionality.

Measure of disproportionality	Type	Expected 'null value'	Conditions	Advantage	Disadvantage
Information component	Point estimate	0	None	• Always applicable • Large numbers of calculations can be made efficiently • Can be used for pattern recognition in higher dimensions	Relatively non-transparent for people not familiar with Bayesian statistics
Reporting odds ratio	Point estimate	1	Cells b and c have to contain reports	• Easy applicable • Different adjustments possible in logistic regression analysis • In logistic regression analysis, interaction terms can be used for the analysis of drug interactions and syndromes • Easy interpretation	• Odds ratio cannot be calculated if denominator is zero (specific ADRs) • Interpretation difficult • Results not always reliable in the event of small numbers in cells a,b,c and d of the contingency table
Proportional reporting ratio	Point estimate	1	Cell c has to contain reports	Easy interpretation	Cannot be calculated for all drug–ADR combinations (see conditions of use)
Yules Q	Point estimate	0		Always applicable	Difficult to interpret
Poisson	Test		Only for rare events	Correction for different covariates can be easily established in Poisson regression	Only p-value provided
Chi square (Yates correction)	Test			Always applicable	
Yules' Q-1.96se	Test		Cells a,b,c and d have to contain reports		Standard deviation cannot always be calculated
ROR-1.96se	Test		Cells a,b,c and d have to contain reports	Correction for different covariates can easily be established	Standard deviation cannot always be calculated
IC-2std	Test		None	Always applicable	

- **Statistical Analysis of Safety Data in Clinical Trials**

Comparing period 22-6-2021 to 22-8-2021

DPAR vs Chi Square

	AEFI of interest	All other AEFI	TOTAL Doses
Vaccine of interest	10	9,586	9,596
All other Covid vaccines /Comparator Vaccine	1	8,928	8,929
TOTAL	11	18,514	18,525

PRR = 9.3

	AEFI of interest	Those without Vasculitis	TOTAL	90% CI
Vaccine of interest	10	4483134	4,483,144	(.00065 .00069)
All other Covid vaccines /Comparator Vaccine	1	5617012	5,617,013	(.00043 .00046)
TOTAL	11	10100146	10,100,157	

P value<0.05

Comparing AZ to all Pfiser Headache



Comparing AZ to all Pfiser



Document 3

Which is the right time period?

Bursitis over 6 month period

	AEFI of interest	All other AEFIs	TOTAL
Vaccine of interest	32	32208	32240
All other vaccines	190	81188	81378
TOTAL	222	113396	113618

PRR = 0.40

Comparing AZ to all other vaccines

	AEFI of interest	All other AEFIs	TOTAL
Vaccine of interest	32	32208	32240
All other adult vaccines	104	41299	41403
TOTAL	136	73507	73643

PRR = 0.4

Comparing AZ to all other adult vaccines

Comparing period 1-2-2021 to 1-8-2021

Document 3

Which is the right DPAR?

Bursitis over 6 month period

	AEFI of interest	All other AEFIs	TOTAL
Vaccine of interest	32	32208	32240
All other non covid vaccines	98	22245	22343
TOTAL	130	54453	54583

PRR = 0. 2

Comparing AZ to all non covid other adult vaccines

	AEFI of interest	All other AEFIs	TOTAL Doses
Vaccine of interest	32	32208	32240
All other Covid vaccines /Comparator Vaccine	6	19054	19060
TOTAL	38	51262	51300

PRR = 3.2

Comparing AZ to Pfiser

Comparing period 1-2-2021 to 1-8-2021

Document 3

DPAR vs Chi Square

Bursitis over 6 month period

	AEFI of interest	All other AEFIs	TOTAL Doses
Vaccine of interest	32	32208	32240
All other Covid vaccines /Comparator Vaccine	6	19054	19060
TOTAL	38	51262	51300

PRR = 3.2

Comparing AZ to Pfiser

	AEFI of interest	Those without a headache	TOTAL	90% CI
Vaccine of interest	32	4483112	4483144	(.00065 .00069)
All other Covid vaccines /Comparator Vaccine	6	5617007	5617013	(.00043 .00046)
TOTAL	38	10100119	10100157	

P value<0.05

Comparing AZ to all Pfiser
Becomes more pertinent when Moderna on board

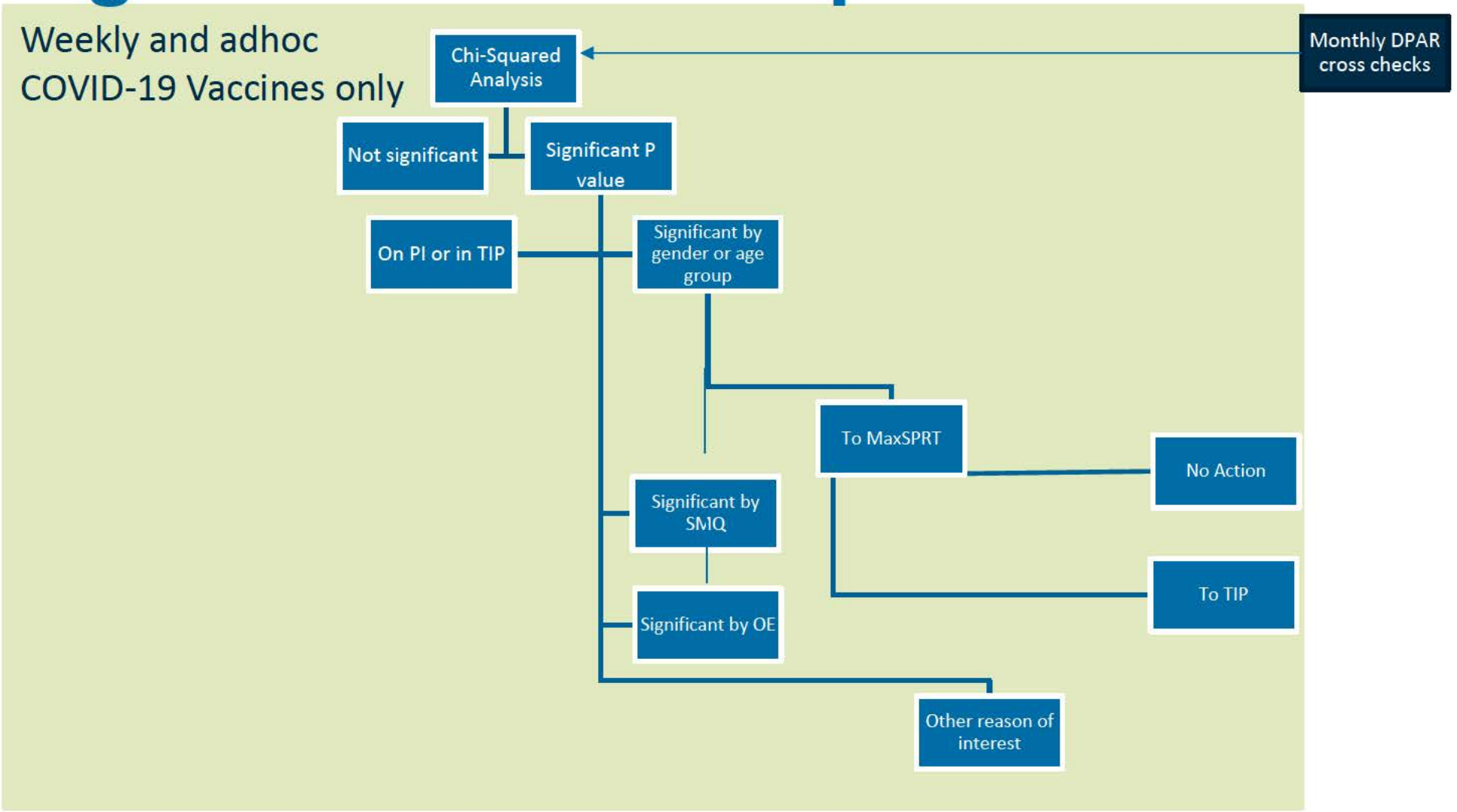
Comparing period 1-2-2021 to 1-8-2021

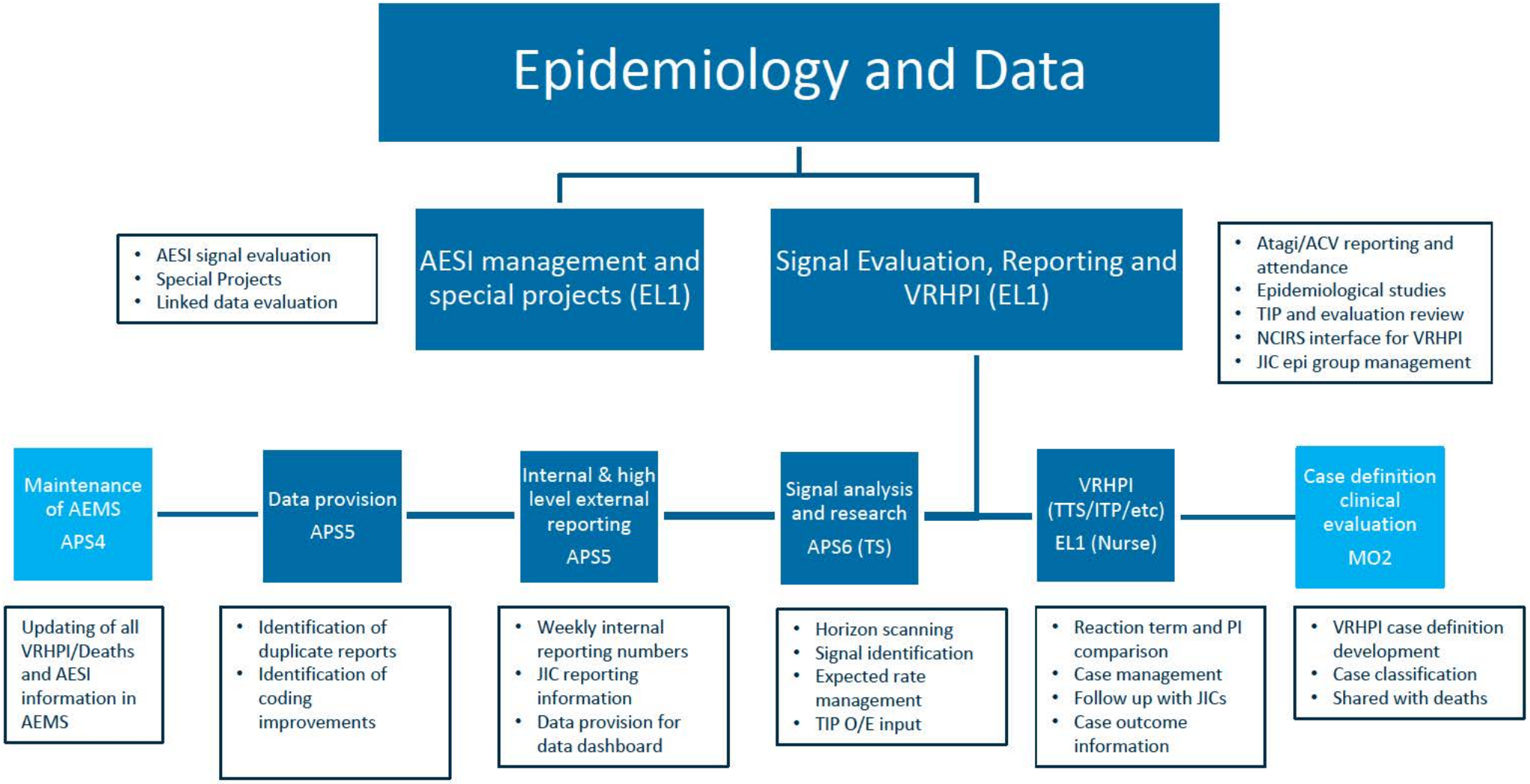
The way forward

- A new process that uses
  - the Chi squared analysis comparing COVID-19 vaccines to identify signals
  - Automated O/E where appropriate and,
  - Use of the maximised sequential probability ratio test (MaxSPRT) method (method currently used by MHRA and CDC)

Signal Identification process

Weekly and adhoc
COVID-19 Vaccines only




Epidemiology and Data
AESI management and special projects (EL1)
Signal Evaluation, Reporting and VRHPI (EL1)
• AESI signal evaluation
• Special Projects
• Linked data evaluation
• Atagi/ACV reporting and attendance
• Epidemiological studies
• TIP and evaluation review
• NCIRS interface for VRHPI
• JIC epi group management
Maintenance of AEMS APS4
Data provision APS5
Internal & high level external reporting APS5
Signal analysis and research APS6 (TS)
VRHPI (TTS/ITP/etc) EL1 (Nurse)
Case definition clinical evaluation MO2
Updating of all VRHPI/Deaths and AESI information in AEMS
• Identification of duplicate reports
• Identification of coding improvements
• Weekly internal reporting numbers
• JIC reporting information
• Data provision for data dashboard
• Horizon scanning
• Signal identification
• Expected rate management
• TIP O/E input
• Reaction term and PI comparison
• Case management
• Follow up with JICs
• Case outcome information
• VRHPI case definition development
• Case classification
• Shared with deaths

Staffing and Automation

- Staffing
  - Reaction list by vaccine -
  - DPAR comparator – APS5 or 6

    - Automation 100% in QLIK
    - Automation 100% in QLIK minor adjustments undertaken in excel

  - MaxSPRT - developed and maintained by EL1

    - Automation 99%
      - Initial coding 80% complete
      - Ongoing coding minimal and maintained by EL1s in R

  - Chi-Squared Analysis - developed and maintained by EL1

    - Automation 100%
      - Initial coding 100% complete
      - Ongoing coding minimal and maintained by EL1s in Stata

Staffing and Automation

- Staffing
  - Observed vs expected - adhoc - APS6 and EL1 checked
    - Automation 50%
      - 50% in O/E calculator (Complete)
      - Ongoing manual (excel)
  - Observed vs expected – all available AEFI - APS6
    - Automation 50% up to 100% over time
      - Initial coding 60% complete
      - Ongoing coding minimal and maintained by APS6
  - Reporting rates – all reactions
    - Automation 100%
      - Initial coding 100% complete
      - Ongoing coding minimal and maintained by APS5 or 6 in Stata
      - Weekly charts in Excel

Staffing and Automation

• Staffing – Comparison of DPAR to Chi-Squared -APS5 or 6	• Automation 100% – Initial coding 90% complete – Output in excel for review
– Comparison of identified reaction to previously reported reaction	• Automation 100% – Initial coding 85% complete – Ongoing coding minimal and maintained by APS5 or 6
– Comparison of identified reaction to PI related reactions Nurse and/or MO2	• Automation 5% – In development at 20% automated and 80% manual – Weekly charts in Excel
– Decision and Escalation of Signals - Vera Epid and med team	• Automation 0% – Weekly meeting review

Comparison Chi-square to DPAR

Outcomes of Chi-squared analysis - 2 monthly

- Chi-squared analysis – identified
  - 200 reactions out of 2322
  - 156 were AZ and 44 were Pfiser

- DPAR analysis identified
- 1048 reactions out of 2322
- 624 were AZ and 424 were Pfiser
- Comparison
  - 133 AZ reactions were concordant
  - 37 Pfiser reactions were concordant

- It is possible to drill down to see the reported reactions and deaths by vaccine which highlighted death was more common in AZ for reports that mentioned Cardiac Arrest, PE, DVT and thrombocytopenia

Comparing period 22-6-2021 to 22-8-2021

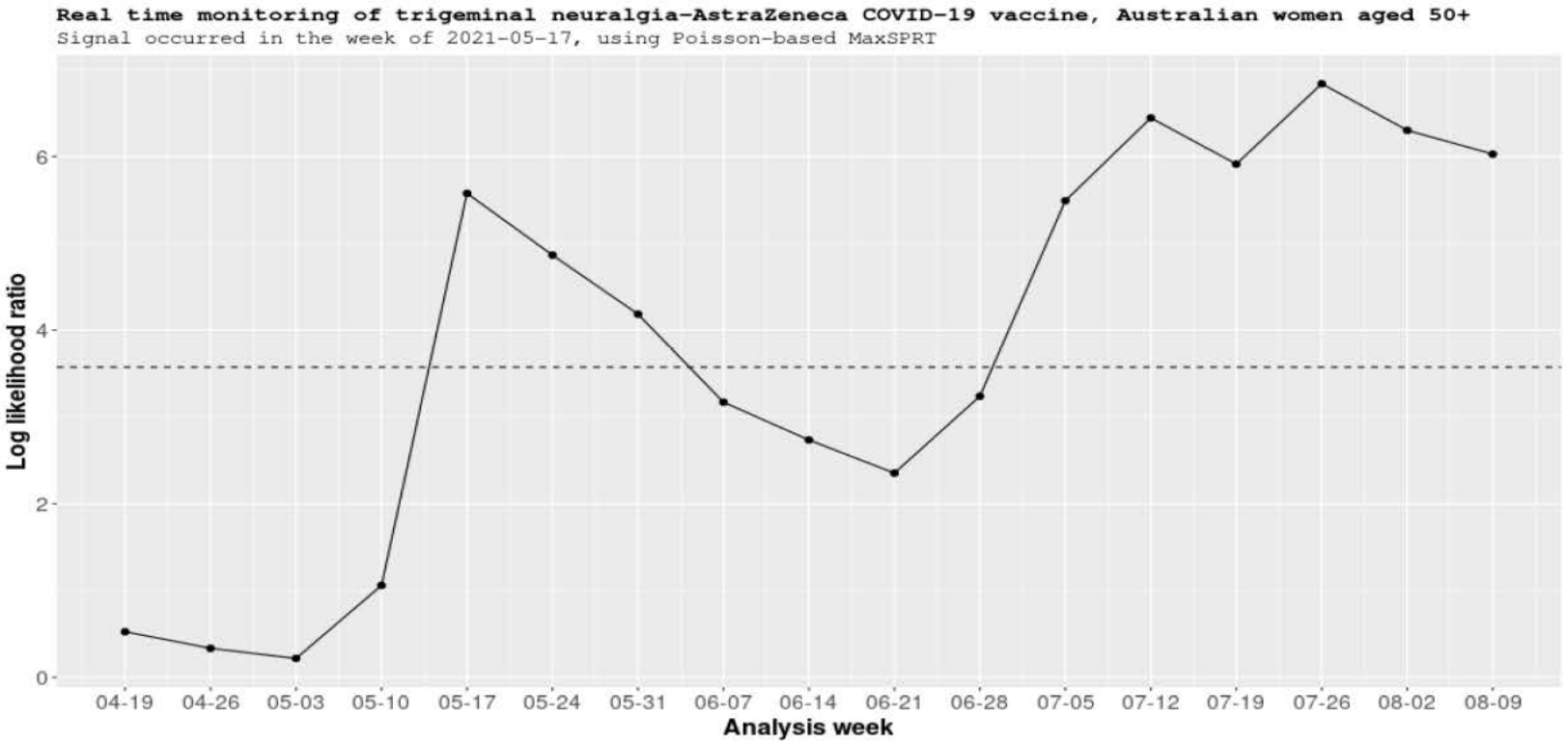
Reactions found by Chi-Squared and not DPAR

AZ	AZ	AZ	AZ
Bursitis	**Hypokinesia**	Oedema peripheral	Somnolence
Concomitant disease progression	Influenza	Peripheral swelling	Urticaria
Constipation	Injection site cellulitis	Rash erythematous	Vasculitis
Dyskinesia	Injection site erythema	Rash pruritic	Vomiting
Faeces discoloured	Injection site mass	Skin discolouration	Weight decreased
Hepatitis	Injection site swelling	Sleep disorder	

AESI Chi Squared Analysis

AESITerm	AZ	Pfiser	TNS	Total	p value		DoseAZ	DosePfiser
Coagulation disorder	**1730**	304	7	2039	0.00		8778717	8053175
Acute cardiac injury	251	**277**	1	529	0.03			
Thrombocytopenia	**465**	37	1	503	0.00			
Anaphylaxis	189	**265**	1	455	0.00			
Peripheral facial nerve palsy	**203**	135	3	341	0.00			
Myocarditis (MVA platform)	79	**230**	1	310	0.00			
Generalised convulsion	147	122	0	269	0.41			
Anosmia, ageusia	**93**	56	1	150	0.01			
Guillain-Barré Syndrome	**87**	7	0	94	0.00			
Acute aseptic arthritis (r-VSV platform)	**61**	32	0	93	0.01			
Liver injury	**50**	28	0	78	0.03			
Acute kidney injury	**32**	14	0	46	0.02			
Rhabdomyolysis	25	12	0	37	0.06			
Single organ cutaneous vasculitis	**22**	6	0	28	0.01			
Encephalitis/Encephalomyelitis	**17**	4	0	21	0.01			
Pancreatitis	13	8	0	21	0.37			
Chilblain-like lesions	5	**15**	0	20	0.02			
Aseptic meningitis (Live viral vaccine platforms)	3	5	0	8	0.41			
Subacute thyroiditis	6	2	0	8	0.20			
Erythema multiforme	5	2	0	7	0.31			
Acute disseminated encephalomyelitis	2	0	0	2	0.18			

Real Time monitoring



Outcomes of Chi-squared analysis – 6 monthly

- Chi-squared analysis – identified
  - 337 reactions out of 2322
  - 281 were AZ and 56 were Pfiser

- DPAR analysis identified
- 1257 reactions out of 2322
- 785 were AZ and 472 were Pfiser
- Comparison
  - 242 AZ reactions were concordant
  - 43 Pfiser reactions were concordant

- It is possible to drill down to see the reported reactions and deaths by vaccine which highlighted death was more common in AZ for reports that mentioned Cardiac Arrest, PE, DVT and thrombocytopenia

Comparing period 1-2-2021 to 1-8-2021

Reactions found by Chi-Squared and not DPAR

AZ	AZ	AZ	AZ
Ataxia	Hepatitis	Injection site swelling	Restlessness
Blister	Incorrect route of product administration	Listless	Rheumatoid arthritis
Bursitis	Injection site cellulitis	Myositis	Skin exfoliation
Chronic obstructive pulmonary disease	Injection site erythema	No adverse event	Sleep disorder
Condition aggravated	Injection site infection	Oedema peripheral	Somnolence
Constipation	Injection site inflammation	Peripheral swelling	Swelling
Diarrhoea haemorrhagic	Injection site mass	Purpura	Urticaria
Dyskinesia	Injection site nodule	Rash	Vasculitis
Encephalitis	Injection site reaction	Rash pruritic	Vomiting

Reactions found by Chi-Squared and not DPAR

Pfiser	Pfiser	Pfiser	Pfiser
COVID-19 immunisation	Extensive swelling of vaccinated limb	Hepatomegaly	Pallor
Drug ineffective	Gastrointestinal stoma output abnormal	Inappropriate schedule of product administration	Unresponsive to stimuli
Drug monitoring procedure incorrectly performed	Gastrointestinal stoma output decreased	Incorrect dose administered	Urine output decreased



Australian Government

Department of Health

Therapeutic Goods Administration

Where to then?

- Questions
  - What can we do better now we have a denominator?
  - What do clinical trials do?
  - What is the comparator?

Australian Government
Department of Health
Therapeutic Goods Administration

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

DPAR Comparison 6 months post COVID-19 vaccine rollout

IN CONFIDENCE AND NOT FOR DISTRIBUTION

Pharmacovigilance & Special Access Branch

August 24 2021

TGA Health Safety Regulation

Why and what DPAR?

- DPAR utilises the number of events reported for each vaccine and statistically screens the database for higher than expected vaccine-event combinations signalling a potential vaccine-associated event [1]

- Why
  - DPAR and PRR was introduced **to overcome the lack of denominator**.
  - "The mathematical basis of Proportional Reporting Ratios (PRRs) is straightforward and has been applied in other contexts where there are **difficulties with denominators** (e.g. proportional mortality ratios)." [2]
  - Passive surveillance has recognized limitations: problems with data quality, underreporting, **missing or inadequate denominators**, and the lack of appropriate comparator groups for signal confirmation.[3]

Niu MT, Erwin DE, Braun MM. Data mining in the US Vaccine Adverse Event Reporting System (VAERS): early detection of intussusception and other events after rotavirus vaccination. Vaccine. 2001 Sep 14;19(32):4627-34. doi: 10.1016/s0264-410x(01)00237-7. PMID: 11535310.
Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001 Oct-Nov;10(6):483-6. doi: 10.1002/pds.677. PMID: 11828828
Williamson, T., Lévesque, L., Morkem, R., & Birtwhistle, R. (2014). CPCSSN's role in improving pharmacovigilance. *Canadian family physician Medecin de famille canadien, 60*(7), 678–680.

Comparing vaccine AEFIs



Comparators

- EMA in “Good Signal Detection Practices: Evidence from IMI PROTECT” [4]
  - Consideration should be given to carrying out comparisons of quantitative signal detection methods across spontaneous report databases matching at the drug-event combination level rather than averaging over all drug-event combinations

- Options
  - All adverse reports
  - All vaccine reports
  - Adult vaccine reports
  - Adult gender based vaccine reports
  - Disease specific Vaccines

Wisniewski AF, Bate A, Bousquet C, Brueckner A, Candore G, Juhlin K, Macia-Martinez MA, Manlik K, Quarcoo N, Seabroke S, Slattery J, Southworth H, Thakrar B, Tregunno P, Van Holle L, Kayser M, Norén GN. Good Signal Detection Practices: Evidence from IMI PROTECT. Drug Saf. 2016 Jun;39(6):469-90. doi: 10.1007/s40264-016-0405-1. PMID: 26951233; PMCID: PMC4871909 D20-3621792

6 months since the first dose of Pfiser

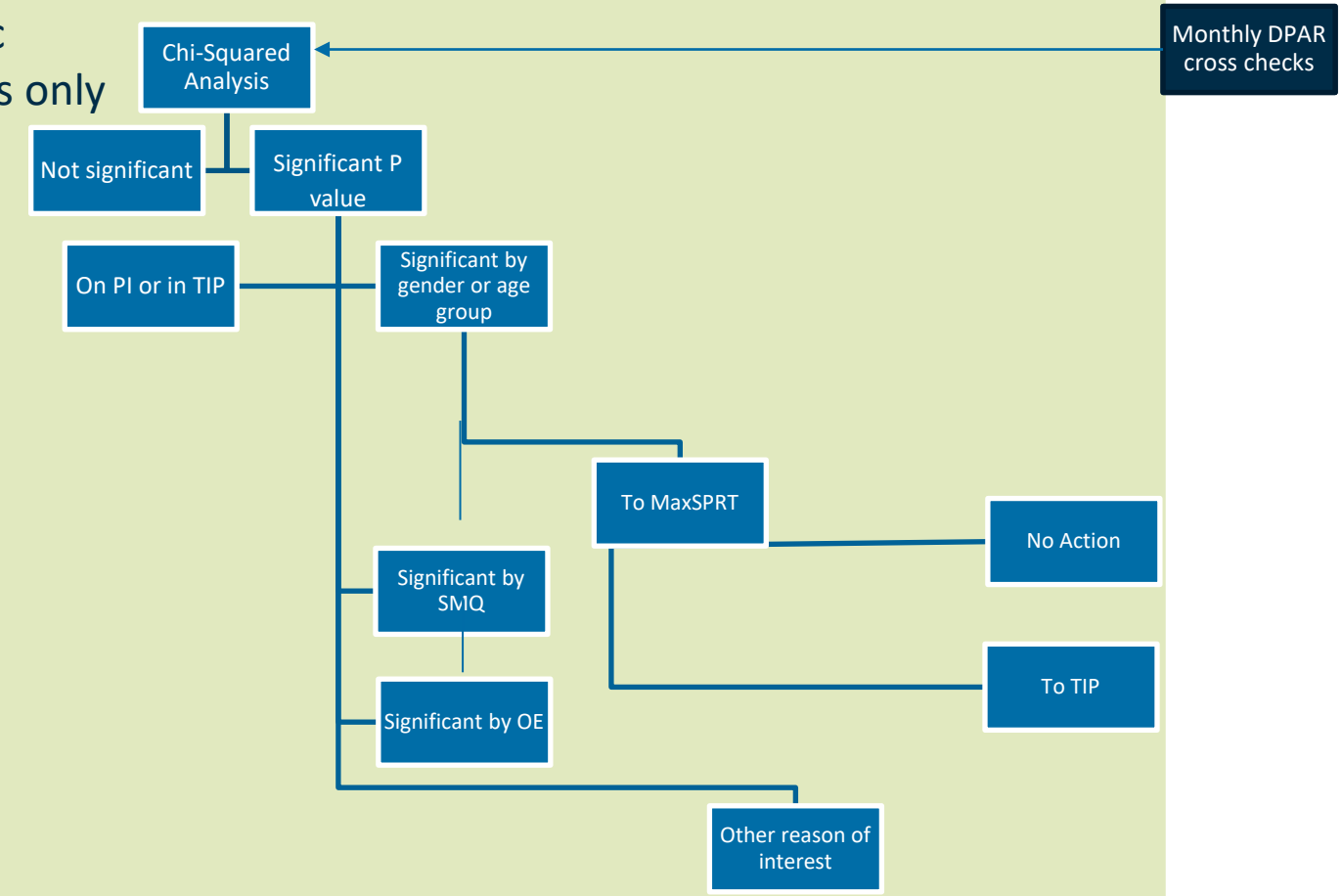
- We have an accurate and timely denominator in the form of AIR data
- COVID-19 vaccines make up 46% of all vaccine reports and 71% of all adult vaccine reports. In the last 2 months we have had 257 adult adverse reports for all other vaccines vs 18,525 COVID-19 reports (VAXz 9596 and Pfiser 8929)
- We have statistical system and capability in the form of Stata and R which was not in the SIU team at the time of ACV
- We can now replicate the process for signal detection used in clinical trials to some degree.

The way forward

- A new process that uses Reporting rate by comparing
  - the Poisson Confidence Intervals and Chi squared analysis comparing COVID-19 vaccines to identify signals
  - Automated O/E where appropriate and,
  - Use of the maximised sequential probability ratio test (MaxSPRT) method (method currently used by MHRA and CDC)

Signal Identification process

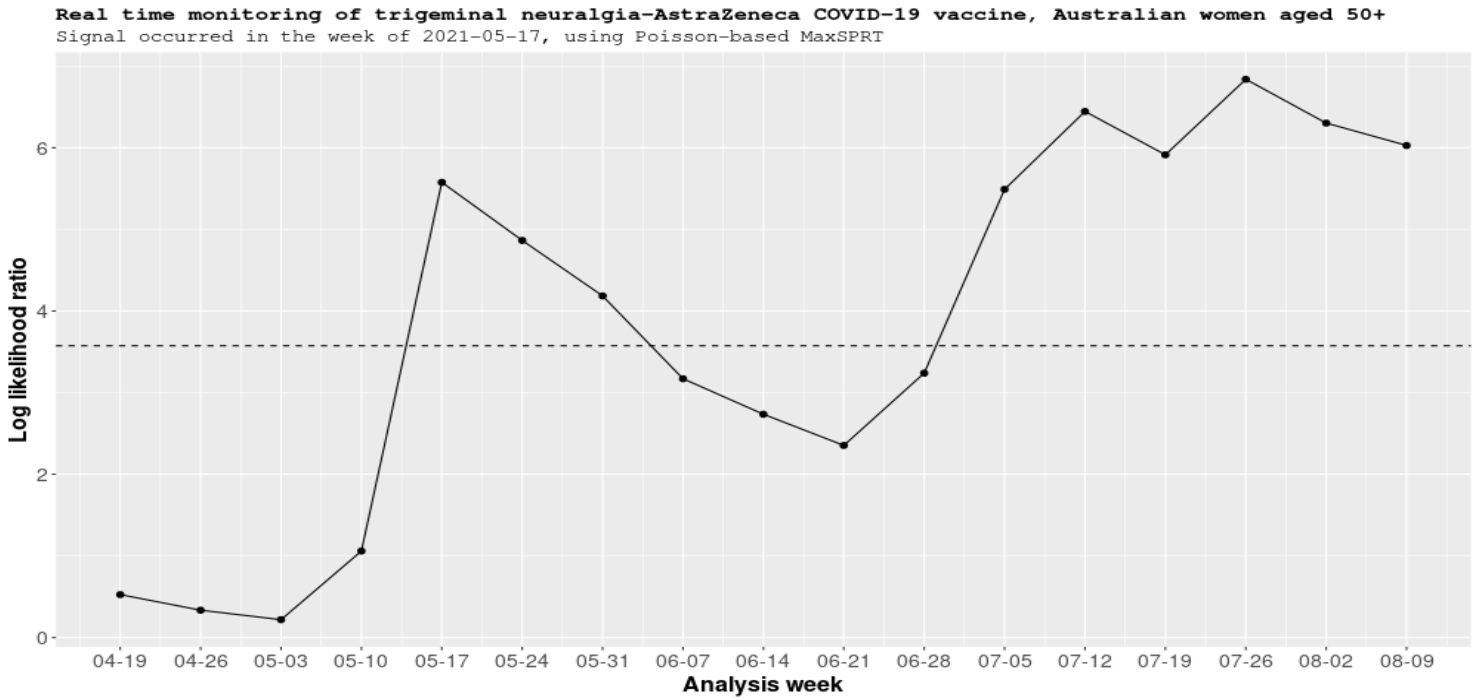
Weekly and adhoc
COVID-19 Vaccines only



AESI Chi Squared Analysis

AESITerm	AZ	Pfiser	TNS	Total	p value		DoseAZ	DosePfiser
Coagulation disorder	**1730**	304	7	2039	0.00		8778717	8053175
Acute cardiac injury	251	**277**	1	529	0.03			
Thrombocytopenia	**465**	37	1	503	0.00			
Anaphylaxis	189	**265**	1	455	0.00			
Peripheral facial nerve palsy	**203**	135	3	341	0.00			
Myocarditis (MVA platform)	79	**230**	1	310	0.00			
Generalised convulsion	147	122	0	269	0.41			
Anosmia, ageusia	**93**	56	1	150	0.01			
Guillain-Barré Syndrome	**87**	7	0	94	0.00			
Acute aseptic arthritis (r-VSV platform)	**61**	32	0	93	0.01			
Liver injury	**50**	28	0	78	0.03			
Acute kidney injury	**32**	14	0	46	0.02			
Rhabdomyolysis	25	12	0	37	0.06			
Single organ cutaneous vasculitis	**22**	6	0	28	0.01			
Encephalitis/Encephalomyelitis	**17**	4	0	21	0.01			
Pancreatitis	13	8	0	21	0.37			
Chilblain-like lesions	5	**15**	0	20	0.02			
Aseptic meningitis (Live viral vaccine platforms)	3	5	0	8	0.41			
Subacute thyroiditis	6	2	0	8	0.20			
Erythema multiforme	5	2	0	7	0.31			
Acute disseminated encephalomyelitis	2	0	0	2	0.18			

Real Time monitoring



Document 4



Australian Government

Department of Health

Therapeutic Goods Administration

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

COVID-19 vaccine signal detection and investigation framework – Working draft

D20-3725525

The COVID-19 vaccine signal detection, investigation and response processes sit within the context of the VSS Vaccines SOP framework

VSS Vaccines SOP TRIM

Plan

COVID-19 Vaccine Pharmacovigilance Plan TRIM

Signal detection

Objective: timely detection of COVID-19 vaccine safety signals.
Characteristics: timely, high sensitivity, high positive predictive value.

AEFI reports

- Entered
- Coded
- Checked

AESI – Lead: s22

- COVID-19 vaccine AESI list D21-2104959
- COVID-19 vaccine AESI cased definitions, MedDRA Preferred Terms and codes D21-2105103

Medically significant AEFI escalation

- Identification by AEMDS
- Escalation to SIU
    - All COVID cases initially, including serious AEFI, AESI, vaccine error

[Document: List and Process for escalating medically significant AEFI]

Individual report review

- Check data completeness
- Check data coding
- Follow-up questions and request for further information

[Document: COVID-19 vaccine specific follow up questions - s22]

- JIC review
- Role of AEFI-CAN

- Temporal association, causation
- Plausibility
- Likelihood

[Document: Vaccine SOP – and s22 document]

AEMS cumulative report review

Observed adverse event numbers and rates (for COVID-19 vaccines registered in Australia) –

Process: Weekly analysis Wed morning of data to end of previous Sunday. Discuss Wed pm.
<TRIM Link from [redacted] – process and governance> [redacted]
Process: Fortnightly general vaccines QLIK sheet review [redacted]

Analysis:

- Serious AEFI - counts for previous week, cumulative totals and cumulative rates. Look for any clustering by batch, location or demographics – [redacted]
- Deaths – counts for previous week, cumulative totals and cumulative rates. Look for any clustering by batch, location or demographics – [redacted].
- AESI counts for previous week, cumulative totals and cumulative rates – [redacted].
- Vaccine error, including multi-dose vials – [redacted].
- Common AEFI – assign.
- Unexpected nature – determine process – Case Line Listing check [redacted]. PRR
- Unexpected clustering – e.g. batch, location, characteristics – as a sub analysis of the above.

Data:

1. AEMS numerator - Qlik automation
2. AIR denominator (1) - Qlik automation
3. VOC SITREP or Dashboard administration denominator (2)

Active surveillance

Analysis

- Cumulative rates as a proportion of responses and as a proportion of surveys distributed. Look for any AEFI that are unexpected in frequency, clustering or nature – [redacted]

Data:

- Daily AusVaxSafety reports
- Data if required

Observed vs expected analyses

Expected adverse event rates (for COVID-19 vaccines registered in Australia) – [redacted]

1. Product Information.
2. Clinical safety profiles.
3. International data.

Background disease rates (for AESI and serious AEFI) – Lead: [redacted] D21-2108023

1. **Literature** rates – Australia – default. [Document: [redacted]]
2. Vaccine AEFI rates - for some AESIs/ AEFIs these will be rates of the AE seen with other vaccines if population rates are not available

3. **Hospital data** – Australia - general population – AIHW data, consider dataset NISI/ Admissions/ Emergency presentations/ Outpatients; national vs jurisdiction; linked by individual or not.
    a. Access to data to determine baseline disease incidence pre-COVID-19 vaccine availability (short term development goal)
    b. Access to data for real time signal detection using sequential methods (long term development goal)
4. **NSW** NCIRS background rate report
5. **Aged Care mortality** data – aged care data warehouse
6. Global Vaccine Data Network rates
    a. Contact s22 to connect
7. EU Vac4U – publishing on BG rates in EU, s22 ?

Comparison of observed and expected adverse event rates – Development by s22

- Use consistent case definitions where possible
- Consider using date of reaction rather than date of report
- Use risk windows
- Observed to expected rate, relative risk, confidence interval

- Consider subgroup analyses
- Consider adjusting for age and other characteristics
    - Numbers may be too small

- Ask other regulators for their analyses

- Confirmatory studies?

Disproportionality analyses – Development by s22 . <D21-2056009> s22 s22

Process: Weekly COVID-19 vaccine DPAR
Process: Monthly COVID-19 vaccine DPAR
Process: 3 monthly general vaccines DPAR (done through to December)

1. Consider weekly calculations for AESI and high frequency serious adverse events - Qlik automation
2. Consider less frequent calculations (e.g. every 1 or 2 or 6 months) for all events to detect rare events - Qlik automation?
3. Testing of PRR thresholds D21-2103979

- **Unexpected frequency** - Go through large volumes of data to see if any occurring more frequently than other vaccines – Unknown unknowns
- Critical events flag? – AESI? Analphylaxis - not disproportionate - (AESI regardless of whether the has been a report) – not in sheet unless reports – dashboard? **Trend analysis (1) weekly**
- New conditions associated with COVID – unable to compare to for proportionality (Enhanced disease, Paediatric inflammatory syndrome)
- Consider comparison to vaccines only or to vaccines and medicines together.
- Each COVID vaccine antigen individually (Brands as one; Trade names individually)
- **Cumulative review – frequency? Weekly – depends on rate of reports – Fortnightly**

- **Graph of PRR over time**
- **Will take time to be useful.**
- Only what has been reported since, though things may have changed due to other vaccine reports – **excel sheet (2)** weekly - everything
- Check weekly commitment (AESI regardless of whetehr the has been a reort)

- Staff processes and allocation for reviewing Disproportionality analyses at particular time of week

Environmental scanning

Jurisdiction signal detection and investigations

- **VICSAEF**
- **WA**

PSUR

- Periodic Safety Update Reports (PSUR) - tbc

Other

1. Clinical study reports - tbc
2. International data VigiBase – tbc – detection or investigation – watch FDA AE (FAE) Database - ICMRA signals

Environmental scanning SIU work instruction D19-5209870 and flow chart D18-10434494.

Routine scanning

- **Regulator alerts** - MHRA, FDA, EMA, other. **Section email (**media scan, subscriptions, news letters etc) **or IRRS** s22 IRRS email (s22 s22 meet)
- **Aggregate spontaneous vaccine AEFI reporting reports from countries** (e.g. Health Canada) (s22) **US** – FAERS (s22 with s22 support)
- **Databases - WHO** – VigiBase (s22) GACVS issues. Committtes; **Eudravigilance** database; Pregnancy - VSAFE – US active including pregnancy, Harvard registry; sponsors
- **IRRS Library - Medline and EMBASE, (MMWR reports within), Fortnightly regulator news (ICMRA and WHO), Monthly vaccine development newsletter, national and international news searches, Media reports of journal articles**

- **WHO sponsored studies, reports**

- **Others**

- **BC Guidelines**

AusVaxSafety

- **Reports**
- **WA active surveillqnce**

Pregnancy registers

RACF information

Additional alerts

- **On call.** Risk based focus. D18-10434494 Work instruction, D20-471851, sponsor to provide information on action and their justification. Signal investigation D17-770082. Use Evaluation of Sponsor Signal template R15-72515. Check OPR/ AEMS/ PI. Review OPR 'how to' work instruction D18-11291890. Roster D20-3011769. For countries with similar vaccines registered
- **Sponsor Significant Safety Issue notifications**
- **Overseas regulators -** Signal notifications

- **ICMRA** PV network s22
- **Regulators Whats App group** with a number of regualtors – Jane and Elspeth

Internal information

- **TGA – Clinical, (nonclinical), RMP, PSUR intelligence (s22 and s22 – s22 meeting with s22 and s22 provisional and clinical studies**

Media scanning

- s22 daily media digest
- s22 notes D21-2001984

Social media scanning for adverse events

- HERD – s22

Signal investigation

Objective: timely investigation and validation of COVID-19 vaccine safety signals.
Characteristics: timely, high validity and strength of evidence

Definition of a signal

Role of officers in signal investigation

- Individual officer assigned as lead for each signal investigation
- Details to be recorded in signal investigation folder in TRIM

Case series review – process development and oversight informed by s22

- Review individual case data for quality, completeness, including temporal information for risk windows
- With statistical team check data on numbers, rates, proportions, comparisons
- Compare with other sources of data (signal amplification)

1. Check with overseas regulators
2. International VigiBase

- Conduct confirmatory studies (epidemiological studies)
    1. Access Australian hospital data through AIHW for specific vaccine-event pair investigations as appropriate; SAEFVIC willing to assist with Victorian data; check with NSW and Qld and WA – development by s22

Vaccine Safety Investigation Group (VSIG) – process development and oversight by s22

- Processes
    - Criteria to convene
    - Chair and key panel members
    - Causality assessment, root cause analysis
    - Communication advice
    - Regulatory response and actions

  [Document: COVID-19 Vaccine VSIG - s22]

- Provide report
    - Case data
    - Cumulative review findings
    - Comparisons with other data
    - Confirmatory studies
    - Causation analysis

    - Consider template of past reports

Response

Communications

- TGA to communicate information related to confirmed safety signals
- TGA to communicate safety signal reassurances

- Involve PSAB Comms, TGA Comms, COVID Vaccine Comms (covidvaccinecomms@Health.gov.au) and Department of Health media unit (news@health.gov.au) – see VOC Communication Protocol

Regulatory responses

Programmatic responses

Reporting

Weekly external report

Weekly CMO report

Weekly JIC report

Based on previous JIC reports

- stratification by jurisdiction, age, sex
- AESI – national and per jurisdiction
- AEFI– national and per jurisdiction

Weekly internal report to inform external reports

1. **Per vaccine name**
2. **Numbers of AEFI reports received**, cumulative per timeframe
    a. **total AEFI reports**
    b. **serious AEFI** (with definition of serious, and limitations)
    c. **individual AESI** and other. Not for public reporting? (Or organ classes SOC, or cluster e.g. neurological – for public)
3. **Individual AESI rates** (**AEMDS/AIR received +/- Distribution data**), **cumulative**; total AEFI, individual AESI and other; e.g. n per 100,000. For public reporting? Not serious event rates.

4. **Proportional Reporting Ratio**, cumulative (with significance, confidence interval); individual AESI and other – subject to interpretation, not for public reporting

- Trend graphs?

5. Confirmed safety signals

6. Data notes, caveats and conditions of use

Automated Qlik display and export function to generate reports?

Confirm day of week for data cut off and for issuing report.

Official key statistics – e.g. number of people immunised consistent with department
Delay of 1 week on reporting data publically

NIR reporting alignment

Monitoring and evaluation

Monitor implementation through PSAB Activities Register

- Confirm indicators for timely investigation. Monitor for timely detection and investigation of AEFI.

Evaluate system performance:

- Usefulness
- Attributes
    - Data quality
    - Sensitivity
    - Positive predictive value
    - Representativeness
    - Simplicity

- Flexibility
- Acceptability
- Timeliness
- Stability

Review and integrate lessons learned into routine vaccine safety surveillance system

Resources

Staff

Software

- Consideration of R Studio, STATA, SAS according to functional requirements, existing department operating software environment, EDW articulation and partner agency compatibility

Expert technical groups – expertise and capacity

1. Consider role of NCIRS
2. Consider role SAEFVIC
3. Consider role others

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance and Special Access Branch (PSAB)

STANDARD OPERATING PROCEDURE – (SOP)

Name of procedure	Vaccine Surveillance SOP- monitoring of adverse events following immunisation (AEFI)– SIU- PSAB
Applicable to	Signal Investigation Unit
Number	TRIM Reference D18-11209492
Written by	Medical and Professional Officers of SIU
Authorised	Dr s22 [redacted]
Date issued	2019
Version no.	1.0

Version history

Version	TRIM Reference	Description of change	Author/s	Effective date
V1.0	Original	New SOP	s22 [redacted]	

Purpose

This Standard Operating Procedure (SOP) provides a standardised approach to monitoring and surveillance of adverse events following immunisation (AEFIs) by the TGA to enable appropriate responses and/or prevention. This SOP does not cover marketing authorization and licensing activities, the system for lot release of vaccines, recall actions, access and use of the laboratory, regulatory inspections of manufacturers for GMP compliance or regulatory oversight of clinical trials. These are covered by other areas of the TGA. Vaccine product defects are covered but are primarily managed by the Adverse Event and Medicine Defect Section (AEMDS) of PSAB with staff in the Signal Investigation Unit (SIU) providing clinical advice as needed.

Responsibility

The SOP is to be followed by staff within AEMDS and SIU who are involved in any aspects of receiving, coding and reporting adverse events following immunisation and the surveillance and monitoring of vaccines used in Australia.

The responsibility for ensuring this SOP is maintained and routinely updated lies with the SIU Vaccine Safety Manager and/or the Director of the SIU. It is anticipated that over time some defined sections of this SOP will be replaced by links to work instructions in TRIM. All documents relevant to vaccine surveillance work undertaken in the SIU is saved under the TRIM placeholder PH19/50214.

Background

Immunization is one of the most effective public health interventions and has been credited with saving millions of lives around the world from vaccine-preventable diseases (VPDs). To maintain the public health benefits it is important for the public to have confidence in the safety of immunisation. The Australian Government invests large amounts of funding and resources into the National Immunisation Program annually to ensure high coverage rates and to support post market monitoring activities (pharmacovigilance).

Pharmacovigilance involves the collection, detection, assessment, monitoring, and prevention of adverse events following immunisation (AEFIs). One key component of pharmacovigilance is effective surveillance i.e. systematic collection of data on medically important events following immunization to enable investigation and, if necessary, follow-up action.

Following an increase in fever and febrile convulsions associated with Panvax and Fluvax influenza vaccines in children in 2010, Professor John Horvath AO was commissioned by the Australian Government to conduct an independent review of the national response to the reported AEFIs to identify ways in to improve the system. The review made seven recommendations around governance, the establishment of protocols and procedures for managing AEFIs, raising awareness of vaccine safety monitoring, improving the timeliness of reporting, improving transparency and enhancing collection of vaccine usage and safety monitoring data to improve vaccine safety monitoring in Australia and all seven were accepted for implementation over the subsequent two years.

An AEFI is any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal, laboratory finding, symptom or disease.[1] Vaccines rarely cause serious adverse reactions; most reactions are minor and resolve with no treatment or sequelae. AEFIs may be due to an individual's reaction to a vaccine or caused by errors in handling (such as deficiencies in cold-chain maintenance) and/or administration of

[1] Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Geneva: Council for International Organizations of Medical Sciences; 2012 (http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf accessed 25 July 2014).

the vaccine or quality issues with the vaccine itself or the accompanying Product Information (PI) and Consumer Medicines Information (CMI) documents.

Reported AEFIs may be either causally related to, or coincidental with, an immunisation. Surveillance of AEFIs includes review of reports of well-recognised adverse events associated with particular vaccines, as well as events not previously associated with a vaccine.

Surveillance can reveal 'signals' or generate hypotheses about previously unknown AEFIs. A vaccine signal is suspected when information (from one or multiple sources) 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.[2] Rigorous scientific techniques may be required to investigate potential signals to determine causality.

Classification of vaccines

Vaccines can be classified as live attenuated, inactivated, subunit and toxoids.

Examples are:

Live attenuated vaccines (LAV)

Bacteria: BCG vaccine, oral typhoid vaccine

Virus: live Japanese encephalitis vaccine, oral poliovirus vaccine, measles, mumps, rubella, live attenuated varicella vaccine (varicella and zoster), rotavirus vaccine, yellow fever vaccine, intranasal influenza vaccine

Inactivated (killed antigen) vaccines

Bacteria: Whole -cell pertussis (wP)- previously on NIP but high rates of reactions

Virus: Inactivated Japanese encephalitis vaccine, inactivated poliovirus vaccine (IPV) (injected, currently on NIP)

[2] https://www.who.int/vaccine_safety/initiative/investigation/New_aide-memoire_AEFI.pdf

Subunit vaccines (purified antigens)

Protein-based: Hepatitis B vaccine, Acellular pertussis (aP) vaccine- currently on NIP

Polysaccharide: Meningococcal polysaccharide vaccine (no longer used in Australia), Pneumococcal polysaccharide vaccine, Typhoid Vi polysaccharide vaccine

Conjugate vaccine

Haemophilus influenzae type b (Hib) conjugate vaccine, meningitis A, C,W,Y and B conjugate vaccines, Pneumococcal conjugate vaccines (PCV-7, PCV-10, PCV-13), Vi conjugate vaccine- Vi-rEPA vaccine- not registered in Australia, appears to be more effective than first two.

Toxoids

Tetanus toxoid, Diphtheria toxoid

Types and causes of vaccine reactions

Vaccine reactions can also be categorised based on seriousness and frequency:

- common or minor reactions;
- rare or serious reactions.

The WHO definition of 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.[3] Any medical event that requires intervention to prevent one of the outcomes above may also be considered serious. The causes of AEFIs can be categorised as in Table 1.

Table 1: The Cause-specific categories of AEFI (CIOMS/WHO 2012)[4]

[3] Global manual on surveillance of adverse events following immunizationhttps://www.who.int/vaccine_safety/.../Global_Manual_on_Surveillance_of_AEFI.pdf.
[4] Global manual on surveillance of adverse events following immunization: https://www.who.int/vaccine_safety/.../Global_Manual_on_Surveillance_of_AEFI.pdf.

Cause-specific type of AEFI	Definitio n
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
Immunization error- related reaction (formerly "programme error")	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization anxiety-related	An AEFI arising from anxiety about the immunization. reaction
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists.

Note: "Immunization" as used in these definitions means the use of a vaccine for the purpose of immunizing individuals. "Use" includes all processes that occur after a vaccine product has left the manufacturing/packaging site – i.e. handling, prescribing and administration of the vaccine.

Most vaccine reactions are minor and subside on their own. Serious AEFIs due to vaccines such as anaphylaxis, seizures, thrombocytopenia, hypotonic-hyporesponsive episodes (HHEs) and persistent inconsolable screaming are rare and usually do not lead to long term problems.

After immunisation with the live attenuated vaccines (LAVs) such as measles/MMRV, live attenuated herpes zoster vaccine (Zostavax) and oral polio vaccine (OPV), the systemic reactions can occur from vaccine virus infection. Measles vaccine can cause fever, rash and/or conjunctivitis but is usually milder than the naturally occurring measles, although can be severe and even fatal in people who are immunocompromised. The mumps component of MMRV can uncommonly result in parotitis, and rubella vaccine can cause joint pains and swollen lymph nodes in children. Such reactions to rubella vaccine can be very common (up to 15%) in adults.

Table 2. Frequency of occurrence of reported adverse reactions

Frequency category	Frequency in rate	Frequency in %
Very common	≥ 1/10	≥ 10%
Common (frequent)	≥ 1/100 and < 1/10	≥ 1% and < 10%
Uncommon (infrequent)	≥ 1/1000 and < 1/100	≥ 0.1% and < 1%
Rare	≥ 1/10 000 and <1/1000	≥ 0.01% and < 0.1%
Very rare	< 1/10 000	< 0.01%

Procedure

The objectives for an effective surveillance system for vaccines[5]

- Identify problems with vaccine lots or brands leading to vaccine reactions caused by the inherent properties of a vaccine
- Detect, correct and prevent immunization errors caused by errors in vaccine preparation, handling, storage or administration
- Prevent false blame arising from coincidental adverse events following immunization, which may have a known or unknown cause unrelated to the immunization
- Reduce the incidence of injection reactions caused by anxiety or pain associated with immunization, by educating and reassuring vaccinees, parents/guardians and the general public about vaccine safety
- Maintain confidence by properly responding to parent/community concerns, while increasing awareness (public and professional) about vaccine risks
- Generate hypotheses about vaccine reactions

[5] adapted from http://vaccine-safety-training.org/aefi-surveillance-components.html

- Estimate rates of occurrence of AEFIs in Australia compared with trial and international data, particularly for new vaccines that are being introduced

Components of AEFI surveillance cover detection and reporting, investigation, causality assessment of AEFIs, and risk/benefit assessments.

Detection and reporting

Across most states and territories adverse event reporting following immunisation by health care professionals is mandatory in Australia, particularly reporting of serious AEFIs and adverse events occurring in state funded programs and for vaccines on the National Immunisation Program (NIP). Sponsors of medicines and vaccines are expected to follow the *Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements Version 2.1, June 2018*[6], which outlines the mandatory reporting requirements and offers recommendations on pharmacovigilance best practice.

AEFIs are usually reported to the TGA by fax or email and are sent by health care providers, consumers, sponsors, State and Territory Health Departments, immunisation coordinators and other external stakeholders such as Poisons Information Centres.

A small proportion of AEFIs are identified by other routes or received elsewhere in the PSAB or other areas of the TGA e.g. Prescription Medicines Authorisation Branch (PMAB) in which case the report(s) would be sent to the AEMDS team for coding and entry. AEFIs may also be identified by evaluators in the SIU from information obtained from a range of sources including media reports and immunisation experts or clinicians in Australia. Only Australian reports are entered into AEMS. When serious AEFI reports are received originating from outside the state and territory immunisation coordinators (i.e reports from consumers and health care professionals) Full Case Details (FCDs) are sent to the respective state and territory offices within 24 hours. FCDs for AEFI reports originating from the respective state and territory and a national list of all cases (Case Line Listing, CLL) are sent every month to each of the immunisation coordinators. During the seasonal influenza season, FCDs and National CLL are sent to the respective state and territory immunisation coordinators weekly. These are prepared by an administrative officer in AEMDS. They are reviewed and sent out by an MO with section 61 delegation within SIU.

[6] https://www.tga.gov.au/sites/default/files/pharmacovigilance-responsibilities-medicine-sponsors.pdf

Adverse Event Management System (AEMS) Database

AEFI reports are coded and entered into the AEMS Database by staff in the AEMDS of PSAB. Where there is insufficient information in a report to determine causality for a serious adverse event AEMDS senior staff will contact the reporter on up to three occasions to elicit further information. AEMDS coders and the director of AEMDS use the WHO definition of 'serious' as a guideline when coding events but this definition it is not consistently applied so cannot be reliably used to search for all serious events, especially historical events.

Since mid-2018 adverse event reports, including those following immunisation, can be sent to the TGA via Electronic Data Interchange (EDI). The EDI is a system to system channel which makes it possible for reporters (as of January 2019 only sponsors submit via EDI) to submit ADR reports directly into the TGA's AEMS from their IT systems. Use of this service eliminates significant manual processing for industry. As of January 2019 AEFIs submitted through EDI will continue to be reviewed by the AEMDS team.

The internationally recognised Medical Dictionary for Regulatory Activities (MedDRA) is used to code all AEFIs which are entered into the AEMS database. MedDRA is endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and is used by the pharmaceutical industry to code AEFI. Academics, health professionals and other organisations that communicate medical information may use MedDRA terminology but many reporters, including S/T health departments, use free text or other coding systems.

Qlik is a graphical data analytics program on the AEMS dashboard used to search for AEFIs for all vaccines, such as when undertaking data mining and signal detection activities. A guide to understanding and using QLIK is at TRIM# D18-11246188. MedDRA 'Preferred terms' are used in QLIK as the 'reaction term' and MedDRA mapping can be performed to find all relevant preferred terms which may be coded in QLIK when looking for a certain type of reaction. For example, when searching for terms that may be related to 'Shoulder Injury Related to Vaccine Administration' (SIRVA), search terms could include the terms 'bursitis', 'bursa injury', 'musculoskeletal stiffness', 'periarthritis' etc.

AEFI reports may be classified by the coder(s) as 'certain, possible, probable, unlikely or unclassifiable/unassessable' to be causally related to immunisation or referred to the Director for causality categorisation. The criteria used to determine unlikely and

unclassifiable/unassessable events are a) there is no reasonable temporal association between the administration of a vaccine and the clinical event; b) the record does not contain enough information for an adequate assessment or the information is contradictory; or c) uncommonly, a clinical event is explained as more likely to have arisen from other causes or is biologically implausible, for example, shingles developing on the same day as immunisation with Zostavax.

Database of Adverse Event Notifications (DAEN)

Since August 2012, there has been a publicly available and searchable database of adverse events, the DAEN, on the TGA website. The DAEN database contains coded terms for all AEFIs except those classified as 'unlikely or unclassifiable/assessable' or those identified as duplicates. Details visible on the DAEN include age, date report entered, gender, vaccines and medicines taken or administered and the MedDRA terms for the reactions which were reported to the TGA. For each vaccine-event pair (and concurrent medicine-event pair) AEFIs are listed as 'suspected' or 'not suspected' based on whether the event is a known or possible AEFI for example *varicella reported following Zostavax (live varicella vaccine) – Suspected; Coversyl (Perindopril) - Not suspected; Crestor (Rosuvastatin calcium) - Not suspected.*

Monitoring AEFI reports

The initial step in monitoring AEFI is escalation of a subsection of adverse event reports in the attached list at TRIM# D18-11331075 from coders to the assistant director of AEMDS for review. The list captures many of the serious AEFI, including all deaths following vaccination, adverse events of special interest (AESI) and serious unexpected AEFIs. 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.

The list is adapted as needed when particular events are under investigation or as requested by immunisation stakeholders. This process covers reports where the sender uses particular terms or diagnoses when reporting the AEFI and also captures the case narratives of some clinical conditions associated with vaccines. Quality control of the data to detect coding inconsistencies is undertaken on a fortnightly basis by the director of AEMDS.

The Assistant Director reports a subset of these serious and/or unexpected AEFIs (such as all deaths, unexpected events or known events of unexpected seriousness, admissions to ICU,

AEFI resulting in prolonged admission to hospital or where patient has not recovered at the time of the report) to one of the medical or professional officers in SIU primarily responsible for vaccine surveillance and monitoring.

Case line listing fortnightly reviews

To detect events which may constitute safety signals and/or clusters, case line listings for all vaccine AEFI are reviewed fortnightly by the vaccine team. Documents to use include the 'Working Template for fortnightly scanning' (TRIM# D18-11263731), which provides a summary of the numbers/types of adverse effects, and a QLIK generated excel sheet of total AEFI reports for the fortnight with pertinent cases highlighted. The criteria for "pertinent" cases are:

- Requiring ICU or PICU admission

- Ongoing admission in hospital (i.e. longer than overnight)

- Ongoing disability

- Serious unexpected AEFI which is not already captured in the AESI table

An AEFI is considered 'unexpected' if it is not listed in the PI document for the vaccine or is listed but causality has not been established.

This scanning helps ensure timely detection of any emergent vaccine adverse events of concern and allows the team to specifically monitor certain adverse effects or vaccine groups which have been highlighted by our various stakeholders as requiring closer monitoring. The review also contributes to quality control of the data. The list of adverse events which are specifically monitored changes over time, with new evolving issues, new schedules and the introduction of new vaccines added as required.

Pertinent cases are included as a standing item on the meeting agendas of the Advisory Committee on Vaccines (ACV) and the Jurisdictional Immunisation Coordinator (JIC) committee. The format allows data to be cut and pasted into the ACV and JIC agenda papers.

Investigation of AEFIs, potential safety signals and/or clusters

Not all AEFI need investigation although even known AEFI such as fevers or febrile convulsions should be monitored for an increase in rate of events, especially if associated with a new vaccine.

The WHO Global manual on surveillance of adverse events following immunisation recommends an AEFI should be investigated if it:

- appears to be a serious event (as defined by WHO) of known or unknown cause;
- belongs to a cluster of AEFI;
- is a previously unrecognized event associated with an old or newly introduced vaccine;
- involves an increased number or rate of known cause;
- is a suspected immunisation error;
- appears on the list of events defined for AEFI surveillance; and
- causes significant parental or public concern[7]

The level of investigation depends on the severity of the event and/or number of events. All serious events are reviewed by the Assistant Director of AEMDS and a selection, as described above, by the TGA Medical Officers (MOs) and professional officers in the SIU vaccine team.

There are serious adverse events designated *adverse events of special interest* (AESI). These AESI include anaphylaxis, Bell's palsy, encephalitis, myelitis and ADEM, Guillain-Barre Syndrome, hypotonic-hyporesponsive episode, multiple sclerosis, neuritis, optic neuritis, seizure, serum sickness, vaccination failure, vasculitis and shingles. Reporters are routinely sent questionnaires to complete to collect further information if the information provided is incomplete or inconclusive. This can only occur when the reporter has provided consent to contact with contact details. These questionnaires are provided at TRIM# 2015/034788.

Serious AEFI including deaths which may constitute a safety signal, potentially generate media interest and/or threaten public confidence in the National Immunisation Program (NIP) should generally be reported to the SIU director, PSAB head and the head of the Office of

[7] Global manual on surveillance of adverse events following immunization: https://www.who.int/vaccine_safety/.../Global_Manual_on_Surveillance_of_AEFI.pdf.

Health Protection Branch. Timeframes for reporting are in table 4, from the Vaccine Safety Investigation Group (VSIG) work instructions, TRIM# D18-10878760.

If only limited information is available, all possible avenues should be explored to source additional information from the reporter or jurisdiction in which the AEFI occurred to obtain inpatient notes, referrals, test results and/or autopsy results, if relevant. Minimum information which should be requested include hospital discharge summary if available, date of vaccination, age, date of first symptoms (onset), postcode or jurisdiction, when and to which hospital they were admitted, any tests (if known), the final diagnosis and name of specialist under whom admission occurred if applicable. If no further information can be gathered consider referral to the Adverse Events Following Immunisation – Clinical Assessment Network (AEFI-CAN; see below for further information).

Once further information has been received and reviewed a more rigorous causality assessment can then be undertaken. The level of causality attributed to the vaccine is recorded in AEMS using the six criteria used by the coders ie ‘certain’ ‘probable’ ‘possible’ ‘unlikely, ‘unclassified’ or ‘unassessable’.

Table 3: Escalation timeframes and pathways for AEFIs (adapted from VSIG WI)

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[8]	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[9]	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[10] and the report contains adequate information[11]			
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
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[12]

[8] The AEMS Coordinator will also request further information from the reporter if required.
[9] If reported directly to the TGA (i.e. not through a jurisdictional public health unit).
[10] 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.
[11] 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/PSAB AS	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

In some instances the case should be referred to the VSIG for a formal causality review by an independent panel and/or to determine if further actions are required. The criteria triggering the formation of VSIG and referral of an AEFI are included in the VSIG work instructions, TRIM# D18-10878760. The new issue should be added to the OPR database.

Detection and investigation of potential safety signals

A safety signal is defined as having a possible causal relationship with the vaccine where the relationship is previously unknown or incompletely documented. Often more than one AEFI report is needed to confirm a safety signal. A signal may be suspected when information from one or multiple sources suggest 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.[13]

Safety signals may be detected via review of cases reported to the senior MO by the assistant director of AEMDS, an analysis of the TGA Adverse Event Management System (AEMS) database including through case line listing reviews, Proportional Reporting Ratio (PRR) analysis or from any other source of adverse event reports such as:

[12] 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

[13] Global manual on surveillance of adverse events following immunization: https://www.who.int/vaccine_safety/.../Global_Manual_on_Surveillance_of_AEFI.pdf.

- World Health Organization (WHO) or immunisation centres or clinicians overseas
- overseas regulatory agencies (e.g. FDA, EMA, MHRA, Health Canada, Medsafe);
- medical literature;
- notifications about safety investigations from elsewhere in TGA
- via Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Reports (PBRERs) or information stemming from Risk Management Plans (RMPs).

Decisions on how to proceed with investigating serious AEFIs which may be safety signals should be made in discussion with the Unit Director, Branch Head or senior colleagues. Potential safety signals may also be discussed with OHP and/or the chair of ACV. As for safety signals associated with medicines, the SOP entitled *Process for conducting a medicine signal investigation* at TRIM# D17-770082 may then be followed. The safety signal should be added to the OPR issues database. Occasionally and if not urgent, it may be appropriate to discuss the issue at the next SIU Meeting. Again, if certain criteria are met, outlined in the VSIG work instructions, the VSIG can be convened to investigate a potential safety signal and/or advise on additional actions. The PSAB head and OHP should be informed in this circumstance and the issue should be added to the OPR database.

Signal detection using the Proportional Reporting Ratio (PRR) Method of Analysis (Disproportionality Analysis Report (DPAR))

Every two months vaccine adverse events with a PRR exceeding the prescribed threshold are reviewed by the vaccine team. The PRR analysis is a well-established quantitative method of detecting safety signals for vaccines and medicines. The concept behind the PRR method is that of disproportionality. The PRR examines how many reports have been received for a given reaction to a given medicine or vaccine compared to the same reaction reported for all other medicines and vaccines combined. For detailed information on how to conduct a DPAR refer to TRIM# D18-11114057.

Vaccine advisory group meetings

Advisory Committee on Vaccines (ACV)

The ACV provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of vaccines supplied in Australia including issues relating to pre-market assessment, post-

market monitoring and safe use in national immunisation programs. Membership comprises professionals with expertise in specific scientific, medical or clinical fields, or consumer health issues. The committee meets approximately six times a year.

Vaccine safety signals or TGA investigations of AEFI and new TGA or OHP vaccine strategies and protocols may be presented to ACV for comment and advice. Submissions for PSAB agenda items should cover the product(s) and sponsor(s), a short summary of the issues, and whether expertise from outside ACV would be useful. Templates are TRIM # D17-276351 as a simple nomination form, or the standard coversheet TRIM # D17-276349 if the request for committee advice is fully developed. These need to be prepared four weeks prior to the meeting and cleared by the PSAB head. Two weeks prior to ACV coversheets and agenda paper (summary of issue, filter or investigation (cleared by the Section Head)), should be placed in agenda container TRIM# E18-307995 for ACV # 'working' agenda papers.

Serious AEFIs occurring in the previous two months are a standard item for noting only on the agenda of ACV. Non urgent causality reviews of AEFIs may be undertaken at the conclusion of ACV by members of the committee and invited experts. Results or conclusions will be reported back to committee members at the next ACV.

Jurisdictional Immunisation Coordinator (JIC)

Regular jurisdictional immunisation coordinator meetings are convened monthly with State and Territory representatives and the Office of Health Protection (OHP). A TGA staff member (currently MO) chairs this meeting. The agenda is developed by the assistant director AEMDS or MO in SIU in consultation with the senior medical and other professional officers (evaluators). The agenda and minutes are filed under the placeholder PH16/113 and a new container is created for each teleconference. The standard agenda template is in TRIM# D19-5008701.

Regular agenda items include serious AEFI, updates of any AEFI received for new NIP vaccines and for any vaccines for which there is enhanced surveillance. A recent example of enhanced surveillance is for extensive limb swelling in children receiving the fifth DTPa dose at 4 years of age. In some instances clusters of clinical symptoms and signs which are not MedDRA terms, for example *serious allergic reactions excluding anaphylaxis* are collated and reported at JIC meetings. In this case the assistant director of AEMDS will search all QLIK reports for a particular vaccine and select the reports which fit these criteria eg wheeze, angioedema,

swollen tongue. The search terms used each month may vary depending on the reports received and the search criteria will be annotated beneath the relevant table.

Other standing agenda items include an AusVaxSafety update and round table discussion. If requested by jurisdictions, AEFIs reported for state/territory-based vaccination programs may also be included. The JIC agenda is based on current issues and can be modified as required by jurisdictional and/or OHP/TGA members.

Adverse events following immunisation - Clinical Assessment Network (AEFI-CAN)

AEFI-CAN is a formal collaboration between state and territory-based vaccine safety clinics and the Therapeutic Goods Administration (TGA) funded by the Commonwealth Department of Health.

As a national network, AEFI-CAN works collaboratively to clinically assess and manage individual patients following serious or unexpected adverse events following immunisation. AEFI-CAN links surveillance with clinical assessment and management. AEFI-CAN can assist in investigating patient outcomes and possible vaccine safety signals.

There is an AEFI-CAN database developed and managed by the Victorian vaccine safety service (SAEFVIC; Surveillance of Adverse Events Following Vaccination In the Community). It was initially funded by the Victorian Department of Health and the expansion in 2018-19 has been partially funded by the Commonwealth via AusVaxSafety. SAEFVIC is the central reporting service in Victoria for any significant AEFI. As of March 2019 the AEFI-CAN database includes all AEFI reports and clinical notes from patients referred to the specialist immunisation clinics (SICs) in Victoria and one of the other states (Western Australia-WAVVS) at this stage. It also has clinical data from the Hunter New England SIC, Newcastle, NSW and Queensland Children's Hospital. Most states and territories are expected to also contribute their clinic data to the database in the near future. It is envisioned that this database will include all serious AEFI in most, if not all, states and territories and that these reports will be transmitted via a Gateway to the TGA AEMS database. Reports will be siloed into individual states and territories, although Victoria will have access to all reports across jurisdictions. The TGA will not have direct access to this database but is currently working with SAEFVIC to enable efficient transmission of data into the AEMS database.

AEFI-CAN meetings are held every four to six weeks and a TGA medical officer attends and reports on current safety investigations and serious AEFI. Through members' clinical and

hospital networks AEFI-CAN may be able to identify seriously ill patients when AEFI reports to TGA do not contain sufficient information to allow investigation. All AEFI-CAN and TGA emails relating AEFI-CAN should be filed in TRIM in a folder for the current year *Meetings - Adverse Events Following Immunisation Clinical Assessment Network (AEFI-CAN) Teleconferences.*

The Australian Technical Advisory Group on Immunisation (ATAGI)

ATAGI is an expert vaccine advisory committee.

ATAGI's role is to:

- advise the Minister for Health on the medical administration of vaccines available in Australia, including those available through the National Immunisation Program (NIP)
- provide advice to research organisations on current immunisation research and areas that need more research
- advise the Pharmaceutical Benefits Advisory Committee (PBAC) on vaccine effectiveness and use in Australia
- consult with relevant organisations to produce the Australian Immunisation Handbook
- consult with relevant organisations in implementing immunisation policies, procedures and vaccine safety.

ATAGI meets for two days, three times annually with an additional industry/ATAGI day midyear adjacent to the ATAGI meeting. ATAGI is usually attended by a senior Medical Officer from the SIU. The MO5 in PMAB Clinical Evaluation Unit 2 (CEU2) is the TGA representative on ATAGI. There is a standing TGA item prepared by PMAB unit 2 head, the PSAB senior vaccine MO and the ACV secretariat. The ACV and PSAB report covers outcomes from the most recent ACV meeting and updates of any current vaccine safety investigations or other vaccine issues. This section of the agenda item is cleared by the PSAB head. The agenda template is at TRIM# D18-11245131. All emails relating to ATAGI should be filed in the folder for current year. The placeholder for ATAGI meetings is PH19/51452.

National Immunisation Committee (NIC OHP) and Jurisdictional Immunisation Coordinators (JIC) The National Immunisation Committee's (NIC) role is to provide advice on

the National Immunisation Program (NIP). A separate Jurisdictional Immunisation Coordinators (JIC) meeting is usually held prior to the NIC meeting for specific jurisdictional issues. The NIC also represents the needs and views of vaccination providers and consumers.

The NIC was established in 1993, at a time when there were no other existing governance committees for immunisation at the national level. The original purpose was to implement the HiB program and co-ordinate roll-out of the vaccine. A committee was required that brought together interest groups such as the Australian Medical Association (AMA), immunisation providers and consumer groups.

This is still a key role of the NIC, which brings together interest groups such as the AMA, RACGP, APNA, ACM, NCIRS, ACCRM, MCaFHNA, CHF, CATSINaM, RDAA, and NACCHO with the Commonwealth and the jurisdictions.

As of April 2019, the Terms of Reference (TOR) and the membership of the NIC are undergoing review. The current TOR are:

- Progress and oversee implementation of the National Immunisation Strategy.
- Provide advice on the strategic direction of the NIP, including policy and program advice that supports the implementation of the Program.
- Represent the views of key immunisation stakeholder groups. These include health professionals, peak bodies, consumers and researchers and the Commonwealth and state and territory governments.
- Consult and collaborate with other peak immunisation related committees. These include the Australian Technical Advisory Group on Immunisation (ATAGI), Jurisdictional Immunisation Coordinators (JIC) and the Communicable Diseases Network Australia (CDNA).
- Provide advice on the development and implementation of NIP communication strategies.

The NIC meets three times a year. The PSAB head is a voting member of NIC but may delegate meeting attendance to the senior MO in vaccines.

The Vaccine Safety Investigation Group (VSIG)

The Vaccine Safety Investigation Group (VSIG) is a time-limited working group which will be convened when specific criteria for an 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.

The role and activities of the VSIG include (but are not limited to) causality assessments, root cause analyses, multi-case investigation; development of communication material and risk communication messages including advice for clinicians, advice on programmatic action and advice on risk minimisation through regulatory action. The Vaccine Safety Investigation (VSIG) Work Instruction and associated templates are in TRIM# E18-338144. All relevant documents pertaining to VSIG Causality Assessment Panels should be saved to TRIM under the place holder PH19/51903.

Liaison with the National Centre for Immunisation Research and Surveillance (NCIRS)

NCIRS is a research organisation that provides independent expert advice on all aspects of vaccine preventable diseases and social and other issues related to immunisation to inform policy and planning for immunisation services in Australia.[14]

Annual AEFI surveillance reports have been prepared by NCIRS in collaboration with the TGA and published in Communicable Diseases Intelligence since 2003. These reports contain valuable information such as the rate at which an adverse event following vaccination is reported. They also contain annual information about serious adverse events and deaths that are reported to have occurred following a vaccine.

AEFI reports are provided by the SIU in de-identified form to NCIRS for these annual reports and other analyses, for example, national immunisation program evaluations, reports to the Australian Technical Advisory Group on Immunisation (ATAGI). The annual national and NSW reports are reviewed by a senior MO in SIU and the PSAB head prior to publication and the PSAB head or senior MO is listed as a co-author.

AusVaxSafety reports

[14] http://www.ncirs.org.au

AusVaxSafety is an active surveillance system, led by the NCIRS and funded by the Commonwealth Department of Health. It operates in more than 270 sites nationwide and sends automated text messages to patients or parents following a vaccination to inquire whether any adverse events may have been experienced. SmartVax and Vaxtracker are the two software programs used to do this. SmartVax reports on events experienced within three days of vaccination, while Vaxtracker reports on events experienced within 16 days post-vaccination. For Vaxtracker, an additional survey is sent at 24 days post-vaccination inquiring whether participants have experienced a chickenpox-like rash or influenza-like symptoms or been hospitalised in the 24 days following vaccination. Replying "yes" to having a rash and influenza-like symptoms and/or requiring hospitalisation triggers an alert for follow-up.

AusVaxSafety currently monitor 5 vaccines – herpes zoster, pertussis booster, maternal pertussis, HPV and influenza. This will be expanded to monitor all vaccines on the NIP in 2019.

A summary of the data is collated and emailed as surveillance reports to the TGA throughout the month for each individual vaccine, to a nominated vaccine team member. The number received per month varies depending on the season. Each report states at the outset whether the NCIRS author has determined that a signal has been detected. This determination is assessed by the TGA staff member reviewing the report. Once each report is reviewed for the month, it is recorded as a task in the issues (OPR) database (Issue #9283), including the date the report was received, the report number and the result (eg – no signals identified) documented. The emails with the reports are also filed to TRIM container E19-502429.

Advisory Committee for the NCIRS Evaluation of the National HPV Vaccination Program

In September 2019, NCIRS invited the TGA to sit on the Advisory Committee for the NCIRS/Department of Health evaluation of the national HPV vaccination program in Australia (begun in 2007), which will build on the evaluation of the 4vHPV vaccination program conducted by NCIRS in 2012/13. The final report is due June 2020. The first teleconference was held on 30/09/19, the second on 16/12/19 and the third is scheduled for March 2020.

Documents pertaining to the TGA's representation on this Advisory Committee are stored in TRIM container E19-528570.

NCIRS and TGA joint research project: Adverse events following HPV vaccination – 11 years of surveillance in Australia

The TGA was approached by Dr s22 from NCIRS/Telethon Kids Institute (TKI) in February 2017 for study investigators to participate in a research project (carried out as part of Dr s22 doctorate) analysing 11 years of HPV vaccine AEFI compared with rates of adverse events with other vaccines. Dr s22 and Dr s22 s22 (senior medical officers in the SIU) agreed to participate as study investigators and provide advice on the extraction, interpretation, and clinical assessment of adverse event reports in AEMS.

An ethics application was submitted by Dr s22 in October 2018 and subsequently approved. The study began in November 2018 and was completed in November 2019. The results were presented at the Public Health Association of Australia Communicable Diseases Control Conference in Canberra on 21/11/19. The manuscript was submitted for consideration to the journal *Vaccine* in November 2019. It was accepted as a major revision, and suggested revisions were made by the primary author and submitted to the TGA for consideration in January 2020.

Documents pertaining to the TGA's involvement in this study are stored in TRIM container E19-528570.

Annual influenza vaccine web statement

The Australian Influenza Vaccine Committee (AIVC) provides advice to the Therapeutic Goods Administration (TGA) on the composition of the seasonal influenza vaccine to be supplied each year in Australia.

The meeting is held annually following the September World Health Organisation (WHO) strain consultation meeting, which makes a decision on vaccine composition for the Southern Hemisphere.

At the meeting the committee reviews and evaluates current available data related to the epidemiology, antigenic and genetic analysis of recent circulating regional and southern hemisphere influenza isolates and serological responses to the previous season vaccines. AIVC is not involved in any decision making process under the *Therapeutic Goods Act 1989*.

The following March each year, ATAGI publishes a web statement on the coming season's influenza vaccines. Based on these statements, the PMAB CEU2 MO5, an MO in the vaccine

area of SIU, PSAB and the director of biomedicines and flu vaccine in the laboratories branch prepare the annual TGA web statement for the coming influenza season.

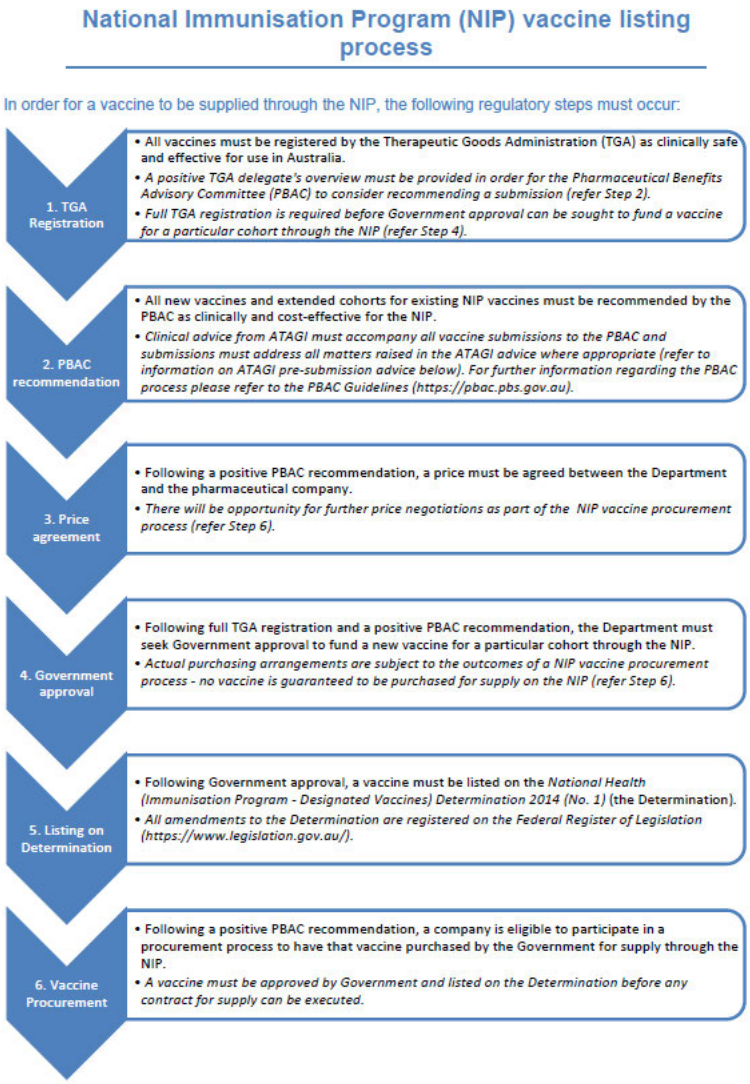
PSAB provides the Assistant Secretary of the Immunisation Branch the opportunity to comment on the draft statement, before it is finalised by the PSAB communications team and uploaded to the TGA website.

Record Keeping

All vaccine related SIU documents should be created and stored in the relevant TRIM containers, with placeholders for easy location.

Responses to inquiries from stakeholders regarding vaccines actioned by the SIU are filed in TRIM container E20-4786.

Attachment 1



https://www.health.gov.au/sites/default/files/nip-vaccine-listing.pdf

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

Australian Government
Department of Health
Therapeutic Goods Administration

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.

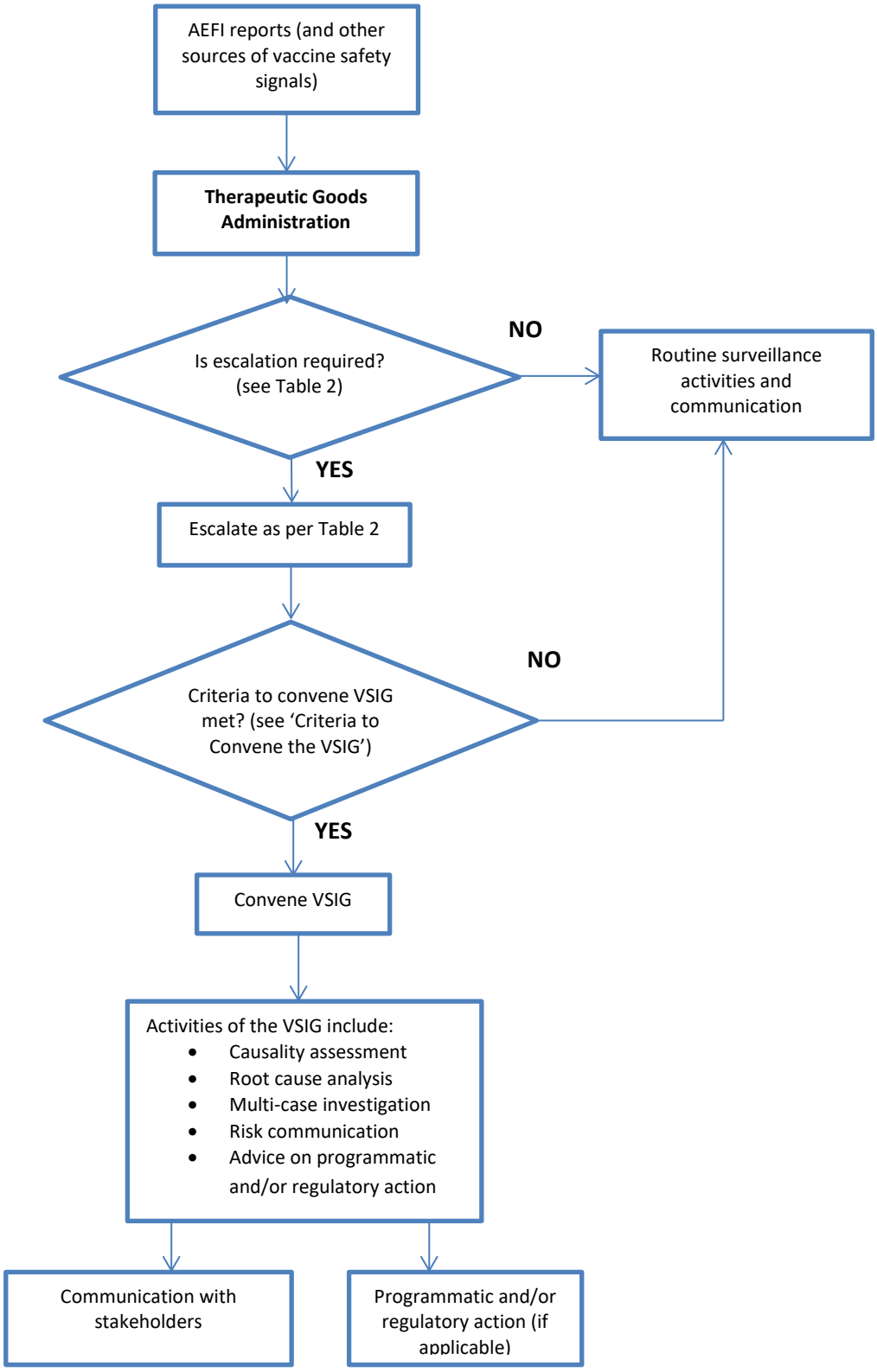
Related Documents

- 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
Dr s22 [redacted]	s22 [redacted], Signal Investigation Unit	7 January 2019

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

INTERNAL USE ONLY

Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance and Special Access Branch

STANDARD OPERATING PROCEDURE – (SOP)

Name of procedure	Process for Conducting a Medicine Signal Investigation – PSAB - SOP
Applicable to	Signal Investigation (Medicines) Unit
Number	TRIM Reference
Written by	Medical and Professional Officers of the Pharmacovigilance and Special Access Branch
Authorised	Dr Jane Cook
Date issued	
Version no.	4.0

Version history

Version	TRIM Reference	Description of change	Author/s	Effective date
V1.0	Original	Working Draft	Dr s22	Working Draft
V2.0	R13/987646	Minor revision & New Filter Template	Dr s22 s22 Mr s22 s22	December 2013
V3.0	R15/118149	Revision of SOP and Filter Template	Dr s22 s22	March 2015
V4.0	D17-770082	Revision of SOP and Signal Investigation Template	s22 s22 s22 ,s22 ,s22	March 2019

INTERNAL USE ONLY

Purpose

This Standard Operating Procedure (SOP) provides a standardised approach for conducting a signal investigation.

Historically, a signal investigation was called a safety filter and was a short appraisal of a new safety signal that aimed to distinguish signals requiring further review or regulatory action from signals that do not require further investigation. However, the safety filter has evolved to become the main tool to further investigate a safety signal and recommend appropriate action if the issue is complex/involves a class and where a direct negotiation with sponsor activity is not appropriate. Accordingly, in 2019 the name was changed from safety filter to signal investigation. In 2019, a targeted signal investigation was introduced. This is a concise assessment of a less complex safety issue.

Responsibility

The SOP is to be followed by officers within the Signal Investigation Unit (SIU) of the Pharmacovigilance and Special Access Branch (PSAB) who prepare signal investigations or are involved in any aspect of their preparation and handling.

The responsibility for ensuring this SOP is maintained and routinely updated lies with the Director of the SIU.

Background

Safety signals are identified by the medical officers and other evaluators of the SIU from information obtained from a range of sources including:

- Disproportionality Analysis Report (DPAR) or other analysis of the TGA Adverse Event Management System (AEMS);
- Referral from elsewhere in the PSAB or other areas of the TGA e.g. Prescription Medicines Authorisation Branch (PMAB);
- Sponsors e.g. Periodic Safety Update Reports (PSURs), other information stemming from Risk Management Plans (RMPs) or notifications about significant safety issues and regulatory action elsewhere;
- Review of the medical literature;
- Overseas regulatory agencies (e.g. FDA, EMA, MHRA, Health Canada, Medsafe, HSA).

Commented [SSC1]: If this list is from IPMST members, then need to include Swissmedic.

Procedure

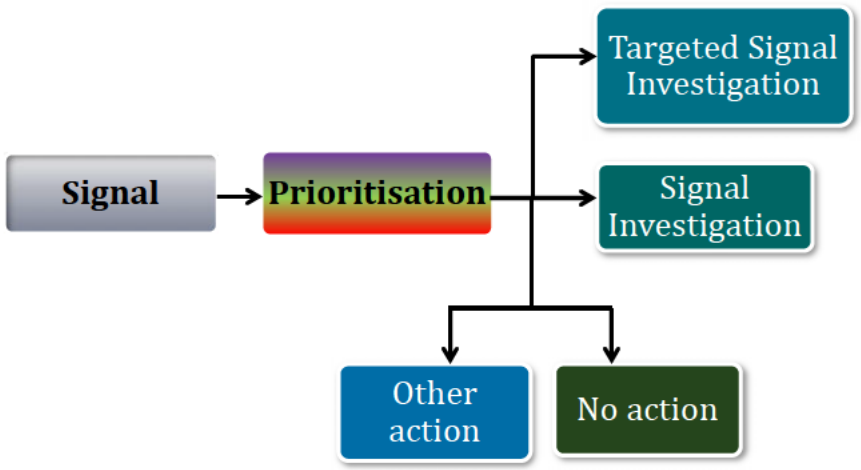
Issues Database

Once a signal is identified, it is added to the OPR Issues Database (herein referred to as the 'Issues Database') by the Signal Investigation Coordinator and is thereafter referred to as an 'issue'. The

evaluator undertakes an initial assessment of the issue to determine what action needs to be taken (e.g. defer, no further action, direct negotiation with the sponsor, targeted signal investigation, signal investigation etc.) and assigns a priority (high, medium or low) based on the risk level. The proposed action and priority are then agreed at the following SIU team meeting.

Refer to the *'OPR Issues Database'* work instruction for further information on the documentation and maintenance of workflow information in the Issues Database (D18-11291890). Refer to the *'SIU Prioritisation'* work instruction (D18-11335152) for further guidance on the prioritisation process.

The possible options for investigating a new issue are illustrated in the diagram below and further explained within the box.



- In many cases a targeted signal investigation is required to assess other action, or no action is indicated and to help prioritise the issue. The targeted signal investigation also serves as a record of the decisions made regarding the issue given the information available at the time. It may also lead to a signal investigation.
- In some cases a signal investigation is required to further assess a complex issue which may involve a class of medicines and/or multiple tasks. If a more comprehensive signal investigation is required to investigate the issue, the evaluator may consider broadening the headings/content of the signal investigation to include pharmacokinetics, pharmacodynamics, a more detailed assessment of the methodology of available safety and efficacy evidence, consideration of TGA-adopted EU guidelines and consideration of safety issues in specific subgroups (where relevant). In this instance, the historical Safety Review SOP (R15/400261) may be a useful guide as well as 'PMAB clinical evaluator training program' documents available from TRIM (2012/019533).
- Sometimes 'other action' is clearly indicated from the outset. The rationale for undertaking other action should be documented in the 'Comments' field for the issue in the Issues Database and the relevant new task/s should be added.
- Sometimes, it is equally clear that no action is required. The rationale for taking no action should be documented in the 'Comments' field for the issue in the Issues Database. There is no need to generate any task. This will show that the signal has been considered by PSAB for future reference.

When a signal investigation is required, a Signal Investigation 'Task' is created for the issue in the Issues Database. Likewise, when a targeted signal investigation is required, a Targeted Signal Investigation 'Task' is created. The evaluator should then allocate themselves to that 'Task' and change

the Issue status from 'New' to 'Work in Progress'. When picking up a task for an issue from the Issues Database, the evaluator should seek clarification of decisions on how to proceed with investigating the issue from their direct supervisor or SIU Director, especially for older issues.

Record Keeping

All PSAB documents should be created and stored in TRIM. The targeted signal investigation/signal investigation (herein referred to as 'investigation' unless otherwise specified) and any documents relating to the investigation (e.g. references, correspondences) should be stored in the relevant TRIM container. A link to the TRIM container can be found under the issue's summary in the Issues Database. If you are unable to locate the correct TRIM container or are unsure about where to save documents, please contact the Signal Investigation Coordinator.

The investigation and other relevant documents should be saved using the same naming convention as the investigation TRIM container to ensure that they are readily identifiable within the container. For example:

DXX-XXXXX Active ingredient (Trade Name) and Adverse Event/Issue – Signal Investigation

DXX-XXXXX Active ingredient (Trade Name) and Adverse Event/Issue – Product Information

The investigation should be marked as DRAFT followed by the date. It is the evaluator's responsibility to mark the investigation as FINAL once it has been cleared.

Use of the Targeted Signal Investigation and Signal Investigation Template

The targeted signal investigation template or signal investigation template should be used to document the evaluation of the safety issue (for Targeted Signal Investigation template see TRIM D19-5190469 and for Signal Investigation template see TRIM D19-5190468).

Scope and Aim of the Targeted Signal Investigation and Signal Investigation

Targeted Signal Investigation

A targeted signal investigation is appropriate for a straightforward issue where a limited amount of additional information is required in order to make a decision about regulatory action.

The aim of the targeted signal investigation is to determine whether there is sufficient evidence to conclude that a signal may be a true signal that warrants regulatory action, if further investigation is required, or if there is insufficient evidence to support the validity of the signal. If the signal is verified, the investigation also aims to assess its clinical impact.

If the safety signal is found to be invalid or has already been acted upon, the evaluator undertaking the investigation will generally make a recommendation for no further action. If a targeted signal investigation has concluded that further investigation is warranted, a signal investigation can be conducted to evaluate the issue/s in greater depth.

Signal Investigation

A signal investigation is recommended for issues that have higher levels of complexity, possibly involving a class of products or where there is likely to be a lot of information that needs to be evaluated and synthesised.

Style and Format of the Targeted Signal Investigation and Signal Investigation

- Font style and size: Cambria (body) size 10 (minimum)
- Paragraph style and referencing:
    - Please refer to Health Products Regulation Group (HPRG) writing guide available at: http://sharepoint.central.health/groups/hprg/Pages/how-to-policies-and-resources/communications/az-writing-guide.aspx
    - Please refer to HPRG formatting guide available: http://sharepoint.central.health/groups/hprg/Pages/how-to-policies-and-resources/communications/az-formatting-guide.aspx

Commented [2]: The TGA writing guide says:

Font sizes
The font size in TGA documents is flexible - you can change these font sizes if there is a good reason to.
Normal text in Microsoft Word documents should be between 9.5 and 11 point, with 11 point being the preferred size.
Multiple column documents usually have slightly smaller type than single column documents.
Headings start large and become smaller. Thus Heading 2 should always be larger than Heading 3, and Heading 3 should always be larger than Heading 4, etc.

As point size 11 is the preferred, should we include "size 11 (preferred)"?

Content of the Signal Investigation

Although the remainder of this SOP outlines the content of a signal investigation, this guidance is also relevant to the more concise targeted signal investigation.

The signal investigation should be clear and concise yet contain enough information to allow the peer reviewer or authoriser to adequately assess the signal and the recommendations made by the evaluator. The signal investigation's header should include the name of the product(s) and the safety issue. It should also include the PSAB Issue number, the task number and the signal investigation document's TRIM record number.

The content of the signal investigation should be structured under the following sections to allow for the logical flow of information to assist reviewers in the assessment of the signal:

Commented [3]: The draft templates have the headings in capitals. The writing guide states minimal capitalisation with only the first word having a capital letter.

1. Introduction

Commented [4]:
For ease of navigation and so that information can be seen easily, I suggest inclusion of 2 subheadings:
- A subheading eg. 'Has this issue been previously considered?' from the previous template could be reinstated
- A subheading eg. 'Purpose of this signal investigation'

2. What Products/Ingredients are involved?
3. What is the safety concern?
4. Current risk minimisation strategies/measures
5. Literature
    - 5a. Search Strategy
    - 5b. Critical Appraisal
6. Post-marketing adverse event reports

6a. TGA Adverse Event Reports

6b. VigiBase data

6c. Published case reports

6d. PSURs

7. Discussion

7a. Validity of the signal

7b. Public health impact of the signal

7c. Recommendations

8. Conclusion

9. Summary of Recommendations

10. References

11. Authorisation

N.B. not all sections need to be completed if they are not relevant to the assessment of the signal. The decision to complete certain sections is at the discretion of the evaluator however the evaluator should seek guidance from their supervisor if required.

1. Introduction

This section should contain a brief description of the signal and how it was identified, including specific details about the timeline and source of the signal. For example, a signal identified from the DPAR may be described as follows:

> *A signal for drug X and adverse event Y was identified on DD/MM/YYYY through the bi-monthly disproportionality analysis report (DPAR) of adverse event reports in the TGA Adverse Event Management System (AEMS). A PRR of <value> was obtained from <value> reports.*

Check the Issues Database to determine if the issue has been investigated by the TGA previously. If it has been investigated previously, what action was taken and what were the reasons for the action? How does the current situation differ? Include the source of the issue, the date it was completed and the issue number.

Commented [5]: See my comments above

The evaluator should conclude this section with a brief summary of the potential impact of this signal in the Australian context, what risk mitigation strategies are currently in place and describe what this signal investigation hopes to achieve. For example:

Commented [6]: See my comments above

> *This signal investigation will analyse the evidence for "signal X". There are currently no warnings or precautions for this signal and therefore this signal investigation will determine whether any regulatory action or risk minimisation activity is required in Australia.*

INTERNAL USE ONLY

2. What Products/Ingredients are involved?

Active Ingredients/Products

This section should identify what active ingredient(s) and/or product(s) are involved in the signal. For example the signal may involve:

- particular active ingredients (innovator products and their generic equivalents) e.g. ramipril (TRITRACE) and its generic equivalents;
- individual products (individual entries on the ARTG) e.g. TRITRACE (ramipril) 1.25mg tablets ARTG 34515;
- a specific class of medicine (e.g. ACE Inhibitors). If the signal investigation concerns a class of drugs it is acceptable to list the individual active ingredients for that class and their respective innovator product noting whether or not there are generic equivalents.

If possible the active ingredients/products should be listed in a table format according to their strength, ~~formulation~~ dosage form, ARTG No., date of first entry into ARTG, sponsor's details etc. For example, a class of medicine can be presented as follows:

Active Ingredient	Innovator trade name	Strength[a]	Formulation	ARTG No.	Date entered in the ARTG	Sponsor	Generic Equivalent (Y/N)
ramipril	TRITACE	1.25mg	Tablets	34515	20 December 1995	Sanofi-Aventis Australia Pty Ltd	Yes, more than 10 brands in the ARTG

Commented [7]:
'Dosage Form' is the relevant AAN.
'Formulation' refers to the active + excipients of a product.

If there are too many active ingredients/products involved to present in a neat table then a brief description of the active ingredients/products available in the ARTG will suffice. It is at the evaluator's discretion to determine which is appropriate.

Determining the class of a medicine
Medicines may be classified on the basis of their chemical structure, mechanism or mode of action, or indication. Consideration of the class of the medicine of interest is important to determine if there are related products on the ARTG that fall into the scope of the investigation. As there is no definitive list of registered products categorised by class, the evaluator will need to exercise judgement in deciding what is relevant.

The WHO classifies medicines using the Anatomical Therapeutic Classification (ATC) system, which is a hierarchical system with five different levels. For further information see:
https://www.whocc.no/atc/structure_and_principles/#principles

You can search for a medicine here:
https://www.whocc.no/atc_ddd_index/

Search results for a medicine will show the higher levels of classification, and these can be used to identify other medicines in the same level or class. This is not a failsafe method and sometime the ATC

[a] Only complete the 'strength' column if the strength of the medicine is relevant to the safety issue. If unsure, discuss with your supervisor.

codes do not group according to class. The Australian Medicines Handbook also groups medicines by class:
https://amhonline.amh.net.au/drugs/monographs

Mechanism of Action

Describe the mechanism of action of the drug.

Registered Indications

This section should identify the registered indications for each active ingredient or product. This information may also be presented in a table format however it is at the evaluator's discretion as to how this information is presented. For example, the indications for a class of medicine (e.g. SGLT2 inhibitors) may be presented as follows:

SGLT2 inhibitor	Trade name of SGLT2 inhibitor	Indication(s)
Canagliflozin	INVOKANA	Indicated in adults with type 2 diabetes mellitus, as an adjunct to diet and exercise, to improve glycaemic control as: • Monotherapy When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. • Add-on combination therapy Combination therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic contro

Regulatory and Pharmaceutical Benefit Scheme (PBS) funding status and Utilisation

ARTG number and date of ARTG entry are already provided in the table under 'Active Ingredients/Products'. Therefore, include in this subsection, any additional relevant information about regulatory status e.g. whether the medicine was approved under Section 60 of the *Therapeutic Goods Act 1989* or Administrative Appeals Tribunal (AAT) decision.

A general search in TRIM, Premier Workflow and/or Docubridge should be undertaken to determine whether there are any PMAB or COMB evaluations in progress for variations to the medicine's entry. A worksheet containing all live and archived submissions can be found here. The evaluator should discuss with their supervisor if they are unsure.

Consideration should be given to how widely the product(s) is prescribed and used in Australia. This will help establish how relevant the safety concern is. For example, consideration could be given to the product indications (i.e. which types of patients are likely to receive this product) and the restrictions on availability due to product scheduling (refer to the latest Poison Standard) and PBS/R-PBS listing (refer to PBS website). For a vaccine, state whether it is on the National Immunisation Program Schedule.

The evaluator should make a comment on the PBS/R-PBS status of the product, making particular reference to the PBS schedule, PBS criteria and any restrictions, for example:

> *Norfloxacin is available on the PBS-RPBS general schedule as an authority required antibacterial for the systemic treatment of acute bacterial enterocolitis or complicated urinary tract infection*

If the product is not listed on the PBS/R-PBS then the evaluator should state this and discuss whether it was previously listed (including reasons for removal) or is being considered for PBS listing by Pharmaceutical Benefits Advisory Committee (refer to PBAC Outcomes and PBAC Summary Documents).

If the products are reimbursed on the PBS then an overview of the relevant usage data should be provided. Where possible, the PBS usage data for the previous 12 months or the previous full calendar year should be captured to ensure that the most up-to-date usage information is analysed in the signal investigation. If applicable, the evaluator may wish to graph the PBS usage over time (e.g. past decade) and comment on the trends and anticipate the usage in the future. Usage numbers may need to be updated before sending for clearance depending on the time it took to complete the signal investigation.

Consider estimating population exposure by dividing the number of prescriptions reimbursed under the PBS with the number of scripts usually dispensed for a year's worth of medication. If the product is not on the PBS and usage data is particularly relevant to the signal investigation, consider contacting the sponsor for sales/distribution data.

PBS usage data will be limited based on the date of PBS listing of a medicine and the evaluator should use their judgement when interpreting this data. For example, if a medicine was recently PBS listed then current usage volume according to PBS statistics will be low, however the evaluator may comment that the usage is expected to increase significantly.

For further information about PBS data, refer to 'Introduction to PBS Data' (TRIM container: E19-524051).

The evaluator should note that PBS usage data will always underestimate the actual usage of a medicine due to non-PBS prescribing including most public hospital usage. If a medicine is not listed on the PBS then the evaluator may seek to capture sales or distribution data by contacting the sponsor.

If the signal investigation pertains to a vaccine, consider obtaining approximate distribution figures if the vaccine is on the National Immunisation Program Schedule by liaising with the Immunisation Policy Section of the Immunisation Branch. Batch release figures from the Laboratories Branch may also be helpful. Discuss with your supervisor before requesting data from either of these sources.

Related products

The evaluator should consider whether there are products related to the medicine in question that are not relevant to the safety concern. Examples include a product in the same therapeutic class but with a different molecular structure or a chemically-related product but with different indications.

If there are related medicines that fall into the scope of the signal investigation, they should be included in the signal investigation.

3. What is the safety concern?

The evaluator should describe the safety concern in sufficient detail for the authoriser to understand it. This should include a discussion of some or all the following points:

- Epidemiology of the adverse event (AE) condition: how frequently does it occur in the general population? This will provide a guide as to whether the number of adverse event (AE) reports the TGA has received is in line or significantly higher/lower than expected (keeping in mind the limitations of underreporting, and accurate exposure estimates).

- Risk factors and pathogenesis of the adverse event disease process. This will help assess confounding in AE reports, and the adequacy of confounder adjustment strategies in observational studies.

- Whether the adverse event or a related/ similar condition can be a consequence of the disease that the drug is treating. For example, in the case of an adverse event such as haemolytic anaemia, can the disease that the drug is treating cause this in itself? In other words can the adverse event condition occur as a disease related condition as well as a consequence of the drug? This issue could be briefly discussed here and elaborated on later in the signal investigation.

- Presentation (symptoms and signs). This helps with determining Qlik search terms and establishing whether the identified adverse event reports represent the safety issue of interest.

- Diagnostic criteria

- Prognosis/morbidity/mortality. This helps with assessing the clinical significance of the safety issue.
- Epidemiology of the condition that the drug is treating.

The evaluator should indicate whether the safety issue applies to the whole population taking the product/ingredient or to subgroups, for example, paediatric patients, the elderly or patients with renal impairment, or only when the product is used for certain indications.

Some reputable sources of information for this section are:

- AIHW website for statistics on disease incidence in Australia: https://www.aihw.gov.au/reports-statistics

- Medical and pharmacological textbooks e.g. 'Harrison's Principles of Internal Medicine', 'Goodman and Gilman's the pharmacological basis of therapeutics', and 'Martindale: the complete drug reference'. Available online from IRRS and http://accessmedicine.mhmedical.com/book.aspx?bookid=1130

- UpToDate (subscription required – check with IRRS): https://www.uptodate.com/contents/search

4. Current risk minimisation strategies/measures

Australian Product Information (PI) and/or Product Package Labelling

In this section the evaluator should discuss whether the safety concern is addressed in the Australian PI or product package labelling (especially in the case of an OTC or complementary medicine[b]).

If the safety concern is included in the PI and/or product package labelling then the evaluator should assess whether the warnings are adequate in light of any new safety information. For example, the evaluator could consider the adequacy of the wording, location or prominence of the text in the PI or product packaging label (consider inserting a direct quote). For example, a statement in the *Precautions* section of the PI is considered stronger than a statement in the *Adverse Effects* section.

Ensure that the last updated date of the PI is included.

[b] Refer to the current Medicines Advisory Statements Specification on the TGA website.

In the case of OTC or complementary medicines, the evaluator should check if there are any mandatory warning or advisory statements that address the signal of interest [refer to the current Required Advisory Statements for Medicine Labels (RASML) available here: https://www.tga.gov.au/publication/required-advisory-statements-medicine-labels-rasml].

Where relevant to the issue at hand, the following guidance documents may be useful to consult:

- Australian regulatory guidelines for over-the-counter medicines (ARGOM)
  - Appendix 3: Guidelines on presentation aspects of OTC applications - https://www.tga.gov.au/publication/argom-appendix-3-guidelines-presentation-aspects-otc-applications
  - Appendix 5: Guidelines on OTC applications for specific substances - https://www.tga.gov.au/publication/argom-appendix-5-guidelines-otc-applications-specific-substances
- Medicine labels: Guidance on TGO 91 and TGO 92 - https://www.tga.gov.au/book-page/1-using-orders

International Product Information (PI)

Similarly, in this section, the evaluator should discuss whether the safety concern is addressed in International PIs (e.g. US FDA Label, Health Canada Product Monograph etc.) or product package labelling and comment on any similarities or differences with Australian labelling. Consider inserting direct quotes from the PIs.

Ensure that the last updated date of the product reference documents is included. Comparative information between Australian and International PIs may be presented in a table format however it is at the evaluator's discretion as to how this information should be presented. For example:

	FDA	EMA	Health Canada	MedSafe NZ
Black box Warning				
Contraindications				
Warnings/Precautions				
Adverse Effects				
Dosage and Administration				
Other (specify)				

Copies of PIs must be saved in TRIM as information contained within these documents change over time.

Signal analyses, safety alerts or other risk communication

In this section, the evaluator should identify and comment on any current or previous signal analyses or safety alerts (or other risk communication) in relation to the safety concern that have been published by:

- Foreign regulatory agencies (e.g. FDA Medwatch, Medsafe prescriber update, Health Canada Product InfoWatch, EMA PRAC signal analyses or recommendations)
- Sponsors (e.g. Dear Healthcare Professional Letters)
- The TGA (e.g. MSUs, web statements, ADRAC Bulletins etc.)

Risk Management Plans (RMP)

If an RMP exists for the product, then the evaluator should discuss whether the signal of interest was considered during the evaluation of the RMP. The RMP Coordinator (RMP.Coordinator@health.gov.au) can advise whether RMPs have been or are currently being evaluated.

For example, the evaluator could consider whether the signal is included in the summary of safety concerns (either as an identified or potential risk or missing information item) and whether pharmacovigilance and risk minimisation activities are proposed. If an RMP was required by the TGA then the Australian Public Assessment Report (AusPAR) will contain a general description of whether risk minimisation activities are required, with additional information on the proposed pharmacovigilance and proposed risk minimisation activities for each identified safety issue (see section on AusPAR below).

General information on RMPs is available from the following:

- Risk management plans for medicines and biologicals http://www.tga.gov.au/publication/risk-management-plans-medicines-and-biologicals
- A presentation given to SIU in September 2017 at D17-888595.

Periodic safety update reports (PSURs)

Comment on whether PSURs for the product are required to be to be submitted to the TGA (the RMP Coordinator can advise on this requirement and if a PSUR has recently been submitted).

Australian Public Assessment Report (AusPAR)

An AusPAR provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve an application. Only prescription medicines entered on the ARTG after November 2009 or which have had a new entry to their ARTG registration since this time will have an AusPAR.

If an AusPAR exists, then the evaluator should discuss whether the signal of interest was considered during the pre-market evaluation and what the pre-market delegate recommended.

Further information about AusPARs is found here:

https://www.tga.gov.au/auspars-questions-answers

Current clinical guidelines

Consider commenting on whether the adverse event is generally well understood by health professionals as being related to the particular medicine. For example, is it mentioned in the Australian Medicines Handbook (AMH) and other sources of prescribing information such as the Therapeutic Guidelines?

Consider current clinical or best practice guidelines (e.g. AMH, Therapeutic Guidelines, RACGP Guidelines) to evaluate whether the safety concern is mitigated (e.g. reduced exposure due to drug not

being a preferred first-line treatment, safety concern well understood and not prescribed to patients at greater risk).

https://amhonline.amh.net.au/

https://tgldcdp.tg.org.au/etgAccess

https://www.racgp.org.au/your-practice/guidelines/

5. Literature

If the source of the safety concern is from the literature, a critical appraisal of the paper is required. The appraisal could include the type of study design (RCT vs case series), and basic parameters such as sample size, open vs blinded design, or aspects that suggest a study has not been well-conducted (e.g. inadequate randomisation process, confounding, bias). See below for links to some critical appraisal tools.

General approach

In this section, the evaluator should identify and discuss any published literature relating to their signal of interest.

The depth of the literature search should be discussed with your supervisor first. If the signal investigation is for a single adverse event and single medicine that is a new signal (e.g. from DPAR), the most relevant literature is likely to be published case reports and/ or case series (e.g. descriptive studies) because larger observational studies are unlikely to have been performed to investigate the association. In this case, this section might be brief as the published case reports/ case series should be described in section 6 below.

If the signal investigation is for an older signal or class of medicines then other studies (case control, cohort and potentially meta-analyses of observational studies or randomised controlled clinical trials) may have been published. In this case, this section is likely to be longer.

Literature that discusses possible mechanisms of action by which the medicine might cause the adverse event is also relevant. Articles that discuss the adverse event more generally may also be relevant. For example, a signal investigation might concern a particular medicine causing Guillain-Barre Syndrome (GBS), but articles about drug-related GBS in general may also be relevant.

Using the TGA Information Resources and Research Services (IRRS)

The evaluator can perform their own literature search or utilise the TGA IRRS. To request the assistance of IRRS, send an email to s22 @health.gov.au, outlining what the aim of your search is and when you require it to be completed by. Consider meeting with them or having a phone conversation to clarify any questions they might have about your request. When you request the search ask them to include the abstracts as well as titles, their search strategy and the date the search was performed.

Which databases to search?

Detailed information is found at:
http://kemh.health.libguides.com/library/search_tips/faqs/difference_between_pubmed_medline_embase

Below is some information from the Ovid help desk via TGA IRRS regarding Medline, Embase and PubMed:

- Medline: Subject coverage = medical & biomedical sciences
- Embase: Subject coverage = Medline + drug & pharmacy journals.

- PubMed: Subject coverage = medical, biomedical & life sciences.
- All of Medline is included in Embase, with the exception of the earliest publisher supplied citations. These citations are only accessible by searching Medline directly, either on PubMed or Ovid Medline.
- All the records from PubMed are in Ovid Medline, but the interface is different. In many ways the Ovid Medline database is easier to use than PubMed.
- The difference between the Medline citations in Embase and the Medline citations in PubMed or Ovid is the indexing - when Medline citations are loaded into Embase, they receive automated indexing to convert the MeSH terms in the citation to equivalent Emtree terms. Sometimes there is no change with the conversion because there is a direct equivalent - e.g. hypertension is a subject heading in both thesauri so there is no change in that case. But where there is no direct equivalent, the MESH term is changed to the nearest equivalent Emtree term. This equivalent Emtree term may not be as granular as the MeSH term. As you know, Medline is a database for medical research across many fields, while Embase is designed for detailed pharmaceutical research, so some MeSH terms aren't included in Emtree because they don't fit the purpose of that database.

Overall, the database to use depends on the topic being searched, and also the terms being used. General advice from TGA IRRS is:

- For the most complete search, use both Embase and Medline and search them separately if performing a subject heading search.
- For a more targeted search:
    - If the researcher is doing a pharmaceutical-focused search and it is keyword based, use Embase
    - If the researcher is using subject headings, check if the subject headings are common to both Embase and Medline. If they are common to both thesauri, use Embase. If some terms are unique to MeSH, do separate searches in Medline and Embase.
- In summary, though all the records from Medline are in Embase, the indexing and emphasis are different. If you are doing a keyword search this shouldn't be a problem but if you are doing a subject heading search, the results from the two data-bases might be different.

Information from IRRS about google scholar:

- It is generally suggested that you not rely on google scholar – inclusion in google depends upon publishers submitting information to google scholar so reliance on google scholar may lead to a less complete search. Also, searches performed in google scholar are not necessarily reproducible and therefore not reportable.

More detailed information about google scholar can be found at:
http://libguides.lib.msu.edu/pubmedvsgooglescholar

Which search terms to use?

If performing a keyword search, generally speaking you search your chosen database for articles with the adverse event term in the title 'OR' abstract, and then combine this (using 'AND') search with a search of your chosen database for articles with the medicine term in the title or abstract (suggest using both the brand name of the medicine and the generic name). For further advice, it is recommended you speak to TGA IRRS. From the results you can choose the relevant articles for your signal investigation. If your results are too large and you need help focussing the search, again it is recommended you speak to TGA IRRS.

Documentation of search strategy

Search strategies should be documented. This is especially important for complex signal investigations that, for example, might end up going to the Advisory Committee on Medicines (ACM). Even for less complex signal investigation, it's a good idea in case another staff member needs to repeat your search.

INTERNAL USE ONLY

The following details should be provided:

- Date of search
- Database searched
- Search terms used

The search results should be saved as a PDF in TRIM.

Critical appraisal

When evaluating the relevant literature, consider any study limitations in light of any supporting evidence for the signal. This section is especially relevant if the source of the signal is a published study. The following website has a number of critical appraisal tools for different study types: http://www.casp-uk.net/casp-tools-checklists

There is also a BMJ Reader's Guide series to critical appraisal of cohort studies:

1. Role and design - http://www.bmj.com/content/330/7496/895

2. Assessing potential for confounding - http://www.bmj.com/content/330/7497/960

3. Analytical strategies to reduce confounding - http://www.bmj.com/content/330/7498/1021

6. Post-marketing Adverse Event Reports

Identifying adverse event reports in Qlik

Qlik is a visual analytical tool which allows users to easily view all available data for a medicine, adverse event or medicine-event pair. It can be used to develop a search strategy by easily expanding or narrowing a search depending on the initial search results.

When developing your search strategy, consideration should be given to using a search that is broad enough to capture PTs that could be used to code the adverse event. This may include PTs for symptoms, signs, clinical complications, a preceding event (e.g. QT prolongation preceding torsades de pointes) and/or laboratory results relating to the adverse event. In some circumstances, a Standard MedDRA Query (SMQ)[c] or System Organ Class (SOC) search may be warranted. MedDRA[d] should be consulted prior to searching to identify the relevant PT(s), SMQ, or SOC(s).

Table 1: Approach to searching in Qlik for specific adverse events.

Adverse Event Characteristic	Approach to searching inQlik
Is it a poorly-defined condition?	Consider broadening your search to include PTs for symptoms, signs, complications, and/or laboratory

[c] Qlik does not have a SMQ searching function however an SMQ search can be manually entered into Qlik as per the MedDRA parameters.

[d] Medical Dictionary for Regulatory Authorities. Further information and resources on MedDRA can be found on the MedDRA website:

- http://www.meddra.org/
- http://www.meddra.org/how-to-use/support-documentation

E.g. next-day impairment	investigation results related to the adverse event. *E.g. lethargy, somnolence, altered state of consciousness, road traffic accident, accident at home, accident at work, accidental death.*
Is it a known under-diagnosed condition? ***E.g. pericarditis***	If so, this may mean that when a patient has developed the condition, it may not have been diagnosed and consequently will not have been reported or coded as the condition of interest. If initial search results are limited, consider broadening your search to include symptoms, signs, complications, and/or laboratory investigation results related to the adverse event. *E.g. orthostatic intolerance, orthostatic heart rate response increased, dizziness postural, tachycardia, heart rate increased, palpitations, vision blurred, fatigue, tremor.*
Is it a broad condition? ***E.g. childhood neurodevelopmental disorders***	Capturing all the appropriate PTs may be difficult. In these cases, after conducting a preliminary search using the PTs you have identified as being relevant, a System Organ Class (SOC) search with the relevant SOCs can be run to ensure that any other relevant cases aren't missed. *E.g. the SOCs "Nervous system disorders" and "Psychiatric Disorders".*

is important to document the parameters of the search strategy in the body of the signal investigation. This should include the date of the search, PTs and medicine search terms used and any other parameters (e.g. suspect and interacting medicines, sole-suspect, age, seriousness, outcome etc.). The full search strategy should be documented, regardless of whether there are AE reports available with the search terms used. This is to ensure that an appropriate search has been carried out. It is also a reference if the search needs to be replicated in the future.

A copy of the results should be stored as a TRIM record in the relevant container. Qlik search results can be obtained using the following methods:

- Export a case line listing (CLL) as an MS excel file by navigating to the CLL sheet, right-clicking the table → choose export data → click download your data file. Then open the excel file and edit as needed.
- Generate a full case detail (FCD) word document from the FCD sheet and save as a PDF. This will include all your search terms on the cover page.
- Export the dashboard sheet with graphs as a whole pdf, or individual graphs by right clicking it → export as an image.

Other tips for searching with Qlik:

- In general, apply the default bookmark before searching (characterisation: suspect, interacting; case decision: accepted; study type: other studies, unknown). This will exclude purely concomitant use, SAS or clinical trial use and general listed cases (causality uncertain) from the search results.

- If trying to identify all drugs in a class (e.g. antipsychotics), searching for ATC codes with the prefix for that class (i.e. 'N05A' for antipsychotics) can be helpful.
- If an AE report has been posted on or prior to 2004 and it is available in CRM but there is no supporting documentation, a hard copy of the original report may be available. Consideration should be given to requesting it. Similarly, if the case is not available in CRM, consider requesting the hard copy report. Requests for hard copy reports should be made to the Database team in an email to adr.reports@health.gov.au. In your request include the case number(s) and the urgency of the request remembering that the documents are stored off-site.
- If a report is being edited in CRM, it will not be searchable in Qlik. Additionally, there will be a delay between the report being "posted" and it being searchable in Qlik. This delay is generally overnight.

Useful Resources

- Qlik website - https://help.qlik.com/en-US/
- Qlik website link which explains what the selection colours mean. This is critical to understanding Qlik – https://help.qlik.com/en-US/sense/September2018/Subsystems/Hub/Content/Sense_Hub/Selections/associative-selection-model.htm
- AEMS Dashboard Guide for SIU – D18-11246188

Analysing TGA AEMS Cases

The overall aim of reviewing AE reports received by the TGA is to evaluate the strength of the evidence on signal validity presented by the case series.

Where possible, prior to analysing and presenting the AE cases in the signal investigation, ensure that incorrect coding and/or duplicate reports have been dealt with.

In general, a descriptive analysis of the AE reports and causality assessment is required. If the number of cases is small, a summary of the clinical picture of each case should be provided with an assessment of causality. Evaluators should ensure that key details relevant to the assessment of causality (see Table 2 below for further information) and clinical significance (e.g. requiring hospitalisation) are included in the case description.

Examples of key details include underlying conditions, concomitant medications, indication for use, temporal association between medicine commencement and adverse event occurrence, objective evidence of the adverse event (i.e. laboratory or radiographic investigation results), dechallenge and rechallenge information (if applicable), and outcome. These details should be included regardless of whether they positively or negatively contribute to the causality assessment. When these details are not provided, and they are relevant to the case, this should also be stated in the signal investigation.

A flow chart to assist with assessing causality of individual cases is available in TRIM (D18-10131651). Further guidance can also be found in a presentation given to SIU in July 2017 on Causality Assessment in Case Series (D17-422755).

Where it is impractical to provide a summary of the clinical picture, due to the volume of relevant cases, an overall summary of the cases should be provided. A summary should include the total number of cases, the number of positive rechallenges and dechallenges, the number of serious cases (including the number of fatal cases if relevant), the age and gender breakdown and the number and proportion of reports where the drug is sole-suspected. It may be relevant to provide a summary of the more relevant AE reports. It may be relevant to track the number of AE reports over time and to identify relevant time points in the analysis, such as the extension of indication of the product to a larger population or the listing of the product on the PBS. Depending on the number of reports, the summary could be presented in a table or flowchart.

INTERNAL USE ONLY

Include a single sentence summary which summarises the quality of AE reports received by the TGA for this signal.

Table 2: Key points to consider when assessing causality in individual AE reports

Factors	Considerations
Temporal Relationship	What was the time relationship between starting treatment and onset of the event? The event must be preceded by medicine exposure. Does this fit with the nature of the adverse event? *E.g. osteoporosis with long-term use of glucocorticoids; anaphylaxis after the first dose of a course of a penicillin (after previous sensitisation).* If treatment was stopped or restarted, did the event subside or reoccur? A positive rechallenge in the absence of alternative causes is generally considered to be strong evidence for causation. Some temporal relationships are well described: • Anaphylaxis (minutes to hours) • Alopecia (several weeks) • Solid organ tumours (years)
Evidence of a valid diagnosis	Has the reporter provided details that support the diagnosis? E.g. symptoms, signs, laboratory and/or radiological investigation results etc.?
Definitive evidence that the adverse event was caused by the medicine	This may include serum drug levels or laboratory evidence of infection with the virus of interest following exposure to a live attenuated vaccine. Note that definitive evidence is rarely present.
Alternative causes	Is there another explanation for the occurrence of this adverse event? All reasonable alternative aetiological explanations should be considered. These may include: • Pre-existing illnesses • Concomitant medications • Other exposures to drugs and toxins prior to the event • Newly acquired illness • Spontaneous occurrence of an event without known risk factors • Emergence of a genetically programmed disease • Surgical or other trauma that leads to a complication • A complication of the condition being treated
Nature of the event	Is the nature of the event suggestive of an association with the medicine? Some clinical events are often caused by medicines and may immediately suggest a relationship. Events with a higher probability of

	drug causality are erythema multiforme, rhabdomyolysis, agranulocytosis, renal failure and anaphylaxis.

Special considerations for the assessment of causality in Adverse Event Following Immunisation (AEFI) reports

- Alternative causes of AEFIs also include:
  - Immunisation anxiety (e.g. vasovagal, hyperventilation, or stress-related disorder).
  - A manifestation of, or complication of, a coincidental infection that was present before or at the time of immunisation, or was incubating, but was not apparent at the time of immunisation.
- Consider whether the adverse event was caused by immunisation error. Examples include:
  - Error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use despite contraindication, use beyond the expiry date etc.)
  - Unsterile administration
  - Abnormal physical condition (e.g. colour, turbidity, presence of foreign substances etc.) at the time of administration
  - Error in vaccine handling (e.g. breach in cold chain during transport or storage)
  - Incorrect administration (e.g. wrong dose, site, route of administration; wrong needle length)
- *Definitive proof that the vaccine caused the adverse event is often only possible for live attenuated vaccines where the live virus can be isolated from clinical specimens and typed.*

Further guidance on causality assessment of individual AE reports is available from the following:

- Presentation given to SIU in July 2017 on the causality assessment of individual case reports: D17-584339
- WHO-UMC Causality Categories - http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf
- World Health Organization. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification (second edition) 2018. Available from: https://www.who.int/vaccine_safety/publications/gvs_aefi/en/

Consider (if the source of the signal was not DPAR) including relevant PRR values based on cases in QLIK.

VigiBase Data

A search of the World Health Organization (WHO) database (VigiBase) should also be undertaken using VigiLyze to obtain a global picture of AE reporting for the drug-event pair of interest. The search of the VigiBase data is expected to be less comprehensive than that of the TGA AEMS as case narratives are not available. The following details should be provided when presenting your findings:

- Dataset date (the date that the VigiBase data was last updated)
- Total number of cases for the medicine of interest
- Total number of cases for the adverse event of interest
- Number of cases for the adverse event with the medicine of interest
- The Information component (IC)[e] and IC_{025} values

[e] The information component is an indicator value for disproportionate reporting (similar to the PRR). The IC_{025} is the lower end of a 95% credibility interval for the IC. A positive IC_{025} value is the traditional threshold used in statistical signal detection.

- Number of fatal cases
- Number of dechallenges and/or rechallenges
- Where relevant, the geographical distribution of reports

The results should be stored as a TRIM record in the relevant TRIM container.

Published Case Reports

Any relevant case reports should be summarised here as outlined for an AE report. Because case reports tend to have more information than AE reports, a more comprehensive summary should be provided. Include any conclusions/comments on causality provided by the authors (see Section 5 above for information about literature searches).

PSURs

If a PSUR for the medicine of interest has been provided to the TGA in the last 3 years, consider reviewing the most recent PSUR/s for global case reports and the sponsor's assessment of causality or signal analyses relating to the signal of interest. Note any limitations in the sponsor's assessment and whether the adverse event is an identified or potential risk. Evaluators should consider the currency of the data in the PSUR or whether more up to date data should be requested from the sponsor.

7. Discussion

a) Validity of the safety signal

In this section, present an overall causal assessment of the association and therefore make an assessment of whether the safety signal is valid. The assessment should be based on the information presented thus far in the signal investigation (e.g., AE reports from TGA AEMS, case reports from the literature, other published studies, AE reports from VigiBase, AE reports from PSURs, signal analyses from other regulators). Evidence both for and against the association should be included. As part of the overall causality assessment, consideration should also be given to the reliability and/or accuracy of the material. If the source is a published study, consideration of the validity of the study should be included.

In your discussion consider using the Austin Bradford-Hill criteria of causation as a conceptual framework to guide your causality assessment (see Table 3 below).

Table 3: Austin Bradford-Hill criteria of causation

Criterion	Explanation	Pharmacovigilance Example
Temporal relationship*	This is the relationship between the timing of exposure to the medicine and when the adverse event first occurred. A temporal relationship assessment should take into account the timing of potential drug interactions (e.g. new medicines commenced, concomitant medication stopped or dose changed), the occurrence of illnesses (e.g. renal impairment) or a physiological state (e.g. dehydration). For a relationship to be considered causal, the medication exposure must have occurred prior	Information on temporal relationships will generally be obtained from AE reports and case reports.

	to the onset of the adverse event. It is important to consider whether the nature of the event was consistent with the timing of exposure to the medication both in respect to the pharmacokinetic and pharmacodynamic characteristics of the medicine and the pathogenesis of the adverse event. *E.g. it would not be plausible for malignancy to be causally associated with a recent medicine exposure.* Adverse drug reactions can be divided into type A[f] (pharmacological) and type B (idiosyncratic) reactions. A consistent pattern with regard to temporal relationship is supportive of a temporal relationship (particularly for type A reactions). However an inconsistent pattern does not exclude a causal relationship.	
Strength	Strength refers to the quantitative measure of the association between the medicine and adverse event. Strong associations are more likely to be causal than weak associations. Weak associations are more likely to be explained by unrelated biases.	High disproportionality statistic (e.g. PRR or IC)** High relative risk in pharmacoepidemiology (PE) studies#
Dose-Response relationship*	A causal association is supported when an adverse event occurs in a dose-dependent manner or from cumulative exposure over a prolonged period of time. *E.g. there is a dose-response relationship between the oestrogen content of combined oral contraceptive pills and the risk of developing a DVT.* N.B. An interacting medicine can increase or decrease plasma concentrations of a drug so it is important to consider the relationship between stopping or starting interaction medicines and the onset of an adverse reaction.	A dose-response relationship may be observed in AE reports, case reports, clinical trials or PE studies. Consider the effects of increasing or decreasing a medicine dose, dechallenges/rechallenges and the addition or cessation of interacting medicines.

[f] Type A: these reactions represent an augmentation of the pharmacological actions of a drug either due to its primary mechanism of action or off-target effects. These reactions are dose-dependent, predictable from drug pharmacology, more common than type B reactions, normally reversible, and may be manageable with dose adjustment (Pirmohamed et al 1998).

Type B: these reactions are idiosyncratic, not dose-related, unpredictable, less common than type A reactions, may be serious and/or irreversible, and indicate that the drug needs to be stopped (Pirmohamed et al 1998).

Consistency	Repeated observations of an association in different populations under different circumstances provides strength for a causal association.	Consistency of findings from PE studies in different populations and/or using different study methods. Consistency of findings across AE reports from a range of reporters, clinical settings (e.g. hospital and community), and geographical locations. Consistency of the temporal relationships for the AE reports and consistency across a drug class (e.g., is the signal present for more than one drug in a class) Consistency of findings across the various types of PV data (i.e. AE reports, case studies, clinical trials, and PE studies). Consistency of findings among different drug regulators.
Specificity^	This refers to the concept that a cause leads to a single effect, not multiple effects i.e. true associations are specific. This is relevant to pharmacovigilance because medicines cause adverse drug reactions through specific mechanisms (which may or may not be known at the time). E.g., renal failure due to a medicine is often caused by interstitial nephritis. *E.g. medicine A is hypothesised to cause a range of different cancers however this is generally not plausible and an example of a non-specific association.*	*This criterion relates to the specificity of the adverse event itself.*
The next four criteria are linked by whether or not the association fits with existing scientific knowledge. While causation is more likely if these criteria are fulfilled, this may not be the case for newly identified associations. There is often overlap between coherence, biological plausibility and experimental evidence.		
Coherence	Coherence is the cause-and-effect interpretation where the data should not seriously conflict with what is generally known about the natural history and pathogenesis of the adverse event.	

	E.g. frusemide will not cause hyperkalaemia N.B. It is however important to keep an open mind to associations which are not coherent with contemporary knowledge.	
Biological Plausibility	The theoretical plausibility of an association between the medicine and adverse event that is consistent with current biological and medical knowledge. *E.g. since we know that anticholinergic medicines can cause urinary retention, if a new drug with anticholinergic properties is reported to cause urinary retention, the association would be considered biologically plausible.* *What is the mechanism of action of the drug and does this relate to the pathogenesis of the adverse event? An example is immune checkpoint inhibitors and immunological reactions. It is biologically plausible that drugs that activate the immune system might lead to immune disorders.*	
Experimental evidence	Experimental evidence is supportive of causal inference. This type of evidence might include studies in biological models, animals and/or humans. It would also include evidence from AE reports, particularly rechallenge/dechallenge information. *E.g. animal studies for medicine A might indicate a high rate of a specific congenital malformation affecting the limbs, this evidence would be supportive a causal association between medicine A and a similar congenital malformation in humans.*	*In vitro* and animal studies Clinical trials AE reports
Analogy	The occurrence of similar reactions with other medicines that have a comparable mechanism of action to the one of interest (e.g. in the same therapeutic class).	Literature and AE reports for similar medicines Product information documents for similar medicines.

#Adverse events detected in pharmacoepidemiology studies generally have a low relative risk (RR). It is rare to find high RRs for serious adverse events (in comparison to placebo or other medicines) with marketed medicines. This is because it is likely that medicines with a high incidence of serious adverse events would not have been marketed due to safety concerns (Shakir and Layton 2002).

*These criteria may not be fulfilled by idiosyncratic drug reactions (also known as Type B reactions).

**Disproportionality analysis assesses how the reporting of this adverse event for this medicine compares to the reporting of this adverse event in general (or this adverse event for similar medicines). It highlights a case series which then needs further clinical assessment.

When using the Austin Bradford-Hill Criteria, judgement is required as there is no simple formula for adding up the criteria and coming to a definitive conclusion. In general, the more criteria that are met, the more likely an association is causal. Absence of any of the criteria does not exclude an association from being causal. It is important to note that even when pharmacoepidemiology studies do not demonstrate an association, causality can still be assessed and demonstrated through other pharmacovigilance data.[g]

When determining if the signal is valid, also consider the number of reports received for the drug-event pair in the context of how widely the medicine is used and how frequently the adverse reaction occurs in the background population. I.e. is the number of reports greater than anticipated (greater than background incidence or incidence in treated population) considering under-reporting?

Special Considerations for Vaccines

There are several issues to consider when assessing a causal association with a vaccine. These include the following.

- Dechallenge data is not available for vaccines.
- A dose-response relationship is often not able to be assessed as the dose and frequency are fixed.
- Consider whether the association could be confounded by the age at which the vaccine is most commonly administered. *E.g. the incidence of SIDs peaks at two months of age, which is also the age of the 2nd schedule point for immunisations on the National Immunisation Program.*
- Vaccines containing the same antigens may have different adverse effect profiles due to differing vaccine components and manufacturing processes. *E.g. the higher incidence of paediatric febrile convulsions observed with Fluvax in comparison to other trivalent influenza vaccines.*

b) Public health impact of the signal

In this section discuss the clinical impact or public health implications of this signal. Some of the factors will have been covered earlier in the document so this section aims to summarise and synthesise the factors that may make this signal a high impact signal. Factors that may be relevant are:

- What is the seriousness of the adverse event?
- Is the population that is being treated with this medicine in Australia large?
- Is the population that is being treated with this medicine in Australia vulnerable (for example, children)?
- Is the condition that the medicine is treating serious? This can influence the benefit-risk balance. For example, if the medicine is for the treatment of metastatic malignancy there is potentially a higher tolerance for experiencing adverse events than if the medicine is being used to treat a less severe condition such as rhinitis.
- Is there treatment available for the adverse event that needs to be instituted rapidly?
- Is this medicine the only treatment option available for the condition? If so, decisions regarding restricting use of the medicine may have high impact for patients and clinicians.
- Who prescribes this medicine in Australia and does this mean that the prescribers are likely to be able to recognise the adverse event in question without further risk minimisation activities being applied? For example, if the medicine is an IV infusion given by specialists in a hospital settings and the adverse event has a quick onset, there may be better recognition of the adverse event than if it is prescribed by GPs in the community.
- Is there potential for this signal to be a class-effect?

[g] Perrio M, Voss S, Shakir S. Application of the Bradford Hill Criteria to assess the causality of cisapride-induced arrhythmia. Drug Safety. 2007;30(4):333-346.

- What is the reporting rate (number of cases per users) over the last year? (If available e.g., a PSUR of sponsor assessment). This indicates whether it is an adverse event that is occurring commonly or not among users and gives a sense of the magnitude of the problem.

c) Recommendations

If the signal has been determined to be valid, assess the current risk mitigation measures in place and if inadequate, outline the relevant risk mitigation options (both regulatory and non-regulatory) available to the TGA. If the signal has not been found to be valid based on the information available at the time, the evaluator may choose to recommend no further action. The clinical impact of the signal is also relevant to this section. For example, if the validity of the signal is uncertain at this point in time, but the consequences of not mitigating the potential risk are high, the evaluator may choose to still recommend further action.

Firstly, briefly comment on the adequacy of the current risk minimisation measures. Even an issue fully captured in the PI may require further action such as an alert communication (e.g. Medicine Safety Update article, TGA web statement or Dear Healthcare Professional Letter [DHCPL]) or increased monitoring. If the PI does already identify the issue, the evaluator should assess whether the new information changes the magnitude or scope of risk, or the certainty of causality. If more than one product is implicated (including generics) the evaluator should consider whether the safety issue is dealt with by the other products. If the product is an OTC or complementary medicine, the evaluator should consider whether the current RASML advice adequately addresses the safety issue.

Regulatory options available to the TGA include, but are not limited to:

- Changes to the PI[h], packaging and/or labelling
- Cancellation from the ARTG
- Risk communication
- Seeking advice from the Advisory Committee on Medicines or the Advisory Committee on Vaccines
- Pharmacovigilance inspection
- Changes to the Poisons Standard (e.g. upscheduling) (see https://www.tga.gov.au/publication/poisons-standard-susmp).

Non-regulatory options available to the TGA include, but are not limited to:

- Adding the medicine to the Intensive Drug Monitoring Program list.
- Requesting further information from the Sponsor.
- Liaison with external organisations such as NPS MedicineWise or the Australian Commission on Quality and Safety in Healthcare if the issue relates to clinical practice or the quality use of Medicines.

Where regulatory action is considered an option, outline the risks and benefits of implementing such action versus no regulatory action. This consideration should take into account the frequency and severity of the adverse event, the expected impact of the regulatory action and the resources required to implement such regulatory action.

Where recommendations are made, clearly articulate what is expected to be achieved by implementing the recommendation.

Ensure that adequate detail is provided regarding the scope and content of the recommended action. For example, where amendments to the PI are recommended, state the section of the PI for the

[h] If considering the addition of a boxed warning, refer to the Boxed Warning guidance - https://www.tga.gov.au/publication/boxed-warning-guidance

proposed amendment and include the text of the proposed changes within the signal investigation. Where it is recommended that advice from an advisory committee be sought, outline the issues that you are seeking advice on.

Consideration should be given to the relevance of the safety issue and proposed actions in the Australian context. Assessment of relevance may be helped by consulting a few key clinical references (e.g. Therapeutic Guidelines) but a full search for specific clinical guidelines is not required for completion of a signal investigation.

A risk communication should be considered when new information regarding the safety profile of a medicine has come to light that health professionals and/or consumers should be aware of. This is particularly relevant when it relates to a serious risk where mitigation of that risk requires a change in clinical practice or consumer behaviour.

There are generally two types of TGA risk communication activities (see Table 4 below).

Table 4: Types of TGA risk communication activities

Type of Risk Communication	Target Audience	Publication Frequency
Medicines Safety Update	Health professionals	Published every 2 months
Web Statement	Health professionals and consumers	Includes 3-4 articles

When considering which type of risk communication is required, consider the following questions:

1. Who is the target audience?
    - For example consider the scheduling of the medicine of interest. If it is available over-the-counter, there is less opportunity for a health professional to provide adequate counselling regarding the medicine's side effect profile and how to safely use the medicine. Therefore, consider a web statement which targets consumers as well as patients.
2. How urgently does the message need to be communicated?
    - If the message needs to be communicated urgently and the timing does not align with the publication of a MSU, a web statement should be considered.

If a risk communication is recommended, outline the key message(s) that need to be communicated based on your signal investigation. If a web statement is recommended, outline the key message(s) for the two different audiences; health professionals and consumers. Also identify the key health professional groups (e.g. paediatricians and intensive care physicians), colleges or societies that the risk communication is relevant to so that the Technical Safety and Improvement Section (TSIS) can notify the relevant professional organisations and medical specialty colleges in the dissemination of the risk communication.[i]

[i] External communications are generally sent to the following organisations: Royal Australian College of Physicians (RACP), Royal Australian College of General Practitioners (RACGP), Australian College of Rural and Remote Medicine (ACCRM), and Consumer Health Forum of Australia (CHF). Medicine Safety Updates are also sent to the

INTERNAL USE ONLY

To assist evaluators in identifying the relevant messages and information that should be conveyed in a risk communication, a TGA Web Statement template is available at D17-413159.

8. Conclusion

Summarise the findings of the signal investigation and include a clear rationale for any recommendations (including no further action).

9. Summary of Recommendations

This section provides a quick reference to the recommendations of the signal investigation which are identified using the tick boxes in the template. Ensure that adequate detail is provided for each recommendation.

10. References

All materials considered in undertaking the signal investigation should be referenced in the signal investigation document and the full citations and TRIM record numbers should be listed in the Reference section.

The preferred referencing style is Vancouver using numerical superscript, with the full reference being cited in the References section at the end of the signal investigation document.

Evaluators are strongly encouraged to use the referencing program EndNote to ensure consistent referencing and to easily accommodate changes to the structure of the signal investigation or additional citations during the drafting process.

As noted in Section 1, a copy of all PIs or other web-based documents referenced must be saved in TRIM as an attachment to the signal investigation. It is not sufficient to provide the web address and date of access as the reference as documents may change over time and previous revisions are often unavailable.

11. Authorisation

Prior to clearance, evaluators should work through the following checklist to ensure that their investigation meets the expected standards.

Have you:

- Done a spellcheck?
- Followed the HPRG writing and formatting guide?
- Followed the Vancouver referencing style?
- Referenced all scientific statements?
- Provided a clear rationale for the recommendation(s)?
- Included the 'last updated' date for all product reference documents?
- Included a title for all tables and figures and referred to them in the body of the report?
- Saved all references (e.g. literature articles, product reference documents, clinical guidelines etc.) in the TRIM container for the investigation?
- Saved all search results (e.g. Qlik, VigiLyze and literature searches) in the TRIM container for the investigation?

Australian College of Nursing (ACN), Pharmaceutical Society of Australia (PSA), the Pharmacy Guild of Australia, and The Society of Hospital Pharmacists of Australia (SHPA).

INTERNAL USE ONLY

Refer to the 'Clearance Processes' work instruction (D18-10130838) for information on the clearance process for signal investigations.

To ensure that finalised signal investigation documents can be identified in TRIM, the evaluator removes the draft watermark and the word 'DRAFT' from the document title and adds 'FINAL' and the date of finalisation in DD MMM YYYY format (separated by single spaces and not slashes i.e. 14 Dec 2013) to the document title. The authoriser then saves the document as final in TRIM.

12. Action following Authorisation

Once the signal investigation has been finalised, the evaluator is responsible for updating the 'Issue' in the OPR Issues Database by either creating new tasks that reflect the recommendations of the signal investigation or closing the issue all together. Consider liaising with the Signal Investigation Coordinator especially when closing an issue.

It is important to ensure that any modifications to the Issue or Issue Tasks in the OPR Issues Database are done accurately and timely for completion.

Consider whether any proposed regulatory actions impact PBS listings for the medicine. If so, any such changes should be communicated to the Pharmaceutical Benefits Division.

If the safety issue relates to a vaccine, consider whether the Office of Health Protection (OHP), Jurisdictional Immunisation Co-ordinators (JIC) and/or the Australian Technical Advisory Group on Immunisations (ATAGI) need to be notified.

Useful References

- Perrio M, Voss S, Shakir S. Application of the Bradford Hill Criteria to assess the causality of cisapride-induced arrhythmia. Drug Safety. 2007;30(4):333-346.
- Pirmohamed M, Breckenridge A, Kitteringham N, Park B. Adverse drug reactions. British Medical Journal. 25 Apr 1998;316:1295-8.
- Shakir S, Layton D. Causal association in pharmacovigilance and pharmacoepidemiology. Drug Safety. 2002;25(6):467-471.
- Talbot J, Waller P, editors. Stephens' Detection of New Adverse Drug Reactions. 5th ed. John Wiley & Sons; 2004.
- Uppsala Monitoring Centre. Analytics in VigiLyze. 23 Jan 2017 [accessed May 2017]. Available from: https://www.who-umc.org/vigibase/vigilyze/analytics-in-vigilyze/
- Waller P. An introduction to pharmacovigilance. West Sussex: Wiley-Blackwell; 2010.
- World Health Organisation. Causality assessment of an adverse event following immunization (AEFI) user manual for the revised WHO classification. Geneva: WHO Press; 2013.

Useful Links

- Signal Investigation Template – D19-5190468
- Targeted Signal Investigation Template - D19-5190469

INTERNAL USE ONLY

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

INTERNAL USE ONLY

Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance and Special Product Access Branch

STANDARD OPERATING PROCEDURE – (SOP)

Name of procedure	Process for Conducting a Medicines Safety Review – PSPAB – SOP
Applicable to	Signal Investigation Unit
Number	TRIM Ref no R15/400261
Written by	Medical and Professional Officers of the PSPAB
Authorised	Dr Jane Cook
Date issued	7 July 2015
Version no.	1.3

Version history

Version	TRIM Reference	Description of change	Author/s	Effective date
V1.0	R13/625085	New document drafted in accordance with the recommendations from the OPR Control Development Project	Dr s22 [redacted]	16/03/2012
V1.1	R13/663529	Minor revisions and general update	Mr s22 [redacted] Dr s22 [redacted]	December 2013
V1.2	R15/400261	Updated with new review template	Dr s22 [redacted]	May 2015
V1.3	R15/400261	Updated with new Branch and Section names	Dr s22 [redacted]	7 July 2015

Purpose

This Standard Operating Procedure (SOP) document outlines elements to be considered in conducting medicine safety reviews in the Pharmacovigilance and Special Product Access Branch (PSPAB).

A Medicines Safety Review and therefore the scope of this SOP, relates only to products that are Registered or Listed on the Australian Register of Therapeutic Goods (ARTG).

The purpose of this SOP is to establish and document a peer reviewed, systematic approach to undertaking a medicine safety review, whilst providing the rationale behind the process.

Responsibility

This SOP should be followed by medical and other professional officers within the PSPAB Signal Investigation Unit (SIU) who conduct medicine safety reviews.

This procedure should be maintained and updated by the Director of the SIU within the PSPAB.

Background

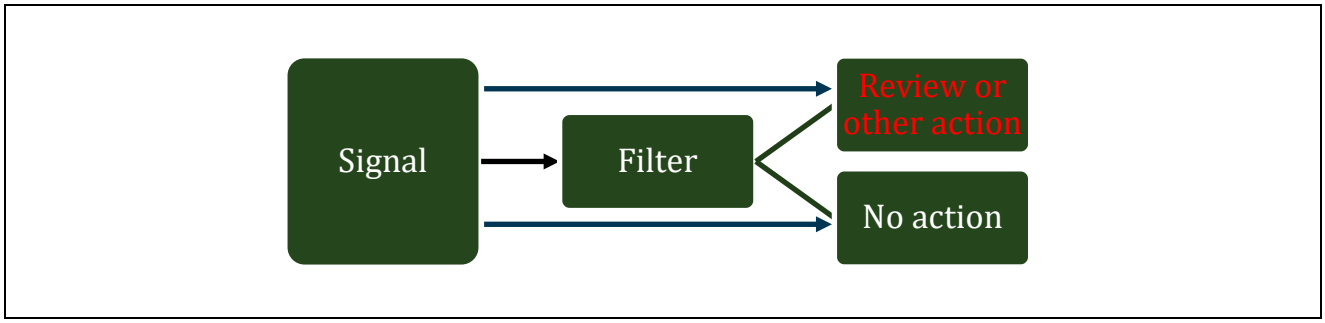
Safety signals are identified by the medical officers and other evaluators of the SIU from information obtained from a range of sources including:

- Proportional Reporting Ratio (PRR) analysis or other analysis of the TGA Adverse Drug Reaction System (ADRS) database;
- elsewhere in the PSPAB or other areas of the TGA e.g. Prescription Medicines Authorisation Branch (PMAB);
- sponsors e.g. Periodic Safety Update Reports (PSURs), other information stemming from Risk Management Plans (RMPs) or notifications about safety investigations elsewhere;
- review of the medical literature;
- overseas regulatory agencies (e.g. FDA, EMA, MHRA, Health Canada, Medsafe).

These safety signals are further considered by the preparation of a 'safety filter' (sometimes referred to as being 'filtered') by the medical officers and other evaluators of the SIU to decide whether a more detailed analysis is required before the issue may be considered to be resolved or before a decision on any regulatory action can be taken (see the PSPAB SOP '*Process for Conducting a Medicines Safety Filter'*).

The more detailed analysis of any given safety issue constitutes a 'Safety Review'. Depending on the nature and urgency of the signal, the issue may be immediately investigated through a Safety Review, without a preceding Safety Filter if considered warranted by the SIU Director and/or the Head of the PSPAB.

The diagram below shows the safety review option (red text) in managing a signal in context with other possible actions.



The size and complexity of safety reviews vary widely. Reviews are not limited to the assessment of risk; an important objective of any review is to describe and/or recommend options for risk management, including writing and publishing a risk communication.

Reviews should be detailed enough to facilitate informed recommendations for appropriate management of the issue and to provide an evidence base for any proposed regulatory actions.

Once a recommendation for a medicine safety review has been agreed by the Director SIU, a priority for the review should be determined. Unless the issue is urgent, this can occur at the next Fortnightly Prioritisation Meeting as described in the PSPAB SOP '*Prescription Medicine Safety Issue Prioritisation*' (see TRIM # R13/662685).

Procedure

Record Keeping

The review document should be stored in TRIM, in its own container, which should also include all relevant filter documentation and attachments (e.g. source documents). All documents used in undertaking the review should also be stored in this container. Where a document is to be attached to the review it should be titled as an attachment using the convention described below.

Naming conventions for safety review containers and documents

In order to maintain continuity and facilitate searching for completed reviews, the TRIM naming convention illustrated below should be used.

Container No: 20xx/xxxxxx -THERAPEUTIC ADMINISTRATION - POST MARKET - Safety Review - NAME OF THE MEDICINE AND ISSUE – Pharmacovigilance and Special Product Access Branch

Record No:

Rxx/xxxx *Oxaliplatin and laryngospasm - Safety Review*

Rxx/.xxxx *Oxaliplatin and laryngospasm - Safety Review - Attachment 1 – (description)*

Rxx/xxxxx *Oxaliplatin and laryngospasm - Safety Review - Attachment 2 – (description)*

Rxx/xxxx *Oxaliplatin and laryngospasm - Safety Filter*

Rxx/xxxx Oxaliplatin and laryngospasm - Safety Filter - Attachment 1 - CLL

All relevant 'Safety Filter' documents are transferred to the specific 'Safety Review' container. This can be done using the 'RELATE RECORDS' function in TRIM. Refer to the current TRIM help card on Relating Records for further information about using this function.

Template

The '*Medicines Safety Review Template in external publication format*' (TRIM R15/543682) should be used. It may need to be tailored, sometimes extensively, according to the scope and objectives of the review. Headings for aspects not included in the review may be retained with 'Not applicable" inserted underneath or deleted with subsequent re-numbering of the headings.

Defining the Objectives and Scope of the Review

The objectives and scope of the review should be:

(a) formally defined in collaboration with the Evaluator's Supervisor and the Director SIU;

(b) clearly stated in the document and;

(c) met.

Some safety reviews consider only one aspect of safety, e.g. hepatotoxicity. Other safety reviews are full risk-benefit reviews, in which case all previous safety and efficacy issues should be considered in context with the overall review. The scope of the review – narrow or broad – should be clearly identified early in the review document.

Sources

A key issue is how wide a net should be cast when collecting information for a review. This is a matter of judgement on a case-by-case basis. Some typical sources are:

- **Literature:**
  - If a literature search is undertaken, record the methodology. It is generally appropriate to include a detailed search strategy as an Appendix. The TGA Information Resources and Research Services (formerly known as the Library) can be requested to assist in designing the search strategy and conducting the searches.
  - If the sponsor has conducted the literature review, evaluate the search strategy.
- **Documents provided by the sponsor:**
  - the Dossiers provided for registration of new chemical entities or major variations to conditions of registration (e.g. extensions of indication)
  - PSURs
  - RMPs
  - ad hoc documents such as the sponsor's reviews of literature articles or other non-submission data
  - information / documents specifically requested for input to the review.

- **TGA documents:**
  - Previous related filters and safety reviews by PSPAB
  - Evaluations of submissions, including Clinical Evaluation Reports and Clinical Overviews [PREMIER and TRIM can be searched; hard copies of clinical files can be retrieved; discussion with relevant PMAB Clinical Evaluation Units may help to identify relevant documents]
  - Evaluations of PSURs and RMPs
  - TGA Advisory Committee documents (e.g. ACPM or ACSOM minutes)
- **Overseas regulatory agency documents:**
  - FDA

    Useful is: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

    Advisory committee transcripts / supporting documents are large but helpful: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm
  - EMA (consider EPARs, alerts, etc)
  - Occasionally, direct liaison with these agencies may be made to request copies of publically unavailable safety reviews or other documentation that these agencies have prepared. These requests should be made in writing, approved by the Director SIU and forwarded by email to 'TGA International'.
- **ADR database information:**
  - TGA ADRS database
  - WHO Vigibase
  - Other overseas databases e.g. the US AERS, VAERS
- **Other databases, for example:**
  - Poisons Information Centres
  - National Coronial Information System

Content of a Safety Review document

The content will depend on the scope and objectives of the review (see 'Template' section above).

1. Title

The title should clearly identify the reason for the review. A clear title also facilitates searches in TRIM.

2. Executive summary

The Executive Summary should summarise the key points of the investigation, the findings and the recommendations of the review.

3. Issue under investigation

This section should briefly describe:

- the issue
- its source (refer to any filter document)
- overall context given the indications and availability of the product.

4. Objectives / scope of review

See 'Define objectives and scope of the review' section above.

5. Product identification

If a specific product (or list of several products) is being reviewed, provide enough detail to clearly distinguish them from unaffected products, particularly where they contain the same ingredient in question.

If a specific active ingredient is being reviewed, list innovator and generic products and indicate the relevant sponsor. For example: Omeprazole - the innovator product is Losec (AstraZenica) and generics are: X (sponsor), Y (sponsor), Z (sponsor).

If a specific class of medicine is being reviewed, describe members of the class. For example: proton pump inhibitors - in Australia the following PPIs are on the ARTG: omeprazole, rabeprazole, pantoprazole and esomeprazole. It may be appropriate to list each product as above.

Where the number of generic products is large, it is appropriate to list the innovator products and add 'and multiple generics'.

Consider the value of including information regarding the sponsor, overall formulation, route of administration, packaging, dose regimen (as recommended in PI) and approved indications:

- Generally, it is important to identify the sponsor of a product, and this information can be found on the ARTG.
- Sometimes, it might be a critical aspect of the review to understand a specific product's formulation or route of administration or dose regimen or indications, or to identify differences between products regarding these parameters.

6. Background

6.1 – Pharmaceutical background

Mechanism of action can be described (for example, this might affect discussion of the biological plausibility of an adverse reaction).

Class effects or the potential for class effects can be discussed.

6.2 – Regulatory history in Australia

Key regulatory events in Australia can be described, e.g. the path to registration, the date of registration, and regulatory actions post-registration e.g. review by ADRAC or ACSOM.

This may require examining clinical files, TRIM and/or the PSPAB Issues Database, etc.

It may be useful to include references to specific documents such as clinical overviews or ACPM minutes or, for complicated issues, to write a chronology of events.

6.3 – Place in clinical practice

Define the target population as described in the PI, based on registered indication and contraindications.

Describe the stated benefit based on:

- the registered indication
- the Clinical Trials section of PI
- focused discussion of the condition/s being treated
    - prevalence / incidence / key epidemiology and risk factors
    - life-threatening vs self-limiting?

Comment on off-label use (especially if known to be common and/or enshrined in influential clinical guidelines).

Describe utilisation (extent of use), considering:

- Poisons Scheduling (S8, S4, S3, etc) - see the *Standard for the Uniform Scheduling of Medicines and Poisons* at http://www.tga.gov.au/industry/scheduling-poisons-standard.htm#electronic
- Product availability e.g. marketed or not, PBS-listed or not, RPBS-listed or not, is authority required
- Discuss PBS usage trends, if relevant:
    - https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml
    - DUSC data (Drug Utilisation Sub Committee of the Pharmaceutical Benefits Advisory Committee) - http://www.pbs.gov.au/info/industry/listing/participants/drug-utilisation-subcommittee

Briefly describe therapeutic alternatives (any or many?) if appropriate, citing clinical guidelines, e.g.:

- Therapeutic Guidelines
- The Clinical Practice Guidelines Portal at http://www.clinicalguidelines.gov.au/
- Specialist college guidelines
- Overseas or literature-based guidelines

6.4 – Regulatory guidelines

Discuss relevant TGA-adopted European guidelines where this may be the case. The context should distinguish pre-registration from post-registration guidelines. Take care if using pre-registration guidelines in the post-market setting as they are likely to differ significantly. Consult the following link for further information http://www.tga.gov.au/industry/pm-euguidelines.htm

6.5 – Regulatory / marketing status in other countries

Describe the regulatory and marketing status in other countries, especially the USA and the EU. If medicine is not registered in these countries, indicate whether it is registered in any other countries and identify the countries.

7. Overview of data

List the data / documents that have been examined as part of the review process. In the event an Australian PI is used as a primary source that conveniently defines the scope of the issue, specify whether it is a current or proposed PI and also specify the source of the document e.g. TGA website PI/CMI search facility, accessed DD MMM YYYY.

8. Pharmacology issues to consider

Discuss relevant pharmacokinetic (PK) and/or pharmacodynamic issues. The section might be irrelevant, in which case write 'not applicable'. If a relationship between a safety issue and exposure (generally C_{max} or AUC) is identified, suitable analysis of the PK data may be required.

9. Efficacy issues to consider

If the review is a 'risk-benefit review', efficacy must be considered.

For a given clinical study, consider internal validity ('reliability') of findings:

- Design (consider NHMRC Levels of Evidence[1])
- Conduct (e.g. patient compliance)
- Statistical significance of any comparison; sample size and power; efficacy in sub-groups; role of post-hoc analyses
- Confirmation of primary outcomes by results of other endpoints

Also consider external validity for each study:

- Clinical relevance of the (primary) efficacy endpoint
- Validation of any adopted comparator scales and outcome measures used; patient-preferred outcomes; use of surrogate endpoints
- Choice of comparator(s)
- Magnitude of treatment effect
- Does the studied population represent the target population? (Inclusion/exclusion criteria...)
- Do the studied dose and formulation equate to the proposed dose and formulation?

What is the evidence across clinical studies (is there consistency?) and/or are pivotal studies supported by other studies?

Is there other evidence of efficacy?

Summarise the efficacy issues that have been discussed.

10. Safety issues to consider

10.1 – Pre-clinical findings

Only the key pre-clinical findings (e.g. those that influence the likelihood that clinical safety signals are real) should be discussed. For relevance to humans, discuss with PSPAB toxicologists.[2]

10.2 – Extent of clinical exposure

Summarise clinical studies and market exposure (noting Australian market exposure). Duration of follow-up in controlled safety studies is a key issue.

[1] http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf (see Table 3)

[2] A useful discussion is presented in: Cohen et al. Evaluating the Human Relevance of Chemically Induced Animal Tumors. *Toxicological Sciences* 2004. 78: 181-186

10.3 – Safety evaluation methodology

Comment on any problems with safety monitoring that might diminish the ability to detect safety issues[3]. Conversely, if a safety signal is not detected despite good monitoring methods, this should be noted.

There are multiple dimensions to AE reporting:

- Categories of report, e.g. adverse events (AEs) vs serious AEs (SAEs) vs suspension or discontinuation of treatment due to AEs vs study discontinuation due to severity of AEs (e.g. mild – moderate – severe – life-threatening; 'serious AEs' and their definition). Consider also duration and reversibility of AEs, and the need for investigation or treatment in response to AEs.
- Known AEs (generally those described in the PI) vs unexpected AEs.
- Causality, in particular 'treatment emergent AEs' vs 'treatment-related AEs'. Consider how the relationship was determined (e.g. investigator vs adjudication panel).

Helpful links include:

- http://aemg.cochrane.org/welcome
- http://aemg.cochrane.org/relevant-publications
- Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE.pdf

10.4 – Mortality

It is often relevant to assess and include in this section all-cause mortality across studies.

10.5 – Other safety issues

These will be guided by the objectives of the review. For example, a full risk-benefit review should consider all safety issues. A new section should be devoted to each discrete issue. Examples include:

- Hepatotoxicity

  The FDA has a useful document about Drug Induced Liver Injury (DILI) but it is (a) not adopted by TGA and (b) for pre-registration guidance

  www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

- QT prolongation

  Extent of QT prolongation should be considered. Not all QT-prolonging medicines have pro-arrhythmic potential. Evidence for pro-arrhythmic effects should be sought.

  The TGA has adopted an EU guideline (pre-registration guideline) with an addendum:

  CHMP/ICH/2/04 – Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs – Adopted by the TGA with the

[3]These problems include:
- Difficulties in rigorously defining unexpected outcomes
- Inadequate monitoring and under-reporting
- Insufficient sample size to measure rare events
- Insufficient follow-up duration to measure rare events
- Exclusion of patients with risk factors for AEs
- Slicing of AE data into many subcategories (with few events in each sub-category)s

following notation: 'QT prolongation would be of regulatory concern if either the estimated QT prolongation was >5ms OR the upper bound of the 95% confidence interval was >10ms.'

10.6 – Safety in subgroups

To be researched and addressed should that be required in order to meet the objectives of the review.

10.7 – Pregnancy and lactation

Consider:

- Exposure in clinical trials.
- Pre-clinical evidence (not necessarily relevant.)
- Does the medicine cross the placenta? Is it excreted in breast milk? Extent?
- Class effects.

10.8 – Drug (and food) interactions

To be researched and addressed if needed to meet the objectives of the review.

10.9 – Potential for abuse and potential for overdose

Consequences and possibility of treatment should be considered. For example, is the molecule likely to be dialysable, and is there clinical trial evidence for this effect?

10.10 – Summary of safety issues

This section should integrate consideration of the pharmacology (e.g. class effects; relationship to exposure) and pre-clinical and clinical safety methodology and associated findings.

11. Current risk mitigation activities

Current risk mitigation activities should be considered before the risk of harm is weighed against the probability of benefit.

Consider the formal Risk Management Plan if one is available:

- The safety specification section of an RMP should inform preceding sections of the review document; there is no need to duplicate information in this current section.
- Proposed pharmacovigilance activities do not influence the current risk-benefit profile of the drug.
- The effectiveness and feasibility of risk mitigation activities are critical considerations.

If an RMP is not available, consider current informal risk mitigation arrangements. Also consider in Section 12 whether a formal RMP should be required.

If risk mitigation activities are proposed, consider their likely effectiveness and feasibility; consult the RMP Unit for advice.

In some cases, this section could be incorporated in Section 10.

12. Risk of harm vs probability of benefit

If the scope of the safety review extends to weighing risks and benefits, in this section a qualitative weighing of harms and benefits should be attempted taking into account risk of harm both before and after the implementation of any proposed risk mitigation strategies.

13. Options to manage risks

There should be a discussion of reasonable options to manage risks. Options include:

- No action
- Seeking additional input to the risk analysis from
  - The sponsor
  - Other TGA offices e.g. OLSS or OSE
  - The Advisory Committee on the Safety of Medicines (ACSOM), the Advisory Committee on the Safety of Vaccines (ACSOV) or other advisory committees
- Increased monitoring by PSPAB
  - consider whether the drug should be added to the 'Drug of Special Interest' (DOSI) list
- Active steps, some of which would only be taken after informal or formal negotiations with the sponsor and some of which require formal decisions under the Therapeutic Goods Act:
  - Cancellation
  - Suspension
  - Recall action
  - Requests for PI changes e.g. via safety-related referrals (SRRs)/ submissions; recommendations for PI changes
  - Changing / adding conditions of registration or listing, directly or via the PMAB or the Complementary and OTC Medicines Branch (COMB).
  - Risk communication:
    - Dear Healthcare Professional Letters
    - TGA web statements
    - Medicines Safety Update or other articles
    - Communications with professional Colleges and organisations
    - National Prescribing Service
  - Changes to legislation
    - Required Advisory Statements for Medicine Labels (RASML)
    - Scheduling
  - Other regulatory action e.g. through referral to the Regulatory Compliance Unit (RCU) or the COMB.

This section of the document could be combined with the 'Conclusions and recommendations' section in many cases.

14. Conclusions and recommendations

In this section the Evaluator should

- Answer the objectives defined in Section 2.
- Identify and make recommendations about options for managing risk.

- Specifically recommend whether the issue should be reviewed, or not, by ACSOM or ACSOV and whether the review should be sent to the sponsor for comment prior to going to the Committee for consideration. In making this recommendation the Evaluator should consider the timelines for notification of issues and sending of papers to the ACSOM Secretariat in relation to the urgency of the issue.

- Formulate questions for ACSOM, if there is a recommendation to seek ACSOM advice.

15. References

Include any references used, regardless of the source, and where possible include a full copy of the reference in the TRIM container established for the review. Include the TRIM Record Number in the reference list.

Process after a review is completed

Evaluators undertaking Safety Reviews should regularly update their supervisors on the progress of reviews as they are being undertaken. Once the Evaluator has completed the Safety Review and, where appropriate, had the document reviewed by his or her supervisor, the Review should be provided to the Director SIU for clearance and advice on further actions. The Director may consult with the Head of the PSPAB to determine the most appropriate actions. These may include:

- Approving the recommendations and implementing them;

- Requesting peer review of the document from another TGA evaluator with appropriate expertise or special experience or from an external evaluator such as a member of a TGA advisory committee;

- Obtaining advice from ACSOM, ACSOV or other TGA advisory committee;

- Seeking comment from the sponsor – this may be before or after advice is sought from the advisory committee.

After input is received from peer review, advisory committee and/or from the sponsor, it may be necessary to update the Safety Review or write an addendum.

All documentation, including the completed Safety Review and any updates or addenda should be filed in TRIM.

References

The current DOSI list can be found at TRIM # R11/479239

The PSPAB SOP *Process for Conducting a Medicine Safety Filter* is at TRIM # R13/723612

Attachments

Attachment 1 - Safety Review Template - filed at TRIM # R15/378564

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

Australian Government
Department of Health

Vaccine Surveillance Section (VSS) – Disproportionality Analysis Report (DPAR) Work Instruction for Vaccines

TRIM reference: D22-6235093

Disproportionality Analysis Report (DPAR) Work Instruction for Vaccines

Background

The TGA receives spontaneous reports of adverse events associated with the use of all medicines, including vaccines. These reports are received from pharmaceutical companies, health professionals, consumers, and state and territory health departments and are entered into the TGA Adverse Event Management System (AEMS) database. Most Adverse Event Following Immunisation (AEFI) reports made for vaccines to AEMS are from Jurisdictional Immunisation Co-ordinators (JICs) in state and territory governments.

Data from the AEMS are used to generate the Disproportionality Analysis Report (DPAR), which is reviewed by staff in the Vaccine Surveillance Section (VSS), the DPAR is reviewed bimonthly.

DPAR is a process for flagging a series of case reports of concern. It involves a clinical assessment of a list of vaccine-event pairs and the prioritisation of detected signals for validation by the VSS team, either via the, or another method.

Conceptual basis

The methods adopted in the TGA DPAR process include the Proportional Reporting Ratio (PRR) and Information Component (IC) statistics. These methods are based on the assumption that a signal of disproportionality is identified for a medicine/vaccine when a reaction is reported relatively more frequently in association with the medicine/vaccine of interest than other medicines/vaccines.

For example, if 6% of all reports for a medicine describe nausea, compared to 2% of all reports for the whole database, excluding the medicine of interest, a PRR = 3 is generated for that particular medicine-reaction pairing.

Table 1: 2x2 contingency table used to compute PRR and IC statistic

	Reaction of Interest	All other Reactions	Total
Vaccine of interest	A	B	A + B
All other Vaccines	C	D	C + D
Total	A + C	B + D	N = A + B + C + D

*Note that all vaccines are currently used for denominator data (C and D values). A recommendation to exclude COVID-19 vaccines from the background dataset when performing a DPAR is currently being explored. This process would therefore include only general (non-COVID-19) vaccines in the background dataset (denominator values of C and D).

PRR Calculation

The PRR is calculated using the following formula:

PRR = $\frac{A/(A+B)}{C/(C+D)}$

PRR Upper and Lower Confidence Intervals Calculation

The upper and lower confidence intervals are calculated for the PRR value using the following formulas:

standard error of PRR: se(PRR) = $\sqrt{\frac{1}{A}+\frac{1}{C}-\frac{1}{A+B}-\frac{1}{C+D}}$

lower bound = PRR / $exp^{1.96*se(PRR)}$

upper bound = PRR * $exp^{1.96*se(PRR)}$

Note: The PRR and PRR LCI will be undefined (in the report) if C = 0; i.e. if the reaction of interest has not been reported with other products. For AEFI-vaccines pairs where there is a C cell with a zero value, the Haldane-Anscombe correction will be applied where 0.5 is added to each cell in that 2x2 contingency table to allow a PRR to be calculated. The PRR will also be very large if A, B, and C are all small – i.e. new product and new reaction term (this happens frequently due to the large range of reaction terms to choose from in MedDRA).

IC calculation

The IC is calculated using the following formula:

expected value: E = $\frac{(A+C)(A+B)}{(A+B+C+D)}$

IC = $\log_2(\frac{A+0.5}{E+0.5})$

IC Lower Confidence Interval Approx. Calculation

The IC lower confidence interval is approximated using the following formula:

IC LCI = $\log_2(\frac{A+0.5}{E+0.5}) - 3.3(A + 0.5)^{-1/2} - 2(A + 0.5)^{-3/2}$

PRR threshold limits

When scanning the DPAR for potential signals, threshold values are applied to the PRR. For a standard product, the threshold applied is PRR ≥3 **AND** at least five total cases or three sole suspect cases of the drug-event pair.

Reduced thresholds for medicines on the Intensive Drug Monitoring Program (IDMP)

The IDMP applies extra scrutiny to certain medicines or vaccines. The IDMP list is maintained in the AEMS Customer Relation Management Database (CRM) 'Special Interest' table with products identified by ingredients. For products on the IDMP list, a lower threshold of PRR ≥2 AND at least two total cases is applied.

Critical Adverse Events

A Critical Adverse Event (CAE) is an adverse event of particular medical significance and is usually potentially life threatening. Lower PRR thresholds for identifying a potential signal apply to CAEs. This list is also stored in in the AEMS CRM 'Special Interest' table. The list of vaccines on the Intensive Drug Monitoring Program (IDMP) and Critical Adverse Events (CAE) used in the Qlik vaccine DPAR app are currently stored in AEMS CRM under the Medicines of Special Interest table. Changes and updates to this list can be made in AEMS CRM.

The process for ongoing maintenance and verification of the IDMP list and the CAE list is outlined in the IDMP work instruction (D18-11080642).

Table 2: PRR threshold Limits

	Not IDMP listed	IDMP listed
Not a CAE	Cases (Total) ≥5 **OR** Sole Suspect (Total) ≥3 **AND** PRR ≥3	Cases (Total) ≥2 **AND** PRR ≥2
CAE	Cases Total ≥2 **AND** PRR ≥2	**Any new case**

Further information on the conceptual basis of PRR is available from the following sources:

- Evans SJW, Waller PC, Davis S. *Pharmacoepi Drug Saf* 2001; 10: 483-486. [These authors define a PRR as significant if PRR ≥2 and if there are three or more cases in the database.]
- The European Medicines Agency document "Guideline on the Use of Statistical Signal Detection Methods in the Eudravigilance Data Analysis System" (Doc. Ref. EMEA/106464/2006 rev. 1, dated 26 June 2008). *Note that in the EMA document (page 6/22) the contingency table rows and columns have been swapped compared to the contingency table shown above.*
- Waller P. *An Introduction to Pharmacovigilance*: 2010; Wiley-Blackwell
- World Health Organisation (WHO). *Promoting safety of medicines for children*: 2007; p43 http://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf

Generating DPARs using Qlik

Open Qlik (https://cwqlcp02.central.health/hub)

Select 'HPRG Published' from the "Streams" menu

Select the *DPAR* icon. The following base sheets are available:

Reference Guide

Medicines vs Medicines

Vaccines vs Vaccines

The STRS analyses the *vaccines vs vaccines* reports bimonthly as part of their routine signal detection processes with the AEMS dataset.

Follow the steps below for any of the disproportionality analysis reports.

1. Under base sheets, select the *vaccines vs vaccines* report

2. Filter the data by reporting period:

   – Click on the reporting period tab and select the desired reporting period. Report periods are monthly and show as year-month (e.g. 2020-10 is the report for October 2020). Click on the green tick to confirm your selection. Multiple reporting periods can be selected if desired.

   – The filters applied appear in the selection (filter) bar. These selections will apply to all reports until removed.

3. Create an excel report:

   – Right click in the tabular section of the report

   – Click on the round circle with '…', select 'Export', then 'Export data'

   – In the Export complete window, click on the link 'Click here to download your data file' to download the report to excel, then click Close.

   – At the bottom left of the window, click on the excel downloaded file.

   – Format the document as follows (there is no need to change the name of the sheet):

      - Go to the 'View' tab, select 'Freeze Panes' button, select 'Freeze Top Row'
      - Highlight columns PRR, PRR LCI, IC, and IC LCI, right click and select 'Format Cells' under 'Number' tab format to two decimal places
      - Right-justify all number columns and adjust column widths as required
      - Select column I ">Limit", go to the ''Home' tab, under 'Editing' select 'Sort & Filter' button, and select Sort Z to A; click 'Expand the selection'. Data with combinations that meet the prespecified criteria (ie, "> Limit" = 1) will appear at the top.
      - Delete the rows (the lower part of the sheet) where ">Limit" = 0.
      - Select column P right click and insert 4 new columns and label the new columns as shown below:

        DPAR date Evaluator Assessment Comment

        The new columns will be P through S, leaving the DPAR Library results on the rightmost edge 'Most Recent Assessment Code', Most Recent Assessment Date', and Most Recent Evaluator's Comment'
      - Fill out DPAR date column with the date the DPAR report was created

Select all the data in the excel document and then select Home – Format as Table –then select 'Medium – Blue (top row)'. This will apply the table format to the excel contents.

4.

   - Save the excel report in the relevant TRIM container within TRIM placeholder PH16/399
     (*SIU – Disproportionality Analysis Report (DPAR)/PRR Trend Analysis*) named

     THERAPEUTIC GOODS REGULATION – Reviews (post market) – Disproportionality Analysis Reports (DPAR) – PSAB – CCYY using the following naming conventions:

DPAR – vaccines – MM/MM CCYY (e.g. DPAR – vaccines – 08/09 2017)

5. Once the rows contained within the DPAR report have been evaluated, the completed document should be saved and filed in TRIM (replace the original document saved in TRIM with the completed version). To do this, open the document in Sharepoint, then under File, save the document to your desktop, then upload the saved excel file to TRIM.

Once the completed DPAR is saved in SharePoint an email should be sent to PSAB Systems (psabsystems@health.gov.au) to advise them that the DPAR assessment is complete. The PSAB team will save a copy of the completed DPAR onto J: drive for upload into the DPAR library in Qlik.

Distributing DPARs

A designated member of the STRS vaccine team will generate the *vaccines vs vaccines* DPAR report, save the document to TRIM, upload the document to the relevant Sharepoint page, and email the VSS team that the vaccine DPAR is ready to be completed.

Completing the DPAR assessments in SharePoint

The DPAR excel report is uploaded to the SharePoint Site DPAR-spreadsheets page (vaccines sheet). Recording of assessments should be undertaken in SharePoint as it allows multiple users to edit the spreadsheet simultaneously and once saved, assessments can then be loaded into the DPAR library on Qlik for future reference.

Assessors need to edit the sheet in the web browser (as opposed to opening an Excel document), when prompted, so that assessments are saved.

Analysing DPARs

VSS staff are allocated a set of vaccine (generic name) – reaction (MedDRA preferred term) pairings to review. The aim of this process is to identify vaccine-event pairings that warrant further investigation, which may be via a Targeted Investigation Process (TIP) review, or through another safety investigation or causality assessment process. In evaluating an association, consider the following points:

1) **Is the vaccine-event association already known?** (is it recorded adequately in the Product Information – refer to the Work Instruction for expectedness assessment for further information on how to approach this located in Appendix 4 and in TRIM at D18-11364307)
2) **Is the association more likely due to other factors?** (such as the disease being treated or other drugs; consider the proportion of total cases that are sole suspected)
3) **Has the signal been detected and worked up earlier?** (refer to the TRIM workflow saved search (see D21-2627652); even if the signal has been reviewed earlier, a large number of new reports might be grounds to re-review the signal). Also review the 'DPAR Vaccine Resources' container on TRIM at E21-425105 to locate any relevant information pertaining to specific vaccine-event pairings.
4) **Has there been a recent increase in reporting of the event?** (compare 'total cases for period' vs 'total cases in database', look at trends over time)
5) **Are the individual reports of sufficiently high quality to support a further investigation?** (if the reviewer proposes that a new vaccine-event association is investigated as a potential signal, it is essential that the reports are briefly reviewed before recommending a Signal Investigation)
6) **Is the vaccine event association supported by external evidence?** (particularly, disproportionality in Vigibase as demonstrated by a positive IC025 value and/or case reports in medical literature and/or inclusion in the product information (PI) documents of international regulatory counterparts; see the VSS Signal Investigation Template at D21-3464876 that contains information to access relevant links and information, including a VigiBase instruction guide at D21-2803517. Give consideration to causality, namely a temporal

relationship (including plausible time to onset), dose response, strength of the association [quantitative measures such as disproportionality], and consistency of report [such as clustering by site or time]; in addition to the specificity of event [i.e. other causes for the event]).

A decision-making tool for the process reflected in 1-6 above can be found at Appendix 2.

CIOMS Practical Aspects in Pharmacovigilance also provides the following points to consider for signal prioritisation

Table 3: Points to consider for initial signal prioritization, not in heirarchical order (taken from CIOMS Practical aspects of signal detection in pharmacovigilance TRIM D22-5759537)

New (not yet reported) adverse reaction
Serious
Medically significant (e.g. severe, irreversible, lead to an increased morbidity or mortality, on list of critical adverse events)
Presence in a "drug-specific" list of surveillance terms (i.e. a limited list of events likely to be associated with a drug)
Rapidly increasing disproportionality score
Important public health impact (e.g. wide usage, number of cases, signifcant off-label use, direct-to-consumer programs)
Data elements from database fields are suggestive of a relationship with the drug (e.g. positive rechallenge, short time-to-onset, presence of literature cases in a case series)
Temporal clustering of events
Reported/observed in a vulnerable population (e.g. paediatric, pregnant women, geriatric, psychiatric)
Occurrence during the first few years post launch (i.e. "newer drug")
Drug with high media attention
Risk perception by general population
More than one data source provides positive evidence of a hazard
Reports from multiple countries
Political obligations (e.g. ministerial concern)

The framework presented below in Appendix 1 can be used during the vaccine DPAR review Evaluation of a potential signal detected during DPAR analysis should be recorded in the comments section of the DPAR and any Vaccine-AEFI pairs that are recommended for a Signal Investigation should be added to the Signal Investigation Surveillance Tracker and Analytics (SISTA) (TRIM D22-5112735) and a separate word document with details of the DPAR assessment for this signal should be created and saved within the 'TIP referrals and related documents' container in TRIM at E21-419218 to assist future DPAR coders and Signal Investigation evaluators. Information related to signals that have not been referred for a Signal Investigation, or that have already had a Signal Investigation completed and continue to signal on DPAR can be saved in the DPAR vaccine resources folder (TRIM E21-425105) and added to the DPAR signal library (TRIM D23-3538572).

If any duplicate case reports are identified in the AEMS database during the DPAR analysis, the case numbers should be emailed to ADR.reports@health.gov.au for removal.

Version history

Version	Description of change	Author	Effective date
1.0	Original publication	s22	21/12/2018
1.1	Additional instructions on completing assessments in SharePoint Additional information relating to COVID-19 vaccine DPAR Additional appendix with new vaccine assessment codes	s22	
1.2	Revision of vaccine assessment codes	STRS team	
1.3	Update of STRS to VSS Update decision making tool flow chart Addition of 'Points to consider for initial signal prioritization'	s22	31 March 2024

Authorisation

Name	Position	Date
s22	s22, Signal Investigation Unit	8 Jan 2019
s22	s22, Vaccine Surveillance Section	31 March 2024

Appendix 1: Coding framework for Vaccine DPAR assessment

While performing the DPAR review, evaluators assess each drug-event pair according to the following coding framework.

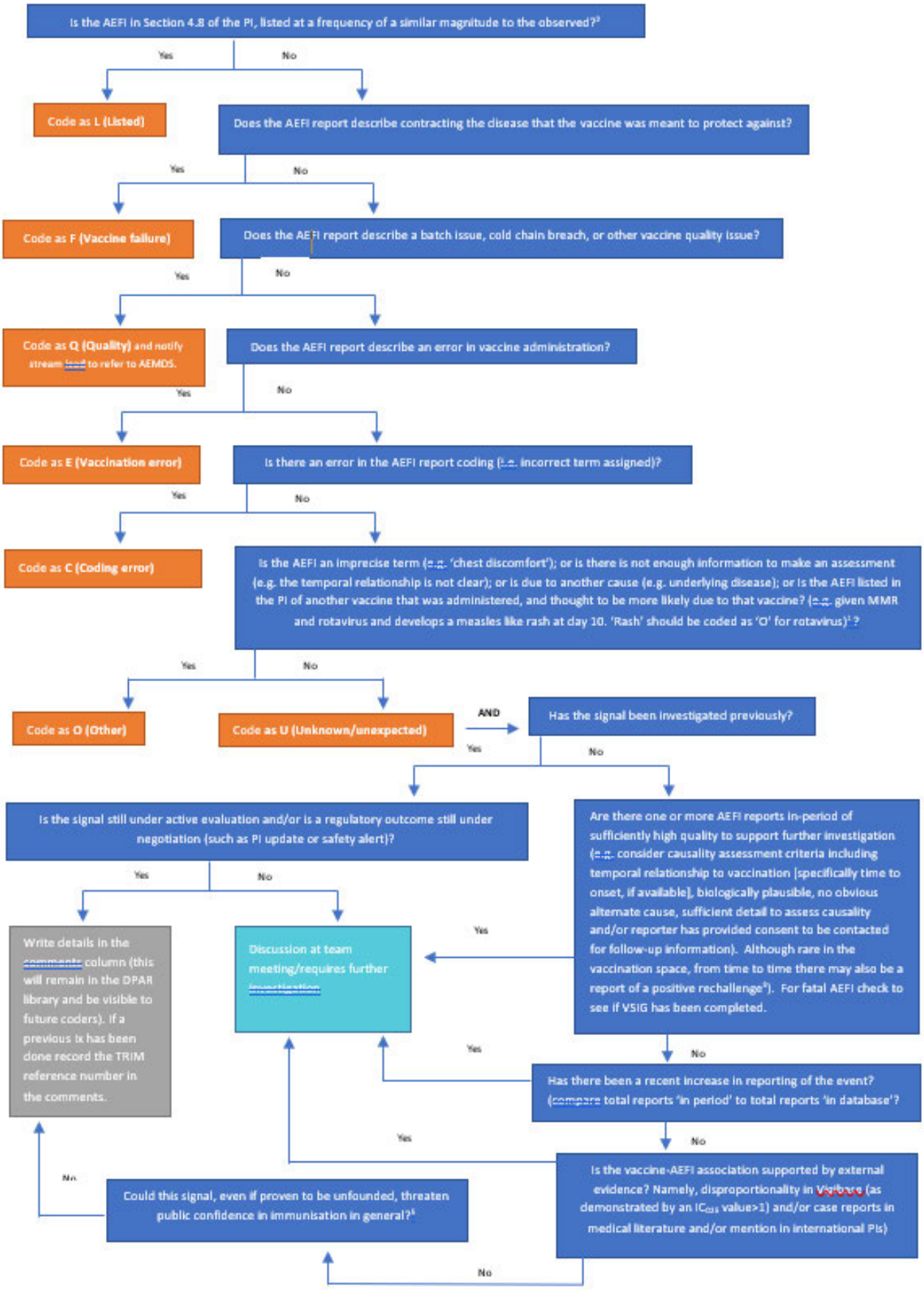
Table 3: Coding framework for assessing causal relationship of a drug-event pair

Code	Assessment	Examples
U	Unknown	An unknown or unexpected AEFI. An AEFI that is not listed in the PI and has not been observed in clinical trials or post-market experience. Codes of U generally require a Signal Investigation to be completed in order to investigate the signal, unless there is a valid rationale for not pursuing a signal investigation (such as the the quality of reports in AEMS is very low, signal not supported in Vigibase or literature).
L	Labelled/included in the PI	AEFI is included in the PI e.g. injection site reactions or fever for many vaccines, intussusception for rotavirus vaccine. Incorporated terms can fall under listed e.g. if case had HHE, then hypertonia, unresponsive, pallor etc. would all be considered listed as they are incorporated under the larger term HHE. This may also include vaccine associated disease such as measles (confirmed vaccine type) or vaccine-associated enhanced disease if it is listed
F	Vaccine failure	Contracting disease vaccine was meant to protect against e.g. getting whopping cough after DTP vaccine
E	Vaccination error	Error in vaccine administration e.g. administered at wrong scheduling, wrong site
Q	Quality	Batch issue, cold chain breach, other quality issues
O	Other	Adverse event was due to another cause e.g. underlying disease such as seizure disorder and vaccine triggered seizure, or other sequelae of a vaccine reaction e.g. case had anaphylaxis to a vaccine (assessed as listed or signal) and because of anaphylactic reaction had chest pain, difficulty breathing, these would be coded as Other (as they're related to anaphylaxis). If an AEFI is not listed on PI for a specific vaccine, but is listed on PI of another vaccine that was administered and thought to be more likely due to that vaccine, then AEFI should be coded as Other for the vaccine where it is not listed on the PI e.g. given MMR and rotavirus and gets a measles like rash at day 10, code 'Rash' as Other for rotavirus. Imprecise terms that are not specific enough to assess e.g. chest discomfort, or lack of sufficient information to make an assessment about a possible association, such as no information on when vaccine was administered and when AEFI occurred.
C	Coding	Report coding needs changing

Appendix 2: Decision making tool for initial triage of DPAR vaccine-event pairs in the Surveillance and Targeted Review Stream (STRS): all vaccines on the ARTG

This is a decision-making tool only. It is designed to provide a framework to assist decision-making and staff should exercise clinical and regulatory judgement to coding, even if this results in a decision that diverges from the general guidance provided below. For additional information/advice on each box, follow the footnote references that appear underneath the decision-making tool graphic.

1. Consider a single vaccine-event pair (product-AEFI pair, i.e. single row on DPAR output, for example, influenza virus haemagglutinin and Guillain-Barre syndrome).
2. Open the National Immunisation Program Schedule, the ARTG PI for the vaccine product in question, and AEMS via the Qlik app. Review the DPAR Vaccine Resources container in TRIM at E21-425105 for any information that may be relevant to a vaccine-event pair flagged on DPAR and check SISTA (TRIM D22-5112735) to see if a Signal Investigation has already been undertaken for this signal.
3. Follow the decision-making tree below.
4. For any vaccine-event pair coded as 'U', please state whether a Signal Investigation is or is not required. Provide additional comment within the DPAR spreadsheet to justify this recommendation. Vaccine-event pairs coded as 'U' and pairs with other coding that are of concern are discussed with the vaccine surveillance team at a DPAR review meeting, scheduled once all evaluators have completed coding their allocated rows. Vaccine-AEFI pairs that are recommended for a Signal Investigation should be added to SISTA (TRIM D22-5112735) and a separate word document with details of the DPAR assessment for this signal should be created and saved within the 'TIP referrals and related documents' container in TRIM at E21-419218 to assist future DPAR coders and Signal evaluators.



Note to edit the decision tree, edit original document at D21-3254984, then copy and paste 'picture' into this document

Explanatory Notes:

1. Vaccines are often administered concomitantly with other vaccines, making causal attribution to a specific vaccine difficult. Reference: Council for International Organizations of Medical Sciences (CIOMS) Vaccine Safety Training: https://vaccine-safety-training.org/tl_files/vs/pdf/CIOMS.pdf

2. Definition of Listed (L): AEFI is listed in the publicly-facing Product Information (PI) document for the vaccine at https://www.tga.gov.au/product-information-0. For example, injection site reactions or fever for many vaccines, and intussusception for rotavirus vaccine. Incorporated terms can fall under listed e.g. if a patient in an AEFI report had Hypotonic-hyporesponsive episode (HHE), then terms such as 'hypertonia', 'unresponsive', 'pallor' etc. would all be considered listed as they are incorporated under the larger term HHE.

   This may also include vaccine associated disease such as measles (confirmed vaccine type) or vaccine-associated enhanced disease if it is listed.

   The threshold for inclusion of information in the RSI/PI may be viewed differently by regulators (and between regulators) than by industry, potentially leading to disagreements on the appropriate safety information. The relative weight of the criteria for inclusion may also vary during the life cycle of a drug.

   The CIOMS V working group advises that expectedness should be based on the inclusion of an ADR term in the Adverse Events (AE)/ADR section (also called Undesirable Effects section) of the PI. In Australia, this section is 4.8 of the PI. This section is usually considered a comprehensive repository of *expected* ADRs with their frequency and grades of severity specified. Thus, even if an ADR term is mentioned in the 'Clinical pharmacology', 'Contraindications', 'Warnings and Precautions', or other sections of the PI, it must be included in the ADR section for it to be considered expected. The associated wording and placement of the ADR term in the PI should be considered within the semantic context of the ADR report, clinical implications and public health impact for surveillance and signal detection.

   The *Work Instruction – Expectedness assessment* at D18-11364307 provides detailed instructions for how to conduct an expectedness assessment in terms of specificity, severity duration and frequency, of the AEFI, as well as consideration of fatal outcomes, overdose, an AEFI class. The *Work Instruction – Expectedness assessment* should be used in conjunction with this Work Instruction and is reproduced at Appendix 4 below for convenience.

3. Consideration of dechallenge and rechallenge differs for vaccines compared with other medicinal products. Vaccines are frequently administered only once or with long intervals, and serious adverse events following immunization often prevent further vaccine administration. Dechallenge may not be applicable to vaccines, given their long-term immunological effects, and rechallenge information is only rarely available. (Reference: CIOMS Vaccine Safety Training: https://vaccine-safety-training.org/tl_files/vs/pdf/CIOMS.pdf)

4. Evaluators in the Vaccine Surveillance Section (VSS)) pick-up vaccine-AEFI pairs to review via Signal Investigation Surveillance Tracker and Analytics (SISTA) (TRIM D22-5112735)

5. Non-serious adverse events following immunization should also be carefully monitored because they may signal a potentially larger problem with the vaccine or immunization or have an impact on the acceptability of immunization in general. (Reference: CIOMS Vaccine Safety Training: https://vaccine-safety-training.org/tl_files/vs/pdf/CIOMS.pdf).

6. Vaccines in shortage. The public register of medicines and vaccines in shortage is available on the TGA website.

Appendix 3: Expectedness Assessment

See D18-11364307

The concept of *expectedness* refers to adverse events following immunisation (AEFIs) which may or may not have been previously observed and documented in the Reference Safety information (RSI) approved by a particular regulatory authority. In Australia, expectedness is assessed according to whether an AEFI is included in approved Product Information (PI). It does not refer to what might have been anticipated (expected in a different sense) from the known pharmacological properties of the vaccine. Depending on the context, *expected* and *unexpected* can refer to:

- *labelled* vs. *unlabelled* (i.e. official data sheets/PI for marketed products); or
- *listed vs. unlisted* (i.e. Investigator's Brochure, Development Core Safety Information (DCSI), or Company Core Safety Information (CCSI)).

An AEFI is considered unexpected when its specificity, severity, frequency or outcome is either not identified, or is not consistent with the terms or description used in the applicable RSI/PI.[1] The purpose of reviewing expectedness is to ensure that all relevant potential AEFIs are described appropriately in the RSI/PI. Ideally, the assessment of expectedness should be consistent between the TGA and for sponsors.

The Council for International Organisations of Medical Sciences (CIOMS) Working Group V endorses the following distinctions established under the International Council for Harmonisation (ICH):

- *Listed* or *Unlisted* are the terms used to refer to AEFIs in association with the Company Core Safety Information (CCSI) within a Company's Core Data Sheet (CCDS) for a marketed product. Similarly, these terms are recommended by the CIOMS Working Group to describe expectedness of AEFIs in association with the DSCI in an Investigator's Brochure.

- *Labelled* or *Unlabelled* (i.e., *Expected* or *Unexpected*) are terms that should be used only in connection with official local/regional RSI for marketed medicines, such as the Australian PI.

The threshold for inclusion of information in the RSI/PI may be viewed differently by regulators (and between regulators) than by industry, potentially leading to disagreements on the appropriate safety information. The relative weight of the criteria for inclusion may also vary during the life cycle of a drug.

The CIOMS V working group advises that expectedness should be based on the inclusion of an AEFI term in the *Adverse Events (AE)/ADR section* (also called *Undesirable Effects section)* of the RSI/PI. In Australia, this section is 4.8 of the PI. This section is usually considered a comprehensive repository of *expected* AEFI with their frequency and grades of severity specified. Thus, even if an AEFI term is mentioned in the '*Clinical pharmacology*', *'Contraindications'*, *'Warnings and Precautions'*, or other sections of the PI, it must be included in the AEFI section for it to be considered *expected*. The associated wording and placement of the AEFI term in the PI should be considered within the semantic context of the AEFI report, clinical implications and public health impact for surveillance and signal detection.

Points to Consider:

- Specificity: An AEFI is considered *unexpected* if the reported AEFI term is more specific than the related AEFI term that appears in the PI. This is because more specific terms may often indicate other associated risks and a different prognosis than expected as per the known safety profile of the drug.

[1] International Conference on Harmonisation (ICH). Harmonised Tripartite Guideline. Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting E2D, 12 November 2003

Example[2]
- *PI lists arteritis; temporal arteritis should be considered unexpected.*

Anatomical and histological specifications may or may not necessarily indicate unexpectedness. The clinical implications must be taken into account for assessment:

- *Example*[2]
  - *PI lists hepatic necrosis; hepatic necrosis with the presence of eosinophils is expected.*
  - *PI lists cerebrovascular accidents; cerebral thromboembolism and cerebral vasculitis is unexpected (greater diagnostic specificity).*
  - *PI lists acute renal failure; interstitial nephritis is unexpected.*

- Severity: An AEFI is considered *unexpected* if the reported AEFI term is more severe than the related ADR term that appears in the PI.

  Example[2]
  - *PI lists liver injury; fulminant hepatitis is unexpected.*
  - *PI lists rash; maculopapular rash is expected; SJS is unexpected.*

- Duration: An AEFI is considered *unexpected* if the reported AEFI term is persistent or chronic in the case summary but related AEFI term that appears in the PI is specified as transient or acute.

  Example[2]
  - *PI refers to acute elevated liver function tests; a raised level lasting three months would be unexpected.*

- Signs and Symptoms: Reported signs and symptoms which are considered to be usually associated with a listed AEFI are individually also considered *expected*. Complications of a listed AEFI term not usually associated with the listed AEFI should be considered *unexpected* when reported.

  Examples
  - *PI lists thrombocytopenia; petechiae are expected.*
  - *PI lists GI irritation; melaena is unexpected.*

- Fatal outcomes: For cases that involve a fatal outcome, AEFI terms should be considered *unexpected* unless the PI specifically states that the AEFI may be associated with a fatal outcome.

- Overdose: If an AEFI has been reported only in association with an overdose, then that same AEFI at usual dosage should be considered *unexpected*.

- Class ADRs: Class-associated AEFIs should not automatically be considered *expected* for the subject medicine. Class AEFIs should be considered *expected* only if described as specifically occurring with the product in the product labeling:

  Examples:
  - *'As with other health products of this class, the following undesirable effect occurs with Product X.'*

[2] Current Challenges in Pharmacovigilance: Pragmatic Approaches- CIOMS Working Group V. (CIOMS Geneva, 2001)

- *'Health products of this class, including Product X, can cause...'*

If the statements such as the following appear in the PI, then the AEFI is considered to be *unexpected* with the use of Product X:

Examples:
- *'Other health products of this class are reported to cause...'*
- *'Health products of this class are reported to cause..., but no reports have been received to date with Product X.'*

- Frequency: Especially when evaluating clusters of cases, it is important to compare the observed frequency of an AEFI to the labeled/expected frequency as mentioned in the PI. A true rise in the observed frequency may warrant further investigation of the AEFI as a potential safety concern.

  Standard categories of known or estimated frequency of AEFIs have been proposed by CIOMS Working Group III:

Very Common	≥1/10 (≥10%)
Common (Frequent)	≥1/100 and < 1/10 (≥1% and <10%)
Uncommon (Infrequent)	≥1/1000and < 1/100 (≥0.1% and <1%)
Rare	≥1/10,000and < 1/1000 (≥0.01% and <0.1%)
Very Rare	< 1/10,000 (<0.01%)

  While evaluating expectedness based on the newly observed frequency compared to the information in the PI, it is necessary to consider the source and type of report. A more accurate observation of frequency will take into account the validity of the estimated denominator (actual patient use/exposure) and the numerator (consider under-reporting with spontaneous reports and 'stimulated' reporting following Health authority prompts and alerts).

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

INTERNAL USE ONLY

Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance Branch

Standard operating procedure (SOP) / Policy document

Name of procedure / policy	Vaccine Surveillance and Targeted Review Stream (Vaccine STRS) – Observed versus expected analyses work instruction
Applicable to	Vaccine STRS
TRIM reference	D21-2715234
Written by	STRS Vaccine Team
Authorised	Dr s22 [redacted]
Date issued	17/09/2022
Version no.	1.0

CONTENTS

PURPOSE 3

What is an O/E analysis? 3

TGA's current use of O/E analysis for vaccine signal investigation 3

Method for undertaking O/E analysis 4

Background incidence rate 4

Person-time at risk 5

Number of people exposed/ vaccinated 7

Determining the observed number for the O/E analysis 7

The O/E ratio 8

Confidence intervals for O/E analyses 8

Age stratified analyses 9

Excel calculator for calculating expected numbers 10

Practical example of undertaking an O/E analysis 10

Appendix A 12

Assumptions used in O/E analyses 12

Assumption 1: The number of doses administered to the population is known 12

Assumption 2: All cases presenting the event of interest after immunization are spontaneously reported. 12

Assumption 3: The background incidence rate in the vaccinated population is the same as the background incidence rate in the population used to calculate the expected 13

Uncertainty analyses to address assumptions 13

References 15

VERSION HISTORY 17

PURPOSE

This policy document contains a work instruction for undertaking and understanding observed – versus- expected (O/E) analyses for COVID-19 vaccine signal investigations within the Medicines and Vaccines Investigation and Surveillance Section (MAVIS) and the Adverse Event and Medicines Defects Section (AEMDS). There is a spectrum of complexity in O/E analysis – from the more rapid and broad, to the more complex – and their application therefore may vary depending upon whether being performed by the Vaccine Surveillance and Targeted Review Stream (Vaccine STRS) or the MAVIS Evaluation Stream. The potential differences are described in this work instruction but there will always need to be judgment regarding the scope of the O/E analysis that is being performed.

What is an O/E analysis?

Analysis of the case details of spontaneous case reports or case series is a qualitative method of signal investigation. Quantitative methods include disproportionality analyses and O/E analyses. The literature [Ref A] describes that:

> *Observed-to-expected (OE) analyses, together with data mining algorithms and pharmacoepidemiological studies, are part of the quantitative pharmacovigilance toolkit for vaccines. While data mining algorithms generate hypotheses about potential safety concerns and pharmacoepidemiological studies test specific hypotheses or measure associations, OE analyses stand in between. The role of OE analyses is to refine previously detected signals when there is not enough information to determine whether further action is necessary [Ref A].*

Spontaneous reports of adverse events following immunisation (AEFIs) can be used as the observed number of cases, and compared with the expected number of cases calculated based on background incidence rates from independent sources, such as published studies or administrative health data. This comparison gives an indicator of whether the observed cases following vaccination are likely to have occurred coincidentally, as part of the background frequency of the condition in question.

> *The core principle of OE analyses is to estimate the expected number of these coincidental cases, under the null hypothesis of no association with the vaccine. Expected numbers are then compared with the number of cases actually reported [Ref A].*

Disproportionality data mining algorithms (such as the TGA's DPAR, and the WHO's VigiLyze statistics) estimate an "O/E ratio" generated based on expected and observed numbers of cases from a single spontaneous reporting system, without the use of background rates or vaccine coverage/ exposure information.

Similar to DPAR analyses, O/E analyses are one component of the assessment of causality. They aid in the assessment of vaccine safety concerns [Ref B] but formal epidemiological studies are generally required to test hypothesis and quantify associations [Ref A].

TGA's current use of O/E analysis for vaccine signal investigation

Prior to 2020, the TGA did not have ready access to vaccine exposure data and relied on disproportionality data mining algorithms for quantitative signal detection. The TGA now has access to vaccine exposure data through the Australian Immunisation Register (AIR), and for the COVID-19 vaccines that were approved in early 2020, began making use of this 'denominator' data for interpretation of spontaneous reports to the AEMS. For example, observed rates have been analysed over time and compared between different COVID-19 vaccines. The TGA has also begun undertaking O/E analyses to compare the observed rates with background rates.

The literature outlines that when O/E analyses are used for continuous signal detection monitoring, inflation of type 1 error rates due to multiple testing can occur [Ref C]. When performing weekly analysis, the FDA uses sequential statistical methods to adjust for the multiple testing inherent in the repeated examinations of the data [Ref F]. The MHRA uses O/E for routine, weekly signal detection for COVID-19 vaccines as they did during the H1N1 pandemic influenza vaccine roll-out in 2009-2010, and views it as a more robust method of signal detection than disproportionality analyses [Ref H], but they also use sequential statistical methods to adjust for the multiple testing that occurs with weekly surveillance (called the maximised sequential probability ratio test (MaxSPRT)) [Ref I].

The TGA's intention in undertaking O/E analyses for COVID-19 vaccines has evolved over time. Initially, before a regular DPAR was established for COVID-19 vaccines, they were used partly for routine weekly signal detection. But once DPAR processes were established, their purpose became signal strengthening. Until the application of sequential statistical methods is available to the TGA, their use for ad-hoc signal strengthening is appropriate. In other words, when signals are detected via usual means such as DPAR, Sponsor notifications (including their own O/E analyses of global data), notifications from international regulators, analysis of observed rates over time, they can then be prioritised for further action or strengthened by the use of O/E analyses.

As of 10 June 2021, the Vaccine Surveillance and Targeted Review Stream (Vaccine STRS) of TGA has been mostly conducting O/E analyses, primarily to aid their Targeted Reviews. As the MaVIS Evaluation Stream is undertaking more detailed evaluations of vaccine safety signals, their use of O/E is likely to differ and may require more detailed analyses.

Method for undertaking O/E analysis

Mahaux et al [Ref A] outlines the method for undertaking O/E analysis. The following is a summary of the article.

The number of cases of a particular event expected to occur by chance alone, within a particular risk period, is estimated based on background incidence rates for that event and total person-time at risk in the vaccinated population.

Expected number within the risk period = background incidence rate * person time at risk

Background incidence rate

The background incidence rate (BG rate) is the number of new cases occurring naturally in the population, expressed in person-time. Person-time means the number of people and the time period. BG rates are often expressed for example, as per 100,000 people (person) per year (time). Estimates of incidence rates for the event of interest are selected through literature reviews and/or database queries (e.g., observational or national health statistics databases).

Evaluators should choose the appropriate rate from the following potential sources:

1. Literature search
2. Previous targeted reviews on the signal in question
3. Repository of background rates prepared mostly for COVID-19 AESIs. These are mostly rates from the published literature. [TRIM D21-2133188]
4. Rates provided by NCIRS based on NSW Health data. These rates are not publicly available so are for internal use only. These rates and information about the methods used to determine these rates can be found at:

   a. Detailed information on methods and rates for AESIs such GBS, convulsions, ADEM, aseptic meningitis, encephalitis, myelitis, Bell's Palsy, thrombocytopaenia, anaphylaxis and all-cause death. D21-2680871
   b. Power point summary of the above information. D21-2410662
   c. Detailed information on methods and rates for coagulation disorder type AESIs D21-2680865
5. The VAC4EU/ EMA ACESS Dashboard Background rates of Adverse Events of Special Interest for COVID-19 vaccines: https://vac4eu.org/covid-19-tool/. These are publicly available rates. Information about how to reference these rates is provided on the website. A report describing the methods, the origin of the data and link to the code sets is available at http://www.encepp.eu/documents/DraftReport.pdf

The choice of BG obviously heavily influences the expected number. For example, the NSW Health rates above in some instances are higher than other rates (GBS) and in some instances lower than other rates (ADEM). Available rates of myocarditis are very variable. Using more than one BG may advisable and also giving consideration to how the observed cases are defined. For example, if coded hospital admission diagnoses are being used as the BG rate, it may be appropriate not to apply the Brighton Criteria Case Definitions to the observed cases.

The BG rates should ideally be estimated from populations that have not been exposed to the vaccine of interest but that have similar demographic characteristics (age, sex, ethnic and geographical) to the vaccinated population. Often for the initial 'first-pass' O/E analysis, a BG rate used is derived from the entire population (e.g., all ages, or all adults). In subsequent analyses, an age stratified analysis (see 'Age-stratified analyses' below) should be performed.

The BG rate can be a single rate or a range (e.g., a review article in the literature might give a range of the incidence of the condition). A single rate makes the calculation of the O/E ratio simpler, but this may not always be available. When a range is used, two O/E ratios can be calculated using the lower and upper BG rate. Undertaking O/E analyses with more than one BG rate may be appropriate to consider the influence of the choice of BG rate on the results.

Examples of previous application of background rates to determine the expected numbers can be found in completed targeted reviews.

Person-time at risk

Total person-time at risk reflects the cumulative time for all persons exposed to the vaccine during a risk period for which there is suspicion and/or medical plausibility that there is a vaccine-associated increased risk of experiencing the event.

In the simple case where the vaccine is administered with only one dose, or the risk period is shorter than the interval between doses, the total person-time at risk is calculated by multiplying the number of persons vaccinated by the risk period.

Person-time at risk = number of people vaccinated (or exposed) * length of the risk period

Multiplying the BG rate by the number of people vaccinated is in effect applying the BG rate to the population that has received the vaccine. But this would then still be reflective of a one year time period (if the BG rate was an annual rate). So this then needs to be multiplied by the risk period (e.g., 21 days) to change it from an annual expected number to a number expected in the risk period.

This adjustment from an annual rate is required because the expected number will be compared to the observed number, and the observed number will also have the same risk period applied. The observed number are the people who have developed the adverse event in question, and we have not been 'observing' them for a year – they also have only contributed a certain amount (the risk period) of exposure time.

The expected number calculation can be re-framed as:

> Expected number within the risk period = BG rate * number of people vaccinated * length of the risk period.

For vaccines scheduled with multiple doses, the calculations can be more complex, it is then important to assess whether there is a dose effect and whether the risk periods overlap. This is important for the Pfizer COVID-19 vaccine, as the time between doses can be as short as 21 days, and there may be some adverse events where the risk period is longer than this (e.g., GBS). For the AZ COVID-19 vaccine, the time between doses is currently usually 3 months, and there are not currently any adverse events that appear to have a risk period this long. For conducting an O/E analysis for the Pfizer vaccine where the risk period is more than 21 days, statistical advice will need to be sought. There is more detail about this issue in Mahaux et al [ref A].

The risk period should be selected by the evaluator based on the biologically plausible window in which an adverse event may be caused by a vaccine. For example, anaphylaxis has a short risk window whereas conditions such as GBS and VTE have longer risk windows. This decision may also be partly based on the time to onset for the spontaneous AEFI reports (or observed cases). The Evaluator should consider whether there is a trend in the TTO for the adverse event based on the AEFI reports, which in

Box 1. Examples of calculation of the expected number of cases for a theoretical event of interest

Example 1: 3,000,000 doses of vaccine X administered according to the AIR by 30 June 2021

Increased risk of event Y within 30 days post immunization, whatever the dose.

Recommended vaccination schedule is three doses at 2, 4, and 6 months of age.

Assumptions: there is no dose effect and all 3,000,000 doses have been administered.

The risk periods following each dose do not overlap.

The person-time at risk: 3,000,000 * 30 [person-days] or 3,000,000 * 30/365.2425 * 1/100,000 = 2.46 [100,000 person-years].

Background incidence rate for event Y is 4.8 cases per 100,000 person-years (measured on unvaccinated population sharing similar demographic characteristics with the exposed population)

The expected number of cases of event Y: 2.46 * 4.8=11.8.

Another way of framing this calculation is as follows:

Expected number of cases of event Y: 4.8/100,000 * 3,000,000 * 30/365.2425 = 11.8

[Expected number of cases = BG rate * number vaccinated * risk window]

Source: Most of the above example is taken from Mahaux et al [Ref A].

itself is part of the causality assessment process. Undertaking O/E with multiple risk windows is appropriate to consider the influence of the choice of risk window on the results.

Number of people exposed/ vaccinated

COVID-19 dose data extracted from the Australian Immunisation Register via the Enterprise Data Warehouse by the Technical and Safety Improvement Section (TSIS) on a fortnightly basis is available at E22-532507. It is updated every 2nd Wednesday and contains data on doses of COVID-19 vaccines reported to the AIR by the Sunday prior. This report should be used to determine the number of people exposed/ vaccinated. These reports are found at E21-254041. The date being used as the cut-off for the vaccine doses should be documented and the TRIM link for the report that is being used as the source of the number of doses should be provided. See below for further information about how this date cut-off relates to the observed number of cases. A pivot table can be constructed using the 'SexAge' sheet to group the data according to the relevant age groups for your analysis.

Determining the observed number for the O/E analysis

The observed number is based on the AEFI reports in AEMS. The number of reports of the adverse event in question occurring in association with the vaccine in question is the observed number. The AEMS search (e.g., Preferred Terms (PTs) used to find cases) should be documented. There are a number of considerations in this assessment:

Risk windows/ time to onset (TTO): as the observed number is compared to the expected number determined based on the selected risk window, the observed number should also correspond to the same risk window. For example, if a 21 day risk window is being used, cases in AEMS with a TTO of 21 days should be included in the observed count. Cases that appear to have a symptom onset prior to vaccination can be excluded. Cases with unknown TTO can be included for a more sensitive analysis. The best approach is to present an analysis with unknown TTO cases included, and if the observed number appears to approach the expected number, an additional analysis with TTO cases excluded can also be presented. When there are very large numbers of AEFI reports in AEMS, and there is insufficient time to determine which cases have TTO within the different risk windows or have TTO unknown, as a 'first pass analysis' it may be appropriate to include all cases, and if this is number is clearly lower than the expected numbers for all risk windows being analysed, there may be no need to further review the TTO of the cases. If this latter approach is being taken, a footnote applied to the observed number should indicate that e.g., TTO has not been used to exclude cases, TTO unknowns have been included etc.

Case definitions: in the 'first pass' analysis, all observed cases regardless of case definition status can be included in the observed count. If the observed number is approaching the expected number, further refinement may be appropriate to exclude those cases that clearly do not have the medical condition in question. Whether or not case definitions have been applied to the observed count should be documented. On the other hand, cases should never be excluded based on causality assessment as it would bias downwards the observed count in contradiction with the null hypothesis [Ref A]. For example, if the observed case has a more likely cause for the adverse event than vaccination, this should not be used to exclude the case from the observed count for the O/E analysis. As discussed in 'Background incidence rates' above, the comparability of the cases in the BG rate and the observed cases should be considered.

Date cut-off: for signal strengthening O/E analyses, it is appropriate to use the same date cut-off for the AEMS cases and AIR doses. For example, if the analysis is using cases reported to AEMS by 30 June, this same date should be used for doses reported to AIR. The most statistically precise method is likely to be to reduce the cut-off for doses reported to AIR (e.g., set it to be one risk period prior to cut-off for AEMS cases, or shorten the risk period that is applied to the BG rate to make it the mid-point of the

risk period rather than the full risk period). But doing this (which in effect will reduce the expected case count) may not be necessary because of the delayed reporting to AIR (i.e., the doses reported to AIR is less than the number that have actually been administered to people, and this already reduces the expected case count). Mahaux et al [Ref A] and Black et al [Ref B] don't explicitly recommend an approach, but they do recommend using the standard risk windows rather than the mid-point. The other consideration is that the reviews being conducted by the STRS are signal strengthening/ prioritisation exercises rather than detailed signal verification reviews, so applying the same cut-off will increase efficiency of the process. This is consistent with the MHRA's approach [see email at D21-2716842]. More detailed O/E analyses by the MAVIS Evaluation stream may modify this approach.

Practically speaking, if the AIR data you are using has a cut off of 2 October 2022, as long as the most recent reported/ observed case has a report date prior to 2 October 2022, it is not necessary to limit the date for the observed/ reported cases.

The O/E ratio

The O/E analysis compares the observed and expected numbers of cases. This may be expressed as the ratio of the observed over the expected. An O/E ratio of one means that the observed number of cases equals the expected number of cases, as stated by the null hypothesis. If the O/E ratio is greater than one, then the observed is higher than the expected signaling an excess of risk. If a range has been used for the BG rate two O/E ratios can be calculated and the O/E ratio described as being between the two calculated values. It is also acceptable, to present the observed and expected number of cases and describe whether the observed is less than, no greater than (if a range of BG rates has been used and the observed number falls between the upper and lower expected number) or greater than the expected number.

Confidence intervals for O/E analyses

The statistical uncertainty will often be driven by the observed number of cases, which is often small (rare events). To deal with this statistical uncertainty around the total number of cases observed over the risk period of interest, a 95% Poisson exact confidence interval (95% CI) can be calculated for the O/E ratio. If the lower limit of the 95% CI of the O/E ratio is greater than one, the observed value is considered significantly higher than expected. If the ratio is greater than one, but the lower limit of the 95% CI of the O/E ratio is less the one, the observed value is considered higher than expected but not significantly at a 95% confidence level. An excel spreadsheet for calculating CI's for the analysis can be found at TRIM D21-2942550 (STRS-TIP Calculators - Prototype). It is recommended that Evaluators use the excel calculator in the 'Observed V expected calculator' sheet to determine the O/E ratio and associated 95% Poisson exact confidence interval (row 3). Below is an example of an O/E analysis presented to ICMR. s45



s45

[redacted]

Age stratified analyses

The need for a stratified analysis may arise when background incidence rates differ between genders, age groups, geographical regions, or calendar time. The expected number of cases for each stratum is obtained by multiplying the incidence rate within the stratum by the number of people vaccinated in that age group and then by the risk window. **The overall expected number of cases is obtained by summing the expected numbers of cases over all strata; however, it may be informative to look at the observed versus expected number within each stratum, as an excess risk might be specific to a particular stratum.** When an overall O/E ratio is calculated using this method, it has been 'adjusted' for age, whereas an O/E ratio that is calculated based on an overall background rate, has not.

See example below.

The number of people vaccinated in different age groups with COVID-19 vaccines is provided in the weekly COVID-19 vaccine safety surveillance reports [TRIM E21-254041.] Consideration of whether

Age stratified calculation of expected numbers

2,000,000 doses of vaccine X have been reported to AIR. 750,000 were administered to those aged 16-44 and 1,250,000 to those aged 45 and over. The risk window is 21 days.

Age group	Age specific BG rate per 100,000 per year	Calculation of expected number of cases	Result
16-44 years	4.5	4.5/100,000 * 750,000 * 21/365.2425	1.94
45 years plus	7	7/100,000 * 1,250,000 * 21/365.2425	5.03
The total number of expected cases = 1.94 + 5.03 = 6.97			

age specific BG rates that match the age breakdown of dosage information is required – but generally speaking, age specific rates in 10 year age groups are often provided (e.g., in the EMA VAC4EU/ ACCESS project and the NCIRS data from NSW) and dosage information in 10 year age groups is available in the weekly report.

An example of an O/E analysis using age specific rates for the signal of GBS with the AZ COVID-19 vaccine is found at D21-2731464.

An example of an O/E analysis using age specific rates and confidence intervals for the signal of myocarditis/ pericarditis is found at D21-2574277.

Excel calculator for calculating expected numbers

A excel spread-sheet that undertakes the calculation of the expected number of cases has been develop [TRIM D21-2942550, STRS-TIP Calculators - Prototype] to assist Evaluators. It also calculates age-specific observed rates and has a worksheet for calculating confidence intervals. The Evaluator enters values for the background rate and dosage information and the expected number corresponding to different risk windows is calculated. Evaluators can however, conduct their own calculations. Evaluators are still required to determine the observed number of cases, and compare this to the expected numbers.

Practical example of undertaking an O/E analysis

Example: The TGA has received 15 reports of Bell's Palsy in association with the Pfizer COVID-19 vaccine up to 6 June 2021. By that date, 1678660 doses of the Pfizer vaccine had been reported to the AIR. The full O/E analysis as at D21-2723254, and includes both COVID-19 vaccines, 3 different risk windows and analyses with TTO included and excluded.

Steps	Considerations	Numbers
Decide on risk period	-What is the biologically plausible time period for which there is an increased risk of Bell's Palsy following vaccination? -Examine the TTO for the reported cases to AEMS (observed cases) to determine if there is a trend.	-There are examples from international regulators and in the literature of using 1, 7 and 14 day risk periods and discussion in the Bell's Palsy Brighton Collaboration Case Definition that this is an acute adverse event. -In this example, 6 cases had a TTO within 1 day, and 13 had a TTO within 7 days. The other 2 had TTO >14 days. TTO was unknown for 2 cases
Observed number of cases	-What will your AEMS search be for observed cases? -Do cases appear to be true cases of Bell's palsy or conditions similar to Bell's palsy being mistaken for Bell's Palsy? -Will you apply Case Definitions (eg Brighton Collaboration)? Important not to exclude cases based on whether or not there is a more likely cause. Only exclude based on TTO or whether they are likely to be truly Bell's Palsy. -Will you perform a sensitivity analysis that adjusts for possible under-reporting to AEMS?	-In this example, only cases with the PT of Bell's Palsy were included. Cases with PTs such as facial droop without Bell's Palsy were not included as they appeared to be cases of e.g., stroke rather than Bell's Palsy. -Case definitions were not applied however, as this was an initial 'first pass' analysis as part of a targeted review. In addition, as no adjustment for under-reporting was being done, it was decided to use a more sensitive rather than specific method of including observed cases. -Analysis with TTO unknown included: observed count=6 for 1 day risk window and 13 for 7 day risk window. -Analysis with TTO unknown excluded: observed count= 4 for 1 day risk window and 11 for 7 day risk window.
Number of people vaccinated/ exposed	-How many have received the vaccine? -Will you use a subpopulation? (what is the age range and sex distribution of observed cases?)	- 1678660 doses of Pfizer COVID-19 vaccine administered according to AIR. -No subpopulation used as cases had a wide age range and roughly equal sex distribution; and an age-stratified analysis was not being performed at this stage.
What background rate will you use?	-Will you use a BG rate that covers the entire population (all ages and both sexes)? -Will you perform an age stratified analysis?	In this example a rate of Bell's Palsy from NCIRS derived from NSW Health data from 2017-2018 of 26.3 per 100,000 per year was selected. This was chosen as it was a rate of Bell's Palsy specifically that was a closer match to the observed cases. Although the incidence of Bell's Palsy does vary with age, because this was a 'first pass' analysis as part of a targeted review, and the observed cases had a wide variety of ages, it was decided at this point not to undertake an age stratified analysis.
What is the expected number of Bell's Palsy cases in a 1 day period following vaccination among those vaccinated? TTO unknown included	Expected number = BG rate * number exposed or vaccinated * risk period = 26.3/100,000*1678660*1/365.25 =1.21 NB: this is one of the calculations done. See full analysis at D21-2723254	
How do you interpret this expected number?	-The observed number was 6, which is greater than the expected number of 1.2 -The observed number is greater than the number of coincidental Bell's Palsy cases that one would expect in 1 day following vaccination among the 1678660 people vaccinated. -An O/E ratio could be calculated = 6/1.2= 5. As this is greater than 1, it supports the hypothesis that there is an increased risk of Bell's Palsy among those vaccinated. -Ideally we would calculate a 95% confidence interval around this O/E ratio to indicate whether the increase above expected is likely to be statistically significant.	
What additional analyses could be performed?	-The expected number could be calculated via an age-stratified analysis if age specific background rates are available. -Sensitivity analyses could be performed to see if the following factors influence the conclusion: • adjust the observed number for different degrees of under-reporting (will increase the ratio) • adjust the observed number to only include cases with known TTO (will decrease the ratio, and was done in this analysis, the ratio was still greater than 1 as only 2 cases had unknown TTO) • adjust the observed number to only include cases that meet the Brighton Collaboration Case Definition (will decrease the ratio) • use different BG rates of Bell's Palsy (a lower rate BG rate will decrease the expected number and increase the ratio)	

Steps	Considerations	Numbers
Some broader considerations about the context of the O/E analysis	O/E analyses are one part of the causality puzzle. How do you results fit in with the other findings of your investigation? How O/E analyses are being conducted (e.g., their purpose and complexity) may vary depending upon whether they are being conducted by STRS or the MAVIS Evaluation Stream.	

Appendix A

Assumptions used in O/E analyses

These assumptions are described to aid the Evaluator's understanding of the limitations of O/E analyses.

Assumption 1: The number of doses administered to the population is known

Prior to having access to AIR data, TGA relied on access to sales data for vaccine coverage or dose information. Having access to AIR data now, and it being compulsory for immunisation providers to report COVID vaccine encounters to the AIR, gives some certainty to the dose information being used in O/E analyses. Although there may be some doses that are not reported to AIR, this is thought to be low. It is acknowledged that there can be a delay in reporting to AIR, and the impact of this on the O/E is discussed further above under 'Determining the observed number for O/E analyses'. This delay may counter the issue of the date cut-off for reported AIR doses being too close to the date cut-off for reported AEMS cases.

Assumption 2: All cases presenting the event of interest after immunization are spontaneously reported.

Spontaneously reported events generally represent only a fraction of the events actually occurring after immunization. This so-called under-reporting is dependent on the risk period considered, as discussed in Assumption 5. Under-reporting is also dependent on the plausibility of the event being causally associated with the vaccination. Other factors, such as the severity of the event, media coverage on the potential association between the vaccine and the event, public awareness, or the presence of the event in the label, also affect the extent of under-reporting. Under-reporting in vaccines spontaneous reporting systems varies and has been estimated for serious events at between 19% and 50%, meaning that between 81% and 50% of the adverse events occurring after vaccination are being reported. Serious adverse events, often covered by the media (e.g., GBS, myocarditis, TTS) and for which a potential causal association has been discussed in the literature tend to be better reported particularly when they occur within a short time period after immunization. Nevertheless, the assumption that all cases are reported tends to lower the sensitivity of most OE analyses.

Over-reporting (more cases reported than the number of cases actually occurring in the vaccinated population) may be observed following extensive media coverage and public awareness, such that an increased number of cases with similar symptoms are reported (over-diagnosing). Over-reporting may also occur because of multiple reports of the same case, where a lack of information makes it difficult to detect and delete duplicates.

During the COVID-19 vaccination program, reporting of associated AEs has been high, so it is assumed that under-reporting is minimal and in some instances there is likely to be over-reporting. Therefore, as of June 2021, analyses to adjust the observed case number for under-reporting have not been required.

Assumption 3: The background incidence rate in the vaccinated population is the same as the background incidence rate in the population used to calculate the expected

This is partially discussed in 'Background incidence rate' above. Of note, background incidence rates derived during pandemic times when health utilisation and infectious disease incidence differs because of lockdowns for example, may not be reliable. Therefore, background rates derived during 2020 and 2021 may not be accurate and data that is still recent but before 2020 is recommended.

Assumption 5: The risk period considered focuses on the time period for which an excess of risk occurs in case of causal association.

The risk period must correspond to the exact period of increased vaccine-associated risk. Overestimation of the risk period may dilute the excess of cases with the event by including periods beyond and/or before the true risk period, during which the vaccine did not generate extra risk for the event. When the risk period is underestimated, the sensitivity is also reduced because it is more difficult to reach statistical significance. Additionally, events occurring a long time after vaccination are less likely to be spontaneously reported than events occurring shortly after vaccination, especially if they are expected, common, or mild. Consequently, a long risk period may include a period characterized by considerable underreporting of the event, reducing the sensitivity of the analysis.

The literature describes that where no clear risk period for the event of interest is defined, the cumulative distribution of the O/E ratio for each day over the whole time window can be used. This would allow potential sub-periods to be detected, where the number of observed cases is higher than expected. This level of sophisticated analysis is beyond the scope of the signal strengthening O/E that the TGA is currently undertaking.

Uncertainty analyses to address assumptions

Providing a single OE ratio estimate is not likely to be sufficient as the qualitative conclusion of the O/E ratio could be reversed depending on how violated the above assumptions are. An uncertainty analysis should determine how much uncertainty would be needed to alter the qualitative conclusion (e.g., the lowest and highest published incidence rates, and possibly adjusting for under-reporting).

As an example of how to better account for uncertainties, Mahaux et al [Ref A] developed a visual framework that determines whether the observed number of events is (significantly) higher or lower than the expected number for simulated values of two sources of uncertainties around the expected. An example (Figure 2) from the paper, considering background incidence rates covering the range of estimates from the literature and under-reporting rates from 100% to 0% (equivalent to a reported fraction of zero to one) is provided below. It is noted that some COVID-19 Sponsors have begun using these visual frameworks in their Summary Safety Reports. Using these visual frameworks at the TGA is an area for consideration.

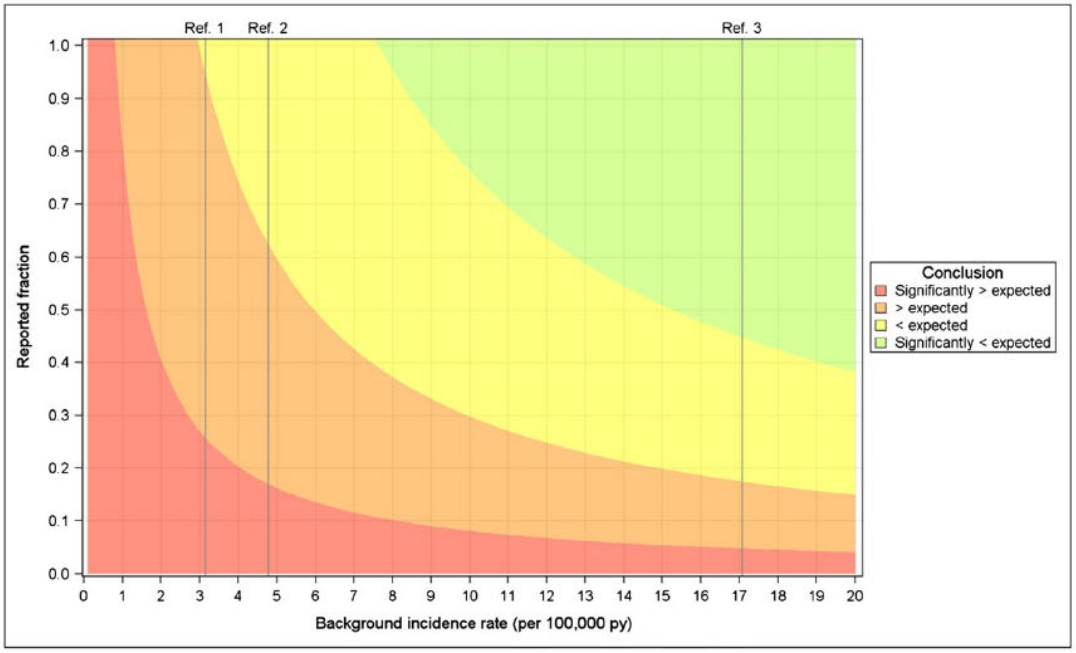


Figure 2. Heat map of the observed-to-expected analysis conclusion in the parameter plane defined by the background incidence rate and the reported fraction. Footnote. Figure 2, drawn from a theoretical example, shows that if Ref. 1 is the correct background incidence rate, the number of cases observed is lower than the number expected only if more than 95% of the cases occurring in the time window at risk were reported. If we take the background incidence rates Ref. 2 or Ref. 3, the number of cases observed is lower than expected only if, respectively, more than 62% or more than 18% of the cases occurring in the time window at risk are reported. Depending on how plausible these values are, an independent reviewer may draw his own conclusions. In most cases, there is no reason to consider that there is a protective effect of the vaccination, so having an observed reporting rate significantly lower than the expected may be an indicator of the range of reported fraction

This visual framework enables independent reviewers such as regulatory authorities to draw their conclusions by making their own assumptions about two sources of uncertainty. When additional sources of uncertainties are deemed to be important then the visualization can be adapted to include these additional uncertainties as illustrated in Figure 3 where the additional uncertainty around case confirmation (i.e., around the observed number of cases) was included in the visualization. This illustrates how additional sources of uncertainties could be incorporated.

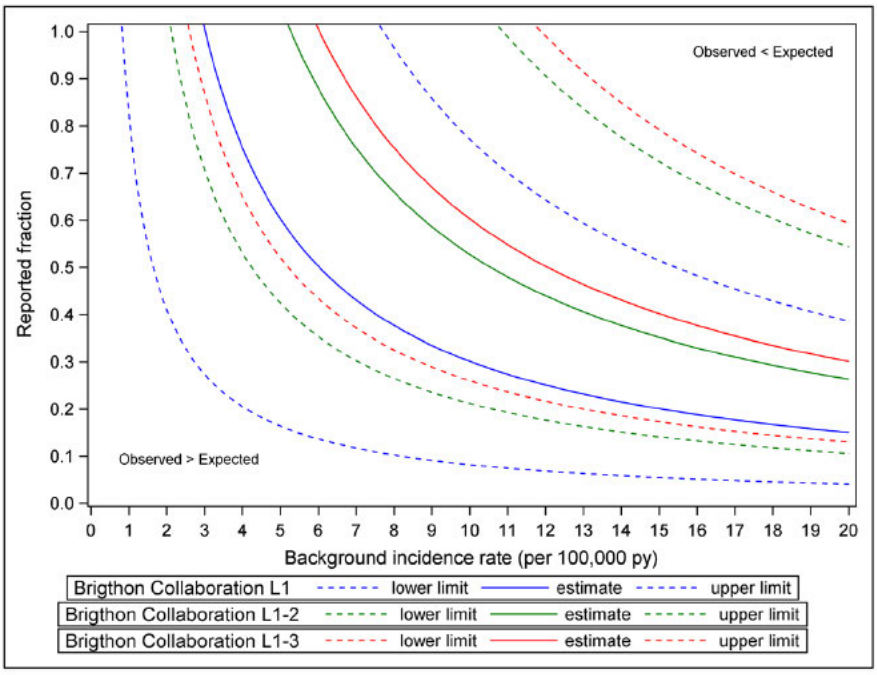


Figure 3. Observed-to-expected (OE) analysis conclusions depending on different scenarios for the reported fraction, the background incidence rate and the case confirmation level.
Footnote. Figure 3 shows the different OE conclusions for the complete range of reported fraction, a specific range of background incidence rate and three scenarios of case confirmation levels. However, this could apply to any other, or a combination of, uncertainty parameters considered as having a significant impact on the conclusion of the OE analysis

References

A. Mahaux O, Bauchau V & LV Holle. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. *Pharmacoepidemiology and Drug Safety 2016;* 25: 215-222. [TRIM D21-2269077]
B. Black S, Eskola J, Siegrist CA, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccine. *Lancet 2009;* 374: 2115-22. [TRIM D20-3568377]
C. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 8). EMA/95098/2010. [TRIM D21-2713255] Available at: http://www.encepp.eu/standards_and_guidance
D. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases. EMA/ 488220/2012 Corr* [TRIM D21-2714264]. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-i-vaccines_en.pdf
E. Leite A, Andrews NJ & SL Thomas. Near real-time vaccine safety surveillance using electronic health records – a systematic review of the application of statistical methods. *Pharmacoepidemiology and Drug Safety 2016;* 25: 225-237. [TRIM D20-3669049]
F. Yih WK, Kulldorf M, Fireman BH, et al. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink Project. Pediatrics 2011; 127: S54-S64. [TRIM D20-3669054]

G. EMA ICMR presentation on Observed to expected analysis for vaccines. February 2021. [TRIM D21-2231609]
H. MHRA presentation on Detecting Drug Safety Signals from Spontaneously Reported Adverse Drug Reaction Data. May 2021. [TRIM D20-3669053]
I. Donegan K, Beau-Lejdstrom R, King B, et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine 2013*: 4961-4967. [TRIM D20-3669043]
J. Presentation given at team training on background rates February 2021[TRIM D21-2280328]

VERSION HISTORY

Version	TRIM Reference	Description of change	Author/s	Effective date
1.0	D21-2715234	Original SOP/Policy	STRS Vaccine Team	17/09/2022

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

1	Consider what background rate you will use			
	noting this method is only applicable for a per person year incidence rate, ie one that looks like x per 100000 people per year			
	if your rate is not in the format please contact the VERA Epidemiology and Data team			
2	Look what stratification options are available			
3	Decide on your risk window		Complete cells Calculation sheet **D4**	The one's highlighted in green
4	Decide what stratification you will use			
	Options	No Stratification	Complete cells Calculation sheet! F4 and i4	The one's highlighted in green
		decade	Complete cells Calculation sheet! F6:15 and i6:15	The one's highlighted in green
		Over or under	Complete cells Calculation sheet! i6:15 B18 & F18:19	The one's highlighted in green
5	Get the appropriate doses from Qlik Sheet		Covid-19 Vaccine Surveillane Platform sheet name 10 year age groups	
	Download the table called Doses Delivered by age by right clicking and selecting three dots and then export data			
	Copy this table into the excel sheet called Doses		Sheet Doses A1:D12	
	If you want to only do first doses			
	Download the table called Doses Delivered by age (people) by right clicking and selecting three dots and then export data			
	Copy this table into the excel sheet called Doses		Sheet Doses F1:J12	

For assistance please contact the VERA Epidemiology and Data team; s22 @health.gov.au : s22 @health.gov.au : s22 @health.gov.au

	Age group	Risk window	Observed	Doses administered	Background incidence rate per 100 000 per annum	Person-years at risk per 100 000 person-years	Expected cases	Ratio O/E	Confidence interval		
		Days	All cases within the risk window and age stratum following the stated number of doses			= number of doses administered * Risk period after a dose 1 (42 days)	= [background incidence rate/100 000] * [person-time at risk]		90%		
	All ages	42	36	7379719	3.5	848609	30	1.21	0.90	1.60	
1	0-19yrs		4	29	8.3	3	0.0	14451.6	4936.37	33070.75	(4936.4 - 33070.7)
2	20-29yrs		7	147,587	8.3	16971	1.4	5.0	2.33	9.33	(2.3 - 9.3)
3	30-39yrs		2	941,587	2.3	108275	2.5	0.8	0.14	2.53	(0.1 - 2.5)
4	40-49yrs		16	1,368,153	7.2	157327	11.3	1.4	0.89	2.15	(0.9 - 2.1)
5	50-59yrs		5	2,600,967	5.8	299091	17.3	0.3	0.11	0.61	(0.1 - 0.6)
6	60-69yrs		1	1,506,699	1.8	173258	3.1	0.3	0.02	1.52	(0 - 1.5)
7	70-79yrs		0	380,383	1.3	43741	0.6	0.0	#NUM!	5.27	(0 - 5.3)
8	≥80yrs		0	158,503	1.4	18227	0.3	0.0	#NUM!	11.74	(0 - 11.7)
	Age not given		1								
	Total		36	7,103,908	8.3	816893	67.8	0.5	0.39	0.70	(0.4 - 0.7)

Age Bracket analysis

Age break	50	Less than-50	29	2,457,356	8.3	282577	23.5	1.2	0.88	1.69	(0.9 - 1.7)
5		Older than-50	7	4,646,552	8.3	534317	44.3	0.2	0.07	0.30	(0.1 - 0.3)

if([DI Perso AZ		COMIRNAT Cumulative	
0 - 9 yrs	15	29	44
10 - 19 yrs	23469	147587	171056
20 - 29 yrs	238577	941587	1180164
30 - 39 yrs	297306	1368153	1665459
40 - 49 yrs	248992	2600967	2849959
50 - 59 yrs	1443954	1506699	2950653
60 - 69 yrs	2419750	380383	2800133
70 - 79 yrs	2387012	158503	2545515
80+ yrs	1192509	275805	1468314
Age not given		6	0
-	2	0	0
	8251586	7379719	15631297

All doses using QLIK 10 years doses

if([DI Perso AZ		COMIRNAT Cumulative		=count(distinct [DI Person ID Encrypted])
0 - 9 yrs	15	27	42	42
10 - 19 yrs	21609	105511	127052	127052
20 - 29 yrs	191862	587769	778754	778754
30 - 39 yrs	236189	859513	1094247	1094247
40 - 49 yrs	170174	1554551	1722679	1722679
50 - 59 yrs	991568	949637	1937522	1937522
60 - 69 yrs	1735897	217461	1951348	1951348
70 - 79 yrs	1479354	89450	1567496	1567496
80+ yrs	736859	147193	883271	883271
Age not giv	0	5	0	5
-	1	0	0	1
	5563528	4511117	10062411	10062417

All doses using QLIK 10 years doses (people)

0	2	2
1860	42076	44004
46715	353818	401410
61117	508640	571212
78818	1046416	1127280
452386	557062	1013131
683853	162922	848785
907658	69053	978019
455650	128612	585043
0	1	0
1	0	0
2688058	2868602	5568886

The difference

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

Date	12/04/2024		Confidence Interval		95%
Single point analysis	Observed	Expected	O/E ratio	Lower CI	Upper CI
Enter the number of Observed events	15	1.67785351	8.94	5.00	14.75

Use .9 for small event numbers or .95 and enter as a decimal

Uses Poisson Exact Confidence Intervals

Under
Over
_

Broad age based analysis			Age Break	50	
	Observed	Expected	O/E ratio	Lower CI	Upper CI
Under_50	6	3	2.00	0.73	4.35
Over_50	6	3	2.00	0.73	4.35
Total	12	6	2.00	1.03	3.49

Detailed age based analysis

	Event	Doses			
0-9 Years	6	3	2.00	0.73	4.35
10-19 Years	6	3	2.00	0.73	4.35
20-29 Years	6	3	2.00	0.73	4.35
30-39 Years	6	3	2.00	0.73	4.35
40-49 Years	6	3	2.00	0.73	4.35
50-59 Years	6	3	2.00	0.73	4.35
60-69 Years	6	3	2.00	0.73	4.35
70-79 Years	6	3	2.00	0.73	4.35
80+ years	6	3	2.00	0.73	4.35
	54	27	2.00	1.50	2.61

Date	12/04/2024		Confidence Interval		90%

Use .9 for small event numbers or .95 and enter as a decimal

Under
Over
_

Single point analysis

	Event	Doses	O/E ratio	Lower CI	Upper CI
Enter the number of events	1	51973	1.92	0.10	9.13

Uses Poisson Exact Confidence Intervals

Broad age based analysis — Age Break 50

	Event	Doses			
Under_50	6	201069	2.98	1.30	5.89
Over_50	57	3205192	1.78	1.41	2.22
Total	63	3406261	1.85	1.48	2.28

Detailed age based analysis

	Event	Doses			
0-9 Years	6	201069	2.98	1.30	5.89
10-19 Years	6	201069	2.98	1.30	5.89
20-29 Years	6	201069	2.98	1.30	5.89
30-39 Years	6	201069	2.98	1.30	5.89
40-49 Years	6	201069	2.98	1.30	5.89
50-59 Years	6	201069	2.98	1.30	5.89
60-69 Years	6	201069	2.98	1.30	5.89
70-79 Years	6	201069	2.98	1.30	5.89
80+ years	6	201069	2.98	1.30	5.89
	54	1809621	2.98	2.35	3.74

Product Information (PI) documents, published on the TGA website, are the most up-to-date reference for adverse events associated with individual COVID-19 vaccines products. The following document may refer to statistical signals that were not confirmed for further review, that were not found to be clinically meaningful, or that were unable to be validated with population-evidence sufficient to confirm an association. Internal TGA Standard Operating Procedures (SOP) and Work Instructions (WI) are designed for use by persons who have undertaken formal TGA induction and on-the-job training. It would be inappropriate for these documents to be utilised as written by someone who is not orientated to the science of pharmacovigilance and the work of the organisation.

INTERNAL USE ONLY

Australian Government
Department of Health
Therapeutic Goods Administration

Pharmacovigilance Branch

Work Instruction (WI)

Name of procedure / policy	Assessment of Individual Adverse Event Following Immunisation (AEFI) reports against Vaccine Safety Investigation Group (VSIG) criteria by the Vaccine Surveillance and Targeted Review Stream (Vaccine STRS)
Applicable to	Vaccine STRS
TRIM reference	D23-5292900
Written by	Vaccine STRS
Authorised	
Date issued	
Version no.	2.0

CONTENTS

PURPOSE 3

Process: assessing AEFI reports against VSIG criteria 4

Legislative Framework 4

Step 1: Referral of AEFI reports by AEMDS to Vaccine STRS 4

Step 3 – Requesting further information 9

Step 4: Assessment of the AEFI report against VSIG criteria 10

Step 5: Advice to the Vaccine STRS Stream Lead 19

Step 6: Updating the ICSR (AEFI report) in AEMS 19

The role of Coroners in Australia 20

Process outside the scope of this WI 20

Medicine adverse event reports 20

References 21

VERSION HISTORY 22

PURPOSE

This Work Instruction (WI) provides a standardised approach to the assessment of individual Adverse Event Following Immunisation (AEFI) reports against Vaccine Safety Investigation Group (VSIG) criteria by the Vaccine Surveillance and Targeted Review Stream (Vaccine STRS) within the Medicines and Vaccines Investigation and Surveillance (MaVIS) section in the Pharmacovigilance Branch (PB).

AEFI reports are referred to Vaccine STRS by the Adverse Event and Medicine Defects Section (AEMDS) for assessment against VSIG criteria. The AEMDS ICSR (Individual Case Safety Report) AEFI Referral and Escalation process is filed in TRIM: D23-5141841.

For **non-COVID-19 vaccines,** fatal AEFI reports and AEFI reports where the patient received care in an Intensive Care Unit (ICU)/Paediatric Intensive Care Unit (PICU) are referred to Vaccine STRS by AEMDS for assessment against VSIG criteria.

For **COVID-19 vaccines**, the relevant serious and fatal reports are referred by AEMDS to the PB PMA (Principle Medical Advisors) for their review and decision about whether the report is subsequently referred to Vaccines STRS for assessment against VSIG criteria.

Regardless of the referral process and whether the vaccine is a COVID-19 vaccine or non-COVID vaccine, once an AEFI has been referred to Vaccine STRS for assessment against VSIG criteria, this WI should be used for completing the assessment.

The aim of this referral and assessment process is the early detection of AEFI reports that meet VSIG criteria, facilitating appropriate and quick regulatory and programmatic responses. This allows for timely action to individual AEFI reports that have the potential to shift the benefit-risk profile of a vaccine, and/or threaten public confidence in immunisation.

The World Health Organisation (WHO) global manual on surveillance of adverse events following immunization[1] recommends that investigations requiring the services of national-level experts (like the VSIG) need to be prioritised. The manual notes that maintaining an active expert committee like the VSIG is a challenge, and that only the most critical cases of national concern be referred[1]. For this reason, this WI only applies where a single AEFI report has the potential to change the entire benefit-risk balance of the vaccine or threaten public confidence in vaccine safety more generally.

It does not apply to clusters of reports that would not individually meet VSIG criteria, but may, in combination, constitute a safety signal. These signals are detected through a variety of other activities undertaken by Vaccine STRS, such as disproportionality analysis (DPAR), environmental scanning, and notifications from international regulatory counterparts.

Sustainability of this internal TGA process depends on the availability of adequate resourcing. In the context of limited staff with expertise and increasing report volumes during the roll-out of COVID-19 vaccines in Australia throughout 2021-22, it was important that only AEFI reports likely to meet VSIG criteria were referred from AEMDS to Vaccine STRS for assessment by clinical evaluators. For this reason, a clear threshold describing which reports are referred was determined. For non-COVID-19 vaccines the threshold (those resulting in ICU/PICU admission or death) was selected in April 2022 based on evidence (a review of all reports referred between September 2021 – February 2022), and agreement between the AEMDS and Vaccine STRS teams, and for COVID-19 vaccines the threshold was agreed by the PB Branch head in consultation with PB PMA and AEMDS. [TRIM D23-5161159]

This WI should be read in conjunction with the Expectedness assessment WI (D18-11364307), which provides detailed instructions for establishing whether an AEFI is adequately described in the vaccine's Product Information (PI); and the WHO Global manual on surveillance of adverse events following immunization[1], which describes the internationally-agreed approach to causality assessment

for AEFI by National Regulatory Agencies (NRAs) like the TGA. An overview of the VSIG process is provided in the VSIG WI (D21-2140941).

Process: assessing AEFI reports against VSIG criteria

Legislative Framework

Under the Therapeutics Goods Act 1989, the TGA is responsible for ensuring the ongoing safety, quality, and efficacy of vaccine products on the Australian Register of Therapeutic Goods (ARTG) and therefore has legal responsibility for acting on vaccine product safety issues within Australian law.

The TGA has the legislative power to undertake rapid regulatory action to mitigate detected risks, such as updates to product information, updates to a vaccine's risk management plan, imposing conditions of registration, facilitating distribution of Dear Health Care Professional Letters or publication of Safety Advisories on the TGA website, and/or recall action. The TGA is therefore an appropriate focal point for vaccine product safety in Australia.

The TGA applies a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy. The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines, vaccines, medical devices and biologicals.

The role of the vaccines team in PB of the TGA is to monitor the safety of vaccines, and to contribute to a better understanding of their possible adverse effects when they are used outside the controlled conditions of clinical trials. As part of this post-market signal investigation work, the TGA use a WHO Organisation (WHO) causality assessment framework to perform causality assessments AEFI reports.

Step 1: Referral of AEFI reports by AEMDS to Vaccine STRS

AEFI reports submitted to the TGA are stored in the AEMS database and entered by the database entry team in the AEMDS.

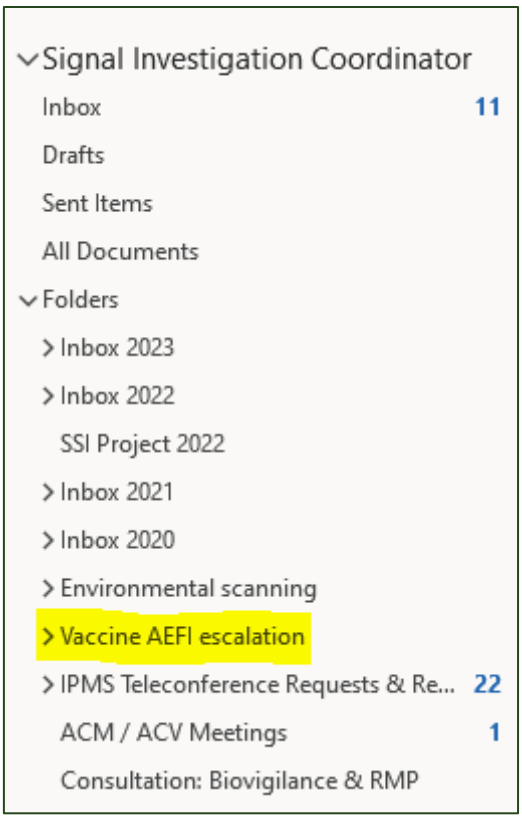
The AEMDS database entry team refer AEFI reports to Vaccine STRS for assessment against the VSIG criteria based on the criteria described in the AEMDS ICSR Referral and Escalation Process (TRIM: D23-5141841].

These reports are referred by the AEMDS from the ADR reports inbox (adr.reports@healthgov.au) to Vaccine STRS by emailing the Signal Investigation (SI) Coordinator (si.coordinator@health.gov.au) and copying in the Vaccine STRS Stream Lead.

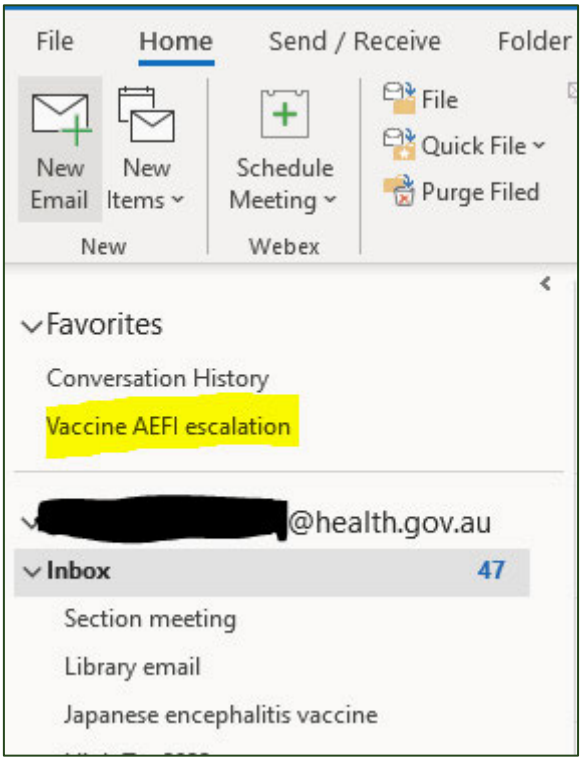
The recommended format of the subject line of the referral email is: AEFI – SERIOUS – [Tradename] – [insert reaction term] – [age & gender] – [State] – AU-TGA-0000#####. This format will assist the SI Coordinator with the early identification of the email and fast track the referral to Vaccine STRS.

The body of the email will contain a link to the ICSR in the CRM database. It may also contain some brief dot points summarising the case.

The SI Coordinator inbox (si.coordinator@health.gov.au) is a generic inbox that is monitored during business hours. Upon receipt of the VSIG assessment referral email, the SI Coordinator moves the email (marked as unread) into the 'Vaccine AEFI escalation' subfolder of the SI Coordinator inbox which is designated for communication with Vaccine STRS.



Vaccine STRS evaluators (with the *Vaccine AEFI escalation* subfolder saved in Favourites in their personal outlook inbox) can see at a glance when a new AEFI report has arrived for assessment. Vaccine STRS evaluators should ensure that they have added this subfolder to their personal Outlook inbox. Favourites are displayed at the top of the Outlook inbox. The instructions for this process are filed in TRIM: D22-5079991.



The Vaccine STRS roster allocates an evaluator to monitor the Vaccine AEFI escalation subfolder for email assessment referrals during business hours. The roster and this work instruction are located on the MaVIS page of the Pharmacovigilance Branch SharePoint site: https://healthgov.sharepoint.com/sites/MVIS/STRS%20AEFI%20WI%20DRAFT/Forms/AllItems.aspx

Allocation of Assessments: Each evaluator only does **1 assessment per week**. If a second+ assessment comes through, the evaluator assigned for that day is to liaise with the evaluator from the previous day (and reassign the assessment to them). If the evaluator from the previous day has already been assigned an assessment that week, then the evaluator is to liaise with the next evaluator assigned to the roster, etc.

As the Vaccine STRS Stream Lead is also copied into these emails, they will also be alert to a new AEFI referral, and can oversee workflow and workloads within the team, including allocation of the referral to a particular evaluator if required.

Step 2: Record keeping

Part A: Check for Duplicates

Before, you start the assessment, it's important to check that the report is not a duplicate report, that is an AEFI that has already been reported to the TGA and an assessment may already have been conducted. This is especially relevant if the assessment is for a fatal or very serious AEFI that occurred more than 6 months ago as fatal and serious AEFIs are usually reported to the TGA close to the date of the date of reaction or outcome.

The following steps will help you find the original report in AEMS, if it exists and exclude the possibility of a duplicate report and assessment.

In QLIK, conduct a search using the reported trade name and reaction term. For fatal AEFI reports use the reported trade name and outcome=fatal.

- You can reduce the number of reports identified in the search by adding in the search parameters of state, gender and age provided in the AEFI report you are assessing.
- If you think you have found a possible duplicate, read the case narrative and check important dates and the reaction details to confirm that it is a duplicate.
- If the report you have been asked to assess is a duplicate, forward the referral email to the ADR report email address and briefly explain why you think it is a duplicate (e.g. same DOB, onset date, reaction, sex, state). Provide ADR reports team with a link to the original report so that the new report can be marked as a duplicate and related to the original.
- You can then file your email to ADR reports (which will contain the original referral) in the TRIM container which was automatically created by AEMS for the referred duplicate AEFI report (not the TRIM container for the original report).
- Email the Vaccine STRS Stream Lead to notify them that the report is a duplicate noting whether an assessment has already been completed and if further information is not included in the report that a new assessment is not required.
- Please Note: An assessment against VSIG criteria is not required if the duplicate contains no new information, as the report would have undergone assessment according to TGA processes in place at the time when the original historical report was received.

Part B: Creating and linking a TRIM File

Although the storage in TRIM for each assessment looks complex there are good reasons for saving the information alternatively within several records in TRIM.

All the information about the assessment of serious AEFI process is stored in TRIM under the main place holder Serious AEFI Investigation Team: PH20/4870.

Within this main placeholder are placeholders named for the different vaccine antigens. These placeholders are libraries of knowledge and great resources for any potential future investigations of serious adverse events for each vaccine and are helpful with Freedom of Information (FOI) requests.

Also within the main place holder is a TRIM folder THERAPEUTIC GOODS REGULATION - Reviews (post market) - Serious AEFI Investigation Team – Year (e,g 2023) referrals for assessment against the VSIG criteria: E22-505282**.** This folder is used to quantify the working being undertaken by the team (team metrics) and is also helpful with FOI requests. A new folder must be created each calendar year.

Before you begin your assessment against VSIG criteria, complete the following record-keeping steps:

1. Create a new TRIM container by selecting New– Record– Digital File and use the Naming Convention – Therapeutic Goods Regulation – Reviews (post market) – Serious AEFI Investigation Team – Fatal or Non-fatal (*as appropriate*) *insert TGA ADR number – insert vaccines – insert Month and year.* All correspondence pertaining to the assessment of the AEFI report against VSIG criteria should be saved to this new TRIM container.
2. Then relate (alternatively within) this container to the following three containers:
    - the original AEFI report TRIM folder which is automatically created by AEMS. This can be located by performing a TRIM 'any word' search, and typing in the TGA case report number, beginning in '0000'. The TRIM container linked to AEMS will be titled according to the following naming convention:
      THERAPEUTIC GOODS REGULATION-Reporting-Adverse Event Individual Case Safety Report (ICSR) AU-TGA-0000 etc
    - the relevant vaccine placeholder (please create new PH if none are relevant)– these are named by the vaccine antigen administered. For example meningococcal vaccines (PH21/38380) or varicella Vaccines (PH20/5130). If multiple vaccines are co-administered, then use the Multiple Vaccines placeholder at TRIM Ref (PH20/4889). If a relevant placeholder is not available, you will need to create a new one and save this alternatively within the main place holder: PH20/4870
    - the TRIM container that contains all reviews referred for assessment against the VSIG criteria for the calendar year. For example for 2022: TRIM E22-505282. This allows the STRs Stream Lead to count your assessment for inclusion in team metrics, easily locate your assessment in the future, and stores your work for education and training purposes.

Save the AEFI referral email to the new TRIM container that you have created for this AEFI report and move the email of the Vaccine AEFI Escalation inbox folder into your personal email inbox to keep the Vaccine AEFI Escalation inbox folder clear for new/unactioned cases.

Part C: Adding the new TRIM container number to the AEFI report in AEMS

You then need to add the number of the newly created TRIM container to the AEFI report in AEMS. This notifies everyone accessing the AEFI report that an assessment against the VSIG criteria is being conducted and where it is located in TRIM. The steps for this are below:

1. Open the AEMS database and type in the TGA ICSR Identifier case number in the search box



2. Click on <u>current version</u> which will open the report with all the latest information visible:



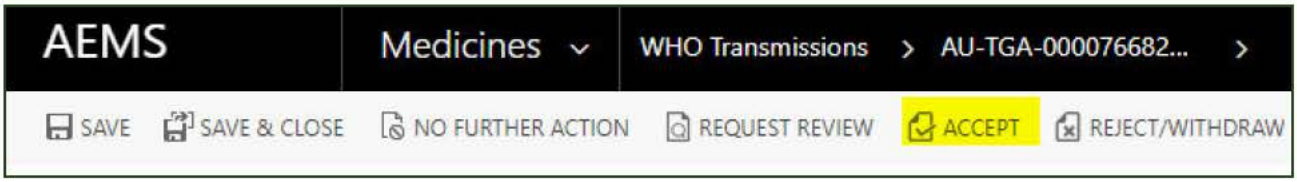
3. Click on the Amend ICSR which is located on the top scroll bar of the AEFI report. This gives you access to edit the report including adding in the information about the assessment.



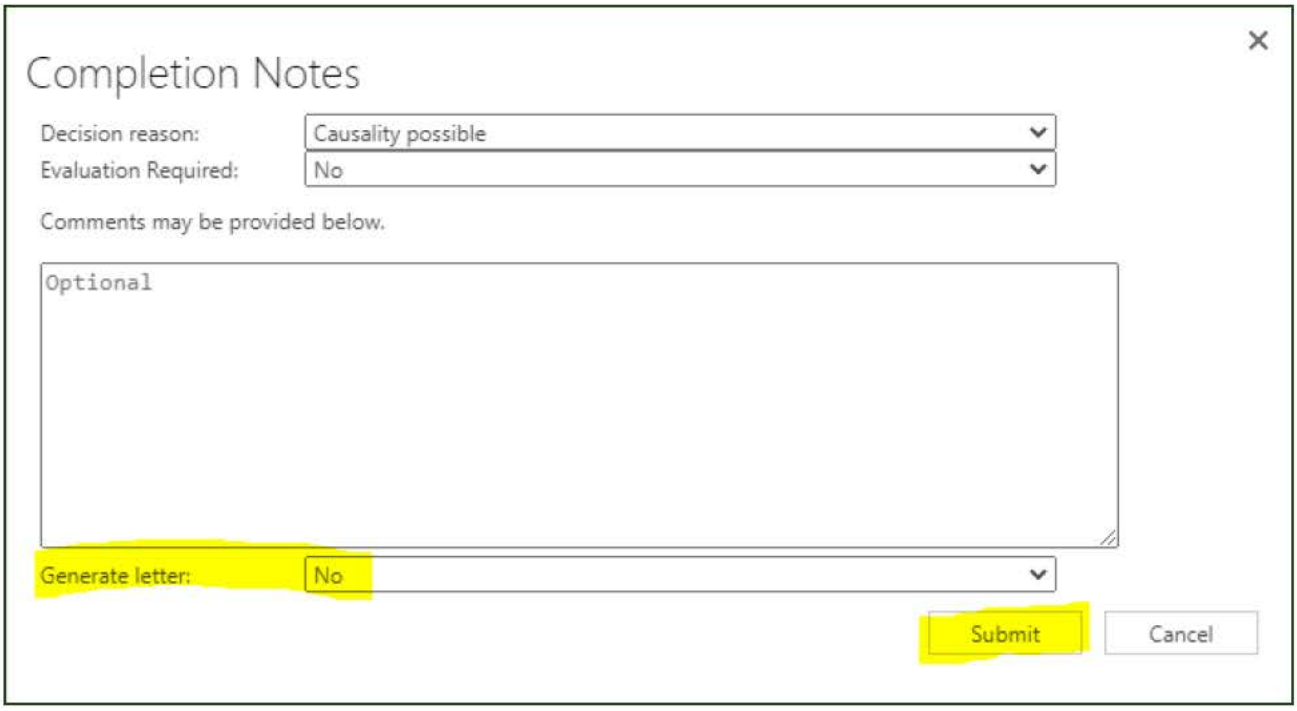
4. Scroll down to Case Narrative and keeping scrolling until you find the Reporters comments. Click under the reporters comments add in the information about the VSIG assessment including the relevant TRIM container:



5. Once this is completed you must then accept the report to push it back into the AEMS database. Accepting the report in AEMS must be completed each time you amend the AEFI report. The following steps are required to complete this:
    1. Return to the Top scroll bar of the report and click accept



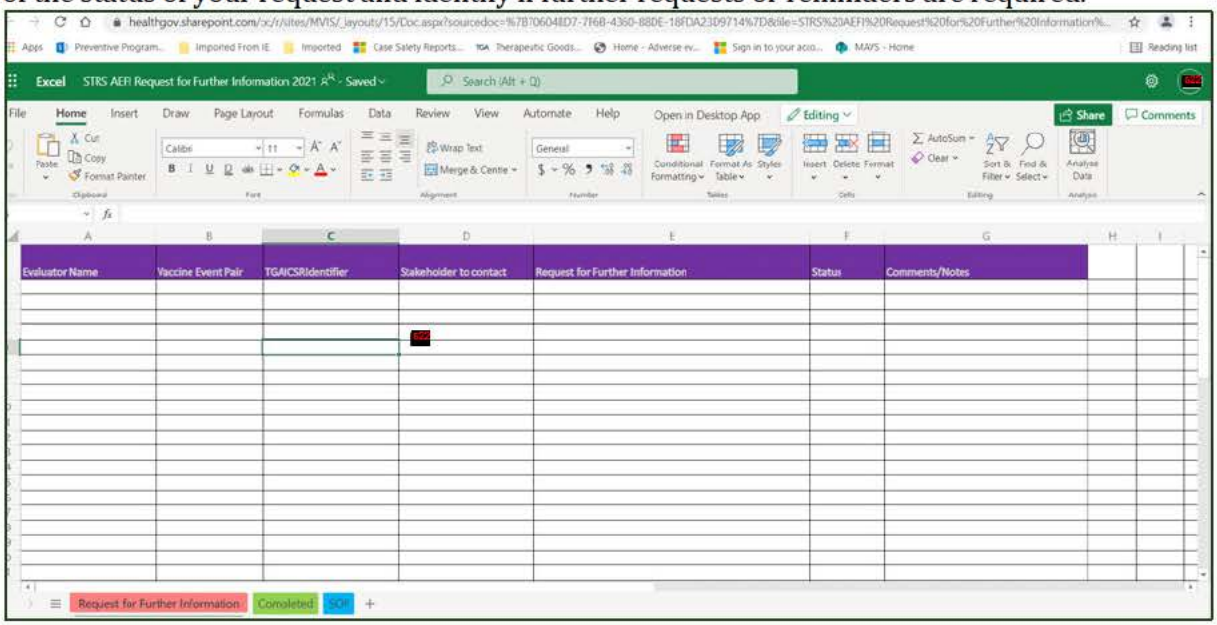
    2. The Completion Notes pop up is then visible. Half way down this pop up there is a Generate Letter drop down list. Ensure that <u>No</u> is selected in the Generate letter dropdown list and then select Submit. The AEFI report is then pushed back into AEMS



Step 3 – Requesting further information

If during the assessment process you decide that you require further information to assist with your assessment, a request for information can be sent to the relevant state or territory public health unit*. The AEFI Coordinator (as of April 2023 this position is held by s22 [redacted]) oversees requests for information and the process is described at: D21-2990399.

Complete the STRS AEFI Request for Further Information (RFI) Spreadsheet on the MaVIS SharePoint site: https://healthgov.sharepoint.com/sites/MaVIS as per the instructions. This will enable visibility of the status of your request and identify if further requests or reminders are required.



Ensure you also send an email to the AEFI Coordinator notifying them of an update to the spreadsheet and describing exactly what information is required and which state or territory the request is to be sent to. The AEFI Coordinator will then send out the request and you will be copied into the RFI email.

The AEFI Co-ordinator will send the evaluator an email once a response to the RFI has been received. The AEFI Coordinator saves all received RFI emails to the TRIM file created for this assessment.

Evaluators review the response to the RFI and assess or re-assess the AEFI report against the VSIG criteria including the newly acquired information following the instructions below in '*Step 4: Assessment of the AEFI report against VSIG criteria'.*

If a response to the request for information has not been received within a week (this timeframe may vary), you can discuss this with the AEFI Coordinator who will send out a reminder email. If after three requests, the information has not been received the request process is considered completed. This information is added to the RFI Spreadsheet, and all the request emails are filed in the assessment TRIM container. The AEFI coordinator overseas this process in consultation with the evaluator undertaking the assessment. As per MO4 email [TRIM: D21-3405399], assessments can be marked as completed after 3 contacted attempts for information. It is then up to the JIC to submit the requested information without TGA follow up.

***** Most vaccine AEFI reports are submitted to the TGA by the relevant state and territory public health unit. When serious AEFI reports are submitted to the TGA from other sources – for example consumers or health professionals, the TGA notifies the state and territory health department via a section 61 notification email. Sub section 61(3) of the *Therapeutic Goods Act (1989)* gives the TGA the authority to release private information to state and territory health departments. To review the conditions of this release, see: https://www.legislation.gov.au/Details/C2019C00066

Therefore, if the initial AEFI report not was submitted to the TGA by a state or territory public health unit, the request for further information may need to include a Section 61 email to firstly notify them of the AEFI report. The AEFI Coordinator will check with the AEMDS team to determine if this has already been completed and then action herself if needed.

Contacting the coroner for information

For most assessments, the requests for information including requests for the autopsy and / or the coroner's report will be made to the relevant state or territory public health unit. If the relevant state or territory public health unit is unable to provide this information or refers you to the coroner, please discuss this with the VSTRS MO4. The most recent wording cleared by TGA legals for your requests: D20-3460954. When drafting your request, consider if you require formal documentation such as a death certificate or if the documented cause of death is sufficient to assist your assessment. The contact information for each state or territory coroner is at: D22-5071463 .

If this information is required urgently (e.g. for a VSIG), each state and territory have their own specific convention for contacting the Coroner directly for information. The information for contacting the coroner is at TRIM: D22-5071463 In these situations, you are asked to discuss your request with the Vaccine STRS Stream Lead who will direct this request as appropriate.

Step 4: Assessment of the AEFI report against VSIG criteria

The role of the Vaccine STRS evaluator is to assess if the AEFI report requires immediate convention of the Vaccine Safety Investigation Group (VSIG). If at any time during the assessment process you consider that a VSIG **may** be required, you are asked to notify the Vaccines STRS Stream Lead as early as possible (even before your assessment is complete).

At the end of this section is a template that can be used to document your findings and recommendations. The template should be copied and pasted into the email referral that you forward to the Vaccine STRS Stream Lead for approval / clearance when the assessment is complete.

The referral email from AEMDS is the first email in the assessment email trail. By selecting forward in response to this email, you can paste the template into the email where you then conduct your assessment. When your assessment is complete you send this email trail to the Vaccine STRS Stream Lead for approval and file the email in your newly created assessment TRIM container. When your assessment is approved, you will receive the approval email from the Vaccine STRS Stream Lead which includes the whole of the email trail. You then file this email in TRIM adding APPROVED at the beginning of the subject of the document as it is filed in TRIM. When the assessment is completed and approved, you then update the name of the TRIM container by adding COMPLETED at the end of the title.

It is recommended that new Evaluators read through some previous assessments for the same vaccine. These can be found in the relevant vaccine placeholder, as outlined in 'Step 2: Record keeping' above. Examples of previous assessments from 2021, 2022 and 2023 can be found in TRIM under placeholder PH20/4870.

Part A: Is the case eligible for assessment?

It is recommended that the Evaluator first check whether the case is considered eligible for assessment (criteria 3 of the VSIG WI D21-2140941). The four elements that are required (name of the vaccine, confirmation that the vaccine was administered before the reported AEFI, a valid diagnosis for the reported AEFI, and adequate supporting information).

If the case is considered ineligible for assessment, it might be important to obtain further information about the case to allow a future assessment against VSIG criteria. This might be warranted if the event appears (based on information currently available) to be an AEFI of concern. Part B of the assessment (below) should, therefore, still be undertaken, based on the information available.

Part B: Has an AEFI of concern been identified?

The next step is confirming that an AEFI of concern has been identified. An AEFI of concern needs to fulfil three criteria:

1. Is serious, AND
2. Is unexpected, AND
3. Does not have an obvious non-vaccine cause

The VSIG work instruction outlines what constitutes a serious AEFI (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).

The VSIG work instruction also outlines that if there is 'Strong evidence against a causal association' [a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) against a causal association between the vaccine and the event] this leads to the VSIG classification of 'Inconsistent causal association to immunization'. Therefore, if the vaccine-event pair you are assessing, has already been investigated and it has been confirmed (e.g., in the Australian Immunisation Handbook) that a safety issue has not been identified, your conclusion for this section can also be that an AEFI of concern has not been identified.

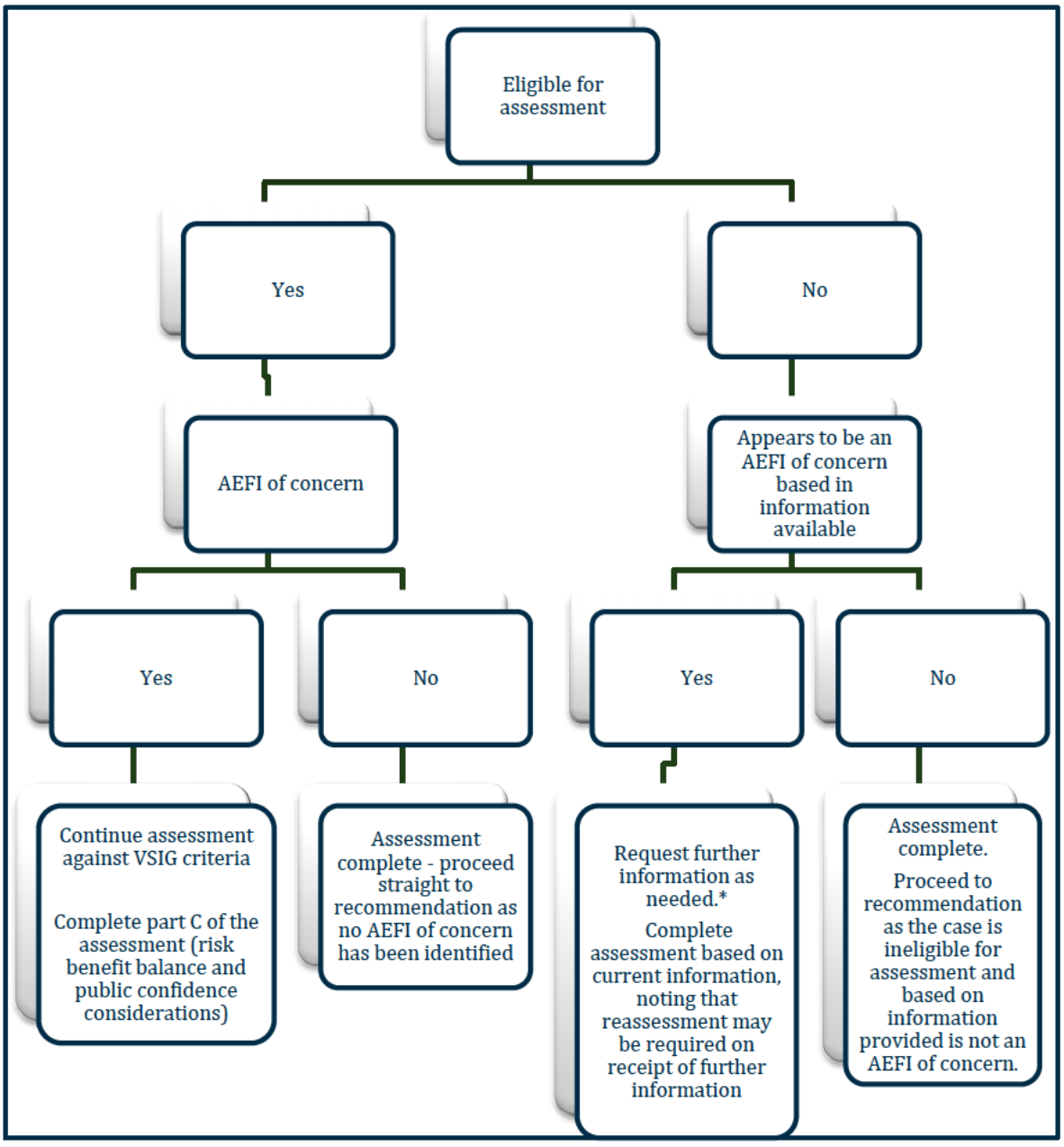
Assessment of expectedness is as per the Work Instruction on Expectedness Assessment at D18-11364307 – noting that the CIOMS V working group advises that expectedness should be based on the

inclusion of an ADR term in Section 4.8 of the Product Information (PI) (that is, an unexpected AEFI is one that is not included in the PI for the product). The work instruction also covers questions of changes in frequency for terms already included in the PI, as well as considerations of the need for more specific preferred terms than those already included in the PI (specificity).

Inclusion of the AEFI in Section 4.4 Special Warning of the PI doesn't indicate expectedness under the CIOMS V working group criteria. However, it does indicate that risk mitigation is in place and for the purposes of this VSIG assessment, the inclusion of an AEFI in Section 4.4 indicates that it is unlikely to be considered an AEFI of concern.

An example of an obvious non-vaccine cause is that the reported AEFI was encephalitis, and the clinical information (such as lumbar puncture results and hospital discharge summary) shows that herpes simplex virus was responsible rather than vaccination.

Consideration of parts A and B



*Request further information to allow future re-assessment against VSIG criteria if required based on the information provided.

Follow the instructions in '*Step 3 – Requesting further information*' above. Information that may be required:

- Name of the vaccine
- Confirmation that the vaccine was administered before the AEFI, including the exact date of vaccination AND the date of the onset of symptoms
- Pathology reports, radiological reports, hospital discharge summaries, GP and specialist letters

The 'assessment of AEFI against VSIG criteria' should continue based on the information you currently hold. Once completed, forward your assessment to the Vaccine STRS Stream Lead with your

recommendation based on the current information and indicating that further information has been requested which may require you to reassess the AEFI report when this information has been received and possibly amend your recommendation. For example:

The report submitted to the TGA does not include adequate information to investigate or assess the case. At present, no supporting documentation including hospital or doctors' notes were submitted with the AEFI report.

The assessment against the VSIG criteria and my recommendation are based on the information that is currently available to the TGA. The TGA will request further information from XXX and when more information is submitted to the TGA, the assessment will be updated and resubmitted to for your approval as required.

Once you receive the requested additional information, you can reassess the AEFI report against VSIG criteria which may (or may not) alter your initial recommendation. On completion of your reassessment, you add this information to the email trail and send back to the Vaccine STRS team lead for approval.

Ensure that any correspondence containing information regarding the AEFI report is attached to the AEFI report in AEMS, which is automatically filed in the AEFI TRIM container.

Part C: Risk benefit balance and public confidence considerations

If an AEFI of concern has been identified, and the case is eligible for assessment, the next step is to consider whether the following VSIG criterion is met:

- Has the potential to change the favourable benefit-risk balance of the vaccine in a National or State Immunisation program OR
- Could threaten public confidence in vaccine safety

As mentioned previously, the aim of assessing serious AEFI against VSIG criteria is not to determine causality, however, some of the following considerations may be useful when assessing the risk-benefit balance and public confidence in the vaccine:

- if the vaccine is part of the NIP/how commonly it is used
- is it a new vaccine?
- level of public concern (often more concern about AEFIs related to new vaccines)
- severity and impact of AEFI
- importance of vaccine for Indigenous health
- other cases of vaccine-AEFI pair (using AEMS data can briefly assess the number and consistency of reporting)
- PRR value from DPAR (is there a disproportionate association between the vaccine-AEFI pair beyond this individual case)
- if there is information about the AEFI- vaccine pair in the literature
- if there is information about the AEFI-vaccine pair in international PIs

Template for assessment

Note, not all sections of the template will need to be completed depending on the case.

PART A: CASE, VACCINE and REACTION DETAILS	
AEMS CASE NUMBER & LINK	
DATE OF BIRTH/ AGE	
GENDER	
ETHNICITY	
JURISDICTION	
DATE OF AEMS REPORT	*[date report was created in AEMS]*
DATE OF REFERRAL FROM AEMS	
DATE OF ASSESSMENT	*[date this form is completed]*
REPORTER	*[Indicate whether consumer/ patient or State JIC or health professional etc]*
VACCINE INVOLVED	
TRADE NAME OF THE VACCINE	
DATE VACCINATION RECEIVED	
DOSE NUMBER IN SERIES	
BATCH NUMBER	
NATIONAL IMMUNISATION PROGRAM (NIP) SCHEDULE **or** **COVID-19 Vaccine roll-out status** *[Last updated date, and trim link]*	*[Indicate when the vaccine in question is recommended to be given according to the NIP schedule or COVID-19 vaccine roll out recommendations]*

DATE OF SYMPTOM ONSET	
AEFI PTS CODED	
MANAGEMENT OF THE EVENT	*[e.g., self, ED presentation, GP management, hospital admission]*
OUTCOME OF THE EVENT	*[e.g., resolved, resolving, fatal]*
OTHER DETAILS ABOUT THE REACTION FROM THE CASE NARRATIVE	

PART B	
Australian product information	
Name, version, date last updated, TRIM link	Indicate whether the AEFI is listed in any sections of the PI (eg 4.2, 4.4, 4.8)
If the AEFI is adequately described in the PI, you do not need to complete the rest of Part B and can proceed to Part C. There are some instances where you might decide to check and document the frequency of the AEFI via an AEMS search even when it is listed in the PI.	
Australian immunisation handbook (AIH) information	
Chapter, date last updated, TRIM link	Indicate whether the AEFI is described in the AIH or whether there is information about evidence against causation
If the AIH describes that there is strong evidence against a causal association, then the Evaluator MAY conclude that an AEFI of concern hasn't been identified. If this is the case, the rest of Section B does not need to be completed. Proceed to Section C.	
The AEMS search, VigiBase search, Literature Search and International PI search boxes below are optional. If the individual AEFI report appears that it might meet VSIG criteria, the evaluator should complete any or all these boxes that they feel are required to confidently determine if VSIG criteria are met.	
AEMS SEARCH	

SEARCH DETAILS	*[This may be required if there is concern about an increased frequency of an AEFI that is listed already in the Aus PI]*
VIGIBASE SEARCH	
SEARCH DETAILS	
LITERATURE SEARCH	
SEARCH DETAILS	
INTERNATIONAL PIS	
NAME, VERSION, DATE LAST UPDATED, TRIM LINKS	

SECTION C: SUMMARY OF ASSESSMENT	
IS THE CASE ELIGIBLE FOR ASSESSMENT?	Yes/ No If no, what information is missing?
AEFI OF CONCERN	
IS THE AEFI SERIOUS?	Y/N and briefly explain
IS THE AEFI UNEXPECTED?	Y/N and briefly explain
IS THERE AN OBVIOUS NON-VACCINE CAUSE?	Y/N and briefly explain
IS THERE STRONG EVIDENCE AGAINST CAUSATION?	Y/N and briefly explain
HAS AN AEFI OF CONCERN BEEN IDENTIFIED?	
1. **NO**	Include a brief justification
2. **YES, A POTENTIAL AEFI OF CONCERN HAD BEEN IDENTIFIED BASED ON INFORMATION CURRENTLY PROVIDED. A REQUEST FOR FURTHER INFORMATION**	Include a brief justification

HAS BEEN SENT AND REASSESSMENT MAY BE REQUIRED ON RECEIPT OF FURTHER INFORMATION.	
3. YES, AND NO FURTHER INFORMATION IS REQUIRED	Include a brief justification

1. If an AEFI of concern has not been identified, do not complete the next table (benefit-risk and public confidence) but proceed straight to the recommendation
2. If an AEFI of concern has been identified (based on current information) but there is insufficient information to complete the assessment, do not complete the next table until further information has been received.
3. If an AEFI of concern has been identified and the case has sufficient information, proceed to the next table.

SECTION D: BENEFIT-RISK AND PUBLIC CONFIDENCE	
Does this individual AEFI report have the potential to change the favourable benefit-risk balance of a vaccine in a National or State Immunisation Program?	Y/N and details
Does the individual AEFI report have the potential to threaten public confidence in vaccine safety?	Y/N and details

Recommendation
e.g., *I have considered this report against the criteria for convening the Vaccine Safety Investigation Group (VSIG), outlined at TRIM D18-10878760. In my opinion, based on the information above, this individual Adverse Event Following Immunisation report* ***does not meet the criteria for convening VSIG*** *because* *- an AEFI of concern has not been identified and the case is considered ineligible for assessment OR* *-an AEFI of concern has not been identified OR* *-an AEFI of concern has been identified but this report does not have the potential to change the favourable benefit-risk balance of a vaccine in a National or State Immunisation Program or to threaten public confidence in vaccine safety.* *e.g., I have considered this report against the criteria for convening the Vaccine Safety Investigation Group (VSIG), outlined at TRIM D18-10878760. In my opinion, based on the information above, this individual Adverse Event Following Immunisation report* ***does meet the criteria for convening VSIG b****ecause the case is eligible for assessment, an AEFI of concern has been identified and the AEFI has the potential to change the favourable*

benefit-risk balance of a vaccine in a National or State Immunisation Program or to threaten public confidence in vaccine safety.

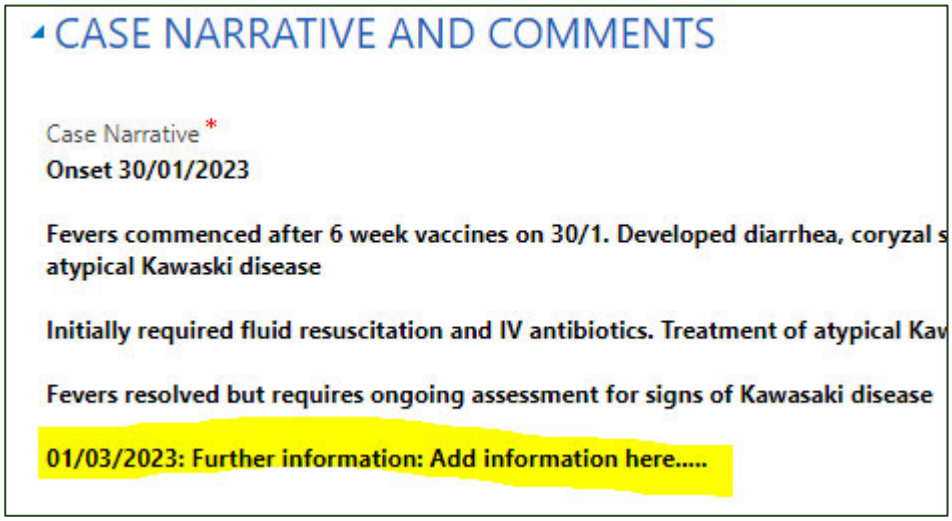
Step 5: Advice to the Vaccine STRS Stream Lead

If VSIG criteria are met, the Vaccine STRS Stream Lead will escalate the AEFI report to the Principle Medical Officer and PSAB Branch Head, as appropriate. The process for convention of the VSIG is described in the Fatal AEFI Workflow at D21-2125934

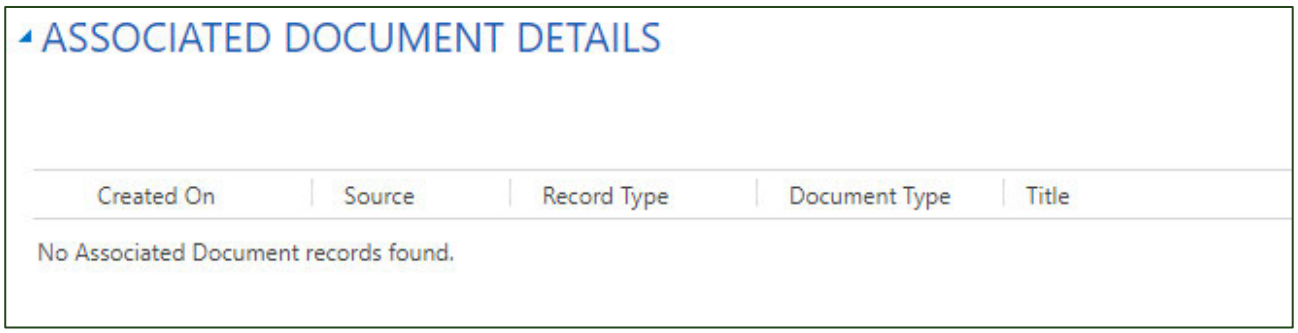
If VSIG criteria are not met, a record will be created (in the form of an email from the Vaccine STRS evaluator to the Vaccine STRS Stream Lead), as described in *Step 4: Assessment of the AEFI report against VSIG criteria* above.

Step 6: Updating the ICSR (AEFI report) in AEMS

If important follow-up information has been obtained during assessment of an AEFI report against VSIG criteria, it is important that the case narrative section of the ICSR in AEMS is updated to reflect this. You may choose to update the narrative of the ICSR in AEMS yourself, or you can email AEMDS via adr.reports@health.gov.au with a request for them to update the narrative. The request email must include the exact wording for inclusion in the narrative. Please note, for legal reasons, information that is obtained via state and territory coroners by the TGA must not be included in AEMS. This information is filed in the AEFI report TRIM container.



Be careful to omit any detail that would render the patient potentially identifiable from the case narrative section, including names of hospitals, places, people (including treating doctors, patients and family members) and very rare conditions, as well as dates. Attach the complete information usually contained in an email to the AEFI report in AEMS (scroll to *Associated Document Details*) which will then automatically file the information in the AEFI report TRIM container.



The AEFI report will be de-identified and published in the Database of Adverse Event Notification (DAEN) on the TGA's website 14 days after it is included in AEMS. The DAEN is available at: www.tga.gov.au/database-adverse-event-notifications-daen . Publication of a report in the DAEN does not mean that the vaccine caused the adverse event, but simply reflects the observations of the person who reported the event.

All fatal AEFI are included in the TGA's internal and external safety monitoring data, even if a coroner or VSIG has concluded it is unrelated to vaccination. For this reason, the causality field of the ICSR is usually left as 'possible' and does not need to be updated once the assessment against VSIG criteria is complete.

The role of Coroners in Australia

The TGA does not undertake autopsies, request coronial investigations, or make formal determinations of the cause of death. In Australia, coroners and treating doctors perform this role. The TGA is not responsible for regulating health professionals or clinical practice. While the process of causality assessment involves determining the possibility of a causal relationship between a vaccine product and a particular adverse event, it does not involve making a formal determination of cause of death, investigating the circumstances surrounding a death, or investigating any clinical practice issues related to appropriate administration of vaccine or clinical management of adverse events. While the TGA works closely with state and territory Coroners, it is important that VSIG causality assessment panels and all other causality assessment processes undertaken at the TGA do not interfere with or unduly influence open Coronial proceedings.

Process outside the scope of this WI

Medicine adverse event reports

While the TGA's Adverse Event Monitoring System (AEMS) includes reports for both medicines and vaccines, this WI only describes the process for assessing adverse event reports pertaining to vaccines once referred to Vaccine STRS for assessment against VSIG criteria.

A much higher level of risk is acceptable for a medicine compared to a vaccine, as vaccines are administered to healthy people for the prevention of disease, while most medicines are used to treat or control disease.

The majority of non-COVID vaccines are administered to infants, with a large number given as part of the National Immunisation Program (NIP) Schedule for children placing them under higher public scrutiny for any concerns and sensitivities about vaccines. Unlike most medicines, vaccines are

administered not only for the benefit of the individual, but also for the benefit of the community. Hence AEFI reports, unlike the other adverse drug reaction reports contained within AEMS, may be perceived as being the responsibility of the community.

In addition, the roll-out of COVID-19 vaccines across Australia has led to a greatly increased public interest in the TGA's monitoring of vaccine safety, and a corresponding increase in AEFI reports submitted to AEMS. For these reasons, the TGA requires an internal AEFI escalation and causality assessment system, separate to that of the medicine adverse event report escalation system.

References

1. Global manual on surveillance of adverse events following immunisation. Geneva: World Health Organization; 2014 (revised March 2016). https://apps.who.int/iris/bitstream/handle/10665/206144/9789241507769_eng.pdf?sequence=1&isAllowed=y [TRIM D23-5145670]
2. Results of 'threshold testing look-back' including summaries of AEFI reports assessed against VSIG criteria by Vaccine STRS September 2021 – February 2022, and AEFI reports escalated from AEMDS prior to 2021 that resulted in consideration of a VSIG [TRIM D23-5161159]

VERSION HISTORY

Version	TRIM Reference	Description of change	Author/s	Effective date
1.0	D22-5070907	Original WI	STRS Vaccine Team	April 2022
	D23-5292900	Updated WI	STRS Vaccine Team	May 2023