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 consideration of whether the pair should be investigated further. The 'Analysing DPAR' section of this work instruction provides guidance on the relevant considerations.

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.

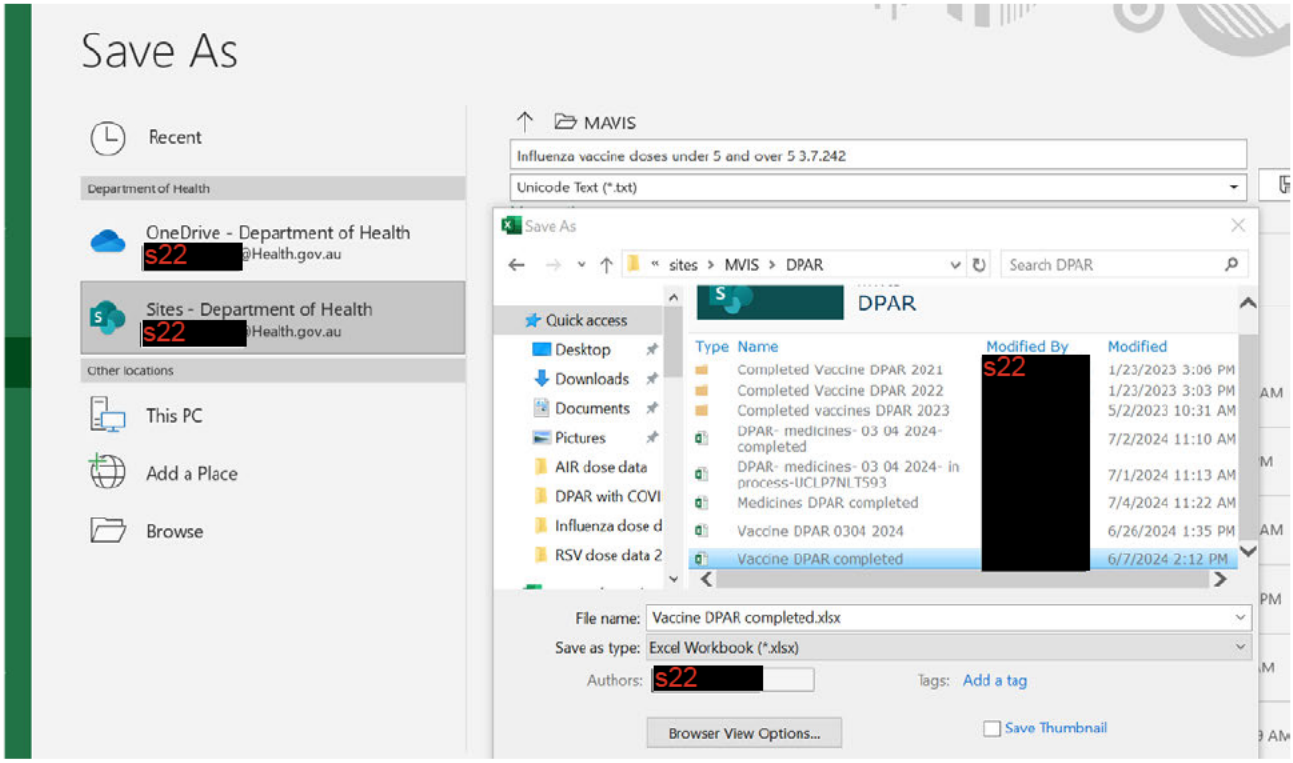
   - Save the excel report in the relevant TRIM container within TRIM placeholder PH16/399
     (*SIU – Disproportionality Analysis Report (DPAR)/PRR Trend Analysis*) named

     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.

2. Once the completed DPAR is saved in SharePoint save to your desktop. This file will then be saved over the original downloaded version in TRIM and should also be saved over the file 'Vaccine DPAR completed.xlxs' in SharePoint, which has a link to the DPAR Qlik app and updates the Qlik DPAR library. To do this go to 'Save As' in the desktop excel file, then navigate to MAVIS/Documents/DPAR and save it over the top of the existing 'Vaccine DPAR completed.xlxs' file. The same file needs to be updated to maintain the link to the Qlik DPAR library.



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. The Vaccine Signal Investigation Tracker and Analytics (SISTA) (TRIM D22-5112735) contains a record of previous, current and planned vaccine safety investigations and safety notification assessments.
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 IC_{025} 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
1.4	Update to add instructions about saving completed DPAR in SharePoint for automatic load to Qlik DPAR library	s22	4 July 2024

Authorisation

Name	Position	Date
s22 [redacted]	Director, Signal Investigation Unit	8 Jan 2019
s22 [redacted]	Director, 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.

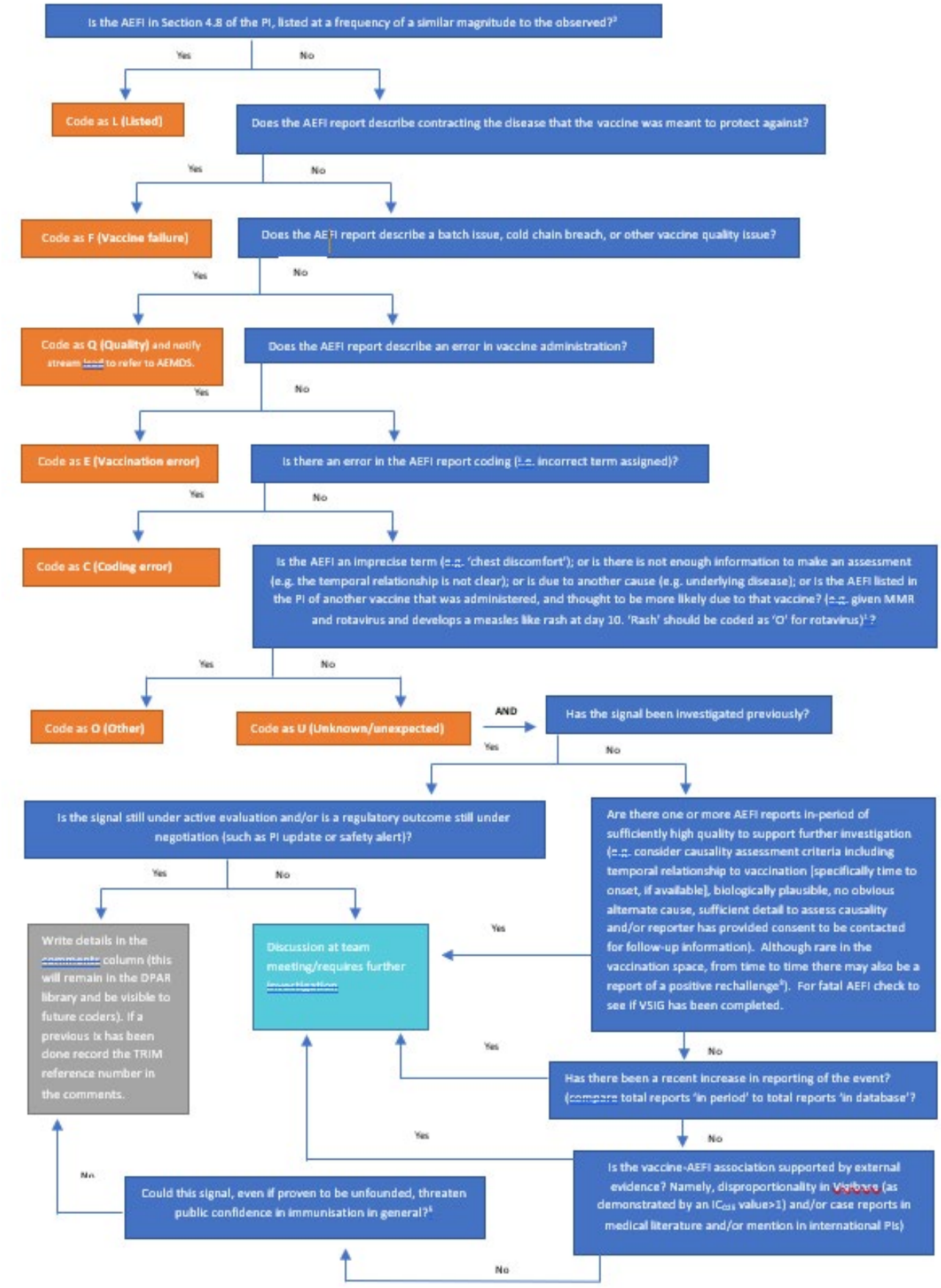
Table 3: Coding framework for assessing causal relationship of a drug-event pair

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).