Contents

COVID-19 vaccine adverse events of special interest (AESI) for evaluation (as of 24 May 2021)

This section describes the current active list of AESI for COVID-19 vaccines. It is a live document based primarily on the evolving Brighton Collaboration AESI list, the adopted TGA AESI list for different vaccine products and considers additional AESI under evaluation from both overseas and Australian sources.

Background

As of May 2020, the Brighton Collaboration with the Safety Platform for Emergency vACcines group (SPEAC) published a list of potential AESIs associated with COVID-19 vaccines (D20-3731994)(1).

An addendum to the priority list dated August 2020 includes a collated AESI list for all CEPI vaccines currently under development, including COVID-19 vaccines (D20-3732003)(2). A quarterly update published 23 December 2020 includes 3 new AESI: subacute thyroiditis, pancreatitis and rhabdomyolysis (D21-2001882)(3). An updated AESI list and completion status for selected case definitions has been published by Brighton Collaboration dated Jan 2021 (D21-2197256)(4).

A repository of resources including case definitions, companion guides and safety templates published by the Brighton Collaboration can be accessed here: https://docs.google.com/spreadsheets/d/1QgF35nYcsaFN3DZTOtV_lP0TYqQzsDMUQBAd5M9brrM/edit#gid=1666959512

Data sources

For the purposes of timely COVID-19 vaccine AESI identification, coding, escalation and investigation by VSS/AEMDS, the list below will be subject to ongoing review for addition of new and emerging AESIs based on the following sources:

- Brighton Collaboration/SPEAC AESI list and published case definitions
- ATAGI COVID-19 Working Group on safety – AESI List (D20-3829580) *For internal use only (confidential document)
- Clinical Evaluation Unit
- Risk Management Section
- Pharmacovigilance Plan Activities – TGA
    - Data analytics
    - AEFI/AESI reporting and escalation
    - AESI discussion and advice from JIC, VSIG, ATAGI, NCIRS, ACV and others

Table 1. TGA AESI list as of 12 Feb 2021 including rationale for inclusion and references

AESI	Included in existing TGA AESI list for escalation from AEMDS to SIU? (General vaccines AESI list - D20-3235571)	Rationale for inclusion	Case definition	Companion guide	Pfizer BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY)	AstraZeneca ChAdOx1-S [recombinant] COVID-19 vaccine
Category 1: AESI related to vaccination in general						
Generalised convulsion	Yes (listed as 'seizures/ convulsions/fits')	Brighton Collaboration Listed	Yes	Yes	✓	✓
Guillain-Barre Syndrome (GBS)	Yes	Brighton Collaboration Listed	Yes	Yes	✓	✓
Acute disseminated encephalomyelitis (ADEM)	Yes	Brighton Collaboration Listed	Yes	Yes	✓	✓
Anaphylaxis	Yes	Brighton Collaboration Listed	Yes	Yes	✓	✓
Vasculitides (incl. single organ cutaneous vasculitis, Kawasaki Disease)	Yes (listed as 'vasculitis')	Brighton Collaboration Listed (initially as vasculitides, then as single organ cutaneous vasculitis)	Yes (multiple case definitions in this group incl. single organ cutaneous vasculitis, Kawasaki disease)		✓	✓
Encephalitis/encephalomyelitis/myelitis (*include transverse myelitis?)	Yes (listed separately as 'encephalitis, myelitis, transverse myelitis')	Brighton Collaboration Listed Consider listing transverse myelitis as separate AESI(5)	Yes	Yes - Acute myelitis(6), acute encephalitis(7)	✓	✓
Idiopathic peripheral facial nerve palsy (see also Category 2 below)	Yes (listed as 'Bell's palsy')	Brighton Collaboration Listed *Highlighted at ACV (Jan 2021) by [redacted] – AE may not result in hospital admission and therefore will need extra PV to capture via primary care/GP.	Yes	Yes	✓	✓

AESI	Included in existing TGA AESI list for escalation from AEMDS to SIU? (General vaccines AESI list - D20-3235571)	Rationale for inclusion	Case definition	Companion guide	Pfizer BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY)	AstraZeneca ChAdOx1-S [recombinant] COVID-19 vaccine
Thrombocytopenia	No	Brighton Collaboration Listed	Yes	Yes	✓	✓
Enhanced disease following immunisation/VAED (also considered a Category 2 & 3 AESI)	No	Brighton Collaboration Listed (proven association with other vaccines – s22 [redacted]	Yes		✓	✓
Category 2: AESI relevant to specific vaccine platforms for potential COVID-19 vaccines						
Live viral vaccines Aseptic meningitis, encephalitis/encephalomyelitis	No	Brighton Collaboration Listed	Yes	Yes – aseptic meningitis(8)	×	×
Recombinant Vesicular Stomatitis Virus (r-VSV) vaccine platform Acute aseptic arthritis	No	Brighton Collaboration Listed	Yes		×	×
Modified Vaccinia Ankara (MVA) vaccine platform Myocarditis	No	Brighton Collaboration Listed – as of Jan 2021, no longer listed as AESI associated with this specific vaccine platform	No. Pending publication on CV injury focussed on myocarditis/pericarditis(3)		×	×
Intranasal e.coli heat labile toxin adjuvanted vaccine platform Idiopathic peripheral facial nerve palsy	No	Brighton Collaboration Listed (in this Category as of Jan 2021)(4)	Yes		×	×
SARS/MERS-CoVs Enhanced disease following immunisation/VAED	No	Brighton Collaboration Listed	Yes		×	×
Category 3: AESI related to COVID-19 disease						
Enhanced disease following immunisation/VAED (also	No	Brighton Collaboration Listed	Yes		✓	✓

AESI	Included in existing TGA AESI list for escalation from AEMDS to SIU? (General vaccines AESI list - D20-3235571)	Rationale for inclusion	Case definition	Companion guide	Pfizer BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY)	AstraZeneca ChAdOx1-S [recombinant] COVID-19 vaccine
considered a Category 1 & 2 AESI)						
Multisystem inflammatory syndrome	No	Brighton Collaboration Listed	Yes		✓	✓
Acute respiratory distress syndrome (ARDS)/vaccine-associated (VA)-ARDS	No	Brighton Collaboration Listed	Yes		✓	✓
Acute cardiac injury (includes myocarditis, pericarditis, arrhythmias, heart failure, infarction)	No	Brighton Collaboration Listed	No. Pending publication on CV injury focussed on myocarditis/pericarditis(3)		✓	✓
Coagulation disorder (includes coagulopathy, thrombosis, thromboembolism, internal/external bleed, stroke, disseminated intravascular coagulation)	No	Brighton Collaboration Listed	Yes – thrombosis and thromboembolism (15 Mar 21)(9)		✓	✓
Acute kidney injury	No	Brighton Collaboration Listed	Recommend use of the international criteria defined by the Kidney Disease Improving Global Outcomes (KDIGO) expert consensus group in 2012(10) as per Brighton Collaboration advice (rather than develop a		✓	✓

AESI	Included in existing TGA AESI list for escalation from AEMDS to SIU? (General vaccines AESI list - D20-3235571)	Rationale for inclusion	Case definition	Companion guide	Pfizer BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY)	AstraZeneca ChAdOx1-S [recombinant] COVID-19 vaccine
			new case definition)(3)			
Acute liver injury	No	Brighton Collaboration Listed	Adopt what has been used in many COVID-19 publications reporting elevations above the upper normal limit of >3 fold for AST/ALT and >2 fold for total bilirubin, GGT and ALP as per Brighton Collaboration advice (rather than develop a new case definition)(3)		✓	✓
Anosmia, ageusia	No	Brighton Collaboration Listed *Highlighted at ACV by s22 s22 – AE may not result in hospital admission and therefore will need extra PV to capture via primary care/GP.	No. Planned development (Tier 3 AESI)(3)		✓	✓
Chilblain-like lesions	No	Brighton Collaboration Listed	No. Planned development (Tier 3 AESI)(3)		✓	✓
Single organ cutaneous vasculitis	Y (listed as 'vasculitis')	Brighton Collaboration Listed	Yes		✓	✓

AESI	Included in existing TGA AESI list for escalation from AEMDS to SIU? (General vaccines AESI list - D20-3235571)	Rationale for inclusion	Case definition	Companion guide	Pfizer BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY)	AstraZeneca ChAdOx1-S [recombinant] COVID-19 vaccine
Erythema multiforme	No	Brighton Collaboration Listed	No. Planned development (Tier 3 AESI)(3)		✓	✓
Subacute thyroiditis	No	Brighton Collaboration Listed	No		✓	✓
Pancreatitis	No	Brighton Collaboration Listed	No		✓	✓
Rhabdomyolysis	No	Brighton Collaboration Listed	No		✓	✓
Category 4: AESI related to TGA clinical evaluation – individual vaccine candidates and safety profile						
Pregnancy and birth outcomes	No, however cases escalated for MO review as per existing VSS processes	'Use in pregnancy and while breastfeeding' is listed as 'Missing information' in EU-RMP (11) and TGA RMP evaluation report (12) . Currently Pregnancy category B1 (COMIRNATY). COMIRNATY PI(13): "Limited experience in pregnant women, administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus." Public interest, potential for intentional/ unintentional off-label use and vaccination in women of childbearing age.	Brighton Collaboration are planning to publish a March 2021 update focusing on COVID-19 disease outcomes in pregnancy and childhood along with long term complications		✓	✓

AESI	Included in existing TGA AESI list for escalation from AEMDS to SIU? (General vaccines AESI list - D20-3235571)	Rationale for inclusion	Case definition	Companion guide	Pfizer BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY)	AstraZeneca ChAdOx1-S [recombinant] COVID-19 vaccine
		International interest: MHRA, EU and FDA have included AESI related to pregnancy and birth outcomes. Listing as AESI to aid monitoring and collection of data to better understand potential risks				
Category 5: AESI related to Australian public interest/expert advice						
Vaccine error	No, however some vaccine error reports may be escalated by AEMDS	Multidose vials – high risk vaccine/administrative errors	No		✓	✓
Thrombosis and thrombocytopaenia syndrome (TTS)		Potential link to AstraZeneca vaccination	Yes(14), as of 13 May 2021 TGA is using a different case definition to Brighton Collaboration, and overlaps with MHRA TTS case definition (see s22 email D21-2638638)		×	✓

Table 2. Potential AESI for consideration from Australian sources

AESI	Rationale for inclusion	Case definition available	Companion guide available	Additional Considerations	References
Category 4: AESI related to TGA clinical evaluation – individual vaccine candidates and safety profile					
BNT162b2 [mRNA] (COVID-19 vaccine) – Pfizer					

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AESI	Rationale for inclusion	Case definition available	Companion guide available	Additional Considerations	References
Pregnancy and birth outcomes – added to VSS AESI list (Table 1)					
ChAdOx1-S [recombinant] (COVID-19 vaccine) – AstraZeneca					
Anaphylaxis – already on AESI list, RMP evaluator has requested sponsor add as important potential risk. Since provisional registration, AZ has detected potential signal for hypersensitivity/anaphylaxis – sponsor is currently evaluating and TGA has requested further information.					
Category 5: AESI discussed by Australian experts					
Vaccine error	Particular interest related to use of multidose vials. Advised on the need to monitor AEs including those that don't result in an AEFI. Consider use in pregnancy. ACV advice on vaccine error/shoulder injury related to vaccine administration (SIRVA) discussed in TGA RMP evaluation report(12) and Delegate's Overview and request for ACV advice(15), for the Pfizer COVID19 mRNA vaccine.				
Shoulder injury related to vaccine administration (SIRVA)	Potential practice and administration AEFI secondary to mass vaccination and rapid rollout/vaccine delivery				

Table 3: AESI from international sources

AESI listed on international AESI lists not currently on TGA AESI list					
AESI	**MHRA (internal correspondence Nov 2020 D20-3918995)**	**EU(16)** *AESI list discussed and agreed with the EMA advisory group monitoring committee on 9th July 2020	**FDA(17)**	**Rationale by other regulators for inclusion**	**TGA evaluation of AESI and current status**
Public interest and concern					
Deaths	Sudden death listed incl. SIDS	Y (any causes) + sudden death	Y	FDA – "Public interest in deaths after vaccination, especially in children (<18 years of age) and recipients of newly licensed vaccines." https://academic.oup.com/cid/article/61/6/980/451431	Routinely escalated by TGA
Pregnancy and birth outcomes	Y – pregnancy outcomes	Y – listed AESI in Maternal: gestational diabetes, pre-eclampsia, maternal death. Neonates: fetal growth restriction, spontaneous abortions, stillbirth, preterm birth, major congenital abnormalities, microcephaly, neonatal death, termination of	Y	FDA – "Public interest and concern over adverse pregnancy events and fetal outcomes." https://www.sciencedirect.com/science/article/abs/pii/S0002937810011051	For TGA evaluation. Reports are routinely monitored and escalated by TGA. Public interest, BC planning March 2021 update focusing on this, potential for intentional/unintentional off-label use and vaccination in women of childbearing age.

		pregnancy for fetal anomaly (TOPFA), induced abortions			
Narcolepsy	Y		Y incl. cataplexy	MHRA – "Narcolepsy based on experience with H1N1 pandemic influenza vaccine." MHRA "Do not have a reason to suspect an association (of CFS/POTS/narcolepsy) with the vaccine at this stage, but will proactively accumulate evidence as the MHRA anticipate receiving reports and media interest/reports in the media of these AESI, so are seeking to have the data to counter this." FDA – "Has been alleged as an adverse events associated with some adjuvanted vaccines; some COVID-19 vaccines might employ adjuvants." 1.https://www.cdc.gov/vaccinesafety/concerns/history/narcolepsy-flu.html	For TGA consideration, potential for public interest, association with adjuvanted pandemic influenza vaccines in 2009[ref]. *Highlighted at ACV by s22 s22 – AE may not result in hospital admission and therefore will need extra PV to capture via primary care/GP.
To distinguish from other complex AESI					
COVID-19		Y (by level of severity): Level 1 – any recorded diagnosis, Level 2 –	Y – VAERS SOP	FDA – "COVID-19 disease can be an indication of vaccine failure. Severe COVID-19	Will be closely monitored by TGA for all COVID-19 vaccines. Reporting form and follow-up questions

		hospitalisation for COVID-19 (confirmed or suspected), Level 3 – ICU admission in those with COVID-19 related admission, Level 4 – ARDS requiring ventilation during hospitalisation for COVID-19, Level 5 – death during hospitalisation for COVID-19 (any cause)		disease can be an indication of VAED."	specific to COVID-19 disease.
Kawasaki disease	Y		Y	MHRA – have referenced MISC but not explained specific rationale. FDA – "Could be confused with MIS-C, which could be an indication of VAED." https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e2.htm	Under TGA consideration for listing outside of vasculitides – may need to be listed as its own entity for surveillance. Has implications for distinguishing from MISC, known association with vaccination and has a BC case definition
Transverse myelitis	Not specifically	Y	Y	FDA – "One report of TM observed in prelicensure clinical trial of ChAdOx1 nCoV-19 vaccine."	For TGA listing as its own separate entity outside of encephalomyelitis/myelitis? Sort of overlaps with ADEM and myelitis, but should be its own entity for monitoring given association with vaccination in the literature and observed with AZ vaccine in clinical trials.
For ongoing TGA evaluation, monitoring and advice					

Multiple sclerosis and other demyelinating disorders	Y		Other acute demyelinating diseases listed		For further TGA discussion and advice
Other peripheral and polyneuropathies	Y				For further discussion
Optic neuritis	Y		?Y – possibly, not clear		Falls along spectrum of demyelinating disorders (for further discussion)
Autoimmune disease	Not as a broad category, specific autoimmune entities listed	List includes separate entities as listed AESI: GBS, ADEM, narcolepsy, acute aseptic arthritis, type 1 diabetes (and broader), idiopathic thrombocytopenia	Y		For further discussion – broad category
Chronic fatigue syndrome (CFS)	Y incl. myalgic encephalomyelitis (ME), Postviral fatigue syndrome (PVFS)			MHRA – "Have included CFS/POTS based on experiences with HPV vaccines and the similarity to cases of so-called long COVID."	For ongoing TGA discussion and advice
Fibromyalgia	Y (Nov 2020, may have been updated since then)				
Post orthostatic tachycardia syndrome (POTS)	Y (Nov 2020, may have been updated since then)				
Myasthenia gravis	Y (Nov 2020, may have been updated since then)				
Non-anaphylactic allergic reactions	N		Y		Routinely monitored by TGA, signal detection via DPAR/other sources

Appendix 1: FDA/CDC AESIs to be monitored for awareness but not abstracted(17)

In addition, selected AESIs will be monitored for awareness but not abstracted. These AESIs and available case definitions are listed in Table 2:

Table 2: AESIs to monitor (but not abstract), with definitions and available case definitions

AESIs to monitor but not abstract*	Reference definitions and available case definitions
Acute Respiratory Distress Syndrome (ARDS)	https://www.thoracic.org/professionals/career-development/residents-medical-students/ats-reading-list/adult/ards.php
Autoimmune disorders	Appendix 4.6 lists specific disorders to monitor
Other clinically serious neurologic AEs:	
Acute disseminated encephalomyelitis (ADEM)	Sejvar et al (2007)
Multiple sclerosis (MS)	NIH (last updated 5 Aug 2019)
Optic neuritis (ON)	Guier et al (last updated 10 Aug 2020)
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Gogia et al (last updated 9 Oct 2020)
Encephalitis	Sejvar et al (2007)
Myelitis	Sejvar et al (2007)
Encephalomyelitis	Merriam Webster (last accessed 7 Nov 2020)
Meningoencephalitis	Merriam-Webster (last accessed 7 Nov 2020)
Meningitis	CDC (last updated 21 Jan 2020)
Encephalopathy	NIH (last updated 27 Mar 2019)
Ataxia	Johns Hopkins Medicine Dept of Neurology and Neurosurgery (last accessed 7 Nov 2020)
Non-anaphylactic allergic reactions	Varies with specific symptom; see Appendix 4.6
Vaccination errors	See Section 4.4

* Will be specified by a list of MedDRA PTs (see Appendix 4.6, p. 27)

As of February 2021, FDA/CDC informed the TGA in confidence of their working list of AESI for monitoring (but not to be abstracted). This list is available in TRIM at: D21-2202182(18)

References:

1. Law B, Sturkenboom M. D2.3 Priority list of adverse events of special interest: COVID-19 https://brightoncollaboration.us/wp-content/uploads/2020/06/SPEAC_D2.3_V2.0_COVID-19_20200525_public.pdf Safety Platform for Emergency vACcines; 25 May 2020.

2. Law B. SO1-D2.0 Addendum to SO1-D2.2 & 2.3 Landscape analyses priority tiers for all CEPI vaccine development adverse events of special interest (AESI). https://brightoncollaboration.us/wp-content/uploads/2020/11/SPEAC_SO1_2.2_2.3-SO2-D2.0_Addendum_AESI-Priority-Tiers-Aug2020-v1.2.pdf Safety Platform for Emergency vACines 9 September 2020.
3. Law B. SO1-D2.1.2 Priority list of COVID-19 adverse events of special interest: Quarterly update December 2020. https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020-review_final.pdf Safety Platform for Emergency vACines 23 December 2020.
4. Brighton Collaboration. COVID-19 updated AESI list Jan 2021. [Internet] accessed on 11 Feb 2021 https://brightoncollaboration.us/wp-content/uploads/2021/01/COVID-19-updated-AESI-list.pdf.
5. Knoll MD, Wonodi C. Oxford–AstraZeneca COVID-19 vaccine efficacy. The Lancet. 2021;397(10269):72-4.
6. Law B. SO2-D2.5.2.1 AESI case definition companion guide for 1st tier AESI: Acute myelitis TRIM D21-2358676. Safety Platform for Emergency vACcines; 5 November 2020.
7. Law B. SO2- D2.5.2.1 - AESI Case Definition Companion Guide for 1st Tier AESI: Acute Encephalitis TRIM D21-2358696. Safety Platform for Emergency vACcines; 21 February 2021.
8. Law B. SO2- D2.5.2.1 - AESI Case Definition Companion Guide for 1st Tier AESI: Aseptic Meningitis. Safety Platform for Emergency vACcines; 21 February 2021.
9. Kidney Disease Improving Global Outcomes. KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements 2012;2(1).
10. EU-RMP Pfizer BNT162b2 COVID-19 mRNA Vaccine Risk Management Plan RMP Version 1.0. 21 December 2020. .
11. TGA Risk Management Plan Evaluation Report Provisional Approval Pathway. COVID-19 Vaccine (BNT162b2 [mRNA]) (COMIRNATY) Pfizer. 25 Jan 2021. .
12. Pfizer. Australian Product Information COMIRNATY (BNT162b2[mRNA]) COVID-19 vaccine. 25 January 2021.
13. Therapeutic Goods Administration (TGA). Delegate's pverview and request for ACV's advice. BNT162b2 [mRNA] COMIRNATY COVID19 vaccine Pfizer Australia Pty Ltd. 11 Jan 2021.
14. Dodd C, Willame C, Sturkenboom M. ACCESS project Protocol: Background rates of adverse events of special interest for monitoring COVID-19 vaccines. Version 1.1 Sep 21. 2020.
15. VAERS Team, Centers for Disease Control and Prevention. Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19 (as of 4 December 2020).
16. RE: Request to obtain information from US CDC/FDA - COVID-19 adverse events of special interest VAERS [SEC=OFFICIAL] - Email 10-02-2021 11:05:46 (0) TGA International - Confidential TRIM D21-2202182.

Version history

Version	Description of change	Author	Effective date

Authorisation

Name	Position	Date
s22		12 February 2021

Vaccine Surveillance Section (VSS) COVID-19 vaccine adverse events of special interest (AESI) – Case definitions and MedDRA preferred terms for coding

This section provides a platform for defining MedDRA preferred terms (PTs) for COVID-19 vaccine AESI to aid MedDRA code mapping for vaccine safety surveillance. In addition, this information will enhance development of COVID-19 vaccine specific follow-up questions for AESI and case investigation.

Sources

The list has been compiled based on the following sources of data and evidence:

- Brighton Collaboration Case Definitions – where there is a published case definition, relevant PTs have been mapped to AESI based primarily on criteria for Level 1 diagnostic certainty. For AESI that do not yet have Brighton Collaboration definitions, Vaccine Monitoring Collaboration for Europe (VAC4EU) Event Definition forms that have been published were consulted(19). This approach was provided by the ATAGI Working Group from their AESI List (in confidence) (D20-3829580).
- Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19 (as of 4 Dec 2020)(17).
- AstraZeneca COVID-19 vaccine EU RMP AESIs and MedDRA PTs(20).
- SPEAC Tier 1 AESI: ICD-9/10-CM and MedDRA Codes(21).

EU MedDRA codes proposed to be available Feb 2021 via the ACCESS/VAC4EU project (will be reviewed to further refine this working list).

Table 1. Category 1: AESI related to vaccination in general

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
Neurologic	Generalised convulsion(22)	**Level 1** Witnessed sudden loss of consciousness **AND** Generalised, tonic, clonic, tonic-clonic, or atonic motor manifestations **Level 2**	• Atonic seizures • Atypical benign partial epilepsy • Autonomic seizure • Clonic convulsion	Was there loss of consciousness or unconsciousne

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
		History of unconsciousness **AND** Generalised, tonic, clonic, tonic-clonic, or atonic motor manifestations **Level 3** History of unconsciousness **AND** Other generalised motor manifestations	• Convulsion in childhood • Convulsions local • Epilepsy • Epileptic encephalopathy • Febrile convulsion • Febrile infection-related epilepsy syndrome • Focal dyscognitive seizures • Generalised onset non-motor seizure • Generalised tonic-clonic seizure • Grand mal convulsion • Idiopathic generalised epilepsy • Myoclonic epilepsy • Neonatal seizure • Partial seizures with secondary generalisation • Partial seizures • Petit mal epilepsy • Seizure anoxic • Seizure cluster • Seizure like phenomena • Seizure • Simple partial seizures • Status epilepticus	ss? If yes, was it witnessed? What motor symptoms did the patient experience during the reported seizure/convulsion? If none, has the patient been/being referred to a neurologist? Has the patient had any of the following investigations: Brain CT/MRI EEG Tests related to drug screening/toxicology Tests related to infection – septic screen etc. *Relevant PmHx (epilepsy/unde

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
			• Temporal lobe epilepsy • Tonic clonic movements • Tonic convulsion • Tonic posturing	rlying neurological conditions/fever)/medications
Neurologic	Guillain-Barré Syndrome (GBS)(23)	**GBS** **Level 1** Bilateral **AND** flaccid weakness of the limbs **AND** Decreased or absent deep tendon reflexes in weak limbs **AND** Monophasic illness pattern AND interval between onset and nadir of weakness between 12 hours and 28 days AND subsequent clinical plateau **AND** Electrophysiologic findings consistent with GBS **AND** Cytoalbuminologic dissociation (i.e. elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/µl) **AND** Absence of an identified alternative diagnosis for weakness (see Appendix A.3 in GBS case definition) **Level 2** Bilateral AND flaccid weakness of the limbs AND Decreased or absent deep tendon reflexes in weak limbs AND Monophasic illness pattern AND interval between onset and nadir of weakness between 12 hours and 28 days AND subsequent clinical plateau AND CSF total white cell count <50 cells/µl (with or without CSF protein elevation above laboratory normal value) OR	• Guillain-Barre Syndrome • Miller Fisher Syndrome • Demyelinating polyneuropathy • Chronic inflammatory demyelinating polyradiculoneuropathy	TTO: progression of symptoms estimated to be over days to weeks (80% reach nadir in 2 weeks)(24) Was there weakness of both limbs/sides of the body? Was there a loss of reflexes? (MFS – Was there weakness involving eye movement of both eyes?) Were investigations

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
		• If CSF not collected or results not available, electrophysiologic studies with GBS OR • Absence of an identified alternative diagnosis for weakness (see Appendix A.3 in GBS case definition) **Level 3** Bilateral AND flaccid weakness of the limbs AND Decreased or absent deep tendon reflexes in weak limbs AND Monophasic illness pattern AND interval between onset and nadir of weakness between 12 hours and 28 days AND subsequent clinical plateau AND Absence of an identified alternative diagnosis for weakness (see Appendix A.3 in GBS case definition) **Fisher syndrome** **Level 1** Bilateral ophthalmoparesis AND bilateral reduced or absent tendon reflexes, AND ataxia **AND** Absence of limb weakness **AND** Monophasic illness pattern AND interval between onset and nadir of weakness between 12 hours and 28 days AND subsequent clinical plateau **AND** Cytoalbuminologic dissociation (i.e. elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/µl) **AND** Nerve conduction studies are normal, OR indicate involvement of sensory nerves only **AND** No alterations in consciousness or corticospinal tract signs **AND** Absence of an identified alternative diagnosis for weakness		ordered, including: Electrophysiology (electromyography and nerve conduction studies) Lumbar puncture/CSF analysis Serum IgG antibodies to GQ1b (for MFS) MRI spine *Relevant PmHx campylobacter jejuni infection/history of infection/medications

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
		For Level 2 and 3 see case definition for details.		
Neurologic	Acute disseminated encephalomyelitis (ADEM)(25)	<u>ADEM</u> **Level 1** Demonstration of diffuse or multifocal areas of demyelination by histopathology **OR** Focal or multifocal findings referable to the central nervous system, including **one or more** of the following: 1. Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 h) 2. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness) 3. Cranial nerve abnormality/abnormalities 4. Visual field defect/defects 5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex) 6. Motor weakness (either diffuse or focal; more often focal) 7. Sensory abnormalities (either positive or negative; sensory level) 8. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes) 9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus **AND** Magnetic resonance imaging (MRI) findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (± gadolinium enhancement on T1 sequences) **AND** Monophasic pattern to illness (i.e. absence of relapse within a *minimum* of 3 months of symptomatic nadir) For Level 2 and 3 see case definition for details. **Exclusion criteria for all levels of diagnostic certainty**	• Acute disseminated encephalomyelitis	Was histopathology performed to confirm the diagnosis? If so, please provide. If not, did the patient have an MRI to confirm the diagnosis?

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
		• Presence of a clear alternative acute infectious or other diagnosis for illness, • Recurrence or relapse of illness at any point following a 3 month period of clinical improvement from symptomatic nadir, or • If known, MRI findings or histopathologic data inconsistent with the diagnosis of ADEM.		
Immunologic	Anaphylaxis(26)	**For all levels of diagnostic certainty** Anaphylaxis is a clinical syndrome characterised by • Sudden onset **AND** • Rapid progression of signs and symptoms **AND** • Involving multiple (≥2) organ systems, as follows: **Level 1 of diagnostic certainty** ≥1 major dermatological **AND** ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion **Level 2** ≥1 major cardiovascular AND ≥1 major respiratory criterion OR ≥1 major cardiovascular OR respiratory criterion **AND** ≥1 minor criterion involving ≥1 different system (*other than* cardiovascular or respiratory systems) OR • (≥1 major dermatologic) AND (≥1 minor cardiovascular AND/OR minor respiratory criterion) Level 3 ≥1 minor cardiovascular OR respiratory criterion **AND** ≥1 minor criterion from each of ≥2 different systems/categories For major and minor criteria see case definition for details.	• Anaphylactic shock • Anaphylactic reaction • Anaphylactoid reaction • Anaphylactoid shock	TTO: sudden onset and rapid progression of signs/symptoms

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
Immunologic	Vasculitides	Individual Brighton Collaboration case definitions exist for the following vasculitides: • Single organ cutaneous vasculitis • Kawasaki disease (KD)		
	Single organ cutaneous vasculitis (SOCV)(27)	SOCV is a syndrome characterised by clinical and histological features of small vessel vasculitis of the skin without involvement of other organ systems. **For all levels of diagnostic certainty** Clinical features: Haemorrhagic papules **OR** Urticaria-like lesions **OR** Purpuric rash involving the face, ears, and extremities AND oedema AND low grade fever (only for acute haemorrhagic oedema of infancy (AHEI)) **Level 1 of diagnostic certainty:** Histology: Perivascular inflammatory cells infiltrates dominated by neutrophils with fragmented nuclei (leukocytoclasia) AND Erytrocyte extravasation or haemorrhage into the dermis AND Fibrinoid necrosis or degeneration of the dermal postcapillary venules AND Exclusion of other vasculitic organ system involvement • Normochromic normocytic anaemia, thrombocytopenia, • Renal involvement (proteinuria, haematuria, hypertension, increased serum creatinine), • Pulmonary involvement (dyspnoea, cough, haemoptysis, patchy or diffuse alveolar infiltrates in chest X-ray),	• Cutaneous vasculitis • Haemorrhagic urticarial • Urticarial vasculitis • Purpura	

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
		• Gastrointestinal involvement (abdominal pain, vomiting, gastrointestinal bleeding) • Liver involvement (elevated liver enzymes and bilirubin), • Serosal involvement (pericardial and or pleural effusion) with ultrasound and/or X-ray examination in case of clinical suspicion, • Arthritis (synovitis) with synovial aspirate in case of clinical suspicion, • Central or peripheral nervous system involvement by neurologic physical examination, • Presence of antinuclear antibodies, ANCA, rheumatoid factor, anti-citrullinated peptides antibodies (CCP), cryoglobulins, • Reduced serum complement factors (C3, C4, C1q), • Serologic evidence of hepatitis C, hepatitis B, Epstein-Barr virus (EBV), Parvovirus B19 serology, antistreptolysin-O titre. For Level 2 and 3 see case definition for details.		
	Kawasaki Disease (KD)(28) *KD is not specifically on our AESI list but is included in MHRA/EU/FDA lists and falls under the category of 'vasculitides' which is on the initial Brighton Collaboration and our AESI list	<u>For definite KD</u> **Level 1a: Complete KD** Autopsy evidence of coronary artery changes consistent with KD OR Fever persisting for 4 or more days **AND** Presence of at least 4 of the following 5 principal features: • Bilateral bulbar conjunctival injection without exudate • Changes in extremities • Polymorphous exanthem • Changes in the lips and/or oral cavity • Cervical lymphadenopathy **AND** No echo abnormalities or echo criteria insufficient to meet criteria **Level 1b: Incomplete KD**	• Kawasaki's disease	Important features: Age Prolonged fever 4 days or more Presence of at least 2 of the principle features for incomplete KD (4 or more for complete) *Relevant PmHx ethnicity, cardiopulmonary disease

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
		Fever persisting for 4 or more days OR Incomplete documentation of fever **AND** Presence of 2 or 3 of the 5 principal features listed in Level 1a **AND** Definitive echocardiographic changes of coronary artery aneurysms (CAA): a) z-score of LAD or RCA≥2.5 OR b) coronary artery features meet Japanese Ministry of Health (JMoH) age-related criteria for aneurysm **For Level 2 and 3 see case definition for details.**		
Neurologic	Encephalitis/ Encephalomyelitis(25)	<u>Encephalitis</u> **Level 1** Demonstration of acute inflammation of central nervous system parenchyma (± meninges) by histopathology <u>Myelitis</u> **Level 1** Demonstration of acute spinal cord inflammation (± meninges) by histopathology For Level 2 and 3 see case definition for details. Exclusion criterion for Levels 2 and 3 also apply.	<u>Encephalitis PTs</u> • Encephalitis post immunisation • Encephalitis <u>Myelitis PTs</u> • Myelitis • Myelitis transverse <u>Other related encephalomyelitis PTs</u> • Encephalomyelitis • Leukoencephalomyelitis • Noninfective encephalomyelitis • Meningoencephalitis viral <u>Consider 2nd Tier PTs:</u> Encephalopathy Leukoencephalopathy Myelopathy	Was histopathology performed to confirm the diagnosis? If so, please provide. If not, did the patient have an MRI to confirm the diagnosis? *Relevant PmHx history of infection/medications

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
			*Evaluate in line with case definition to see whether the case meets Level 2/3 diagnostic criteria	
Neurologic	Peripheral facial nerve palsy(29)	Peripheral facial nerve palsy Initially, the diagnosis of acute-onset peripheral facial nerve palsy needs to be confirmed. Peripheral facial nerve palsy is defined as a weakness of the facial muscles innervated by cranial nerve VII, which is either complete (paralysis) OR incomplete (paresis) and may manifest unilaterally OR bilaterally. **Level 1** Manifests with the acute-onset decreased ability (paralysis OR paresis) • to wrinkle the forehead OR • to raise the eye brows at the affected side. Level 2 and 3 diagnostic certainty not applicable. Idiopathic peripheral facial nerve palsy (Bell's palsy) **For all levels of diagnostic certainty** Idiopathic peripheral facial nerve palsy has an unknown aetiology, which: Has a sudden onset AND Shows initial rapid progression of symptoms and signs AND Shows resolution. Level 1 Remains unexplained after excluding known causes by: Review of clinical history AND Physical examination AND Laboratory investigations AND Radiological studies.	• Facial paralysis • Facial paresis • Bell's phenomenon (related to peripheral facial nerve palsy but not specific to Bell's palsy) • Bell's palsy	TTO: Bells' palsy - acute onset within 2 days, range from 24hours to 10-14 days (longer than 2 weeks may be more suggestive of a tumour)(30) Is there a known cause? If yes, please provide details of history, examination findings, laboratory investigations and/or radiological studies (a known cause rules out Bell's palsy).

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
		Level 2 – if radiological studies absent Level 3 - if both laboratory investigations and radiological studies absent For explanatory notes on facial muscle weakness, decreased facial muscles movement, unilateral versus bilateral palsy, sudden onset, rapid progression, resolution occurs and multiple causality (after excluding known causes) see case definition.		
Haematologic	Thrombocytopenia(31)	**Level 1:** Platelet count less than 150×10^9 L^{-1} **AND** Confirmed by blood smear examination OR the presence of clinical signs and symptoms of spontaneous bleeding **Level 2 (unconfirmed TP):** Platelet count less than 150×10^9 L^{-1} **Level 3** – not applicable	• Thrombocytopenia • Platelet count decreased • Immune thrombocytopenia • Thrombocytopenic purpura	Platelet count and blood smear result or clinical signs/symptoms of spontaneous bleeding *Relevant PmHx/medications
Immunologic	Vaccine-Associated Enhanced Disease (VAED)(32)	**Level 1 (definitive case):** The Brighton Collaboration working group considers that a Definitive Case (LOC1) of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED. **Level 2 (probable):** Rationale for Level 2: Ascertainment is based on confirmed infection with known (2A, higher level of certainty) or without previously known (2B, lower certainty) serostatus, clinical and epidemiologic criteria, and available histopathology. • Level 2a: A probable case of VAED is defined by the occurrence of disease in a *previously seronegative vaccinated* individual with: ○ **Laboratory confirmed infection** with the pathogen targeted by the vaccine AND	*No MedDRA PT available for VAED Reports which may trigger suspicion of VAED would include: Serious/severe/fatal COVID-19 associated disease (multiple PTs associated with severe COVID-19 disease) AND COVID-19 vaccination ▪ Individuals assumed to be at lower risk for	Has the patient had confirmed or suspected COVID-19 infection? If yes, provide date and details of positive test and/or symptom onset.

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
		Clinical findings of disease involving one or more organ systems **(a case of VAERD if the lung is the primarily affected organ)** AND **Severe disease** as evaluated by a **clinical severity index/score (systemic in VAED or specific to the lungs in VAERD)** AND Increased **frequency** of **severe outcomes** (including severe disease, hospitalisation and mortality) when compared to a non-vaccinated population (control group or background rates) AND **Evidence of immunopathology** in target organs involved by histopathology, when available, including any or the following: ▪ Present or elevated tissue eosinophils in tissue ▪ Elevated pro-inflammatory Th2 cytokines in tissue (IL4, IL5, IL10, IL13) ▪ C4d tissue deposition (evidence for complement activation through immune complex deposition) ▪ C1q assessments of immune complexes in fluids ▪ Low C3 levels as evidence complement consumption AND No identified alternative aetiology • Level 2b: A probable case of VAED is defined by the occurrence of disease in a vaccinated individual with *no prior history of infection and unknown serostatus,* with: ○ **Laboratory confirmed infection** with the pathogen targeted by the vaccine AND Clinical findings of disease involving one or more organ systems **(a case of VAERD if the lung is the primarily affected organ)** AND **Severe disease** as evaluated by a **clinical severity index/score (systemic in VAED or specific to the lungs in VAERD)** AND	severe COVID-19 having more severe disease ▪ Individuals at known risk for severe COVID-19 (e.g. older or immunocompromised) having higher rates of fatal outcomes ▪ Observation of an unfavourable imbalance in severe COVID-19 cases in vaccinated individuals when compared to those not vaccinated <u>PTs indicating COVID-19 confirmed or suspected:</u> • Asymptomatic COVID-19 COVID-19 • Suspected COVID-19 • COVID-19 pneumonia • COVID-19 treatment <u>Laboratory PTs:</u> • SARS-CoV-2 antibody test positive • SARS-CoV-2 test positive Note: for cases where COVID-19 confirmed/suspected has	Confirm the date of COVID-19 vaccination and details (vaccine details, dose number etc) Determine severity of post-vaccination COVID-19-associated disease (EU AESI criteria of severity for 'COVID-19'): Level 1 – any recorded diagnosis, Level 2 – hospitalisation for COVID-19 (confirmed or suspected), Level 3 – ICU admission in those with COVID-19 related admission, Level 4 – ARDS requiring ventilation

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs[version 23.1]	Key information for follow-up
		Increased **frequency** of **severe outcomes** (including severe disease, hospitalisation and mortality) when compared to a non-vaccinated population (control group or background rates) AND Evidence of immunopathology in target organs involved by histopathology, if available, including any of the following: ▪ Present or elevated tissue eosinophils in tissue ▪ Elevated pro-inflammatory Th2 cytokines in tissue (Il4, IL5, IL10, IL 13) ▪ C4d tissue deposition (evidence for complement activation through immune complex deposition) ▪ C1q assessments of immune complexes in fluids ▪ Low C3 levels as evidence complement consumption AND No identified alternative aetiology	not been coded, consider PTs for exposure during signal investigation (PTs Exposure to SARS-CoV-2, Occupational exposure to SARS-CoV-2) To meet the definition for VAED, cases should have confirmed/likely seronegative status for COVID-19 disease ***prior to/at the time*** of COVID-19 vaccination: This information will likely be derived from case narratives/in follow-up questionnaire if not reported at the time of report submission	during hospitalisation for COVID-19, Level 5 – death during hospitalisation for COVID-19 (any cause)

Table 2. Category 2: AESI relevant to specific vaccine platforms for potential COVID-19 vaccines

BODY SYSTEM	VACCINE SPECIFIC PLATFORM AESI	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
Neurologic	Aseptic meningitis(33) (Live viral vaccines)	**Level 1** • Clinical evidence of acute meningitis such as fever, headache, vomiting, bulging fontanelle, nuchal rigidity or other signs of meningeal irritation, AND Pleocytosis in CSF determined as: o >5 leukocytes/mm^3 (µL) if patient is 2 months of age or older, o >15 leukocytes/mm^3 (µL) in infants younger than 2 months,	• Meningitis • Meningitis aseptic • Meningitis viral • Meningoencephalitis viral	Clinical presentation – signs and symptoms CSF analysis result including microscopy and culture

BODY SYSTEM	VACCINE SPECIFIC PLATFORM AESI	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
		AND Absence of any microorganism on Gram stain of CSF, AND Negative routine bacterial culture of CSF in the absence of antibiotic treatment before obtaining the first CSF sample. **Level 2** • Clinical evidence of acute meningitis such as fever, headache, vomiting, bulging fontanelle, nuchal rigidity or other signs of meningeal irritation, AND Pleocytosis in CSF determined as: ○ >5 leukocytes/mm^3 (µL) if patient is 2 months of age or older, ○ >15 leukocytes/mm^3 (µL) in infants younger than 2 months, AND Absence of any microorganism on Gram stain of CSF, AND *Negative bacterial culture of CSF obtained, OR negative culture in the presence of antibiotic treatment before obtaining the first CSF sample.* **Level 3** Not applicable If the case meets criteria for aseptic meningitis and encephalitis case definition, it should be reported only as encephalitis.		
Immunologic	Acute aseptic arthritis(34) (r-VSV platform)	**Acute aseptic arthritis (AAA):** AAA is a clinical syndrome characterised by **acute onset of signs and symptoms of joint inflammation for a period of no longer than 6 weeks**, synovial increased leucocyte count and the *absence of microorganisms on Gram stain, routine culture and/or PCR*. For all levels of diagnostic certainty: One or more of the following clinical signs and symptoms assessed by a health care provider • Articular or peri-articular swelling • Articular effusion • Articular or peri-articular erythema • Increased warmth palpable over capsular contour of the joint • Restricted range of movement	General arthritis PTs: • Arthritis • Polyarthritis • Oligoarthritis • Periarthritis Immunologic/autoimmune PTs: • Autoimmune arthritis • Immune-mediated arthritis • Arthritis allergic	Clinical presentation – signs and symptoms Duration of symptoms History of recent trauma Synovial fluid analysis and result including microscopy and culture

BODY SYSTEM	VACCINE SPECIFIC PLATFORM AESI	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
		AND • Duration of less than 6 weeks until complete resolution of symptoms AND • Absence of recent articular trauma Level 1 of diagnostic certainty • Increased leucocyte count in synovial fluid determined as: o >2000 leukocytes/mm^3 on aspirate regardless of age AND o <50% white blood count polymorphonuclear (PMN) in synovial fluid AND • Absence of pathological synovial fluid cells • Absence of any microorganism on Gram stain, microscopy or PCR in synovial fluid • No bacterial growth on routine culture of synovial fluid • Absence of antibiotic treatment before obtaining the first synovial fluid sample **Level 2** • Negative bacterial blood cultures AND • Negative routine bacterial culture of synovial fluid	<u>Inflammatory arthritis PTs:</u> • Arthritis reactive • Crystal arthropathy • Gout • Gouty arthritis • Rheumatoid arthritis • Seronegative arthritis Other aseptic arthritis: • Arthritis viral *Note, septic arthritis is more common in a joint with pre-existing arthritis e.g. RA, OA, gout, pseudogout, Charcot arthropathy.	
Other	Myocarditis (MVA platform)	No Brighton Collaboration case definition exists yet. **ACCESS/VAC4EU(19)** has begun a draft Event Definition Form for myocarditis/pericarditis based on clinical guidelines, expert consensus, and/or published references. It has not established diagnostic criteria for either as per other of its Event Definition Forms.	See Myocarditis PTs below in category 3 *MVA platform associated myocarditis may differ from COVID-19 related myocarditis – await publication of case definition from BC	

Table 3. Category 3: AESI related to COVID-19 disease

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
Immunologic	Multisystem inflammatory syndrome (in children and in adults)(35)	**Level 1 – Definitive case:** Age <21 years (MIS-C) *OR* ≥21 years (MIS-A) **AND** Fever ≥3 consecutive days **AND** 2 or more of the following clinical features: • Mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral non-exudative conjunctivitis, erythema/oedema of the hands and feet) • Gastrointestinal (abdominal pain, vomiting, diarrhoea) • Shock/hypotension • Neurologic (altered mental status, headache, weakness, paresthesias, lethargy) **AND** Laboratory evidence of inflammation including any of the following: - Elevated CRP, ESR, ferritin, *or* procalcitonin[b] **AND** • 2 or more measures of disease activity: • Elevated BNP *or* NT-proBNP *or* troponin[b] • Neutrophilia, lymphopenia, *or* thrombocytopenia[b] • Evidence of cardiac involvement by echocardiography[c] *or* physical stigmata of heart failure[d] • EKG changes consistent with myocarditis or myo-pericarditis[e] **AND** Laboratory confirmed SARS-CoV-2 infection[f] *OR* Personal history of confirmed COVID-19 within 12 weeks *OR* Close contact with known COVID-19 case within 12 weeks *OR* Following SARS-CoV-2 vaccination[g] **Level 2 – Probable:**	• Multisystem inflammatory syndrome in children *MIS-A PT not available in MedDRA yet	Patient age Clinical presentation – signs and symptoms Laboratory results particularly inflammatory markers, troponin and FBC Imaging results: - Echocardiogram - ECG COVID-19 status (infection, presentation and tests) COVID-19 vaccination status

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
		Level 2a: Same as Level 1 except: 1 measure of disease activity **AND** Within 12 weeks of a personal history of known or strongly suspected COVID-19 OR Within 12 weeks of close contact with a person with known or strongly suspected COVID-19 OR Following SARS-CoV-2 vaccination[g] Level 2b: Same criteria as Level 1 except: Fever lasting 1-2 days and can be subjective For all other levels of diagnostic certainty (Level 3 possible, Level 4 insufficient evidence and Level 5 not a case of MIS-C/A) see published case definition for details. **Footnotes:** Note: At all levels of certainty, minimal to mild respiratory symptoms may be present and their presence does not exclude a case of MIS-C/A, however, a case must be excluded if there is concern for acute COVID-19-related pulmonary disease. Further, one of the critical components of the case definition is that it is only applied when there is no clear alternative diagnosis for the reported event. [b]laboratory values are defined as low or high based on local laboratory normal ranges [c]echocardiographic signs: dysfunction, wall motion abnormality, coronary abnormality (dilation, aneurysm, echobrightness, lack of distal tapering), valvular regurgitation, pericardial effusion		

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
		[d]physical stigmata of heart failure: gallop (IF diagnosed by expert) *or* rales, lower extremity oedema, jugular venous distension, hepatospenomegaly [e]EKG changes consistent with myocarditis or myo-pericarditis: abnormal ST segments *and/or* arrhythmia *and/or* pathologic Q waves *and/or* AV conduction delay *and/or* PR segment depression *and/or* low voltage QRS [f]laboratory evidence of SARS-CoV-2 infection: ▪ Serologic evidence of SARS-CoV-2 infection *or* ▪ SARS-CoV-2 nucleic acid amplification positivity or ▪ SARS-CoV-2 antigen positivity [g]if a known or suspected COVID-19 infection has not occurred within the preceding 12 weeks		
Respiratory	Vaccine-Associated Acute Respiratory Distress Syndrome (VA-ARDS)(36)	The Brighton Collaboration case definition provides diagnostic criteria for adult and paediatric ARDS based on Berlin and PALICC definitions respectively. **Level 1 confirmed ARDS:** Adult Must meet ALL of the following criteria: 1 Hypoxaemia – P/F ratio ≤300 2 Positive Pressure Requirement – PEEP/CPAP ≥5cmH20 3 Imaging – Chest imaging with bilateral chest opacities not explained by other process 4 Origin of oedema: not related to fluid overload or cardiogenic oedema 5 Timing – within 1 week of known clinical insult* Paediatric Must meet ALL of the following criteria: 1 Hypoxaemia – P/F ratio ≤300 or S/F ≤264 for non-intubated patients – OI ≥4 or OSI ≥5 for intubated patients 2 Positive Pressure Requirement – PEEP/CPAP ≥5cmH20 3 Imaging – Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease 4 Origin of oedema: new infiltrate not related to fluid overload or cardiogenic oedema	• Acute respiratory distress syndrome	ICU discharge summary for information on: - Timeline: TTO, COVID-19 status, COVID-19 vaccination status - Hypoxaemia (P/F ratio or S/F, OI or OSI) - PEEP/CPAP - Imaging results

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
		5 Timing – within 1 week of known clinical insult* *Timing criteria for ARDS, may vary after vaccination **For Levels 2-5 see case definition for details.**		
Cardiac	Acute cardiac injury including: •Microangiopathy •Heart failure and cardiogenic shock •Stress cardiomyopathy •Coronary artery disease •Arrhythmia •Myocarditis, pericarditis •Infarction	There is no Brighton Collaboration case definition yet. A case definition for myocarditis/pericarditis is planned for 2021. **ACCESS/VAC4EU(19)** has begun drafting Event Definition Forms for the following: • Microangiopathy • Heart failure • Stress cardiomyopathy • Coronary artery disease • Arrhythmia • Myocarditis/pericarditis	Microangiopathy PTs: • Microangiopathy • Cerebral microangiopathy • Thrombotic microangiopathy Heart failure and cardiogenic shock PTs: • Cardiac failure • Cardiac failure acute • Cardiac failure chronic • Cardiac failure congestive • Cardiac failure high output • Cardiopulmonary failure • Cardiogenic shock Stress cardiomyopathy PTs: • Stress cardiomyopathy • Cardiomyopathy acute • Congestive cardiomyopathy	Hospital discharge/specialist letters Cardiology management and investigations/confirmation of diagnosis (echocardiogram, ECG and other relevant investigations) Co-morbidities, cardiac/autoimmune risk factors (smoking, alcohol etc), medications and family history important

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Hypertensive cardiomyopathy • Hypertrophic cardiomyopathy • Ischaemic cardiomyopathy • Non-obstructive cardiomyopathy • Restrictive cardiomyopathy • Tachycardia induced cardiomyopathy • Toxic cardiomyopathy • Viral cardiomyopathy <u>Coronary artery disease PTs:</u> • Coronary artery disease • Microvascular coronary artery disease <u>Arrhythmia PTs:</u> • Arrhythmia • Arrhythmia supraventricular • Bradyarrhythmia • Nodal arrhythmia • Paroxysmal arrhythmia • Supraventricular tachyarrhythmia	

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Tachyarrhythmia • Ventricular arrhythmia • Ventricular tachyarrhythmia <u>Myocarditis/pericarditis PTs:</u> • Myocarditis • Autoimmune myocarditis • Eosinophilic myocarditis • Giant cell myocarditis • Lupus myocarditis • Hypersensitivity myocarditis • Immune-mediated myocarditis • Myocarditis infectious • Myocarditis post infection • Myocarditis septic • Viral myocarditis • Pericarditis • Autoimmune pericarditis • Pericarditis adhesive • Pericarditis constrictive • Pericarditis infective • Purulent pericarditis • Pericarditis lupus	

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Viral pericarditis • Pericarditis uraemic • Pleuropericarditis <u>Infarction (myocardial) PTs:</u> • Acute myocardial infarction • Myocardial infarction • Silent myocardial infarction	
Haematologic	Coagulation disorder •Deep vein thrombosis •Pulmonary embolus •Cerebrovascular stroke •Limb ischemia •Haemorrhagic disease	DRAFT Brighton Collaboration case definition for thrombosis and thromboembolism(9). Case definition and levels of diagnostic certainty of venous or arterial thrombosis/thromboembolism (should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms) Level 1 – Definitive case **Imaging study findings consistent with thrombosis/thromboembolism** Imaging studies include any of the following, depending on the location of the lesion • Ultrasound – Doppler • Computed Tomography (CT scan) – contrast/angiography • Magnetic resonance venography (MRV) or arteriography (*MRA*) • Echocardiogram • Perfusion V/Q scan • Conventional angiography/Digital substraction angiography OR Procedure that confirms the presence of a thrombus (eg. Thrombectomy)	<u>DIC PTs:</u> • Disseminated intravascular coagulation <u>VTE PTs:</u> • Thrombosis • Deep vein thrombosis • Pulmonary embolism • Pulmonary thrombosis • Pulmonary venous thrombosis • Subclavian vein thrombosis • Axillary vein thrombosis • Transverse sinus thrombosis • Cavernous sinus thrombosis	Hospital discharge/specialist letters Haematology management and investigations/confirmation of diagnosis Imaging: - MRV/MRA - CT – contrast/angiography - Doppler USS - Echocardiogra - Perfusion V/Q scan - Conventional angiography/digital substraction angiography

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
		OR Pathology consistent with thrombosis/thromboembolism including biopsy or autopsy Notes: LOC 1 is Independent of clinical findings or presence of risk factors. Most appropriate imaging test depends of the location of the lesion. Any of the tests listed may be used as available. Based on radiologist/expert interpretation. Abnormal laboratory results are not required for confirmation as they can be normal in presence of thrombotic/thromboembolic events. When present, they can be supportive of the diagnosis, including: • D-dimer elevated above the upper limit of normal for age • Shortened PT, PTT– below the lower limit of normal for age • Elevated fibrinogen **For Levels 2-5 see case definition for details.**	• Cerebral venous thrombosis • Cerebral venous sinus thrombosis • Vena cava embolism • Vena cava thrombosis • Venous thrombosis • Venous thrombosis limb • Embolism venous • Hepatic vein thrombosis • Mesenteric vein thrombosis • Portal vein thrombosis • Jugular vein thrombosis • Pelvic venous thrombosis • Renal vein thrombosis • Splenic vein thrombosis • Retinal vein thrombosis • Visceral venous thrombosis <u>General stroke PTs:</u> • Basal ganglia stroke • Brain stem stroke • Cerebellar stroke • Embolic stroke	Laboratory tests are only diagnostic if positive (absence does not exclude the diagnosis of thrombosis/thromboembolism) - D-dimer elevated above upper limit of normal for age - Shortened PT, PTT – below the lower limit of normal for age - Elevated fibrinogen Co-morbidities, thrombophilia/stroke risk factors (surgery, immobilisation, pregnancy etc), medications and family history important

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Lacunar stroke • Spinal stroke • Thrombotic stroke • Vertebrobasilar stroke • Cerebral infarction • Infarction • Cerebrovascular accident <u>Peripheral limb ischaemia PTs:</u> • Peripheral ischaemia <u>Ischaemic stroke PTs:</u> • Ischaemic stroke • Cerebral small vessel ischaemic disease • Ischaemic cerebral infarction • Transient ischaemic attack <u>Haemorrhagic stroke PTs:</u> • Haemorrhagic cerebral infarction • Haemorrhagic stroke • Haemorrhagic transformation stroke	
Renal	Acute kidney injury (AKI)	There is no Brighton Collaboration case definition yet. *Update Dec 2020: BC recommends use of the international criteria defined by the Kidney Disease	• Renal injury • Renal tubular injury • Acute kidney injury	

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
		Improving Global Outcomes (KDIGO) expert consensus group in 2012 (rather than develop a new case definition). **ACCESS/VAC4EU** in their Event Definition Form lists the definition of **KDIGO** (Kidney Disease: Improving Global Outcomes) as the European standard. AKI definition (as per KDIGO)(10): AKI is defined as any of the following *(Not Graded)*: • Increase in SCr by ≥0.3 mg/dl (≥26.5 lmol/l) within 48 hours; OR • Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; OR • Urine volume <0.5 ml/kg/h for 6 hours.	• Renal failure • Hepatorenal failure • Postrenal failure • Prerenal failure • Renal transplant failure • Renal impairment • Renal tubular necrosis • Anuria • Oliguria • Nephritis • Tubulointerstitial nephritis	Hospital discharge/specialist letters Nephrologist management and investigations/confirmation of diagnosis (renal function, CT-KUB/ urogram/renal USS, urine tests and relevant special tests) Co-morbidities, renal risk factors (chronic/acute dehydration etc), medications and family history important
Gastrointestinal	Liver injury	There is no Brighton Collaboration case definition yet. Proposal to adopt of what has been used in many COVID-19 publications rather than develop a new case definition. Brighton Collaboration propose the following definition of acute liver injury be used(3): • >3-fold elevation above the upper normal limit for ALT or AST OR • >2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP **ACCESS/VAC4EU** have included some classification systems of acute liver failure in their draft Event Definition Form.	<u>Elevated liver enzyme PTs:</u> • Hepatic enzyme increased • Hepatic enzyme abnormal • Liver function test abnormal • Liver function test increased • Liver disorder <u>Liver injury PTs:</u> • Liver injury • Drug-induced liver injury • Hepatocellular injury	Hospital discharge/specialist letters Gastroenterology management and investigations/confirmation of diagnosis (MRI/CT/USS, liver function tests/liver panel and other relevant tests) Co-morbidities, hepatic risk factors (herbal and complementary

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Cholestatic liver injury • Mixed liver injury • Extrahepatic biliary tree injury • Acute hepatic failure • Acute on chronic liver failure • Hepatic failure • Subacute hepatic failure • Hepatitis • Hepatitis acute • Hepatitis toxic • Hepatotoxicity • Hepatitis cholestatic • Hepatitis fulminant • Immune-mediated hepatitis • Liver transplant • Hepatic necrosis	medicines use, alcohol, obesity etc), medications and family history important
Neurologic	Anosmia, ageusia	There is no Brighton Collaboration case definition yet. **ACCESS/VAC4EU** has begun a draft Event Definition Form but it does not include diagnostic criteria.	• Anosmia • Ageusia	Duration and history of persistence/resolution of symptoms History of sinusitis/ENT problems and surgery or trauma
Dermatologic	Chilblain-like lesions	There is no Brighton Collaboration case definition yet, nor any international standard clinical definitions of chilblain-like lesion.	• Chilblains • Pernio-like erythema	Clinical presentation – signs and symptoms

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
		ACCESS/VAC4EU has begun a draft Event Definition Form but it does not include diagnostic criteria		Association with temperature change particularly cold Hospital discharge/specialist letters Rheumatologist management and investigations/confirmation of diagnosis (biopsy result, vascular imaging, relevant blood tests) Co-morbidities, autoimmune risk factors, medications and family history important
Dermatologic	Erythema multiforme	There is no Brighton Collaboration case definition yet. **ACCESS/VAC4EU** has begun to draft an Event Definition Form which includes consensus classification of Erythema multiforme based on morphological criteria.	• Erythema multiforme	Hospital discharge/specialist letters Dermatologist/immunologist management and investigations/confirmation of diagnosis (biopsy result, relevant tests) Co-morbidities, other risk factors, medications and family history important

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
Endocrine	Subacute thyroiditis	There is no Brighton Collaboration case definition yet.	• Autoimmune thyroiditis • Immune-mediated thyroiditis • Silent thyroiditis • Thyroiditis acute • Thyroiditis subacute • Thyroiditis	Hospital discharge/specialist letters Endocrinologist management and investigations/confirmation of diagnosis (thyroid function tests, USS/nuclear medicine imaging, relevant tests) Co-morbidities, thyroid/autoimmune risk factors, medications and family history important
Gastrointestinal	Pancreatitis	There is no Brighton Collaboration case definition yet.	• Pancreatitis • Autoimmune pancreatitis • Immune-mediated pancreatitis • Pancreatitis acute • Pancreatitis viral	Hospital discharge/specialist letters Gastroenterologist management and investigations/confirmation of diagnosis (CT/USS, amylase/lipase and other relevant tests) Co-morbidities, pancreatitis risk factors (alcohol etc), medications and family history important

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
Musculoskeletal	Rhabdomyolysis	There is no Brighton Collaboration case definition yet. Uptodate(37): Diagnosis based on presence of elevated serum CK (all cases – signifies muscle necrosis/rhabdomyolysis) +/- myoglobinuria (not all cases) +/- hx. of myalgia/hx. muscle pain, injury (not always). Complications of rhabdomyolysis include acute kidney injury, rarely DIC.	• Rhabdomyolysis • Blood creatine phosphokinase MM increased • Blood creatine phosphokinase increased • Blood creatine phosphokinase abnormal • Myoglobinuria • Myoglobin urine • Myoglobin urine present • Chromaturia	Hospital discharge/specialist letters Nephrologist management and investigations/confirmation of diagnosis (Serum CK, CT-KUB/USS, urinalysis/urine tests) Co-morbidities, risk factors (muscle trauma/injury), medications and family history important

Table 4. Category 4: AESI added by TGA following clinical evaluation

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
Special populations	Pregnancy and birth outcomes	There is no Brighton Collaboration case definition yet. Brighton Collaboration plan to publish update in March 2021 focusing on COVID-19 disease outcomes in pregnancy and childhood along with long term complications(3).	Pregnancy outcomes: • Abortion • Aborted pregnancy • Abortion complete • Abortion complete complicated • Abortion complicated • Abortion early • Abortion incomplete • Abortion incomplete complicated	

Commented [s22]: Multiple specific pregnancy adverse outcomes listed by AZ RMP PTs list including eclampsia/pre-eclampsia, GDM, placenta praevia etc – for review to include?

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Abortion induced • Abortion late • Abortion missed • Abortion spontaneous • Abortion spontaneous complete • Abortion spontaneous complete complicated • Abortion spontaneous complicated • Abortion spontaneous incomplete • Abortion spontaneous incomplete complicated • Abortion threatened • Imminent abortion • Selective abortion • Exposure during pregnancy • Maternal exposure during pregnancy • Foetal death • Foetal exposure during pregnancy • Foetal growth restriction • Foetal malformation	

Commented s22: PT in MedDRA but not included in FDA PT terms – includes abortion induced - complete, - complete complicated, - complicated, - incomplete, - incomplete complicated

Commented s22: Not in FDA PTs list

Commented s22: Mutiple foetal PTs

BODY SYSTEM	AESI TYPE	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			Congenital/birth outcomes: • Congenital anomaly • Congenital anomaly in offspring • Low birth weight baby • Premature baby • Premature labour • Stillbirth Neonatal outcomes: • Death neonatal • Neonatal deformity	

Commented $22 Multiple specific PTs included by AZ RMP PTs list including anencephaly, malformations, septal defects, congenital cataract, cleft lip etc – to review for inclusion?

Commented $22: Note: there are many neonatal PTs for various adverse outcomes/conditions. May need to rely on DPAR to pick up specific neonatal outcomes.

Table 5. AEFI for enhanced monitoring and signal detection – public interest/expert advice

CATEGORY	RATIONALE FOR INCLUSION	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
Vaccine error	Multidose vials requiring dilution with normal saline and drawing up of very small volumes for injection(13). Storage and cold-chain handling requirements	N/A – but could be developed from other sources/literature	Administration errors • Accidental exposure to product • Drug administered in wrong device • Exposure via contaminated device • Inadequate aseptic technique in use of product • Incorrect product formulation administered • Incorrect route of product administration • Intercepted product administration error • Occupational exposure to product • Product administration error	Vaccine details: Brand name, batch/Lot number, dose number Multidose vials: Provider details/location Was the dose early in the vial, late in the vial?

CATEGORY	RATIONALE FOR INCLUSION	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Product commingling • Product leakage • Product use complaint • Product use issue • Product use in unapproved indication • Unintentional use for unapproved indication • Wrong device used • Wrong technique in device usage process • Wrong technique in product usage process Equipment • Device issue *Other device PTs – breakage, failure, difficult to use • Exposure to contaminated device • Exposure via contaminated device • Incorrect dose administered by device • Wrong device used • Needle issue • Syringe issue • Product container issue • Product container seal issue General • Medication error • Intercepted medication error • Product use issue • Vaccination error Inappropriate schedule of drug administration • Inappropriate schedule of product administration • Product administered to patient of inappropriate age • Wrong schedule	Storage details (if applicable)

Commented s22 Not sure if device relevant, whether some might report device to mean syringe and needle?

Commented s22 Wondering if container could also mean vial?

Commented s22 Unsure whether to include – getting into specific off-label territory

CATEGORY	RATIONALE FOR INCLUSION	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			Incorrect dose • Accidental overdose • Accidental underdose • Booster dose missed • Dose calculation error • Extra dose administered • Incomplete course of vaccination • Incorrect dose administered • Incorrect product dosage form administered • Overdose • Underdose • Product dose omission in error • Product dose omission issue • Single component of a two-component product administered • Wrong dose • Wrong strength Prescribing and dispensing • Drug dispensed to wrong patient • Intercepted product dispensing error • Intercepted product preparation error • Intercepted product selection error • Product dispensing error • Product dispensing issue • Product preparation error • Product preparation issue • Product selection error • Prescribed overdose • Prescribed underdose Product quality • Expired product administered	

Commented s22 : If given undiluted

Commented s22 Dispensing error – given >6hours after dilution for example

CATEGORY	RATIONALE FOR INCLUSION	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Poor quality product administered • Product contamination • Product contamination chemical • Product contamination microbial • Product contamination physical • Suspected product contamination • Product quality issue • Product quality control issue • Suspected product quality issue • Product reconstitution quality issue • Product sterility lacking • Product storage error Product labelling/packaging • Product confusion • Product design confusion • Product name confusion • Product container issue • Product dosage form confusion • Product identification number issue • Physical product label issue • Product label confusion • Product label issue • Product label on wrong product • Product lot number issue • Product packaging issue • Product outer packaging issue • Product packaging confusion Wrong product • Interchange of vaccine products • Intercepted wrong patient selected • Product substitution error	

CATEGORY	RATIONALE FOR INCLUSION	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Wrong patient received product • Wrong product administered • Wrong drug	
Thrombosis and thrombocytopaenia syndrome (TTS)	Potential link to AstraZeneca vaccination	Any patient presenting with both acute venous or arterial thrombosis AND New onset thrombocytopaenia And no known recent exposure to heparin Level 1 – definite Low platelet count <150 x 10^9/L with a confirmatory peripheral smear showing reduced platelets without clumping (falsely low platelet count) AND Thrombosis/thromboembolism confirmed by at least 1 of: Imaging (USS/Doppler, CT contrast/angiography, MRV/MRA, ECHO, perfusion V/Q scan, conventional angiography/DSA) Surgical Pathologic examination	*See thrombosis PTs – add in CVST/MI to search *See thrombocytopaenia PTs DIC PTs: • Disseminated intravascular coagulation Myocardial Infarction • Coronary artery disease • Microvascular coronary artery disease • Acute myocardial infarction • Myocardial infarction • Silent myocardial infarction VTE PTs: • Thrombosis • Deep vein thrombosis • Pulmonary embolism • Pulmonary thrombosis • Pulmonary venous thrombosis • Subclavian vein thrombosis • Axillary vein thrombosis • Transverse sinus thrombosis • Cavernous sinus thrombosis • Cerebral venous thrombosis • Cerebral venous sinus thrombosis* • Sagittal sinus thrombosis • Vena cava embolism	Platelet count and peripheral smear Imaging reports +/- surgical/pathologic to confirm thrombosis Signs and symptoms reported to confirm thrombosis/thrombosis syndrome D-dimer level *See s22 s22 /international f/u questions form (CRF TTS): D21-2646209 *See VOC f/u questions form (VITT form): D21-2646217

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CATEGORY	RATIONALE FOR INCLUSION	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			• Vena cava thrombosis • Venous thrombosis • Venous thrombosis limb • Embolism venous • Hepatic vein thrombosis • Mesenteric vein thrombosis* • Portal vein thrombosis* • Jugular vein thrombosis • Pelvic venous thrombosis • Renal vein thrombosis • Splenic vein thrombosis* • Retinal vein thrombosis • Visceral venous thrombosis • Splanchnic vein thrombosis (LLT)* General stroke PTs: • Basal ganglia stroke • Brain stem stroke • Cerebellar stroke • Embolic stroke • Lacunar stroke • Spinal stroke • Thrombotic stroke • Vertebrobasilar stroke • Cerebral infarction • Infarction • Cerebrovascular accident Peripheral limb ischaemia PTs: • Peripheral ischaemia	

CATEGORY	RATIONALE FOR INCLUSION	BRIGHTON COLLABORATION AESI CASE DEFINITION LEVELS OF DIAGNOSTIC CERTAINTY/COMPANION GUIDE	MedDRA PTs	Key information for follow-up
			Ischaemic stroke PTs: • Ischaemic stroke • Cerebral small vessel ischaemic disease • Ischaemic cerebral infarction • Transient ischaemic attack Haemorrhagic stroke PTs: • Haemorrhagic cerebral infarction • Haemorrhagic stroke • Haemorrhagic transformation stroke *See also CDC MedDRA PTs for TTS as of 12 May 2021 (Appendix 1)	

Commented [s22]: For review and discussion

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Version history

Version	Description of change	Author	Effective date
1.0	Approved VSS COVID-19 vaccine AESI MedDRA codes – working document.	s22	January 2021
2.0	Added Table 4 – 'Category 4: AESI added by TGA following clinical evaluation' - Pregnancy and birth outcomes added – rationale: special population of interest, missing information in RMP, potential for COVID-19 vaccine administration in this population Added Table 5 – 'AEFI under consideration for enhanced monitoring and signal detection' - Vaccine error added – rationale: special interest from Australian experts, potential risk with multi-dose vial	s22	

Authorisation

Name	Position	Date
s22		28 January 2021

Appendix 1

From CDC presentation to ACIP: "Update: Thrombosis with thrombocytopaenia syndrome (TTS) following COVID-19 vaccination (ACIP) May 12, 2021. Tom Shimabukuro, Vaccine Safety Team.

Slide 40:

Proposed VAERS MedDRA PT and text string search terms for TTS

MedDRA PTs for large vessel thrombosis and embolism in unusual locations Aortic embolus, aortic thrombosis, aseptic cavernous sinus thrombosis, brain stem embolism, brain stem thrombosis, carotid arterial embolus, carotid artery thrombosis, cavernous sinus thrombosis, cerebral artery thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, mesenteric artery embolism, mesenteric artery thrombosis, mesenteric vein thrombosis, splenic artery thrombosis, splenic embolism, splenic thrombosis, thrombosis mesenteric vessel, visceral venous thrombosis, hepatic artery embolism, hepatic artery thrombosis, hepatic vein embolism, hepatic vein thrombosis, portal vein embolism, portal vein thrombosis, portosplenomesenteric venous thrombosis, splenic vein thrombosis, spontaneous heparin-induced thrombocytopenia syndrome, femoral artery embolism, iliac artery embolism, jugular vein embolism, jugular vein thrombosis, subclavian artery embolism, subclavian vein thrombosis, obstetrical pulmonary embolism, pulmonary artery thrombosis, pulmonary thrombosis, pulmonary venous thrombosis, renal artery thrombosis, renal embolism, renal vein embolism, renal vein thrombosis, brachiocephalic vein thrombosis, vena cava embolism, vena cava thrombosis, truncus coeliacus thrombosis

MedDRA PTs for more common thrombotic events Axillary vein thrombosis, deep vein thrombosis, pulmonary embolism

MedDRA PTs for thrombocytopenia Autoimmune heparin-induced thrombocytopenia, Heparin-induced thrombocytopenia, Immune thrombocytopenia, Non-immune heparin associated thrombocytopenia, Spontaneous heparin-induced thrombocytopenia syndrome, Thrombocytopenia, Thrombocytopenic purpura

Text string for"thrombocytopenia" or "low platelets" in symptom text

Special interest identifier	Special interest type	Tradename	Ingredient	MedDRA	Interest Reason
SI000001	MedDRA term			Acute hepatic failure	Critical adverse event
SI000002	MedDRA term			Acute kidney injury	Critical adverse event
SI000003	MedDRA term			Acute myocardial infarction	Critical adverse event
SI000004	MedDRA term			Agranulocytosis	Critical adverse event
SI000005	MedDRA term			Anaphylactic reaction	Critical adverse event
SI000006	MedDRA term			Anuria	Critical adverse event
SI000007	MedDRA term			Aplastic anaemia	Critical adverse event
SI000008	MedDRA term			Blindness	Critical adverse event
SI000009	MedDRA term			Bone marrow failure	Critical adverse event
SI000010	MedDRA term			Cardiac arrest	Critical adverse event
SI000011	MedDRA term			Cardiac failure	Critical adverse event
SI000012	MedDRA term			Cardiomyopathy	Critical adverse event
SI000013	MedDRA term			Cataract	Critical adverse event
SI000014	MedDRA term			Cerebrovascular accident	Critical adverse event
SI000015	MedDRA term			Chronic hepatic failure	Critical adverse event
SI000016	MedDRA term			Completed suicide	Critical adverse event
SI000017	MedDRA term			Congenital anomaly	Critical adverse event
SI000018	MedDRA term			Death	Critical adverse event
SI000019	MedDRA term			Electrocardiogram QT prolonged	Critical adverse event
SI000020	MedDRA term			Encephalitis	Critical adverse event
SI000021	MedDRA term			Epilepsy	Critical adverse event
SI000022	MedDRA term			Glaucoma	Critical adverse event
SI000023	MedDRA term			Guillain-Barre syndrome	Critical adverse event
SI000024	MedDRA term			Haemolytic anaemia	Critical adverse event
SI000025	MedDRA term			Haemorrhage intracranial	Critical adverse event
SI000026	MedDRA term			Hepatic failure	Critical adverse event
SI000027	MedDRA term			Hyperkalaemia	Critical adverse event
SI000028	MedDRA term			Hyponatraemia	Critical adverse event
SI000029	MedDRA term			Intraocular pressure increased	Critical adverse event
SI000030	MedDRA term			Leukaemia	Critical adverse event
SI000031	MedDRA term			Liver transplant	Critical adverse event
SI000032	MedDRA term			Lymphoma	Critical adverse event
SI000033	MedDRA term			Malignant melanoma	Critical adverse event
SI000034	MedDRA term			Myocardial infarction	Critical adverse event
SI000035	MedDRA term			Neoplasm	Critical adverse event
SI000036	MedDRA term			Optic neuritis	Critical adverse event
SI000037	MedDRA term			Pancreatitis	Critical adverse event
SI000038	MedDRA term			Pancytopenia	Critical adverse event
SI000039	MedDRA term			Papilloedema	Critical adverse event
SI000040	MedDRA term			Paralysis	Critical adverse event
SI000041	MedDRA term			Pathological fracture	Critical adverse event
SI000042	MedDRA term			Progressive multifocal leukoencephalopathy	Critical adverse event
SI000043	MedDRA term			Pulmonary fibrosis	Critical adverse event
SI000044	MedDRA term			Renal failure	Critical adverse event
SI000045	MedDRA term			Renal failure chronic	Critical adverse event

Special interest identifier	Special interest type	Tradename	Ingredient	MedDRA	Interest Reason
SI000046	MedDRA term			Respiratory failure	Critical adverse event
SI000047	MedDRA term			Seizure	Critical adverse event
SI000048	MedDRA term			Stevens-Johnson syndrome	Critical adverse event
SI000049	MedDRA term			Subacute hepatic failure	Critical adverse event
SI000050	MedDRA term			Suicidal ideation	Critical adverse event
SI000051	MedDRA term			Torsade de pointes	Critical adverse event
SI000052	MedDRA term			Toxic epidermal necrolysis	Critical adverse event
SI000053	MedDRA term			Ventricular arrhythmia	Critical adverse event
SI000054	MedDRA term			Ventricular tachyarrhythmia	Critical adverse event
SI000342	MedDRA term			Multisystem inflammatory syndrome	Critical adverse event
SI000343	MedDRA term			Multisystem inflammatory syndrome in children	Critical adverse event
SI000344	MedDRA term			Multisystem inflammatory syndrome in adults	Critical adverse event
SI000345	MedDRA term			MIS-A	Critical adverse event
SI000346	MedDRA term			MIS-C	Critical adverse event
SI000347	MedDRA term			Paediatric inflammatory multisystem syndrome	Critical adverse event
SI000348	MedDRA term			Paediatric multisystem inflammatory syndrome	Critical adverse event
SI000349	MedDRA term			Pediatric inflammatory multisystem syndrome	Critical adverse event
SI000350	MedDRA term			Pediatric multisystem inflammatory syndrome	Critical adverse event
SI000351	Tradename	TN011710 COMIRNATY ORIGINAL/OMICRON BA.1 COVID-19 Vaccine - (tozinameran/riltozinameran)			New chemical entity
SI000352	Tradename	TN011319 COMIRNATY Original/Omicron BA (TNS) COVID-19 Vaccine - (tozinameran/not specified)			New chemical entity
SI000353	Tradename	TN011711 COMIRNATY ORIGINAL/OMICRON BA.4-5 COVID-19 Vaccine - (tozinameran/famtozinameran)			New chemical entity
SI000354	Tradename	TN011214 Spikevax Bivalent Original / Omicron COVID-19 vaccine - (elasomeran/imelasomeran)			New chemical entity
SI000355	Tradename	TN011724 SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 COVID-19 vaccine - (elasomeran/davesomeran)			New chemical entity
SI000356	Tradename	TN011725 SPIKEVAX BIVALENT (TNS) ORIGINAL/OMICRON COVID-19 vaccine - (elasomeran/not specified)			New chemical entity
SI000360	Active ingredient		AI010705 riltozinameran		New chemical entity
SI000361	Active ingredient		AI010780 famtozinameran		New chemical entity
SI000362	Active ingredient		AI010565 imelasomeran		New chemical entity
SI000363	Active ingredient		AI010735 davesomeran		New chemical entity
SI000364	Active ingredient		AI011004 raxtozinameran		New chemical entity
SI000365	Active ingredient		AI010980 andusomeran		New chemical entity