COVID-19 vaccines: Thromboembolic events with thrombocytopenia

CHM 27 March 2021

Medicines & Healthcare products Regulatory Agency

Background

- Reports of cerebral venous and other central venous thromboses occurring with thrombocytopenia
- AZ vaccination programme temporarily suspended in some EU MS
- MHRA statement published on 18 March:
  - Available evidence does not suggest venous thromboembolism caused by AZ vaccine
  - On-going review of very rare cerebral sinus vein thrombosis occurring together with thrombocytopenia (5 UK cases, < 1 in 1 million vaccinated people at that time)
  - Benefit continues to outweigh the risk
- EMA similar statement published on 18 March (18 cases CVST, 7 DIC) – some but not all MS who paused have restarted vaccination programme
- Further EMA statement 25 March updating on review progress

Thrombosis and thrombocytopenia in COVID-19

- Both thrombosis and thrombocytopenia occur in COVID-19 infection
- Incidence of thrombocytopenia on admission (36.2%, Liao et al)
- Thromboembolic event rates range from 20-70%, with higher rates in ICU
- Venous TE rate 21% , 31% in ICU (Malas et al)
- Correlation with more severe disease and death
- Thrombosis can occur after recovery from acute infection, even seemingly mild
- Case series from Brazil thrombotic events 2- 4 weeks following recovery (Vechi et al)

Case validation

- Confirmed :

Venous/ arterial thrombosis + Platelet count < 150 + D-dimer > 4000 + anti-PF4 antibodies +

- Probable:

Venous/ arterial thrombosis + Platelet count < 150 + D-dimer > 4000

- Possible case:

Venous/ arterial thrombosis + Platelet count < 150

- Unlikely:

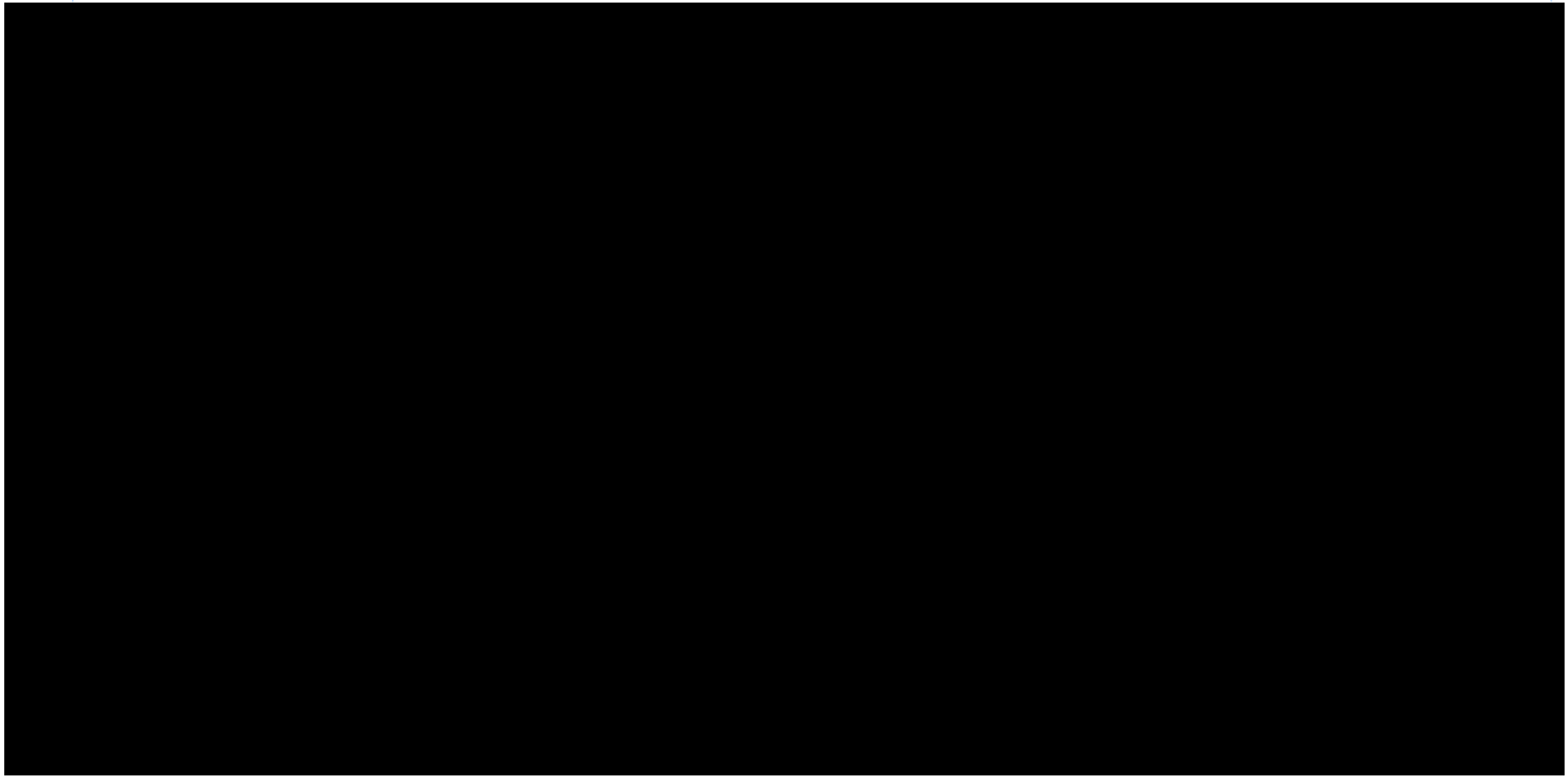
Criteria met for any of the above BUT alternative diagnosis more likely to explain event.

- Criteria not met:- one or none of the criteria met

CVST in YC database

	Cerebral venous sinus thrombosis
CHADOX1 NCOV-19	31
ETHINYLESTRADIOL	26
LEVONORGESTREL	17
CARBOPLATIN	7
CYCLOPHOSPHAMIDE	7
DOXORUBICIN	7
PACLITAXEL	7
NORETHISTERONE	6
ADALIMUMAB	5
ESTRADIOL	4

Thrombo-embolic reports with thrombocytopenic related reactions[1] vs CVST/SSST reactions* vs cumulative UK usage up to 24/03/2021



Data reviewed

- UK Yellow Card cases up to DLP of 24th March
- Cases individually evaluated by WHO causality criteria
- Assessed against case validation criteria
- Evaluate likelihood of being identified case
- Independent adjudication of individual cases by 2 haematologists
- Final results summarised and in circulated spreadsheets

Summary AZ CVST

- 25 cases total
- Overall age range (19- 70, more details on next slide)
- Dose 1 (22/25), 3 unknown
- Gender (7 M, 18 F)
- Fatal (25- 68, med 50.5, mean 28.23)

Category	Number meeting criteria	Notes
Confirmed	5	2 lacking D-dimers, had PF4
Probable	2	D-dimers (>10000, >30000)
Possible	15	2 borderline unlikely (1 ACS and nightly pyrexial spikes unknown origin)
Unlikely	3	AIH, pancreatic cancer, alcohol abuse
Criteria not met	0	N/A

Overview of age by classification- CVST + thrombocytopenia

Overall age range: 19-70

Overall mean age: 45

Classification	Age range	Mean age	No. cases
Confirmed	26-55	45	4
Probable	30-39	34	3
Possible	19- 70	47	15
Unlikely	25-58	46	3

Comparative exposure data – 1st doses

Age group	Estimated number of first AZ doses in UK (1,000,000s)	%	Estimated number of first Pfizer doses in UK (1,000,000s)	%
18-29 yrs	[redacted]	[redacted]	[redacted]	[redacted]
30-39 yrs	[redacted]	[redacted]	[redacted]	[redacted]
40-49 yrs	[redacted]	[redacted]	[redacted]	[redacted]
50-64 yrs	[redacted]	[redacted]	[redacted]	[redacted]
65+ yrs	[redacted]	[redacted]	[redacted]	[redacted]
Total*	18.1	100	10.9	100

* Includes 2 patients with unknown age

Incidence rate – further analysis of CVST (all cases assumed to be after 1st dose)

Age group	Estimated number of first doses in UK (1,000,000s)	Total number of cases	Case incidence rate (per 1 million doses)	Exc. unlikely cases	Case incidence rate (per 1 million doses)	Number of fatal cases (inc. unlikely)	Fatal incidence rate (per 1 million doses)
18-29 yrs	[redacted]	5	[redacted]	4	[redacted]	1	[redacted]
30-39 yrs	[redacted]	5	[redacted]	5	[redacted]	2	[redacted]
40-49 yrs	[redacted]	4	[redacted]	4	[redacted]	1	[redacted]
50-64 yrs	[redacted]	6	[redacted]	4	[redacted]	2	[redacted]
65+ yrs	[redacted]	3	[redacted]	3	[redacted]	2	[redacted]
Total*	18.1	25	1.4 (0.9,2.0)	22	1.2	8	0.4

* Includes 2 patients with unknown age

Incidence rate – further analysis of CVST (all cases assumed to be after 1st dose)

Age/sex group	Estimated number of first doses in UK (1,000,000s)	Total number of cases	Case incidence rate (per 1 million doses)
Males <50	[redacted]	7	[redacted]
Males 50+	[redacted]	1	[redacted]
Total	8.5	8	0.9 (0.4,1.9)

Age/sex group	Estimated number of first doses in UK (1,000,000s)	Total number of cases	Case incidence rate (per 1 million doses)
Females <50	[redacted]	7	[redacted]
Females 50+	[redacted]	8	[redacted]
Total*	9.6	17	1.8 (1.0,2.8)

* Includes 2 patients with unknown age

Summary AZ non - CVST

- 10 cases total
- Overall age range (25-73, med 61, mean 54)
- Dose 1 (10/10),
- Gender (3 M, 7 F)
- Fatal (1 fatality- [redacted])

Category	Number meeting criteria	Notes
Confirmed	0	
Probable	1	
Possible	7	[redacted]
Unlikely	0	
Criteria not met	2	[redacted]

Overview of age by classification AZ non - CVST

Overall age range: 25-73

Overall mean age: 54

Classification	Age range	Mean age	No. cases
Confirmed	0	0	0
Probable	73		1
Possible	25-64	47	7
Criteria not met	60-70	65	2

Overview of age by classification AZ CVST and non – CVST combined

Overall age range: 19 -73

Overall mean age: 47

Classification	Age range	Mean age	No. cases
Confirmed	26-55	45	4
Probable	30-73	44	4
Possible	19-70	47	22
Unlikely	25-58	46	3
Criteria not met	60-70	65	2

Incidence rate – further analysis (CVST + other TE, all cases assumed to be after 1st dose)

Age group	Estimated number of first doses in UK (1,000,000s)	Total number of cases	Case incidence rate (per 1 million doses)	Exc. unlikely cases	Case incidence rate (per 1 million doses)	Number of fatal cases (inc. unlikely)	Fatal incidence rate (per 1 million doses)
18-29 yrs	[redacted]	6	[redacted]	5	[redacted]	1	[redacted]
30-39 yrs	[redacted]	7	[redacted]	7	[redacted]	3	[redacted]
40-49 yrs	[redacted]	4	[redacted]	4	[redacted]	1	[redacted]
50-64 yrs	[redacted]	10	[redacted]	7	[redacted]	2	[redacted]
65+ yrs	[redacted]	5	[redacted]	4	[redacted]	2	[redacted]
Total*	18.1	35	1.9	30	1.7	9	0.5

* Includes 3 patients with unknown age

Pfizer UK Reports

Two UK cases of CVST with the Pfizer COVID-19 vaccine – neither of these report concurrent thrombocytopenia and so **do not** meet the case definition criteria

- [redacted]

[redacted]

TTP – 1 case - case definition not met

- [redacted]

Pfizer non-UK cases – thrombosis and thrombocytopenia

Probable Case

- [redacted]

Possible Case

- [redacted]

Unlikely Case

- [redacted]

Criteria not met

- [redacted]

Pfizer – US publication

Publication of series of cases reporting thrombocytopenia within 2 weeks of vaccine with mRNA COVID-19 vaccines in US data sources

Two cases identified reporting thrombotic events with thrombocytopenia following Pfizer vaccine:

1. 44/F - hospitalized for nausea, vomiting and chest pain on the day of vaccination. Platelet count of 85 × 10^9 /L and a peak troponin level of 4 ng/mL (normal < = 0.04 ng/ mL). The patient was diagnosed with myocarditis but did not require treatment for thrombocytopenia. Her platelets were 61 × 109 /L on discharge, but subsequent platelet counts were not reported.
2. Unknown age or gender reported thrombocytopenia, neutropenia and a pulmonary embolism at an unspecified time following the Pfizer vaccine. This patient was hospitalized and passed away.

No cases of interest were identified with the Moderna vaccine

Janssen data

[redacted] **Clinical trial case**:

- [redacted]

Company Comments:

- [redacted]
- Janssen's safety database including all Ad26-based vaccines no risk for hypercoagulability or thrombotic events.

[redacted]

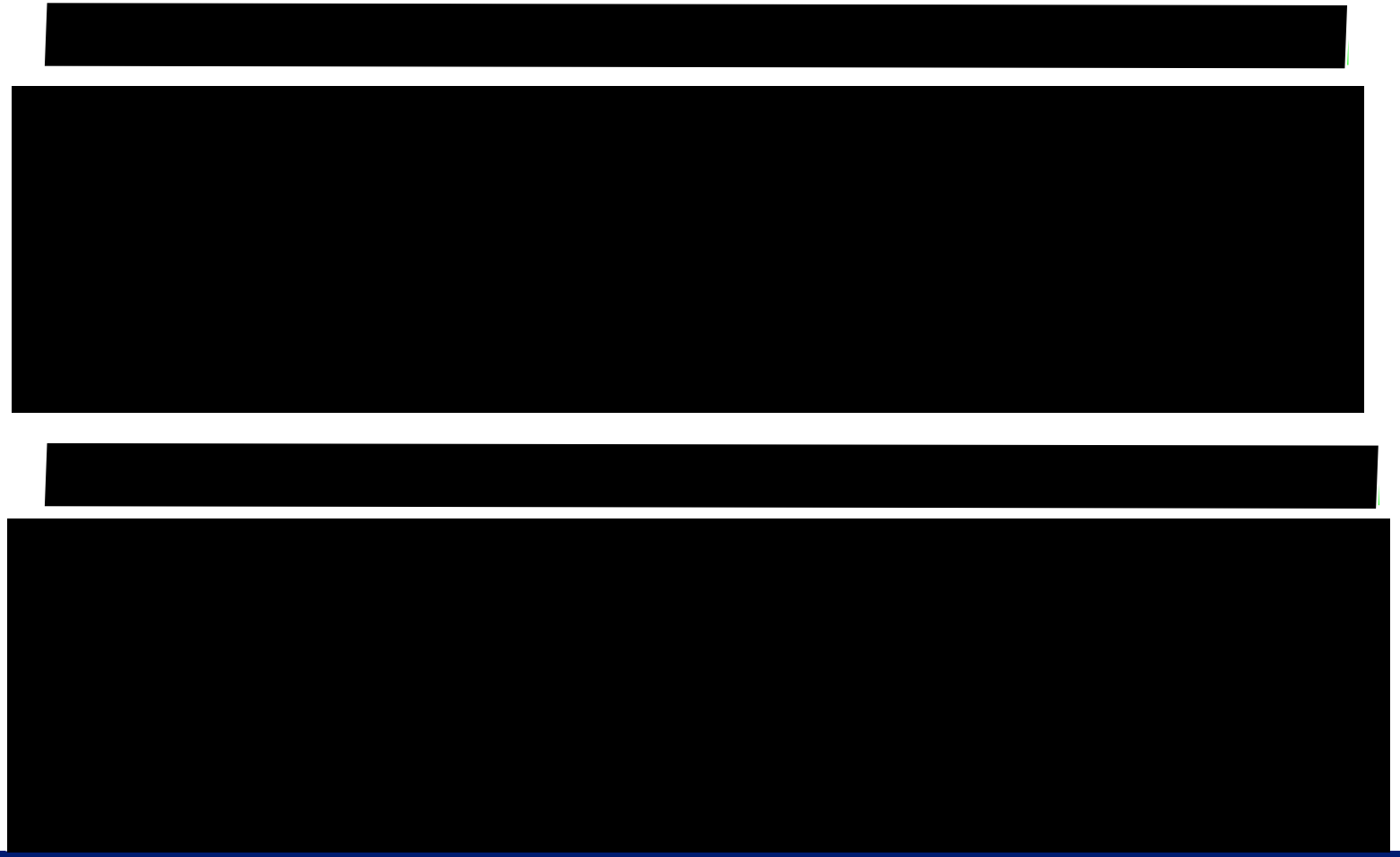
Epidemiology analysis – signal strengthening

Analyses conducted by PHE [redacted]

Hospital inpatient admissions in all ages from the Secondary Uses Service

[redacted]

Epidemiology analysis – signal strengthening



Epidemiology analysis – signal strengthening

3) [redacted]

[redacted]

Benefit risk assessment

Estimates of vaccine effectiveness have been calculated by PHE.

Using these estimates have been made of the number of cases, long COVID cases (persistence of cluster of symptoms beyond 5 week), hospitalisations, and deaths (within 28 days of positive test) prevented per 1,000,000 vaccinations over an assumed third wave.

The vaccine effectiveness estimates used are:

- Against being a case (any case, and a long COVID case) = [redacted]
- Against hospitalisation = [redacted]
- Against death = [redacted]

Benefit risk assessment

- Cases and long COVID – [redacted]

Age group	Number of cases prevented per 1m vaccinations	Number of long COVID cases prevented per 1m vaccinations*
20-29	[redacted]	[redacted]
30-39	[redacted]	[redacted]
40-49	[redacted]	[redacted]
50-59	[redacted]	[redacted]
60-69	[redacted]	[redacted]
70-79	[redacted]	[redacted]
80+	[redacted]	[redacted]

* Assumes 10% of cases experience long COVID

Benefit risk assessment

- Hospitalisation and mortality (per 1 million doses)

Age group	Number of hospitalisations prevented [redacted]	Number of deaths (within 28 days) prevented*	No. of cases of CVST exc. unlikely (95% CI)	No. of fatal cases of CVST inc. unlikely (95% CI)
20-24				
25-29				
30-34				
35-39				
40-44				
45-49				
50-54				
55-60				
60-64				
65-70				

* Assuming 2 doses given

Benefit risk assessment

- Hospitalisation and mortality (per 1 million doses)

Age group	Number of hospitalisations prevented [redacted]	Number of deaths (within 28 days) prevented*	Number of cases of CVST+TE (exc. unlikely)	Number of fatal cases of CVST+TE (inc. unlikely)
20-24				
25-29				
30-34				
35-39				
40-44				
45-49				
50-54				
55-60				
60-64				
65-70				

* Assuming 2 doses given

Opportunities for further epidemiological analysis

- Case ascertainment is the biggest challenge – reporting from haematologist/neurologists supported by follow up of possible cases in SUS
- Vaccination status (and details) should be available – need COVID test data
- Case-crossover or self-controlled case series design preferred approach or both given confounding – risk window?
- May have to be multi-country study to achieve enough sample size – however, we should pursue UK study independently
- Collaborative work with PHE
- Potential for further comparison of reported cases across vaccines using quantitative bias assessments

Questions to EWG

1. On the case definition:

a. Does CHM agree with the definition of cases as venous AND Platelet count of less 150 x 10 9/L, D-dimer more than 4000 and positive anti-PF4 antibodies?

b. Should the case definition include CVST and all cases of major vein thrombosis with thrombocytopenia?

c. Should the case definition also include major arterial thrombosis?

2. On benefit risk: Based on the evidence presented does the CHM consider the benefit:risk remains positive?

3. Is there an age threshold below which the risk benefit of vaccination is not clearly in favour of vaccination?

4. Does the CHM consider the benefit:risk is positive for males and females?

5. What is the CHM's view on the risk:benefit of the vaccine in pregnant women?

Questions to EWG

6. Dose relationship: Does the CHM consider there is any evidence of risk for the second dose of the vaccine?

7. Background rate: Can CHM advise on any data sources to evaluate the background rate of thrombosis with thrombocytopenia, including the impact of COVID-19?

8. Risk in children: Can the CHM advise on the continuation of clinical trials in children?

9. Risk communication: Can the CHM advise on appropriate communication based on the current evidence?

Additional slides

EU product information – section 4.4

Thrombocytopenia and coagulation disorders

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, mesenteric vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of these cases occurred within the first seven to fourteen days following vaccination and occurred in women under 55 years of age, however this may reflect the increased use of the vaccine in this population. Some cases had a fatal outcome.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

Search criteria

Any cases in the Embolic and thrombotic events (SMQ) which also report any term from the thrombocytopenia related list of events:

Acquired amegakaryocytic thrombocytopenia, Amegakaryocytic thrombocytopenia, Autoimmune heparin-induced thrombocytopenia, Autoimmune thrombocytopenia, Congenital thrombocytopenia, Haemangioma-thrombocytopenia syndrome, Heparin-induced thrombocytopenia, Heparin-induced thrombocytopenia test, Heparin-induced thrombocytopenia test positive, Idiopathic thrombocytopenic purpura, Immune thrombocytopenia, Immune thrombocytopenic purpura, Neonatal alloimmune thrombocytopenia, Non-immune heparin associated thrombocytopenia, Petechiae, Platelet count abnormal, Platelet count decreased, Purpura, Purpura non-thrombocytopenic, Severe fever with thrombocytopenia syndrome, Thrombocytopenia, Thrombocytopenia neonatal, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura

Additonal separate search for any cases in the HLT Cerebrovascular venous and sinus thrombosis and any reports of the PT Disseminated intravascular coagulation

Table 2. WHO-UMC Causality Categories

Causality term	***Assessment criteria****
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

* All points should be reasonably complied with

COVID-19 VACCINE UK Clinical trials with paediatric subjects

2020-001228-32	**ChAdOx1 nCoV-19 vaccine / SA-optional booster added to Groups 4 and 6 @4-12 wks**	**University of Oxford**	**A phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 Investigating a Vaccine Against COVID-19** **Heathly subjects - Adults aged 18 or older (group 4); Adults aged 56 or older (groups 1 and 2); Children aged 5-12 inclusive (group 3)/ Note - 13th August 2020 'Seasonal Flu Vaccine' now not excluded.**
2020-005765-13	ChAdOx1 nCoV-19||Bexsero	UNIVERSITY OF OXFORD	A single-blind, randomised, phase II study to determine safety and immunogenicity of the Coronavirus Disease (COVID-19) vaccine ChAdOx1 in UK healthy children and adolescents (aged 6-17)
2020-005720-11	Ad26.COV2.S	Janssen	HORIZON 2 - A Randomized, Double-blind, Placebo-controlled, Phase 2/3 Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Different Dose Levels of Ad26.COV2.S Administered as a Two-dose Regimen Followed by a Booster in Healthy Children From Birth to 17 Years Inclusive When Compared to the Administration of One- and Two-doses of Ad26.COV2.S (in a Two-dose Regimen) in Healthy Adults Aged 18 to 55 Years Inclusive
2020-002584-63	Ad26.COV2.S (also known as Ad26COVS1)||Ad26.COV2.S (also known as Ad26COVS1)	JANSSEN VACCINES & PREVENTION BV	A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate a Range of Dose Levels and Vaccination Intervals of Ad26.COV2.S in Healthy Adults Aged 18 to 55 Years Inclusive and Adults Aged 65 Years and Older and to Evaluate 2 Dose Levels of Ad26.COV2.S in Healthy Adolescents Aged 12 to 17 Years Inclusive

Investigating a Vaccine Against COVID-19 (COV002) [COVID-19] [UPH] - Health Research Authority (hra.nhs.uk)

A phase II study of a candidate COVID-19 vaccine in children (COV006) [COVID-19] - Health Research Authority (hra.nhs.uk)

Phase 2a COVID-19 Vaccine Study - VAC31518COV2001(COVID-19)(UPH) - Health Research Authority (hra.nhs.uk)