Appendix A

Guidelines for data collection, analysis and presentation of thrombosis and thromboembolism

It was the consensus of the Brighton Collaboration *Thrombosis and Thromboembolism Working Group* to recommend the following guidelines to enable meaningful and standardized collection, analysis, and presentation of information about thrombosis and thromboembolism. However, implementation of the guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographical region, and whether the source of information is a prospective clinical trial, a post-marketing surveillance or epidemiological study, or an individual report of thrombosis and thromboembolism. These guidelines have been developed by the Brighton Collaboration working group for guidance only, and are not to be considered mandatory requirements for data collection, analysis, or presentation.

Data collection

These guidelines represent a desirable standard for the collection of data on thrombosis and thromboembolism following immunization to allow for comparability of data, and are recommended as an addition to data collected for the specific study question and setting. The guidelines are not intended to guide the primary reporting of thrombosis and thromboembolism to a surveillance system or study monitor. Investigators developing a data collection tool based on these data collection guidelines also need to refer to the criteria in the case definition, which are not repeated in these guidelines.

Guidelines 1, 2, 5, 6, 9, 11-14, 17-20 and 22-24 below have been developed to address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,[a] and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences.[b] These data elements include an identifiable reporter and patient, one or more prior immunizations, and a detailed description of the adverse event, in this case, of thrombosis and thromboembolism following immunization. The additional guidelines have been developed as guidance for the collection of supplementary information to allow a more comprehensive understanding of thrombosis and thromboembolism following immunization.

Source of information/reporter

For all cases or study participants, as appropriate, the following information should be recorded:

1) Date of report.
2) Name and contact information of person reporting[1] and/or diagnosing the thrombosis and thromboembolism as specified by country-specific data protection law.
3) Name and contact information of the investigator responsible for the subject, as applicable.
4) Relationship to the patient (e.g., immunizer [clinician, nurse], family member [indicate relationship], other).

[a] ICH. Post-approval safety data management: definitions and standards for expedited reporting E2D 2003 Available from: https://database.ich.org/sites/default/files/E2D_Guideline.pdf. [Last accessed: 16 December 2021]

[b] CIOMS. Available from: https://cioms.ch/wp-content/uploads/2019/11/Fillable-Form_CIOMS-to-E2B.pdf. [Last accessed 16 December 2021]

Vaccinee/Control

Demographics

For all cases or study participants, as appropriate, the following information should be recorded:

5) Case/study participant identifiers (e.g. first name initial followed by last name initial) or code (or in accordance with country-specific data protection laws).
6) Date of birth, age, and sex.
7) For infants: gestational age and birth weight.

Clinical and immunization history

For all cases or study participants, as appropriate, the following information should be recorded:

8) Past medical history, including hospitalizations, underlying conditions, diseases or disorders, including pregnancy status, allergies, risk factors for thrombosis and thromboembolism, pre-immunization signs and symptoms including identification of indicators for thrombosis and thromboembolism.
9) Any medication history (other than treatment for the event described) prior to, during, and after immunization including prescription and non-prescription medication as well as medications or treatments with long half-life or long-term effect. (e.g., immunoglobulins, blood product transfusion, anticoagulation therapies, immunosuppressants).
10) Immunization history (i.e. previous immunizations and any adverse event following immunization (AEFI)), in particular occurrence of thrombosis and thromboembolism after a previous immunization and history of allergy to vaccines or vaccine components.

Details of the immunization

For all cases or study participants, as appropriate, the following information should be recorded:

11) Date and time of immunization(s).
12) Description of vaccine(s) (name of vaccine, manufacturer, lot number, dose (e.g. 0.25mL, 0.5 mL) and number of dose if part of a series of immunizations against the same disease).
13) The anatomical sites (including left or right side) of all immunizations (e.g. vaccine A in proximal left lateral thigh, vaccine B in left deltoid).
14) Route and method of administration (e.g. intramuscular, intradermal, subcutaneous, and needle-free (including type and size), other injection devices).
15) Needle length and gauge.

The adverse event

16) For all cases at any level of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet the case definition should be recorded.

Specifically document:

17) Clinical description of signs and symptoms of thrombosis and thromboembolism, and if there was medical confirmation of the event (i.e. patient seen by physician, specific testing).
18) Date/time of onset[2], first observation[3] and diagnosis[4], end of episode[5] and final outcome[6].
19) Concurrent signs, symptoms, and diseases.
20) Measurement/testing
    - values and units of routinely measured parameters (e.g., laboratory tests such as D-dimers), in particular, those indicating the severity of the event;
    - method of measurement (e.g. imaging studies such as Doppler ultrasound; angiography, magnetic resonance);
    - timing of measurement in relation to clinical manifestations;
    - results of laboratory examinations, surgical and/or pathological findings and diagnoses, if present.

21) Treatment given for the thrombotic/thromboembolism event, (specify what treatment and provide dosage information.
22) Outcome[6] at last observation.
23) Objective clinical evidence supporting classification of the event as 'serious' [7].
24) Exposures, other than the immunization, 24 hours before and after immunization (e.g. food, environmental) considered potentially relevant to the reported event.

Miscellaneous/ General

25) The duration of surveillance for thrombosis/thromboembolism should be predefined based on:
    - characteristics of the vaccine e.g., live attenuated versus inactivated component vaccines, vaccine platform;
    - biologic characteristics of the vaccine-targeted disease;
    - biologic characteristics of the thrombosis and thromboembolism, including patterns identified in previous trials (e.g. early-phase trials); and
    - biologic characteristics of the vaccinee (e.g., underlying disease, presence of risk factors).
26) The duration of follow-up reported during the surveillance period should also be defined. It should continue until resolution of the event.
27) Methods of data collection should be consistent within and between study groups, if applicable.
28) Follow-up of cases should attempt to verify and complete the information collected as outlined in data collection guidelines 1 to 24, above.
29) Investigators of patients with thrombosis/thromboembolism should provide guidance to reporters to optimize the quality and completeness of information provided.
30) Reports of thrombosis/thromboembolism should be collected throughout the study period regardless of the time elapsed between immunization and the adverse event. If this is not feasible due to the study design, the study periods during which safety data are collected should be clearly defined.

Data analysis

The following guidelines represent a desirable standard for analysis of data on thrombosis and thromboembolism to allow for comparability of data, and are recommended in addition to data analyzed for the specific study question and setting.

31) Reported events should be classified in one of the following five categories, including the three levels of diagnostic certainty. Events that meet the case definition should be classified according to the levels of diagnostic certainty as specified in the case definition. Events that do not meet the case definition should be classified in the additional categories for analysis.

Event classification in 5 categories[8]

Event meets case definition:

1) Level 1: *Criteria as specified in the thrombosis/thromboembolism case definition*
2) Level 2: *Criteria as specified in the thrombosis/thromboembolism case definition*
3) Level 3: *Criteria as specified in the thrombosis/thromboembolism case definition*

Event does not meet case definition

Additional categories for analysis

4) Reported case of thrombosis/thromboembolism with insufficient evidence to meet the case definition[9]
5) Not a case of thrombosis/thromboembolism

32) The interval between immunization and reported event of thrombosis/thromboembolism could be defined as the date/time of immunization to the date/time of onset[2] of the first symptoms or signs consistent with the definition. If few cases are reported, the actual times could be analyzed for each case but when there are many cases, data can be analyzed in the following increments:

Individuals with thrombosis/thromboembolism by interval to presentation

Interval	**Number / (%)**
≤4 days after immunization	
5-14 days after immunization	
15-28 days after immunization	
29-42 days after immunization	
≥42 days after immunization	
TOTAL	

33) The duration of a possible case of thrombosis/thromboembolism could be analyzed as the interval between the date/time of onset[1] of the first symptoms or signs consistent with the definition and the end of episode[5] or final outcome[6]. Whatever start and ending are used, they should be used consistently within and across study groups.

34) If more than one measurement of a particular criterion is taken and recorded, the value corresponding to the greatest magnitude of the adverse experience could be used as the basis for analysis.

35) The distribution of data (as numerator and denominator data) could be analyzed in predefined increments (e.g., measured values, times), where applicable. Increments specified above should be used. When only a small number of cases is presented, the respective values or times course can be presented individually.

36) Data on thrombosis/thromboembolism obtained from subjects receiving a vaccine should be compared with those obtained from an appropriately selected and documented control group(s) to assess background rates of hypersensitivity in non-exposed populations, and should be analyzed by study arm and dose where possible, e.g., in prospective clinical trials.

Data presentation

These guidelines represent a desirable standard for the presentation and publication of data on thrombosis/thromboembolism following immunization to allow for comparability of data, and are recommended in addition to data presented for the specific study question and setting. Additionally, it is recommended to refer to existing general guidelines for the presentation and publication of randomized controlled trials, systematic reviews, and meta-analyses of observational studies in epidemiology (e.g., statements of Consolidated Standards of Reporting Trials (CONSORT), of Improving the quality of reports of meta-analyses of randomized controlled trials (QUORUM), and of Meta-analysis Of Observational Studies in Epidemiology (MOOSE), respectively).[c]

37) All reported events of thrombosis/thromboembolism should be presented according to the categories listed in guideline 31.

38) Data on possible thrombosis/thromboembolism events should be presented in accordance with data collection guidelines 1-24 and data analysis guidelines 31-36 when applicable.

[c] Available from: https://www.equator-network.org/

39) Terms to describe thrombosis/thromboembolism such as ‘low-grade’, ‘mild’, ‘moderate’, ‘high’, ‘severe’ or ‘significant’ are highly, prone to varied interpretation, and should be avoided, unless clearly defined.

40) Data should be presented with numerators and denominators (n/N) and not only in percentages, if available.
Although immunization safety surveillance systems denominator data are usually not readily available, attempts should be made to identify approximate denominators. The source of the denominator data should be reported and the calculations of estimates be described, e.g., manufacturer data such as total doses distributed, reporting through Ministry of Health, coverage/population based data.

41) The incidence of cases in the study population should be presented and clearly identified as such in the text.

42) If the distribution of data is skewed, medians and ranges are usually more appropriate statistical descriptors than a means and standard deviations. However, the mean and standard deviation should also be provided.

43) Any publication of data on thrombosis or thromboembolism should include a detailed description of the methods used for data collection and analysis as possible. It is essential to specify:
- the study design;
- the method, frequency and duration of monitoring for thrombosis or thromboembolism;
- the trial profile, indicating participant flow during the trial, including drop-outs and withdrawals to indicate the size and nature of the respective groups under investigation;
- the type of surveillance, e.g., passive or active surveillance;
- the characteristics of the surveillance system e.g., population-based, mode of reporting;
- the search strategy in surveillance databases;
- comparison group(s), if used for analyses;
- the instrument for data collection, e.g., standardized questionnaire, diary card, report form;
- whether the day of immunization was considered ‘day one’ or ‘day zero’ in the analysis;
- whether the date of onset[2] or the date of first observation[3] or the date of diagnosis[4] was used for analysis; and
- use of this case definition for thrombosis/thromboembolism, in the abstract or methods section of a publication.[11]

Notes for guidelines

[1]If the reporting center is different from the vaccinating center, appropriate and timely communication of the adverse event should occur.

2The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative for thrombosis/thromboembolism occurred. This may only be possible to determine in retrospect.

3The date and/or time of first observation of the first sign or symptom indicative for thrombosis/thromboembolism can be used if date/time of onset is not known.

[4]The date of diagnosis of an episode is the day post immunization when the event met the case definition at any level.

[5]The end of an episode is defined as the time the event no longer meets the case definition at the lowest level of the definition.

[6] E.g., recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death.

[7]An AEFI is defined as serious by international standards if it meets one or more of the following criteria: 1) it results in death, 2) is life-threatening, 3) it requires inpatient hospitalization or results in prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, 5) is a congenital anomaly/birth defect, 6) is a medically important event or reaction.

[8]To determine the appropriate category, the user should first establish, whether a reported event meets the criteria for the lowest applicable level of diagnostic certainty, e.g., Level three. If the lowest applicable level of diagnostic certainty of the definition is met, and there is evidence that the criteria of the next higher level of diagnostic certainty are met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event could be determined. Major criteria can be used to satisfy the requirement of minor criteria. If the lowest level of the case definition is not met, it should be ruled out that any of the higher levels of diagnostic certainty are met and the event should be classified in additional categories four or five.

[9]If the evidence available for an event is insufficient because information is missing, such an event should be categorized as ‘reported case of thrombosis/thromboembolism with insufficient evidence to meet the case definition’.

[10]An event does not meet the case definition if investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as ‘not a case of thrombosis/thromboembolism’.

[11]Use of this document should preferably be referenced by referring to the respective link on the Brighton Collaboration website (https://brightoncollaboration.us/).