Safety Platform for Emergency vACcines

SO1-D2.7 Guidance for vaccine safety data collection, presentation and analysis

Work Package: WP2 Standards and tools

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Description of the deliverable	This deliverable summarizes Brighton Collaboration guidance on the collection, interpretation analysis and presentation of safety data relevant for CEPI candidate vaccine trials. Summary checklists are provided so CEPI developers can check the degree to which their protocols and case report forms are harmonized with published Brighton collaboration safety data guidelines for vaccine pre- and post-licensure clinical trials including those for pregnant women. It also includes sample AEFI CRFs, guidance on solicited local and systemic reactogenicity and Tier 1 AESI.
Key words	AEFI, AESI, Brighton case definitions, anaphylaxis, thrombocytopenia, generalized convulsion, aseptic meningitis, encephalitis, myelitis, acute disseminated encephalomyelitis, Guillain Barré syndrome, Miller Fisher syndrome, peripheral facial nerve palsy/Bell's palsy, injection site abscess / cellulitis, fatigue, diarrhea.

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DEFINITIONS & ACRONYMS

ADEM	Acute disseminated encephalomyelitis
AE	Adverse event
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
ARDS	Acute Respiratory Distress Syndrome
BC	Brighton Collaboration
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness Innovations
CHIKV	Chikungunya virus
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central nervous system
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
DSMB	Data and safety monitoring board
GBS	Guillain Barré Syndrome
GAIA	Global Alignment of Immunization Safety Assessment in Pregnancy
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
LF	Lassa Fever
MERS	CoV Middle East respiratory syndrome coronavirus
MISC	Multisystem Inflammatory Syndrome of Children
MVA	Modified Vaccinia Virus Ankara
NiV	Nipah virus
RSV	Respiratory syncytial virus
RVF	Rift Valley fever
rVSV	Recombinant vesicular stomatitis virus
SPEAC	Safety Platform for Emergency vACcines
VAED	Vaccine associated enhanced disease
WHO	World Health Organization
YF	Yellow fever

1. Background

The need for standardization

To maximize the learnings about vaccine safety in clinical trials, it is essential to have standard approaches to vaccine safety data collection, presentation and analysis.

Without globally accepted standard case definitions for assessing adverse events following immunization (AEFIs), it is difficult, if not impossible, to compare safety data across studies with any validity. Global standardization might enable comparability of vaccine safety data collected from clinical trials, surveillance systems, individual case reports, and retrospective epidemiologic studies.

In the Brighton Collaboration's first published guidance on collection analysis and presentation of safety data for pre- and post-licensure vaccine trials it was noted: "…in early phase trials, even a single serious AEFI can lead to a comprehensive review to assess whether the AEFI was causally related to the experimental vaccine or not. Pending outcome of the review, the trial may be halted" This has recently been observed in COVID-19 vaccine trials. Further it was pointed out that "…the level of detail, accuracy and completeness of AEFI reports is a vital factor in the generation of reliable data on vaccine product safety".

CEPI has partnered with the Brighton Collaboration, through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key part of the SPEAC activities related to harmonization has been to develop lists of potential adverse events of special interest (AESI) based on events known to follow immunization or linked to specific vaccine platforms as well as events that are theoretically possible because they are seen with wild type disease arising from viral replication and/or immunopathogenesis. Table 1 summarizes the AESI, by body system, which have been identified for the current CEPI target diseases and provides the rationale for their inclusion. It also identifies those which already have a Brighton case definition and those which are under active development and targeted for completion by December 2020.

TABLE 1. COLLATED AESI IDENTIFIED FOR LASSA FEVER(LF), MERS, NIPAH VIRUS INFECTION (NiV), RIFT VALLEY FEVER (RVF), CHIKUNGUNYA(CHIKV) AND COVID-19. AESI in red font have published Brighton case definitions. AESI in blue font have Brighton case definitions under active development.

BODY SYSTEM	AESI Rationale for inclusion (see table footnotes for explanation)	Target Diseases and/or Vaccine Platforms
Immunologic	Anaphylaxis[1]	All vaccines
	Vaccine associated enhanced disease (VAED)[1,2,5]	MERS, COVID-19; Formalin-inactivated measles/RSV[2]; HIV vaccine[2]; Chimeric YF Dengue vaccine[2]; SARS/MERS-CoV vaccines, mouse model[5]
	Multisystem inflammatory syndrome in children (MISC)[3,4]	COVID-19
Respiratory	Acute respiratory distress syndrome (ARDS)[3,4]	COVID-19, MERS, NiV
Cardiac	Acute cardiovascular injury [3,4] (includes myocarditis, pericarditis, arrhythmias, heart failure, infarction)	COVID-19, LF, CHIKV, MVA platform
Hematologic	Thrombocytopenia [1,3,4]	COVID-19, CHIKV

BODY SYSTEM	AESI Rationale for inclusion (see table footnotes for explanation)	Target Diseases and/or Vaccine Platforms
	Coagulation disorder [3,4] (includes coagulopathy, thrombosis, thromboembolism, internal/external bleed, stroke)	COVID-19, LF, RVF, MERS
Renal	Acute kidney injury[3,4]	COVID-19, MERS, RVF, CHIKV
Gastrointestinal	Acute liver injury[3,4]	COVID-19, RVF, CHIKV
Neurologic	Guillain Barré Syndrome[3]	COVID-19, RVF, CHIKV, some inactivated vaccines (*seasonal & pandemic flu, Rabies Semple vaccine, Tetanus toxoid)*
	Acute disseminated encephalomyelitis (ADEM)[3]	COVID-19, MERS, CHIKV
	Aseptic meningitis [2]	COVID-19, LF, NiV, CHIKV, live vaccines
	Meningoencephalitis[2,4]	COVID-19, LF, MERS, NiV, RVF, CHIKV, live vaccines
	Generalized convulsion[1,2,4]	COVID-19, NiV, RVF, CHIKV, live vaccines
	Peripheral facial nerve palsy [1,2,3,4]	COVID-19, CHIKV, E. coli heat labile toxin adjuvanted intranasal influenza vaccine (Nasalflu, Berna Biotech)
	Sensorineural hearing loss [3]	LF
	Anosmia, ageusia[3,4]	COVID-19
	Optic neuritis[3]	CHIKV
Eye	Visual loss (including uveitis, retinitis)	RVF, CHIKV
Dermatologic	Chilblain-like lesions[3,4]	COVID-19
	Single organ cutaneous vasculitis[3,4]	COVID-19
	Erythema multiforme[3,4]	COVID-19
	Alopecia	COVID-19, LF, CHIKV
Musculoskeletal	Acute aseptic arthritis[2]	rVSV platform
	Acute & chronic inflammatory rheumatism[3,4]	CHIKV
Pregnancy / Foetal / Neonatal	Maternal / Neonatal death [4]	LF, MERS
	Spontaneous abortion / stillbirth [3,4]	LF, MERS, CHIKV
	Miscarriage [4]	RVF
	Neonatal sepsis [3,4]	CHIKV
	Neonatal encephalopathy [3,4]	CHIKV
	Neonatal neurodevelopmental delay [3,4]	CHIKV

1. *Proven association with immunization encompassing several different vaccines*
2. *Proven association with vaccine that could theoretically be true for CEPI vaccines under development*
3. *Theoretical concern based on immunopathogenesis.*
4. *Theoretical concern related to viral replication during wild type disease.*
5. *Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.*

In addition to ensuring standard case definitions are available for the AESI, SPEAC is developing tools and resources to aid in the application of the case definitions so a uniform approach is taken to gathering the data needed to meet a case definition and to using the data to assign level of certainty. This will facilitate identification and interpretation of safety signals should they arise during the clinical trials.

CEPI funded vaccine developers are responsible for safety monitoring of their products and have the responsibility to comply with regulatory requirements. Many have years of experience in vaccine research and as part of that have developed their own case report forms. Others are newer to the field and may not yet

have a standard set of clinical trial documents and tools. Most do not have specific forms to gather data related to the many AESI.

This deliverable is designed to assist all CEPI vaccine developers in determining whether their existing clinical trial protocols and CRFs follow Brighton guidelines for safety data collection. It is important to note that all the published guidelines[1,3,4] were harmonized with existing ICH and CIOMS guidelines but also extended the minimum set of information to be gathered on vaccine safety.

This deliverable also provides sample CRFs for AEFI, and specific guidance related to solicited local and systemic reactogenicity as well as the following AESI: anaphylaxis, thrombocytopenia, generalized convulsion, aseptic meningitis, encephalitis, myelitis, acute disseminated encephalomyelitis, Guillain Barré Syndrome and idiopathic peripheral facial nerve palsy. Guidance for other AESI will be provided in future updates planned for February 2021.

The focus of this deliverable is for CEPI sponsored vaccine development targeting Lassa Fever, MERS, Nipah virus, Rift Valley Fever and Chikungunya. That said, it should also be useful for COVID-19 vaccine developers since it adds to the preliminary guidance document from August 2020 in terms of checklists to assess protocol/CRF harmonization with Brighton guidance on pre- and post-licensure clinical trials including those involving pregnant women and it provides guidance on the AESI noted above.

2. Objectives of this deliverable

1. To outline the scope of existing Brighton Collaboration guidance on vaccine safety data collection analysis and presentation for pre- and post-licensure clinical trials, including those involving pregnant women.
2. To summarize the published guidance noted above into checklists that can be used by CEPI vaccine developers to determine the degree to which their clinical protocols/CRFs are aligned with the Brighton guidelines.
3. To provide Brighton Collaboration AEFI report forms for developers who may not have them.
4. To share a SPEAC Memory Aid created and submitted as a recommendation to the WHO COVID-19 Solidarity Protocol, along with SPEAC guidance on solicited local and systemic reactogenicity.
5. To provide guidance on real-time AESI investigations that will facilitate assessing the level of certainty against a given case definition as well as to gather evidence for causality assessment to distinguish between coincidental events and those that could represent vaccine product related adverse events. The focus for this deliverable will be on Tier 1 AESI which include: anaphylaxis, thrombocytopenia, generalized convulsion, aseptic meningitis, encephalitis, myelitis, acute disseminated encephalomyelitis, Guillain Barré syndrome and idiopathic peripheral facial nerve palsy (Bell's palsy).

3. Methods

Previously published Brighton Collaboration Guidelines were reviewed in depth. These included:

- 2009 guidelines on collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies.
- 2013 template protocol for clinical trials investigating vaccines with a focus on safety elements.
- 2016 guidance for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women.
- 2016 guidance on case report form variables to assess safety in clinical trials of vaccines in pregnancy.

Checklist tabular summaries were created based on the guidelines, capturing key recommendations for safety aspects of the clinical trial protocol as well as the variables that should be collected in the clinical trial in general, and separately for trials involving pregnant women.

A previously completed SPEAC deliverable on **Preliminary guidance on safety data collection for COVID-19 vaccine safety (D2.4)** was used as the source of Data collection forms for safety which were originally published in the 2013 template protocol.[3] Similarly the sample SPEAC Memory Aid for Solidarity Protocol and SPEAC guidance on solicited local and systemic reactogenicity were obtained, unchanged, from the D2.4 COVID-19 vaccine safety guidance document.

Using the same tabular structure from the guidance document on solicited local and systemic reactogenicity a table was developed for the Tier 1 AESI to summarize the essential 'real-time' clinical assessment and investigations needed to meet each AESI case definition as well as to guide data analysis, based on careful review of the original Brighton publications. [6-12]

4. Results

4.1 Recommended safety data collection, analysis and presentation

Appendix 1 contains tabular summary checklists for vaccine safety data made in the 2009 guidelines that apply in general to clinical trial protocols addressing vaccine safety and that were endorsed in the more recent 2013 template protocol and the 2016 guidelines specific to clinical trials involving pregnant women. These include:

- Table 1. Recommended roles and responsibilities for AEFI reporting
- Table 2. General recommendations for AEFI data collection
- Table 3. General recommendations for AEFI data analysis
- Table 4. General recommendations for AEFI data presentation

Appendix 2 presents a CRF for vaccine trial safety data, that was published in the 2013 Brighton template protocol for vaccine trials. [3] This may serve as a resource for developers framing their own CRFs. It includes:

- Appendix 2-I. Baseline assessment form: to be used for baseline information collection for each participant independent from AEFI.
- Appendix 2-II. AEFI report form: to be used when an AEFI is reported for the first time.
- Appendix 2-III. AEFI follow-up form: to be used for all follow-up visits after the first.

Appendix 3 presents tabular checklists that summarize the data captured by the recommended Brighton clinical trial template presented in Appendix 2. These are structured in 3 tables corresponding to the Baseline assessment, AEFI report and AEFI follow-up report to enable assessments of the degree to which the CRFs planned for use in the clinical trial meet the Brighton guidelines.

Appendix 4 provides an example of a subject memory aid for collection of local and systemic solicited reactogenicity data on AEFI. This was initially developed by IAVI for their VSV vaccine platform. IAVI gave permission for SPEAC to adapt it as a sample for the COVID-19 Solidarity protocol and it was included in the SPEAC guidance deliverable 2.4 on COVID-19 vaccine trials. It is reproduced here as relevant guidance for CEPI sponsored vaccine trials focused on Lassa Fever, MERS, Nipah virus, Rift Valley Fever and Chikungunya.

Appendix 5 provides the SPEAC guidance on presentation and analysis of solicited local and systemic reactogenicity data. Similar to the memory aid noted above it is provided to assist all developers with standardized collection of safety data to facilitate comparability across clinical trials.

Appendix 6 provides the SPEAC guidance on presentation and analysis of the priority tier 1 AESI specifically: anaphylaxis, thrombocytopenia, generalized convulsion, aseptic meningitis, encephalitis, myelitis, acute disseminated encephalomyelitis, Guillain Barré syndrome and idiopathic peripheral facial nerve palsy (Bell's palsy). It also includes a glossary of terms relevant to anaphylaxis and the neurologic case definitions.

Appendix 7 presents tabular checklists that summarize the GAIA recommendations for safety data variables to be collected in clinical trials involving pregnant women. These are presented in several tables as follows:

- Table 1. Recommended clinical trial site background data collection for maternal, fetal and neonatal outcomes.

- Table 2. Recommended pre-vaccination screening data including maternal demographics, medical and obstetric history, physical exam, laboratory investigation; and fetal data.
- Table 3. Recommended study vaccine administration and related data for pre-vaccination measurements, procedures related to the investigational vaccine and immunization procedures and post vaccination safety data.
- Table 4a. Recommended maternal/fetal/birth and neonatal data to capture following vaccination.
- Table 4b. Recommended maternal and infant follow-up data to capture, following delivery or early termination of pregnancy.
- Table 5. Recommended AEFI data collection and monitoring data to collect in the vaccinated mother or fetus/neonate/infant of the vaccinated mother.
- Table 6. 2009 Brighton recommendations for safety data analysis[1]
- Table 7. 2009 Brighton recommendations for pre- and post-licensure vaccine trial safety data presentation[1]
- Supplemental Table A Priority 1 recommendations for testing related to infections that may have impact on the immunogenicity, efficacy and/or safety of pregnancy vaccines or aid interpretation of events that occur in the mother, fetus, neonate or infant.[4]
- Supplemental Table B. GAIA guide to data to collect to inform obstetrical risk assessment.[5]

4.2 Recommendations on safety data collection for Lassa Fever, MERS, Nipah, Rift Valley Fever, Chikungunya vaccine trials.

These align with the SPEAC preliminary guidance on safety data collection for COVID-19 vaccine safety (specifically recommendations 2 through 7, 10, and 12 through 14). They also extend that guidance in terms of providing the CRF checklists and recommendations for AESI. As such these recommendations (1, 2 regarding assessing existing CRFs as well as 8 and 10 below) also apply to CEPI COVID-19 vaccine developers.

1. CEPI vaccine developers are encouraged to review the Brighton 2009 guidance on safety data collection, analysis and presentation.[1] As an aid, Appendix 1 contains tabular checklists that summarize the 2009 guidance.
2. If possible, all study sites should use a common vaccine safety Case Report Form (CRF) as published in the Brighton 2013 guideline[3] and presented in Appendix 2. It is understood that many if not most developers already have their own CRFs. In this case the CRF should be reviewed using the tabular checklists in Appendix 3 which capture all the recommended safety data variables. Ideally any gaps in safety data collection can be remedied using the appropriate portion of the CRF in Appendix 2.
3. All participants should be followed for local (pain, tenderness, induration/swelling, erythema) and systemic (fever, fatigue/malaise, myalgia/body ache, headache, nausea, chill, arthralgia/joint pain, shivering and lymphadenopathy) reactogenicity from Day 0-7 post each injection via a subject diary (or equivalent technological application). This is the minimum information one would use to inform new vaccinees about what they might expect in terms of common adverse events. An example of a memory aid for collection of these data is provided (Appendix 4).
4. Grading of adverse events should be standardized to promote comparison between vaccine candidates. The FDA Guidance for Industry (September 2007): "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" offers a standardized and broadly accepted tool for this purpose. It can be accessed at: https://www.fda.gov/media/73679/download .
5. All non-solicited Adverse Events (AEs) for 30 days post-each injection should be collected.
6. All participants should be followed for Serious Adverse Events (SAEs) for the duration of the study until resolution.
    - If the trial is a 'First in Humans' trial data collection for SAEs should be continued for a minimum of 6 months following immunization.

- If vaccine enhanced disease has been identified as a possible AESI (true for MERS and COVID-19 vaccine candidates) there should be a minimum of 3-years follow-up for such events if possible.

7. All participants should be followed for new onset chronic disease for the duration of the study.
8. All participants should be followed for the duration of the study for AESIs defined by SPEAC as part of their landscape analysis of CEPI target disease. SPEAC recommends that the developers take a uniform approach to the identification, assessment, investigation, analysis and reporting of any AESI should it occur during a clinical trial. Some AESI are common to all vaccines and others are limited to those developed against a specific target disease or based on a specific type of vaccine platform. These are outlined below:
   - All vaccine candidates regardless of target disease or vaccine platform: anaphylaxis, GBS, ADEM, thrombocytopenia, generalized convulsion.
   - All target disease live vaccines: aseptic meningitis, meningoencephalitis, generalized convulsion
   - rVSV vaccine platform: acute aseptic arthritis
   - MVA vaccine platform: myocarditis
   - Lassa Fever vaccine candidates: sensorineural hearing loss; encephalopathy; coagulopathy; pericarditis; maternal death; neonatal death; spontaneous abortion; stillbirth; alopecia.
   - MERS vaccine candidates: vaccine enhanced disease; ARDS, coagulopathy including stroke; encephalitis; acute kidney injury; maternal death; neonatal death; spontaneous abortion; stillbirth.
   - Nipah Virus vaccine candidates: ARDS; encephalitis/encephalomyelitis.
   - Rift Valley Fever vaccine candidates: unilateral or bilateral blindness/decreased vision; meningoencephalitis; acute liver injury; acute kidney injury; coagulopathy; spontaneous abortion; stillbirth.
   - Chikungunya vaccine candidates: acute and chronic inflammatory rheumatism; meningitis; encephalitis; myelitis; generalized convulsion; sensorineural abnormalities including cranial nerve palsies; myocarditis/pericarditis; arrhythmias; uveitis/retinitis; acute kidney injury; acute liver injury; spontaneous abortion/stillbirth; neonatal infection; neonatal encephalopathy; neonatal neurodevelopmental delay.

     It is possible that new entities will be added to the AESI lists based on updated literature reviews, newly generated vaccine safety templates and occurrence of unexpected serious AEFI during clinical trials involving CEPI candidate vaccines. Should this occur developers will be notified immediately.
9. Study protocols should identify the predefined AESI along with specific plans for whether they will be monitored routinely during the clinical trial or if not routinely monitored, how they will be identified, investigated and followed should one or more occur as an AEFI. Appendix 6 provides specific recommendations for the Tier 1 AESI, which include: anaphylaxis, thrombocytopenia, generalized convulsion, aseptic meningitis, GBS, encephalitis, myelitis, acute disseminated encephalomyelitis and idiopathic peripheral facial nerve palsy. Similar recommendations will be provided for the AESI assigned to Tiers 2, 3 and 4 in due course and once ready, developers will be notified.
10. All pregnancies occurring on study should be followed using a standardized pregnancy registry to collect information on the maternal and neonatal outcomes. For safety data collection in pregnancy we refer to the Brighton Collaboration case definitions delivered by the GAIA project. For collection, analysis and presentation of safety data see Appendix 7 which summarizes the GAIA guidelines[4,5] including identification of safety data variables considered essential or complementary related to maternal, fetal, birth, neonatal and infant outcomes.
11. For clinical trials that include pregnant women, the CRFs should be compared to the checklists summarizing GAIA published guidance for safety data collection, analysis and presentation[4,5] (Appendix 7) to determine completeness of safety data collection. Any gaps in safety data collection for essential variables should be remedied.
12. All participants should be followed for clinical signs of the respective target disease using a standardized case definition and suggested evaluation plan (to include laboratory confirmation, clinical severity scores that will aid in evaluation of possible enhanced disease, if relevant).
13. Stopping rules and pause rules should be in place prior to study start.

14. Data should be entered electronically at the site within 24 hours of each visit and coded by experienced data managers to allow for timely IDMC review. AEs should be coded into Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The number and percentage of subjects experiencing each specific adverse event should be tabulated by severity and relationship to study product. A complete listing of AEs for each subject should provide details including severity, relationship to study product, onset, timing post-last vaccination, duration and outcome.

5. Conclusions and recommendations

This guidance document was created to support CEPI developers of vaccines targeting Lassa Fever, MERS, Nipah virus, Rift Valley Fever and Chikungunya. They are also relevant to COVID-19 vaccines in terms of the checklists described below as well as guidance on AESI that were not included in the separate COVID-19 guidance document.

It provides:

- Several checklists that summarize published Brighton Guidance for safety data collection, analysis and presentation in pre- and post-licensure clinical trials. These are intended for use by the developers to assess the degree to which their trial protocol and CRFS meet the recommended guidelines. Specifically:
  - Appendix 1 provides a checklist for safety aspects of the study protocol
  - Appendix 3 provides a checklist for the recommended CRF safety data elements
  - Appendix 7 provides several checklists for CRF safety data collection in trials involving pregnant women including fetal/neonatal outcomes and further categorizes the data as essential or non-essential/complementary priority.
- Forms that can be used for safety data collection related to baseline assessment, AEFI reports and AEFI follow-up reports. These were originally published in the 2013 guidance[3] and are reproduced in Appendix 2.
- A sample SPEAC memory aid for solicited local/systemic reactions in Appendix 4.
- Condensed SPEAC guidance on data collection and analysis for solicited local and systemic reactions, including as appropriate, specific recommendations from published Brighton case definitions.
- Specific recommendations for data collection and investigation of the following unsolicited but important local and systemic reactions:
  - Injection site abscess
  - Injection site cellulitis
  - Injection site nodule
  - Fatigue
  - Diarrhea
- Condensed SPEAC recommendations for data collection, investigation and analysis of the following AESIs :
  - Anaphylaxis
  - Thrombocytopenia
  - Generalized convulsion
  - Aseptic meningitis
  - Guillain Barré Syndrome and Miller Fisher Syndrome
  - Encephalitis, myelitis, acute disseminated encephalomyelitis
  - Peripheral facial nerve palsy (Bell's palsy)

The SPEAC team recommends that developers (CEPI or otherwise funded) use the guidance document for collection of safety data, as this will allow for better comparison across trials and vaccines.

The SPEAC team also recommends that CEPI requires developers who have their own CRFs to use the checklist tools provided in this guidance document to assess and report back on the degree to which they are harmonized with the Brighton guidelines.

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ANNEXES

ANNEX I:

Brighton Collaboration Guidance for Vaccine Safety Data Collection, Analysis and Presentation in Pre- and Post-licensure Clinical Trials

This captures key Brighton recommendations for clinical vaccine trial safety data first published in 2009[1] and updated in 2013[3]. The recommendations are presented as checklists for use by CEPI Vaccine Developers to indicate the degree to which their protocol and related instruments and methodologies meet the guidelines.

Checklist for Brighton Recommendations for AEFI reporting Vaccine Safety Data Collection, Analysis and Presentation

TABLE 1. RECOMMENDED ROLES AND RESPONSIBILITIES FOR AEFI REPORTING[3]

Investigator	☐ Accurate documentation of event ☐ Follows-up to ensure completeness of information related to the event ☐ Respects notification deadlines ☐ Provides the sponsor with all necessary information ☐ Gives access to source documents if requested by sponsor
Sponsor	☐ Specified requirements for investigator to report to trial sponsor including: o Responsible individual reporters o Method of reporting o Minimal required information o Time frames for SAE, expedited and non-expedited AEFI / AESI reporting o Data privacy regulations ☐ SAE reporting required as soon as the site is alerted to it (≤24h) ☐ Specified that preliminary notification for SAE to be made by phone or other specified immediate reporting method containing minimal required information: o Reporter information o Trial participant ID number o Study vaccine, immunization date o Event description and severity o Investigator's causality assessment ☐ Clearly specifies any non-serious AESI that require expedited reporting ☐ Clearly specified that full regular AEFI report form with all event details to be submitted following preliminary notification
Sponsor reporting to regulatory authorities	☐ Regulatory reporting requirements specified for each country where product is registered, and trial being done including: oTimelines for reporting SAE, unexpected AEFI, deaths, life-threatening events, pre ☐ Method of reporting clearly stated (fax, mail, email, other; phone/fax numbers / address to be used) ☐ Any third party, such as contract research organization charged with pharmacovigilance or safety matters is clearly identified along with method of reporting
Sponsor reporting to data safety monitoring board (DSMB) if applicable	☐ Note if sponsor responsible for informing the DSMB of any SAE ☐ Planned reporting procedure is described

TABLE 2. AEFI DATA COLLECTION THE TABULAR CHECKLIST BELOW IS BASED ON AN AMALGAMATION OF RECOMMENDATIONS PUBLISHED BY THE BRIGHTON COLLABORATION FOR PRE- AND POST-LICENSURE VACCINE CLINICAL TRIALS.[1,3]

<table>
<tr><th colspan="2">Solicited AEFI</th></tr>
<tr><td>Duration of post-immunization follow up</td><td>☐ Daily for 7 days
☐ Daily for 14 days
☐ Other (specify)</td></tr>
<tr><td>Instrument(s)</td><td>☐ Subject diary
☐ Subject Memory aide
☐ Other (describe)</td></tr>
<tr><td>Solicited Local AEFI
Check all that are being collected and indicate how defined and severity classification</td><td>
<table>
<tr><th>Injection site:</th><th>Case definition</th><th>Intensity scale</th></tr>
<tr><td>Pain</td><td>☐ Brighton
☐ Other (specify)</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Tenderness</td><td>☐ Specify:</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Swelling</td><td>☐ Brighton
☐ Other (specify)</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Induration</td><td>☐ Brighton
☐ Other (specify)</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Redness</td><td>☐ Specify:</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Other(specify)</td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Solicited Systemic AEFI</td><td>
<table>
<tr><th>Systemic event</th><th>Case definition</th><th>Severity rating</th></tr>
<tr><td>Fever</td><td>☐ Brighton
☐ Other (specify)</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Fatigue</td><td>☐ Brighton
☐ Other (specify):</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Chills</td><td>☐ Other (specify)</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Headache</td><td>☐ Other (specify)</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Nausea</td><td>☐ Other (specify):</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Malaise</td><td>☐ Other (specify):</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Myalgia</td><td>☐ Other (specify):</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Arthralgia</td><td>☐ Other (specify):</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Diarrhea</td><td>☐ Other (specify):</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Vomiting</td><td>☐ Other (specify):</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
<tr><td>Other</td><td>☐ Other (specify):</td><td>☐ FDA toxicity scale
☐ Other (specify)</td></tr>
</table>
</td></tr>
</table>

Unsolicited AEFI	
Plans for surveillance and reporting	☐ Predefined duration of surveillance. ___Yes __No If yes describe: ☐ Any special reporting requirements for selected participants? If yes specify AEFI report form that will be used ☐ CIOMS form ☐ Brighton recommended AEFI report form from 2009 guidance[1] ☐ Brighton recommended AEFI report from from 2013 guidance[3] ☐ Other – specify and complete the tabular checklist for recommended AEFI report form data elements or submit to SPEAC for review AEFI follow up report form that will be used ☐ CIOMS form ☐ Brighton recommended AEFI report form from 2009 guidance[1] ☐ Brighton recommended AEFI follow-up report form from 2013 guidance [3] ☐ Other - specify and complete the tabular checklist for recommended AEFI follow-up report form data elements or submit to SPEAC for review
SAE	☐ All SAE occurring during entire trial period will be recorded. Includes from time participant signs informed consent through last follow-up visit, early termination visit or death – whichever comes first For First in Human studies indicate duration of SAE follow-up: ☐ At least 6 months ☐ <6 months (specify:) ☐ Not applicable
AEFI instructions: The Protocol / Study procedures manual should specify each of the following for AEFI. Check all that are specified and for any that can't be checked, indicate how it will be handled.	☐ Timeline for validating AEFI and SAE ☐ Time frame for completion and submission of all AEFI reports ☐ Separate AEFI report to be submitted for each AEFI ☐ Time frame for completion and submission of AEFI follow-up form ☐ Management of study participants with AEFI including: o Access to health care and necessary treatments offered for AEFI of interest including all SAE o State that compensation criteria and mechanisms for compensation are provided in a separate compensation guidance. o Procedure and timeline for communicating safety-relevant information from current trial and other relevant studies
AESI	Predefined AESI have been designated and will be monitored: ☐ Yes – as recommended by SPEAC in whole or in part. List the ones to be monitored and describe how and for how long they will be monitored. Explain why any of the SPEAC recommended AESI are not being included.

	☐ Yes – in addition to those recommended by SPEAC. List the ones to be monitored and describe how and for how long they will be monitored. ☐ No
AEFI/AESI Specimen management and biobanking for future investigation	☐ Any differences in management from what is done as part of routine study investigations is described detailing how specimens will be processed, labelled, handled, shipped, stored and documented.
Causality assessment of individual cases	☐ Specified method for assessing causality. Describe including the classification categories to be used
Causality assessment on a population basis	Plans for population-based causality assessment? ☐ Yes (describe) ☐ No ☐ Not applicable given sample size
Criteria for modifying protocol or halting trial	☐ Clearly specified in protocol ☐ Decision making responsibility clearly assigned ☐ Communication strategy with trial stakeholders, investigators and participants provided ☐ Appropriate regulatory requirements detailed including communications between stakeholders ☐ Potential unblinding procedures for individual or all study codes for safety evaluation specified
Regulations and guidelines applicable to AEFI management	☐ All relevant specific legislation or regulations applicable for all trial settings identified

TABLE 3. CHECKLIST FOR GUIDELINES RELATED TO VACCINE SAFETY DATA ANALYSIS. THESE FOLLOW THE 2009 GUIDELINES[1] WHICH WERE ENDORSED AND RECOMMENDED FOR USE IN THE 2013 GUIDELINE[3]

AEFI to be analyzed by:	☐ Study arm ☐ Study dose ☐ Vaccine lot ☐ Vaccinated subjects vs control subjects. If yes specify the control:
AEFI/AESI with a Brighton Case Definition	The guidelines recommend, for AESI with a Brighton case definition, that the following classification be used: ● Event meets the case definition: ▪ Level 1 of diagnostic certainty ▪ Level 2 of diagnostic certainty ▪ Level 3 of diagnostic certainty ● Event does not meet the case definition ▪ Level 4: Reported event but insufficient evidence to meet definition ▪ Level 5: Not an event as defined In this trial: ☐ Level of certainty will be determined ___Yes __No __Undecided If yes who will determine the level of certainty: ☐ Site investigator ☐ CRO monitor

	☐ Sponsor b19ased on reported information ☐ Other – describe If No or undecided, describe analysis plans for AEFI/AESI:
AEFI with no Brighton Case Definition	Describe analysis plans for AEFI with no Brighton case definition:
AEFI onset	Interval (hours, days, weeks, months, years as appropriate) from date & time of immunization to date / time of (indicate which one used): ☐ AEFI Onset – first sign/symptom noted ☐ AEFI First Observation – first objective documentation of sign/symptom ☐ AEFI diagnosis – when case definition first met ☐ Other – specify:
AEFI duration	Interval from AEFI onset/first observation/diagnosis (using same definition as above) to (indicate which one used): ☐ End of episode (time the event no longer meets the case definition) ☐ Final outcome ☐ Another endpoint – specify:
For any AEFI that occur intermittently	☐ Event will be categorized corresponding to the greatest magnitude of adverse event (e.g. highest recorded temperature). ☐ Frequency and pattern of re-occurrence will be analyzed ☐ Specify any other plan for analyzing AEFI that occur intermittently
For AEFI defined by measurement of a particular parameter AND there is >1 value for the parameter (e.g. fever)	☐ Categorization will be based on the parameter value corresponding to the greatest magnitude of the adverse event (e.g. highest body temperature). ☐ Analysis will be done for other characteristics like qualitative patterns of criteria defining the event (e.g. periodicity, frequency, fever-days, etc) . Specify:
Analysis of AEFI data distribution	For AEFI that have measured parameters (fever, injection site reaction size, laboratory abnormalities) analysis will be done using predefined increments: ☐ Yes, and according to Brighton case definition guidelines if they exist ☐ Yes, and specified in the protocol but not based on Brighton case definitions ☐ No ☐ Undecided Plans for presenting AEFI frequency (check all that apply): ☐ numerator and denominator data ☐ Percentage ☐ graphical illustrations

TABLE 4. CHECKLIST FOR GUIDELINES INDICATING DESIRABLE STANDARDS FOR PRESENTATION OR PUBLICATION OF ANALYZED AEFI DATA TO ALLOW COMPARABILITY OF DATA.

Check all that apply using a checkmark for what is planned and an 'X' for what is not planned. For any 'X's provide alternate approach or rationale for not following guideline.
☐ For skewed data, where median and range would be the appropriate statistical descriptors, mean and standard deviation will be provided to permit meta-analysis
☐ Incidence of AEFI events that meet the Brighton or other appropriate case definition will be presented. Check all that apply ☐ Cumulative incidence rate (# AEFI among all doses administered) ☐ Incidence rates (# AEFI per specified time point (day after immunization) or study point (after each planned dose)
☐ Methods for data collection and analysis clearly described including study design, study group(s) and comparison group(s)
☐ Methods specified for method, frequency and duration of monitoring for AEFI.
☐ Day of immunization will be clearly defined as either day 0 or day 1 for analysis purposes.
☐ The trial profile will be provided indicating participant flow during the study including drop-outs and withdrawals.
☐ Reference cited for any Brighton case definitions or other case definitions used.

ANNEX II

Data Collection Forms for Safety

This is obtained in whole from Appendix B in the original Brighton Collaboration template protocol[3]
It may be of use to developers who have not yet created safety CRFs.
As described in Section 3.1, the procedure of safety data collection can typically be classified into three stages: baseline assessment, case identification, and follow-up. To prevent duplicate data collection at different stages, the data collection forms are classified into three forms for different purpose of use:

Appendix II-I. Baseline assessment form:
to be used for baseline information collection for each participant independent from AEFI.

Appendix II-II. AEFI report form:
to be used when an AEFI is reported at the first time.

Appendix II-III. Follow-up form:
to be used for all follow-up visits after the above stage.

Appendix II-I. Baseline Assessment Form

Trial ID:_____
Participant ID:_____
Medical record ID:_____
Date:_____
Site: _____

A. Vaccinee /Control
1) participant ID: ___/___/____ (DD/MM/YYYY)
2) Sex: □M □F
3) Ethnicity or race:_____
4) Weight (kg): _____
5) Height (cm): _____
6) Infants: Gestational age (weeks/days):____/_ ___
7) Infants: Birth weight (g)_____

B. Medical History
8) Pre-vaccination signs or symptoms on day of vaccination (e.g. cold, fever):

□Yes □No □Unknown

If YES, please describe:

_____
_____
_____

9) Underlying or concomitant disease(s): □Yes □No □Unknown

If YES, please describe (including resource of the diagnoses when available, e.g. contact information of physician or hospital):

_____
_____
_____

10) Any other significant medical history including treatment (e.g., hospitalizations, pregnancy, allergies, seizures, events similar to or related to the solicited AEFI, and the resource information of the diagnoses)

_____
_____
_____

11) Any previous exposure to either the vaccine specific infectious agent or - if vector based vaccine- the vector (e.g., previous vaccination, resident of endemic area)

_____

_____
_____

12) Any medication 3 months prior to, during, and after the AEFI including prescription and non-prescription medication (e.g., herbal or homeopathic medication) as well as medication with long half-life or long term effect (e.g., immunoglobulins, blood transfusion, immunosuppressants, oral or intravenous corticosteroids), that could affect the evaluation of an AEFI, but other than treatment given for the AEFI.

□Yes □No □Unknown

If YES, please specify including the date(s), that the medication was given:

_____
_____

13) Relevant family history?

□Yes □No □Unknown If yes, please specify:

_____
_____
_____

14) Any local disease outbreaks?

□Yes □No □Unknown

If yes, please specify:

_____
_____
_____

C. Recorder:

15) Date of this report: ___/___/___ (DD/MM/YYYY)

16) Time of this report (hh:mm; 24-hour clock) ___:____

17) First name _____ 18) Last name: _____

Appendix II-II. AEFI Report Form

Trial ID:_____
Participant ID:_____
Medical record ID:_____
Event identifier:_____

Participant and reporter identity is confidential. Complete the form to the best of your abilities. Should you require more space than provided to report all relevant data, please use additional pages and refer to the respective item number.

A. Source of Information/ Reporter

1) Date of this report: ___/___/___ (DD/MM/YYYY)
2) Time of this report (hh:mm; 24-hour clock) ___:____
3) First name: _____ Middle initial: _____ Last name:
4) Phone [+country code (area code) phone number]: +____ (_____)_____
   E-mail:_____
5) Organization: _____
6) Street: _____
7) Postcode/ ZIP: _____
8) City: _____
9) State/Province: _____
10) Country: _____

11) Primary source of information:
- □ Investigator
- □ Patient/Family member (indicate relationship)_____
- □ Manufacturer_____
- □ Other(specify)_____

12) Modality to capture event:
- □ Scheduled trial follow-up visit
- □ Self-presentation to health facility
- □ Other: _____

B. Adverse Event* (AEFI)
* If more than one event, complete one form per event

13) Initial diagnosis: _____
14) Date of diagnosis: __ _/__ _/___(DD/MM/YYYY)
15) Was the participant seen by a physician for the present complaint?
□ Yes □ No □ Unknown
16) Contact information of Physician: _____

17) Was the participant hospitalized for the present complaint?
□Yes □No □Unknown

IF yes, contact of hospital: _____

18) Admission date: ___/___ /____ (DD/MM/YYYY)

19) Date and time of

□ onset (first sign indicative of AEFI) ___/___/___ (DD/MM/YYYY) ___/___ (hh:mm 24-hour clock) or

□ first observation (if onset unknown) ___/___/___ (DD/MM/YYYY) ___/___ (hh:mm 24-hour clock)

20) Detailed history of present complaint (e.g., type of pain, progression of symptoms and signs after the first observation) including times and dates:

_____
_____
_____
_____

21) Findings on physical examination including times, dates, and values and units of routinely measured parameters.

_____
_____
_____
_____
_____
_____
_____
_____
_____

22) Further investigations (e.g., laboratory findings, radiographs surgical and/or pathological findings and diagnoses).
For each investigation, provide investigation name, date, findings and diagnosis, and source of information:

_____
_____
_____
_____

23) Detailed record of treatments given for the AEFI including times, dates, progress of clinical condition and treatment provider:

_____
_____
_____
_____
_____

24) Was there recurrence of the event after initial AEFI or did the participant experience any AEFI to previous doses of the same vaccine?

□Yes □No □Unknown □ N/A

If YES, describe in detail including dates of occurrence:

_____
_____
_____
_____
_____

25) Any other significant medical history including treatment (e.g., hospitalizations, pregnancy, allergies, seizures, events similar to or related to the AEFI)

_____
_____
_____
_____

26) Did the event meet any criteria for a SAE?

□ Yes □No □ Unknown

□ Hospitalized for the AEFI Admission: ___/___/___ (DD/MM/YYYY) Discharge:___/___/___ (DD/MM/YYYY)

□ Not recovered; persistent signs and symptoms:

_____

□ Disability resulting from AEFI:

_____

□ Life-threatening:

_____
_____

□ Death Date of death : ___/___/___ (DD/MM/YYYY)

Cause of death is based on autopsy □ Yes □ No □ Unknown
If YES, please specify

_____

□ Other medically important condition (e.g., New onset chronic disease):_____

C. Most Recent Immunization(s) prior to AEFI

27) Date ___/___/___ (DD/MM/YYYY) Time ___/___ (hh:mm 24-hour clock)

28) Location (e.g. field site, hospital, physician's office, home, other): _____

29) Please list all past routine and experimental immunizations. For each immunization, provide vaccine name and administration date

	Investigational Vaccine	Co-administered Vaccine(s)
30) Vaccine		
31) Manufacturer		
32) Lot number		
33) Lot of diluent(s)		
34) Multi- or monodose vial		
35) Expir. date (DD/MM/YYYY)		
36) Volume		
37) No. of dose in series (e.g., 1st, 2nd, 3rd)		
38) Route		
39) Anatomical site of injection		
40) Device (e.g., type of syringe including needle length and gauge, biojector, electroporation, patch or other device)		
41) Source of information (e.g., vaccination record, key interview, investigator's report etc.)		
42) Any violation of administration protocol for vaccine		

Appendix II-III. AEFI Follow-up Form

Should you require more space than provided to report all relevant data, please use additional pages and refer to the respective item number.

Trial ID:_____
Participant ID:_____
Medical record ID:_____
Event identifier:_____
Date of initial report:

A. Source of Information/ Reporter

1) Date of this report: ___/___/___ (DD/MM/YYYY)
2) Time of this report (hh:mm; 24-hour clock) ___:____
3) First name: _____ Middle initial: _____ Last name: _____
4) Phone [+country code (area code) phone number]: +____ (_____) _____Fax: +____ (_____) _____
E-mail:_____
5) Organization: _____
6) Street: _____
7) Postcode/ ZIP: _____
8) City: _____
9) State/Province: _____
10) Country: _____
11) Primary source of information:
□Investigator □Other(specify)_____
12) Modality to capture event:
□ Scheduled trial follow-up visit □Self-presentation to health facility
□ Other: _____

B: AEFI Follow-up (only to be completed if form is specified as follow-up form in title of the form)

13) Final Diagnosis of AEFI: _____
14) Date of final diagnosis: ___/____/_____(DD/MM/YYYY)
15) Has causality assessment been done?

□ Yes □ No □ Unknown

If YES, is the AEFI causally related?

□ Related □ Not related □ Unknown

Describe in detail how the causality assessment has been done and contact information of the correspondent of the assessment

_____

_____
_____

16) Has participant's condition returned to pre-vaccination health status?

□ Yes □ No □ Unknown

□ Life-threatening:

_____
_____

If YES, indicate when pre-vaccination heath status was reached:
___/___/___(DD/MM/YYYY)

If NO, what is the current status? (e.g. therapeutic intervention, persistence of the event, sequelae, death, or description of any other outcome.

In the case of death, post mortem findings should be specified, if available._____
_____
_____

17) Did the event meet any criteria for a SAE?

□ Yes □ No □ Unknown

□ Hospitalized for the AEFI
Admission: ___/___/___ (DD/MM/YYYY)
Discharge:___/___/___ (DD/MM/YYYY)

□ Not recovered; persistent signs and symptoms:_____

□ Disability resulting from AEFI_____

□ Life-threatening:

□ Death
Date of death: ___/___/___ (DD/MM/YYYY)
Cause of death is based on autopsy
□ Yes □ No □ Unknow
If YES, please specify

□ Other medically important condition (e.g., New onset chronic disease):_____

18) Was the participant revaccinated with the investigational vaccine(s)

□ Yes □ No □ Unknown

If YES, describe the doses and respective outcome

_____
_____

If NO, the reason was

□ exclusion from further vaccination □ No further vaccination sched

ANNEX III

Tabular Checklist to Assess Trial CRF Capture of Recommended Elements for Safety Data Collection

The checklist captures the elements recommended in the original Brighton Collaboration template protocol.[3] Appendix 1 provides the actual CRFs as presented in the 2013 Template protocol publication.[3]

For situations where a study protocol CRF has already been developed, we encourage a review of the planned CRF against the tabular checklist presented below to determine the extent to which recommended safety data elements are being captured in a standard way, harmonized with the Brighton guidance.

Recommended formats for frequently collected data items. Checkmark if format used, 'X' if not used (indicate alternate format used)

- ☐ Date – DD/MM/YYYY Alternate format:
- ☐ Time – hh:mm; 24-hour clock Alternate format:
- ☐ Height – centimeters Alternate format:
- ☐ Weight – kilograms Alternate format:
- ☐ Gestational Age – weeks+days Alternate format:

TABLE 1. BASELINE ASSESSMENT

Data Category	Key Data Elements to be captured in CRF (check all that are captured and note any differences in recommended format shown in brackets; mark NA if not applicable to vaccine trial)
Trial	☐ ID ☐ Medical record ID ☐ Trial site
Vaccinee or Control	☐ Participant ID ☐ Enrolment date ☐ Date of birth ☐ Sex ☐ Ethnicity or race ☐ Weight ☐ Height ☐ Infants (≤ 12 months of age): Birth weight, Gestational Age, Head circumference
Medical History	☐ Pre-vaccination signs/symptoms (yes, no, unknown; if yes describe) ☐ Underlying or concomitant diseases (yes, no, unknown; if yes describe) ☐ Any other significant medical history including treatment (e.g. hospitalizations, pregnancy, allergies, seizures, resource information of diagnoses) ☐ Previous exposure to either the vaccine specific infectious agent or vector (if vector-based vaccine) (e.g. via previous vaccination, resident of endemic area) ☐ Other immunization history if relevant and available ☐ Previously documented AEFI – especially for predefined AESI ☐ Medication taken (yes, no, unknown; if yes describe, with dates given: prescription/non-prescription medication noting any with long half-life/ long term effect such as immunoglobulins, blood transfusion or immunosuppressants that could affect the evaluation of an AEFI o 3 months prior to enrolment o at time of enrolment ☐ Relevant family history (yes, no, unknown; if yes describe) ☐ Any relevant local disease outbreaks
Recorder	☐ First and last name ☐ Report date ☐ Report time (hh:mm; 24 hour clock)

TABLE 2. AEFI REPORT FORM

Data Category	Key Data Elements to be captured in CRF (check all that are captured and note any differences in recommended format shown in brackets; mark NA if not applicable to vaccine trial)
Identifiers	☐ Trial ID ☐ Participant ID ☐ Medical record ID ☐ AEFI unique ID
Reporter / Source of Information	☐ Report date ☐ Report time ☐ Contact information (name, phone, email, fax, organization, address ☐ Source (investigator or other(specify) ☐ How was event identified o Scheduled trial follow-up visit o Self-presentation to health facility(identify) o Other(describe)
Adverse event	☐ Date and time of onset of first sign indicative of AEFI (describe) ☐ Date and time of first objective observation of AEFI ☐ Initial diagnosis ☐ Date of diagnosis ☐ Seen by a physician for the AE? (yes, no, unknown) o If yes MD contact information ☐ Hospital admission for AE? (yes, no, unknown) o If yes hospital contact information captured o Admission date ☐ History of present complaint including times/dates ☐ Physical exam findings including times, dates, values and units of routinely measured parameters ☐ Results of laboratory examinations, surgical and/or pathological findings ☐ Treatments given for AEFI including times, dates, progress of clinical condition and treatment provider ☐ Event recurrence after initial onset (yes, no, unknown; if yes describe in detail including dates of recurrence) ☐ Other significant medical history e.g. hospitalizations, pregnancy, allergies, seizures, events similar to or related to AEFI ☐ SAE (yes, no, unknown) o If yes, specify all seriousness criteria that were met including relevant dates (e.g. hospital admission / discharge dates) o If death: cause of death and note if cause based on autopsy ☐ Brighton case definition level of certainty (if enough information to assign)
AEFI history	☐ Similar AEFI to previous doses of the same vaccine (yes, no, unknown, N/A) o If yes, describe in detail including dates of occurrence

Most recent immunizations prior to AEFI	For both investigational vaccine and any co-administered vaccine(s) provide: ☐ Vaccine specifics (name, manufacturer, lot number, diluent(s) lot number, multi or monodose vial, expiration date) ☐ Number of dose in series (e.g. 1st, 2nd, 3rd) ☐ Route and anatomical site of injection ☐ Device (e.g. type of syringe including needle length and gauge, biojector, electroporation, patch or other device) ☐ Source of information (e.g. vaccination record, key interview, investigator's report, other-specify) ☐ Any violation of administration protocol

TABLE 3. AEFI FOLLOW-UP FORM

Data Category	Key Data Elements to be captured in CRF (check all that are captured and note any differences in recommended format shown in brackets; mark NA if not applicable to vaccine trial)
Identifiers	☐ Trial ID ☐ Participant ID ☐ Medical record ID ☐ AEFI unique ID ☐ Date of initial AEFI report
Reporter / Source of Information	☐ Report date ☐ Report time ☐ Contact information (name, phone, email, fax, organization, address) ☐ Source (investigator or other(specify) ☐ How was event identified o Scheduled trial follow-up visit o Self-presentation to health facility (identify) o Other(describe)
AEFI follow-up	☐ Final diagnosis of AEFI ☐ Brighton definition level of certainty (if AEFI has a case definition) o Date AEFI first met any case definition level of certainty (1, 2 or 3) o Date AEFI no longer met case definition – considered end of episode ☐ Date of final diagnosis ☐ Causality assessment done (yes, no, unknown) o If yes indicate causality assessment and describe in detail how it was done along with contact information of the correspondent of the assessment ☐ Resolution of AEFI o Spontaneous resolution o Resolved with treatment (specify) o Not yet resolved (date of last observation) ☐ Outcome of AEFI o Back to pre-vaccination baseline o Recovering but not yet back to baseline o Permanent disability o Death (provide date, postmortem findings if available) o Other (describe)
Trial status post AEFI	☐ Indicate if: o Further vaccination given per protocol (describe outcome and whether any AEFI recurrence) o Further vaccination scheduled per protocol but not yet given o Excluded from further vaccination o No further vaccination planned o Withdrawn from study

ANNEX IV

Sample SPEAC Memory Aid for Solidarity Protocol

Local Reactions: If reaction is not present, record zero (0). If reaction is present, record severity grade as 1, 2, 3, or 4. Record measurements of redness or hardening in centimeters (cm).

Group Number: ¦___¦

☐ L arm

☐ R arm

Day:	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date	¦__¦__¦¦__¦__¦__¦ (ddMMMyyyy)	¦__¦__¦¦__¦__¦__¦ (ddMMMyyyy)	¦__¦__¦¦__¦__¦__¦ (ddMMMyyyy)	¦__¦__¦¦__¦__¦__¦ (ddMMMyyyy)	¦__¦__¦¦__¦__¦__¦ (ddMMMyyyy)	¦__¦__¦¦__¦__¦__¦ (ddMMMyyyy)	¦__¦__¦¦__¦__¦__¦ (ddMMMyyyy)	¦__¦__¦¦__¦__¦__¦ (ddMMMyyyy)
Oral Temp (°C)	¦__¦__¦ . ¦__¦	¦__¦__¦ . ¦__¦	¦__¦__¦ . ¦__¦	¦__¦__¦ . ¦__¦	¦__¦__¦ . ¦__¦	¦__¦__¦ . ¦__¦	¦__¦__¦ . ¦__¦	¦__¦__¦ . ¦__¦
Time	¦__¦__¦:¦__¦__¦ am/pm	¦__¦__¦:¦__¦__¦ am/pm	¦__¦__¦:¦__¦__¦ am/pm	¦__¦__¦:¦__¦__¦ am/pm	¦__¦__¦:¦__¦__¦ am/pm	¦__¦__¦:¦__¦__¦ am/pm	¦__¦__¦:¦__¦__¦ am/pm	¦__¦__¦:¦__¦__¦ am/pm

Day:		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Local Reactions: If reaction not present, record zero (0). If reaction present, record severity grade as 1, 2, 3 or 4 (See below).									
Pain (pain without touching)		Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦
Tenderness (pain when area is touched)		Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦	Injection site: ¦__¦

Day:		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Swelling/ Hardening or thickening of skin		Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm
Redness of skin/ dis-coloration		Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm	Width ¦__¦__¦ . ¦__¦ cm Height ¦__¦__¦ . ¦__¦ cm

Day:		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Systemic Reactions: If reaction not present, record zero (0). If reaction present, record severity grade as 1, 2, 3 or 4 (See below).									
Chills		¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦
Headache		¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦

Nausea (Feel like vomiting)		¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦
Malaise (Feeling unwell)		¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦
Day:		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Myalgia (muscle pain)		¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦
Arthralgia/ Joint Pain		¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦	¦__¦

Severity Grading Scale for Local and Systemic Reactions

Grade	Meaning
0	None: No signs or symptoms present.
1	Mild: Signs or symptoms causing no or little disruption of your usual daily activities
2	Moderate: Signs or symptoms causing some disruption of your usual daily activities
3	Severe: Signs or symptoms that make you unable to perform your usual daily activities
4	Very severe: Signs or symptoms that prevent you from being able to take care of yourself OR require medical intervention to prevent persistent disability or death

Important: In the event of any other observations of concern, contact the study staff at [phone number] during regular work hours. After hours, the emergency mobile is [phone number].

GENERAL INSTRUCTIONS:

This Memory Aid is given to you to record any signs or symptoms you may have following study injection. Please record the highest severity for each day and bring this card with you every time you visit the clinic.

HOW TO COMPLETE THE MEMORY AID

- Complete the Memory Aid every day, starting the day of injection (Day 0) after leaving the clinic and continue for 6 more days (for a total of 7 days). Volunteers who require help completing the Memory Aid should telephone [study site name] for assistance.
- Assess signs or symptoms, including your temperature, and fill out the Memory Aid in the evening before going to bed, around the same time every day. Document the time you assessed your symptoms in the space above.
- If you feel feverish, you may take your temperature again and record above.
- Fill out all the spaces each time. If you have no reactions, write 0 in all the boxes.

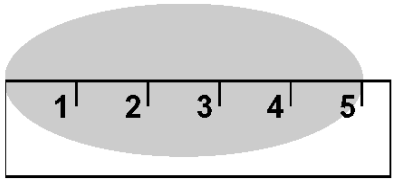
HOW TO TAKE MEASUREMENTS

If you notice redness of skin or skin discoloration, swelling or hardening or thickening in the area where you got your injection over the next 7 days (starting the day of injection, Day 0, after leaving the clinic and continuing for 6 more days), please measure the area using the tool the clinical staff gave you.

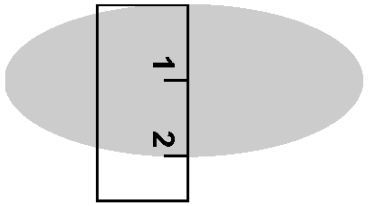
If needed, you may get someone to help you. Record the measurement in the space provided. To measure the area, do the following:

- Measure the widest part of the area from left to right
- Measure the longest part of the area from top to bottom
- Record measurements of skin discoloration or hardening in centimeters (cm)

Left to right



Top to bottom



In the example to the left, the area measures 5 centimeters (cm) from left to right and 2 centimeters (cm) from top to bottom. Record both measurements on the Memory Aid.

Contact the Research Nurse or Doctor…

- If you have any measured temperature greater than or equal to 38.6 °C.
- If you have any severe (Grade 3) or very severe (Grade 4) signs or symptoms. This includes malaise (feeling unwell), fatigue (feeling tired), muscle aches, headache, pain at the injection site, or any other event that prevents any of your daily activity or requires you to see a doctor and medical care.

If you have any concerns or questions about completing the Memory Aid or about any unusual or severe signs or symptoms you are experiencing, please contact the study staff at [phone number]. during regular work hours. After hours, the emergency mobile is [phone number].

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

ANNEX V

SPEAC Guidance on Solicited Local and Systemic Reactogenicity

TABLE 1. EVENTS LISTED ON THE SAMPLE MEMORY AID.

Event	BCCD exists	Key elements of CD or recommended alternate source	Data Collection Guidelines	Data Analysis Guidelines
Local Reactogenicity (all defined as present at or near the injection site)				
Local Reaction (general)	Yes	Any description of morphological or physiological change at or near the injection site. 2 levels of certainty: Level 1: assessed by a health care provider Level 2: assessed by any other person	See individual components of local reaction below for data collection. Document duration from onset to end of episode	Number of events in each category: • Level 1 or 2 of local reaction • Level 4: Reported local reaction that fails to meet level 1 or 2 • Level 5: Not a case of local reaction at the injection site For interval from immunization to new onset of local reaction, % subjects with onset from: 0-24 hrs, 25-48 hrs, 49-72 hrs, 73 hrs to 7 days, >7 days Size of reaction as % of subjects following into incremental categories of: 0-1.0 cm, then 2.5 cm increments up to <10 cm, then 5 cm increments up to <30 cm, and >30 cm.
Pain and Tenderness	Yes	For all 3 levels of certainty: an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage AND occurring at the immunization site at the time of administration or following the procedure.	Level 1 - need a subject self-report of pain or distress assessed using validated or verified instruments. For pre- or non-verbal subjects need observer report using validated age-appropriate tools. Level 2 - need other observer or reporter assessment of subject pain or distress using a validated or verified instrument. Level 3 – no additional description of pain/distress or assessment by validated method	Number of events in each category: • Level 1 -3 of pain at injection site • Level 4: Reported pain that fails to meet level 1-3 • Level 5: Not a case of pain at the injection site For interval from immunization to pain onset, % of subjects with pain onset in intervals of: <5min, 5min - ≤24 hr, 25-≤48 hr, 49-≤72hr, 73hr-≤7days, 8 - ≤14 days, >14 - ≤28 days; >28 days Validated assessment methods are provided in the published case definition. All are scored out of 10. Suggested arbitrary grading of event as: • Mild (Grade 1): score of 1-3 out of 10 • Moderate (Grade 2): score of 4-6 out of 10 • Severe (Grade 3): score of 7 or higher out of 10
Swelling	Yes	Visible enlargement of an injected limb with or without objective measurement. See 'Local reaction for	Need to distinguish from injection site abscess, cellulitis, nodule and induration. Also need to distinguish swelling from induration and vice versa. Objective measurements of the size of the reaction	Number of events in each category: • Level 1 or 2 of swelling at injection site • Level 4: Reported swelling that fails to meet level 1 or 2 • Level 5: Not a case of swelling at the injection site

		levels of certainty'	should be made where possible, measuring greatest diameter and describing anatomical location and specify whether it includes or does not include the injection site as well as whether or not it extends from joint to joint, or crosses joints See Memory Aid	The case definition suggests analyzing the % with swelling or erythema lasting: 0-24hrs; >24-48hrs; >48-72hr; >72-96hrs; >96-168 hr; >7-14 days; >14-21 days; Where cases are limited, 2 categories are suggested (<=7 and >7 days). It is also suggested to present the % that fall into size increments for <2.5, 2.5-5, 5-<10, 10-<15, 15-<20, 20-<30, >30 cm. If relevant specify the proportion with swelling or erythema that crosses a joint, and/or extends from joint to joint
Induration	Yes	Palpable thickening, firmness or hardening of soft tissue (subcutaneous tissue, fat, fascia or muscle). See 'Local reaction for levels of certainty'		
Redness/ Erythema	No	FDA 2007 Toxicity Grading Scale defines severity Grades 1 <15mm, 2 15-30mm, 3 >30mm		
Systemic Reactogenicity				
Fever	Yes	Only Level 1 of certainty: At least one elevated body temperature ³38.0°C irrespective of device, anatomic site, age, environmental conditions	Measure at least once/day, at same time of day, after immunization and whenever fever is suspected. Duration of surveillance depends on vaccine biologic characteristics. If fever is detected it should be followed, ideally with 2/day(morning/evening) measurements until two consecutive measures <38°C	Number of events in each category: • Level 1 • Level 4: Reported fever that fails to meet level 1 • Level 5: Not a case of fever Duration analyzed as number of days with ³ 1 measured temperature that meets Level 1 Degree of fever: % of subjects falling within 0.5°C increments from <38.0 °C to >41.0 °C Analyze by study arm, dose and control group as appropriate to trial design
Fatigue	Yes	Detailed case definition with 3 levels of certainty for 3 different events: a. Fatigue state b. Specified fatigue syndrome c. Other fatigue syndrome	All 3 events need data to confirm it is: a new symptom; primary complaint; not relieved by rest AND interferes with normal function. Impairment should be confirmed using valid, reliable measures (see published CD). For fatigue syndromes, also need data on accompanying	Number of events in each category: • Level 1-3 (a, b or c) • Level 4: Reported event with insufficient information to meet case definition at any level • Level 5: Not a case of fatigue. Duration of fatigue using following descriptors: • Acute: <1 wk in duration • Transient: ≥1 wk to <1 mo duration • Prolonged: ≥1 mo to <6 mo duration • Chronic: ³6 mo duration

		Level 1 applies only to persons [3] 5 years old Levels 2 & 3 apply to all ages.	symptoms + signs. Exclusion criteria for all 3 events: • Concurrent onset of laboratory diagnosed medical or psychiatric disorders for which fatigue is a known symptom. • Concomitant use of a drug (therapeutic or recreational) known to cause fatigue	Duration of each of the accompanying symptoms/signs should also be captured. Chronic fatigue state requires 4 of 8 specified symptoms to be present for >6 mo AND recommended medical, psychiatric and laboratory investigations done 6 mo or more after onset do not reveal an alternative diagnosis.
Chills	No	Not in FDA 2007 document but could use same levels of severity noted below.	Memory Aid for subjects has instructions CRF to capture memory aide data	% of subjects falling into each severity level Time to onset and duration using similar categories to those recommended for local reactions
Headache, Nausea, Malaise, Myalgia, Arthralgia	No	FDA 2007 Toxicity Grading Scale defines severity Grades 1 (mild), 2 (moderate), 3 (severe) and 4 (potentially life-threatening).		

TABLE 2. EVENTS NOT LISTED ON THE MEMORY AID BUT MAY BE INCLUDED IN SOLICITED REACTOGENICITY AND/OR PRESENT AS UNSOLICITED / SERIOUS AEFI. ALL HAVE BRIGHTON CASE DEFINITIONS.

Event	BCCD exists	Key elements of Case Definition (CD)	Data Collection Guidelines	Data Analysis Guidelines
Local Reactogenicity (all defined as present at or near the injection site)				
Nodule	Yes	Single level 1 of certainty: Discrete or well-demarcated soft tissue mass or lump that is firm, in the absence of all the following: erythema, warmth, abscess formation	Document outcome: • Spontaneous resolution • Status quo (follow 3months) • Excision • Sterile abscess development • Other (describe) Pathologic exam of any tissue. Append pathology report to AEFI report.	Number of events in each category: • Level 1 nodule at injection site • Level 4: Reported nodule that doesn't meet level 1 • Level 5: Not a case of nodule at the injection site Describe time course from immunization to onset including % subjects with nodules at 2 week intervals from 0-12 weeks after immunization and 4 week intervals thereafter. Describe size in 0.5 cm increments Describe duration and outcome

Abscess	Yes	Need to distinguish between infectious and sterile.	Clinical description/photo; spontaneous resolution or drainage (surgery or aspiration); Microbiology (gram stain, culture); antibiotic timing relative to sampling for culture; time course to onset; duration & outcome;	Number of events in each category: • Level 1 or2 of infectious abscess • Level 1 or 2 of sterile abscess • Level 4: insufficient information to meet any level of the infectious/sterile abscess definitions • Level 5: Not a case of injection site abscess
Cellulitis	Yes	Need to distinguish true infectious cellulitis from a non-infectious local reaction	Clinical description / photograph; Microbiology (gram stain, culture); antibiotic timing relative to sampling for culture; time course to onset; duration & outcome;	Number of events in each category: • Level 1, 2 or 3 of cellulitis • Level 4: insufficient information to meet any CD level • Level 5: Not a case of injection site cellulitis
Systemic Reactogenicity				
Diarrhea	Yes	Increase in frequency of bowel movements, above normal or baseline, AND that are runny or of liquid consistency (meets level2) For level 1 need to specify the increase is by 3 or more bowel movements within a 24 hour period.	Detailed clinical description of event including concurrent signs and symptoms. Presence of dehydration as a secondary outcome Describe stool consistency: 1=firm; 2=soft; 3=runny and/or takes shape of container; 4=brown liquid; 5='rice water'	Number of events in each category: • Level 1-2 of case definition • Level 4: Reported diarrhea with insufficient information to meet any CD level • Level 5: Not a case of diarrhea For interval from immunization to diarrhea onset, % of subjects with onset interval: <5min, 5min - ≤24 hr, 25-≤48 hr, 49-≤72hr, 73hr-≤7days, 8 - ≤14 days, >14 - ≤28 days; >28 days % of subjects meeting severity grades as included in the FDA toxicity guidelines (case definition proposes similar ones and also the WHO criteria for dehydration)

ANNEX VI

Summary Guidance Regarding Investigation of Included AESI

6.1 Brighton guidelines applicable to all AESI.

Duration of AESI Surveillance For all AESI this should be based on the biologic characteristics of:

- The candidate vaccine plus any other concomitantly administered vaccine(s)
- The vaccine-targeted disease
- The specific AESI event, including patterns identified in previous trials
- The vaccinee including relevant risk factors for the event. SPEAC is preparing risk factor tabular summaries for each AESI and these can be found in the Developer Toolbox. In general, should consider genetic characteristics, nutrition, underlying diseases, past history of occurrence of a given AESI prior to entering the trial.

Data Collection Guidelines

- All the following should be documented:
  - Date (DD/MM/YYYY) and time (hh:mm; 24-hour clock) of AESI:
    - Onset: when first major/minor criterion occurred
    - First observation: when first major/minor criterion observed – if unable to determine onset
    - Diagnosis – when event first met any level of certainty for CD
    - End of episode – when event no longer meets the CD (response to treatment,spontaneous resolution).
    - Final outcome – specify one of
      - Recovery to pre-immunization status
      - Spontaneous resolution
      - Improving with therapeutic intervention
      - Persistence of event
      - Permanent sequelae
      - Death
      - Other – specify
  - Concurrent signs, symptoms and diseases
  - Objective clinical evidence supporting classification of the event as 'serious'.
- Duration of follow-up: should be predefined and should aim to continue to resolution of the event or a documented final outcome
- For all neurologic AESI: Document the final outcome and disposition at last observation as follows:
  - Neurologic / functional outcome using the categories:
    - Recovered, no sequelae present at time of final follow up
    - Recovered, neurologic sequelae present at time of final follow up
    - Died
    - Outcome unknown
    - Other outcome (describe)
  - Disposition at last follow-up using the categories:
    - Disposition to home, independent living
    - Disposition to home, dependent living
    - Disposition to pre-illness residence other than home (e.g. nursing home), independent living or pre-illness baseline status
    - Disposition to assisted living or rehabilitation
    - Died
    - Disposition unknown
    - Other disposition (describe)

Data Analysis Guidelines

- All AESI should be defined in one of 5 categories:
  - Event meets case definition at: (note: specify the highest level of certainty attained with 1 the highest and 3 the lowest. Most but not all AESI have 3 levels of certainty – this is pointed out, as appropriate for each AESI.
    - Level 1 of certainty

        - Level 2 of certainty
        - Level 3 of certainty
    - Event does not meet case definition
        - Level 4: Reported AESI event with insufficient evidence to meet the case definitions
        - Level 5: Not a case of the AESI event

Data Presentation Guidelines

- All reported individual AESI events should be presented according to the levels defined above
- Data should be presented with numerator and denominator and not only in percentages
- The incidence of cases in the study population should be presented and clearly identified as such in the text
- If the distribution of data is skewed, median and range are usually the more appropriate statistical descriptors than a mean. However, mean and standard deviation should also be presented to enable meta-analyses.
- AESI publication should include a detailed description of methods for data collection and analysis including:
    - Study design
    - Method, frequency and duration of monitoring
    - Trial profile indicating participant flow during the study including drop-outs and withdrawals
    - Type of surveillance used – i.e. passive or active
    - Characteristics of the surveillance system (e.g. population served, mode of report solicitation)
    - Search strategy in surveillance databases if applicable
    - Comparison group(s) if used for analysis
    - Instrument of data collection (e.g. standardized questionnaire, diary card, report form, SPEAC or other data abstraction form)
    - How was day of immunization treated: day zero or day one
    - Which variable was used for analysis: Onset date, First observation date, diagnosis date. The choice should be used consistently across all cases for subjects and controls.

6.2.1 Anaphylaxis

- Key elements of Case Definition (CD) Predominantly a clinical diagnosis relying on objective assessment of dermatologic, cardiovascular, respiratory and gastrointestinal presentations which make up the major and minor case definition criteria.
- Duration of Surveillance for Anaphylaxis:
  - Relevant biologic characteristics of the study subjects/controls may help to define this including: history of atopy, past episodes of anaphylaxis, nutrition, underlying disease.
  - Reports of anaphylaxis should be collected throughout the study period regardless of the time elapsed between immunization and adverse event. If not feasible, the study periods during which safety data are collected on anaphylaxis should be clearly defined.
- Recommendations for real time assessment
  - Table 1 provides a symptom/sign checklist corresponding with the case definition major and minor criteria. This can be provided to clinical trial immunization providers as an aid for what should be documented and to append to the AEFI report. It also provides the rules for assigning level of certainty – which could be included or reserved for use of the site investigator or study monitor. This is not meant to guide treatment. Many of the criteria can rapidly be assessed by one staff member as others are providing treatment. It is especially important to have objective documentation rather than historical report of urticaria, angioedema, and upper airway swelling
  - Laboratory – the only supportive laboratory test is mast cell tryptase which is a marker for anaphylaxis
    - Levels peak between 15 and 120 minutes from onset
    - Samples need to be taken within 6 hours of the event onset
    - Elevation above the upper normal limit is considered a minor criterion because it is helpful but not definitive for anaphylaxis
    - Recommendation: determine which study sites are able to measure mast cell tryptase and include it if feasible in the early assessment of anaphylaxis
- Data Collection Guidelines
  - Treatment given for anaphylaxis (especially epinephrine, steroids, volumen, antihistamines) including date / time given
  - Determine exposures other than immunization for the 24-hour period before and after immunization (foods, environmental)
- Data Analysis Guidelines
  - If few cases are reported in the trial the concrete time course should be analyzed for each including interval from immunization to onset
  - If there are many cases, they should be analyzed as the number and percentage following into each interval:
    - <30 minutes after immunization
    - 30-≤60 minutes after immunization
    - 60 -≤90 minutes after immunization
    - 90-≤120 minutes after immunization
    - Hourly increments therafter

ANAPHYLAXIS TABLE 1 TABULAR CHECKLIST FOR CASE DEFINITION ESSENTIAL (1.1&1.2), MAJOR AND MINOR CRITERIA

1. COURSE OF ILLNESS: must be able to check both 1.1 AND 1.2 to meet any level of certainty for anaphylaxis	
☐ 1.1 SUDDEN ONSET of signs & symptoms Working group defines this as "an event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition"	☐ 1.2 RAPID PROGRESSION of signs & symptoms Working group did not define this and further noted that "Using an arbitrarily restrictive setpoint might bias future data collection unnecessarily." Accordingly it is open to judgement.

[3] 2 body systems involved: check all symptoms/signs present by checking appropriate boxes in rows below. Ideally these should be documented in writing (E.G. AEFI report, clinical record in immunization clinic, Emergency room, or other clinical setting. Alternatively, a verbal report from a professional (R.N., M.D, Pharmacist) who witnessed the event.

Body System	B. MAJOR CRITERIA	C. MINOR CRITERIA	
SKIN *excluding hereditary angioedema	☐ Generalized urticaria (hives) ☐ Generalized erythema ☐ Angioedema* (general or localized) ☐ Generalized pruritus WITH skin rash	☐ Localized injection site urticaria ☐ Red AND itchy eyes ☐ Generalized prickle sensation ☐ Generalized pruritus WITHOUT skin rash	
RESPIRATORY (RESP)	☐ Bilateral wheeze (bronchospasm; by stethoscope) ☐ Stridor ☐ Upper airway swelling (lip, tongue, throat, uvula, larynx) ☐ ≥ 2 indicators of respiratory distress: ○ Tachypnea ○ Cyanosis ○ Grunting ○ Chest wall retractions ○ - use of accessory respiratory muscles	☐ Persistent dry cough ☐ Hoarse voice ☐ Sensation of throat closure ☐ Sneezing OR rhinorrhea ☐ Difficulty breathing WITHOUT wheeze or stridor	
CARDIO-VASCULAR (CV)	☐ Documented hypotension ☐ ≥ 3 signs of uncompensated shock: ○ Tachycardia ○ Capillary refill >3 seconds ○ Reduced central pulse volume ○ Decreased level or loss of consciousness	☐ ≥ 2 signs of reduced peripheral circulation ○ Tachycardia ○ Capillary refill >3 seconds ○ Decreased level of consciousness	
GASTRO-INTESTINAL(GI)	NONE	☐ Nausea ☐ Abdominal pain	☐ Vomiting ☐ Diarrhea
LABORATORY	NONE	☐ Elevated mast cell tryptase	

ANAPHYLAXIS TABLE 2A – GLOSSARY OF TERMS (FROM GOLD MS, GIDUDU J, ERLEWYN-LAJEUNESSE M ET AL. CAN THE BRIGHTON COLLABORATION CASE DEFINITIONS BE USED TO IMPROVE THE QUALITY OF ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI) REPORTING? ANAPHYLAXIS AS A CASE STUDY. VACCINE 2010; 28: 4487-4498.)

Accessory muscles	Muscles, primarily in the neck (sternocleidomastoid which elevates sternum; scalene group which elevates upper ribs) which assist but don't play a primary role in breathing. When used at rest they indicate a level of respiratory distress or increased work of breathing.
Angioedema	Areas of deeper swelling of the skin and/or mucosal tissues in either single or multiple sites which may not be well circumscribed and usually not itchy. (Reported symptoms of "swelling of the tongue" or "throat swelling" should not be documented as angioedema unless there is visible skin or mucosal swelling). NOTE: hereditary angioedema, usually with a history of recurrent episodes of swelling, should be excluded (affects 1in 50,000)
Capillary refill time	The time required for normal skin colour to reappear after a blanching pressure is applied for 5 seconds. Usually assessed by pressing on the nail bed to cause blanching and then counting the time it takes for the blood to return to the tissue indicated by a pink colour returning to the nail. It normally takes < 3 seconds.
Cyanosis	A dark bluish or purplish discolouration of the skin and/or mucous membranes due to lack of oxygen in the blood
Dry cough	Rapid expulsion of air from the lungs and not accompanied by expectoration/sputum (a non-productive cough)
Erythema	Abnormal redness of the skin without any raised skin lesions
Generalized	Involving >1 body site – that is each limb is counted separately as is the abdomen, back, head and neck
Grunting	A sudden and short noise with each breath when breathing out
Hoarse voice	An unnaturally harsh cry in an infant or vocalisation in and adult or child
Hypotension	An abnormally low blood pressure(BP) documented by appropriate measurement. For infants and children: age specific systolic BP <3-5th percentile OR >30% decrease from that person's baseline; For adults: Systolic BP of <90mm Hg or >30% decrease from that person's baseline.
In-drawing or retractions	Inward movement of the muscles between the ribs (inter-costal), in the lower part of the neck (supra-clavicular or tracheal tug) or below the chest (sub-costal). The movements are usually a sign of difficulty with breathing which results in increased use of 'accessory respiratory muscles' (sternocleidomastoid and intercostal).
Injection site urticaria	Urticaria which is continuous with the injection site or involves other aspects of the injected limb
Localised	Involving one body site only
Loss of consciousness	Total suspension of conscious relationship with the outside world as demonstrated by an inability to perceive and respond to verbal, visual or painful stimulus
Mast cell tryptase	Inflammatory mediator released by mast cells during acute anaphylaxis. Typically levels peak between 15 and 120 minutes after onset; samples for measurement should be taken within 6 hours of onset of signs/symptoms.
Prickle sensation	An unpleasant skin sensation that provokes the desire to run and/or scratch to obtain relief
Pruritus	Itchiness
Red and itchy eyes	Redness of the whites of the eyes (sclera) with sensation that provokes the desire to rub and/or scratch to obtain relief.
Retractions	Indrawing of skin while breathing in (implies an obstruction to breathing); may be supraclavicular (above the collarbone), suprasternal (above the sternum), intercostal (between the ribs), substernal (below the sternum) or subcostal (abdomen just below the rib cage)
Rhinorrhea	Discharge of thin nasal mucus

Sensation of throat closure	Feeling or perception of throat closing with a sensation of difficulty breathing
Sneezing	An involuntary (reflex), sudden, violent, and audible expulsion of air through the mouth and nose.
Stridor	A harsh and continuous sound made on breathing in
Tachycardia	Faster than normal heart rate which varies by age – see table below
Tachypnoea	Faster than normal respiratory rate which varies by age – see table below
Urticaria	Localized redness of superficial layers of skin that is itchy, raised, sharply demarcated and transient (that is skin changes at any location are usually present for less than 12 hours)
Wheezing	A whistling, squeaking, musical or puffing sound made on breathing out

ANAPHYLAXIS TABLE 2B. AGE-RELATED UPPER LIMITS FOR RESPIRATORY AND HEART RATE. NOTE: THESE SHOULD BE COMPARED TO NORMS FOR STUDY POPULATION AND ANY DIFFERENCES RELEVANT TO THE LOCAL POPULATION CAPTURED. (FROM GOLD MS, GIDUDU J, ERLEWYN-LAJEUNESSE M ET AL. CAN THE BRIGHTON COLLABORATION CASE DEFINITIONS BE USED TO IMPROVE THE QUALITY OF ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI) REPORTING? ANAPHYLAXIS AS A CASE STUDY. VACCINE 2010; 28: 4487-4498.)

Age in years	Respiratory rate: upper limit in breaths / minute	Heart rate: upper limit in beats/minute
<1 year	60	160
1 – 2 years	40	150
2 – 5 years	35	140
5 – 12 years	30	120
>12 years	16	100

ANAPHYLAXIS TABLE 3. CASE DEFINITION LEVEL OF CERTAINTY DETERMINATION (BASED ON DATA IN TABLE 1)

Level of Certainty	Logic to reach level of certainty for Anaphylaxis
Level 1, 2 & 3	Must meet both of the following criteria (if one or both not met, it is not a case – level 5): ☐ Sudden onset of symptoms/signs ☐ Rapid progression of symptoms/signs
Use the pattern of MAJOR and minor criteria met for skin, respiratory, cardiac and gastrointestinal (GI) systems and laboratory result from table 1 to determine the highest level of diagnostic certainty (with level 1 > level 2 > level 3).	
Level 1	³ 1 Skin MAJOR AND [³ 1 Respiratory MAJOR AND / OR ³ 1 Cardiac MAJOR]
Level 2 NOTE: 4 different ways to meet level 2	1. ³ 1 Skin MAJOR AND [³ 1 Respiratory minor AND / OR ³ 1 Cardiac minor]
	2. ³1 Respiratory MAJOR AND ³ 1 Cardiac MAJOR
	3. ³1 Respiratory MAJOR AND ³ 1 minor from a different system (Skin, Cardiac, GI, lab)
	4. ³1 Cardiac MAJOR AND ³ 1 minor from a different system (Skin, Respiratory, GI, lab)
Level 3 NOTE: 2 different ways to meet level 3	1. ³1 Respiratory minor AND ³ 1 minor from each of 2 different systems (Skin, Cardiac, GI, lab)
	2. ³1 Cardiac minor AND ³ 1 minor from each of 2 different system (Skin, Respiratory, GI, lab)
Level 4	Reported anaphylaxis with insufficient evidence to meet any of levels of diagnostic certainty
Level 5	Not a case of anaphylaxis: if unable to check 1.1 and 1.2 (i.e. onset not sudden and did not progress rapidly)

6.2.2 Thrombocytopenia

- Key elements of Case Definition (CD)
  - There are only two levels of certainty (1, 2) based on platelet count (150 X 10^9/L), whether or not a peripheral smear was done to rule out clumping as a cause of thrombocytopenia and clinical evidence of spontaneous bleeding

- The working group deliberately avoided defining ITP (idiopathic thrombocytopenia or idiopathic thrombocytopenic purpura) because the observed event is thrombocytopenia with or without clinical manifestations. Labelling an event ITP was considered to imply causality to vaccine was already excluded. The case definition aims to assist in studying whether and to what extent immunizations may cause thrombocytopenia.

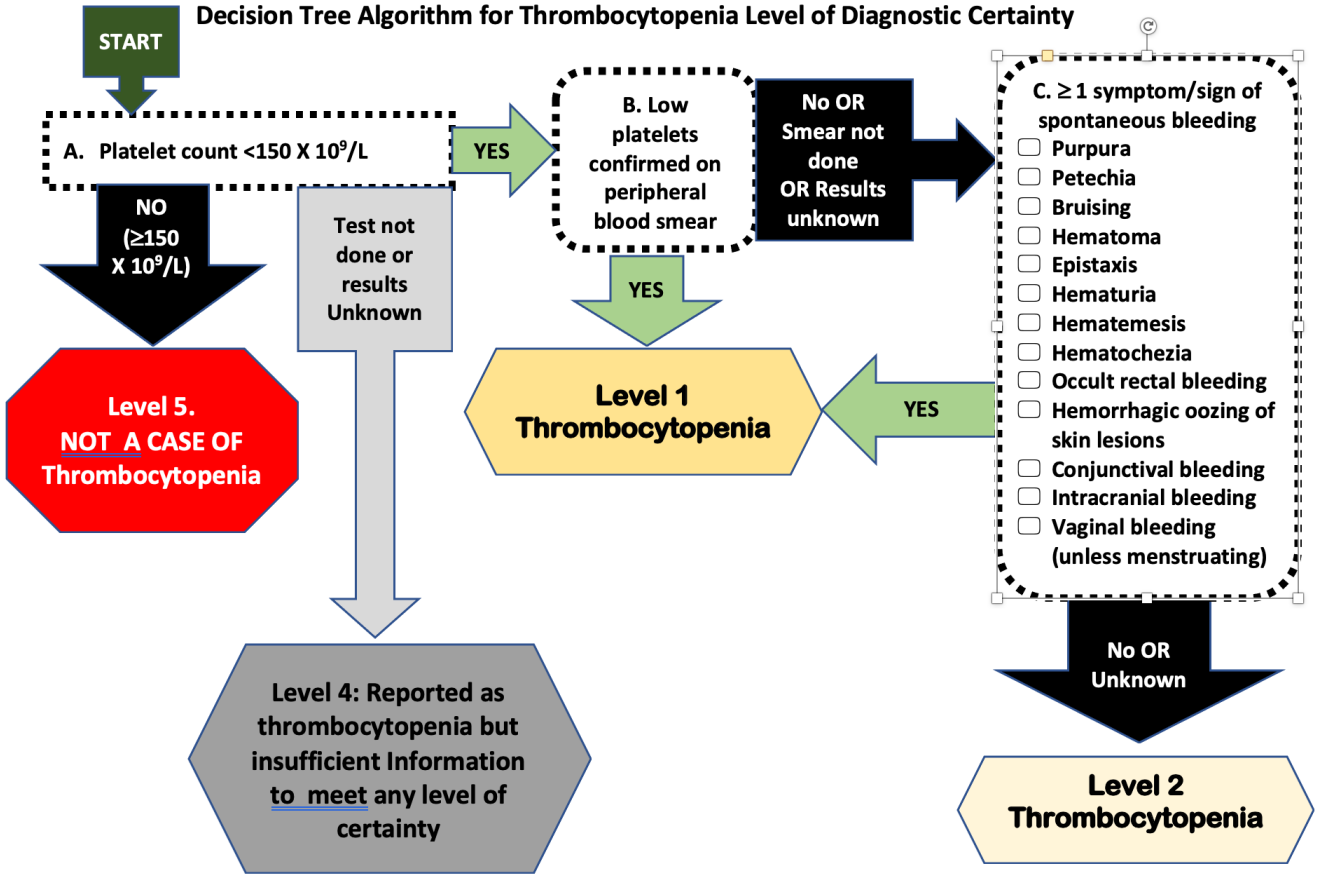
- Duration of Surveillance for thrombocytopenia
  - Reports of thrombocytopenia should be collected throughout the study period regardless of the time elapsed between immunization and the adverse event. If not feasible the study periods during which such data are being collected should be clearly defined.
  - Occurrence of thrombocytopenia should be monitored at a predefined frequency. For early phase clinical trials, it is recommended to monitor at days 1, 7, 14, 21 and 28 following immunization.

- Recommendations for real time assessment
  - Figure 1 summarizes the key laboratory and clinical data needed to meet the case definition. The checklist for evidence of spontaneous clinical bleeding can be based on the contents of box C.
  - Laboratory –
    - All platelet counts should be presented by date
    - Method of measurement should be specified (e.g. automated hematology analyzer, cell count slide or other)
    - Review of a blood smear is recommended to exclude pseudo-thrombocytopenia due to platelet aggregations in the test tube
    - Additional laboratory examinations are not required for the case definition but may help in causality assessment including:
      - Bone marrow cytology and histology
      - Anti-platelet antibodies
      - Serum cytokine levels
      - Surgical and/or pathological findings and diagnoses

- Data Collection Guidelines
  - Therapeutic intervention: note type, duration and date.
  - Hospitalization if applicable: note type, duration and date
  - Any re-occurrence of thrombocytopenia after the initial onset and recovery should be noted
  - Provide a detailed description of the final outcome at the last observation (with date)
  - Provide details of medical confirmation of the event (contact information of diagnosing physician or identify as site investigator/other site personnel as appropriate

- Data Analysis Guidelines
  - Determine time to onset as number and % of events occurring: on day of immunization; and specified intervals following immunization: day 1-6, day 7-13, day 14-20 or <20 days.
  - For duration of thrombocytopenia: number of consecutive days (or weeks, months or years) with a platelet count <150 X 10^9/L
  - If thrombocytopenia occurs intermittently: include first episode and the one with the lowest platelet count. Also the frequency and pattern of re-occurrence should be analyzed.
  - Group degree of thrombocytopenia as number/% subjects with counts: <10, >10-20, >20 to 50, >50-100, >100-150.
  - If detailed analysis in the increments noted above is not posible, at a mínimum use the overall number of subjects with a platelet count <150 X 10^9/L as a basis for analysis of incidence and prevalence
  - If few cases are reported in the trial platelet count values over time can be presented individually

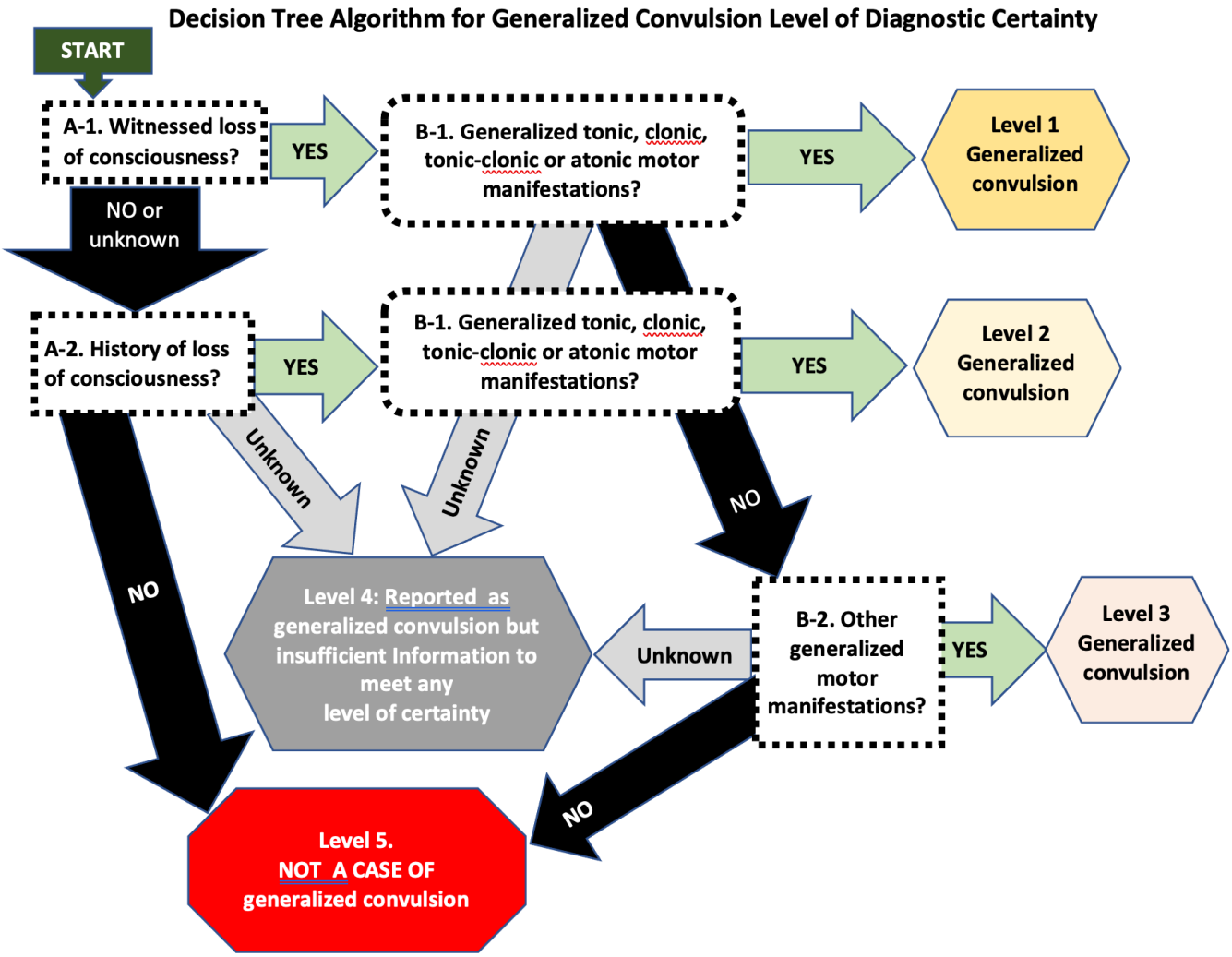
THROMBOCYTOPENIA FIGURE 1. KEY LABORATORY AND CLINICAL DATA AND ALGORITHM FOR ASSESSING LEVEL OF CERTAINTY



6.2.3 Generalized Convulsion

- Key elements of Case Definition (CD)
  - There are three levels of certainty based on observed or history of loss of consciousness and presence and type of generalized motor manifestations.
  - Fever is not part of the case definition but should be documented since febrile seizures are the most common seizure disorder in infants and children and the most common type of non-epileptic seizure observed following immunization.
- Duration of Surveillance for Generalized Convulsion
  - Most cases of febrile convulsion occur during the timeframe that local and systemic reactogenicity is monitored – usually 7 days. However, for live attenuated vaccines surveillance should continue through the expected incubation period of the vaccine agent. Peak occurrence of seizures following live attenuated measles vaccines is 7 – 10 days following immunization.
  - For any seizure still present on the last day of scheduled follow-up, the period should be extended until recovery or a final outcome is reached.
- Recommendations for real time assessment (and see figure 1)
  - A witnessed loss of consciousness is required for level 1 and efforts should be made to document this at the time of first awareness of the event occurrence and to include details of type of witness and contact information (parent/other caregiver, healthcare personnel, other – describe).
  - Seizure is part of the criteria for both encephalitis and acute disseminated encephalomyelitis (ADEM) and could be a presenting feature of aseptic meningitis albeit not a part of the case definition criteria. Accordingly, these should all be considered and if possibilities would require further investigation as outlined in sections 6.2.4, 6.2.6 and 6.2.8)
- Data Collection Guidelines
  - For trials involving children baseline assessment should include history of premature birth, developmental stage at time of immunization, any past or family history of febrile seizure.
  - Ensure collection of information about specific predisposing conditions for generalized convulsion including drug withdrawal, hypoxia, head trauma, CNS infection, neoplasm and metabolic causes (e.g. uremia, hypoglycemia, electrolyte disorders).
  - Provide detailed clinical description of convulsion including temperature and postictal drowsiness.
  - Describe concurrent signs, symptoms and diseases
  - Describe any concurrently administered medications
  - Include EEG/laboratory examinations, surgical and/or pathological findings and diagnoses.
- Data Analysis Guidelines
  - Determine time to onset as number of subjects with seizure occurring within hourly intervals for the first 24 hours following immunization (e.g. ≤ 1, >1-2, >2-3 etc) and then in 24-hour intervals (e.g. >24-48, >48-72 etc). The study population denominators should be specified for each time point along with % having a seizure.
  - Duration of seizure should be analyzed in increments of minutes as: 0 - <1, 1-5, 6-10, 10-15, 16-30, 31-45, 46-60 etc in 15-minute intervals.
  - If generalized convulsion occurs intermittently base the analysis on the value corresponding to the longest seizure.
  - The prevalence and incidence of cases should be presented and for each case definition level of certainty the numerator/denomitor should be presented for febrile, afebrile, unknown fever episodes.

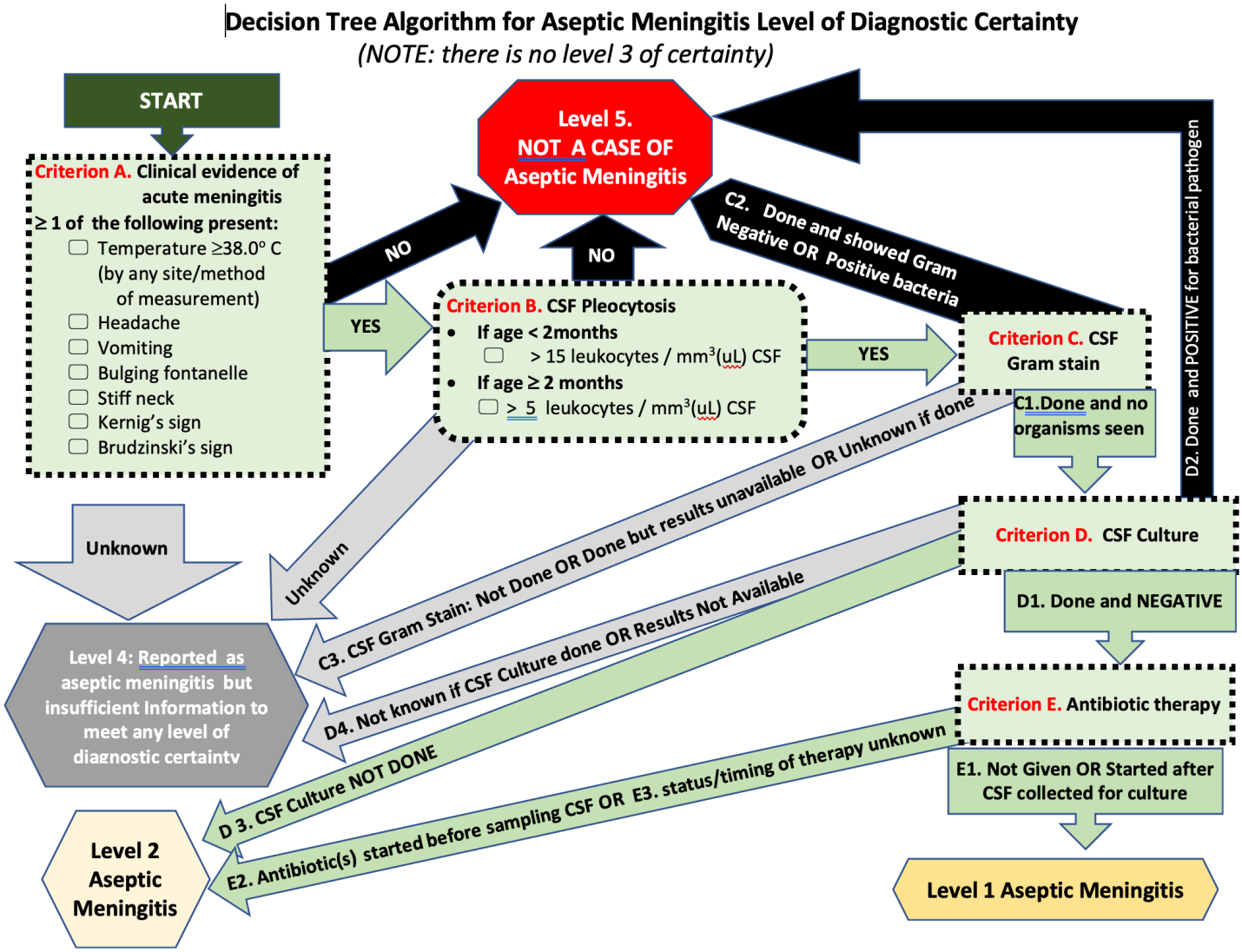
GENERALIZED CONVULSION FIGURE 1. KEY LABORATORY AND CLINICAL DATA AND ALGORITHM FOR ASSESSING LEVEL OF CERTAINTY.



6.2.4 Aseptic Meningitis

- Key elements of Case Definition (CD)
  - Only 2 levels of diagnostic certainty
  - Lumbar puncture for CSF examination is critical to meeting the case definition, with WBC pleocytosis and results of a gram stain being more important than culture results (See Figure 1 below)
- Duration of Surveillance for Anaphylaxis:
  - All reports of aseptic meningitis should be collected regardless of the time elapsed between vaccination and the adverse event. If not feasible study periods during which safety data are being collected should be clearly defined.
- Recommendations for real time assessment
  - If any features of encephalitis are present that should be used instead of aseptic meningitis as the adverse event. (see Appendix 6.2.6 Encephalitis).
  - A lumbar puncture (LP) for collection and examination of cerebrospinal fluid (CSF) is absolutely required to meet any level of the case definition. At a mínimum there needs to be a white blood cell (WBC) count and a gram stain.
  - Ensure that the date and time of CSF collection and first dose of antibiotic therapy are documented
  - CSF investigation for posible causes of meningitis
    - For live attenuated vaccine platforms: PCR or culture as appropriate for the vaccine/vector strain
    - For trial sites in target disease endemic areas: test as appropriate for the wild type strain
    - Depending on laboratory capacity, CSF should be sent for viral, fungal, protozoan and parasitic pathogens known to be common to the geographic area (by stain techniques, culture, PCR as appropriate)
    - CSF should also be tested for typical meningeal bacterial pathogens as appropriate for age
  - Blood should be collected for serologic studies (preferably as paired acute & convalescent samples)
  - For each trial site a list of the common local causes of viral meningitis should be compiled and feasibility for investigation determined. Variation in etiology by age should also be determined.
  - Peripheral blood may contaminate the CSF if the lumbar puncture is traumatic. The case definition provides guidelines for interpretation based on peripheral blood WBC and RBC counts as follows:
    - Visual threshold for blood contamination of CSF is 400 RBC/uL.
    - If there is a traumatic LP, CSF pleocytosis is defined as one of the following:
      - If blood WBC and RBC counts are known:
        - Calculate predicted CSF WBC: CSF RBC X (Blood WBC/Blood RBC)
        - CSF pleocytosis exists if the ratio of observed CSF WBC:predicted CSF WBC >1:1
      - If blood WBC and RBC counts are not known:
        - CSF pleocytosis exists if ratio of CSF WBC: CSF RBC is >1:500
- Data Collection Guidelines
  - document date and time of onset of signs and symptoms suggestive of meningitis (see Figure 1)
  - CSF: document date and time of 1st simple; CSF WBC and RBC count; CSF gram stain and culture results including if not performed; document all investigations for possible microbial pathogens
  - Document details of antibiotic therapy including timing of first dose relative to obtaining CSF simple
  - Document date and time of recovery and presence of any sequelae including fatal outcome.
- Data Analysis Guidelines
  - In addition to classifying cases by level of certainty, where possible also classify as:
    - Confirmed vaccine associated etiology
    - Probable vaccine associated etiology
    - Posible vaccine associated etiology
    - Unknown etiology
    - Non vaccine-associated etiology
  - The interval between immunization and onset of aseptic meningitis should be analyzed in predefined increments such as 1st week (0-7 days), 2nd week (8-14 days) etc up to >10 weeks (>71 days).
  - If few cases are reported the respective values of time to even should be presented individually.

ASEPTIC MENINGITIS FIGURE 1. KEY LABORATORY AND CLINICAL DATA AND ALGORITHM FOR ASSESSING LEVEL OF CERTAINTY.



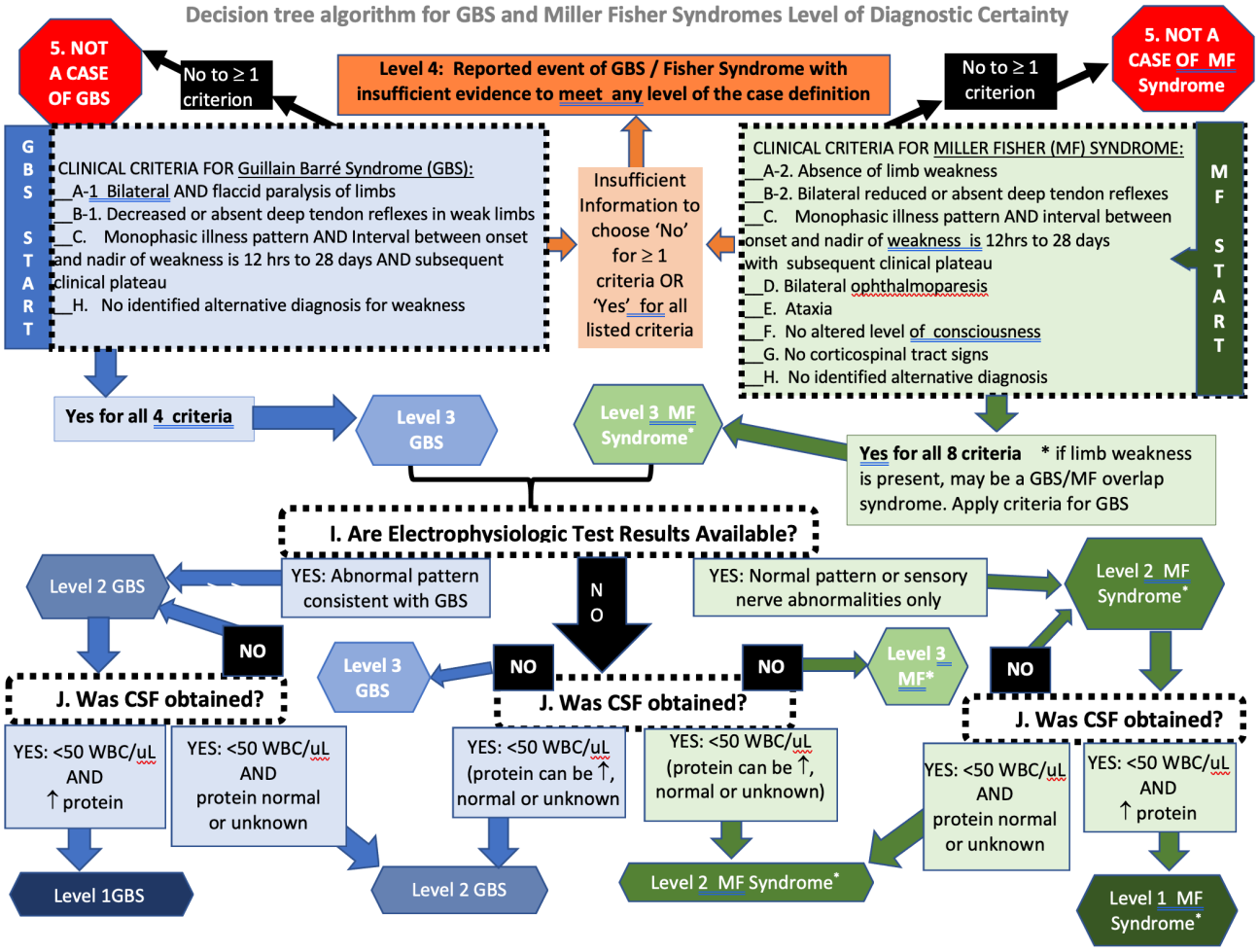
6.2.5 Guillain-Barré (GBS) and Miller Fisher (MF) Syndromes

- Key elements of Case Definition (CD)
    - Both GBS and MF have 3 levels of diagnostic certainty and the lowest, level 3, is based totally on clinical findings without need for laboratory investigation.
    - Critical for GBS to meet CD level 3 is demonstration of absent or decreased deep tendon reflexes in the same limbs that are weak. Without this it cannot meet any level of certainty.
    - Miller Fisher is an infrequent GBS subtype that includes bilateral ophthalmoparesis and ataxia usually without limb weakness. It is possible to have GBS/MF overlap syndromes where there is weakness and features of MF. (See figure 1). In such cases the level of certainty should be based on the GBS criteria, but it can also be described as GBS/MF overlap syndrome.
    - For both GBS and MF there must be sufficient follow-up to demonstrate a monophasic illness pattern (see Figure 1) and no alternative diagnosis for weakness. That said lack of testing for alternative diagnoses does not impact on the ability to meet the case definition.
- Recommendations for real time assessment (see Figure 1)
    - Ensure that the degree and distribution of limb weakness is assessed and that deep tendon reflexes are assessed in all weak limbs.
    - If possible, seek assessment by a neurologist and ask that the following assessments be recorded: Manual muscle testing using the Medical Research Council scale; Deep tendon reflexes; sensory and cranial nerve examination; presence or absence of ataxia. Measures of functionality or disability would also be helpful. These are provided in the published case definition appendices.
    - Full assessments should ideally be done at:
        - Initial presentation to medical care
        - At clinical nadir (see below)
        - At all subsequent points where there is significant change in neurologic status until a final outcome endpoint is reached (recovery, death, end of follow-up). If not possible assessments should be done weekly for 4 weeks, monthly for 5 months and then once every 3 months.
    - A date/time for the clinical nadir (defined as the worst state of clinical symptoms) should be determined. Normally for GBS and MF there is a steady progression in weakness to a nadir point followed by a plateau, fatal outcome or gradual improvement. Therapies such as immunoglobulins or steroids may cause fluctuations in levels of weakness – all of which should be carefully documented. These don't usually extend beyond the first 9 weeks.
    - Level 1 of certainty requires CSF WBC and protein results showing cytoalbuminologic disassociation (WBC >50, elevated protein) and characteristic electrophysiological test results (EMG, nerve conduction studies) as outlined in Figure 1. Of note electrophysiological tests can be normal if obtained in the first 7 days after symptom onset. If normal, testing should be repeated if possible.
    - Level 2 of certainty can be reached with either CSF or electrophysiologic testing rather than both.
    - If real time assessment is not possible the SPEAC data abstraction tool can be used in conjunction with medical records to gather the information needed to assess the level of diagnostic certainty.
        - Immunotherapy: rendered (e.g. IVIG, plasmapheresis, corticosteroids) or not rendered
- Data Collection Guidelines
    - Gather detailed clinical descriptions of symptoms/signs and time course including severity of weakness at the clinical nadir, additional neurologic signs of GBS (e.g. fasciculations, atrophy, myoclonus).
    - Document other concurrent signs, symptoms and diseases.
    - Document the dates and results of all:
        - electrophysiologic studies (electromyography [EMG] and nerve conduction velocity studies [NCS].
        - additional neurophysiologic studies including electroencephalography [EEG], neuroimaging studies (computed tomography [CT] or magnetic resonance imaging [MRI].
        - CSF examinations including WBC (cells/uL), RBC (cells/uL), differential WBC count if available, protein (mg/dL), glucose (mg/dL) and if done a concomitant serum glucose. The upper limits of normal for the laboratory performing the CSF analysis should be documented.

- Tests done to identify and/or rule out alternative etiologies for weakness.
- Document nature and dates of all therapy given for GBS/MF.
- Document the neurologic/functional outcome and disposition at last observation as detailed in the general Data Collection Guidelines for all AESI (Section 6.1)

- Data Analysis Guidelines
  - In the setting of pre-licensure trials, it is unlikely that more than one or a few cases will be reported. The guidelines in the published case definition provide suggestions for data analysis and presentation of scenarios where several cases are assessed (e.g. self-controlled case series study). These are not reproduced here but can be easily found in the published guidelines section 3.2.[11]

GBS AND MF FIGURE 1. KEY LABORATORY AND CLINICAL DATA AND ALGORITHM FOR ASSESSING LEVEL OF CERTAINTY



6.2.6 Encephalitis

- Key elements of Case Definition (CD)
  - Figure 1 details the key criteria needed to meet the encephalitis CD. Characteristic brain biopsy findings of encephalitis are all that are needed to meet level 1 but it is recognized this will rarely be obtained. Of critical importance to meet level 2 or 3 is documentation of either encephalopathy or focal/multifocal neurologic signs along with evidence of brain inflammation (fever, CSF pleocytosis, characteristic CT/MRI/EEG findings in encephalitis) and absence of alternative diagnoses.
  - Encephalitis may be accompanied by evidence of myelitis. See section 6.2.7. If so and both reach the same level of certainty the case is one of encephalomyelitis. If so but both reach different levels of certainty specify separately for each.
  - There is a great deal of overlap between encephalitis and ADEM (section 6.2.8). A level 3A of certainty can be used to specify cases where there are insufficient data to allow distinction between Level 3 encephalitis and Level 3 ADEM. However, if one of the two entities achieve a higher level of certainty that should be the basis for categorization: e.g. level 2 encephalitis and level 3 ADEM should be reported as level 2 encephalitis.

- Recommendations for real time assessment
  - Neurologic consultation should be obtained when possible, as early as possible in the illness course.
  - Neurologic consultation should be obtained when possible, as early as possible in the illness course.
    In addition to notes summarizing the neurologic exam findings, neurologic status should be measured using Glasgow Coma Scale/Pediatric Coma Score, Mini-Mental State Examination, Barthel Index, Modified Rankin Functional Score. (All can be found in the Brighton published CD[10] and are reproduced in the SPEAC encephalitis/myelitis/ADEM data abstraction and interpretation form to be found in the Developer's toolbox for AESI)
  - Recommended frequency of neurologic assessment is at initial presentation to medical care, at the clinical nadir (defined as when clinical status is at the worst), at all subsequent points of significant change in neurologic status until the end of the clinical course (recovery, death or end of follow-up).

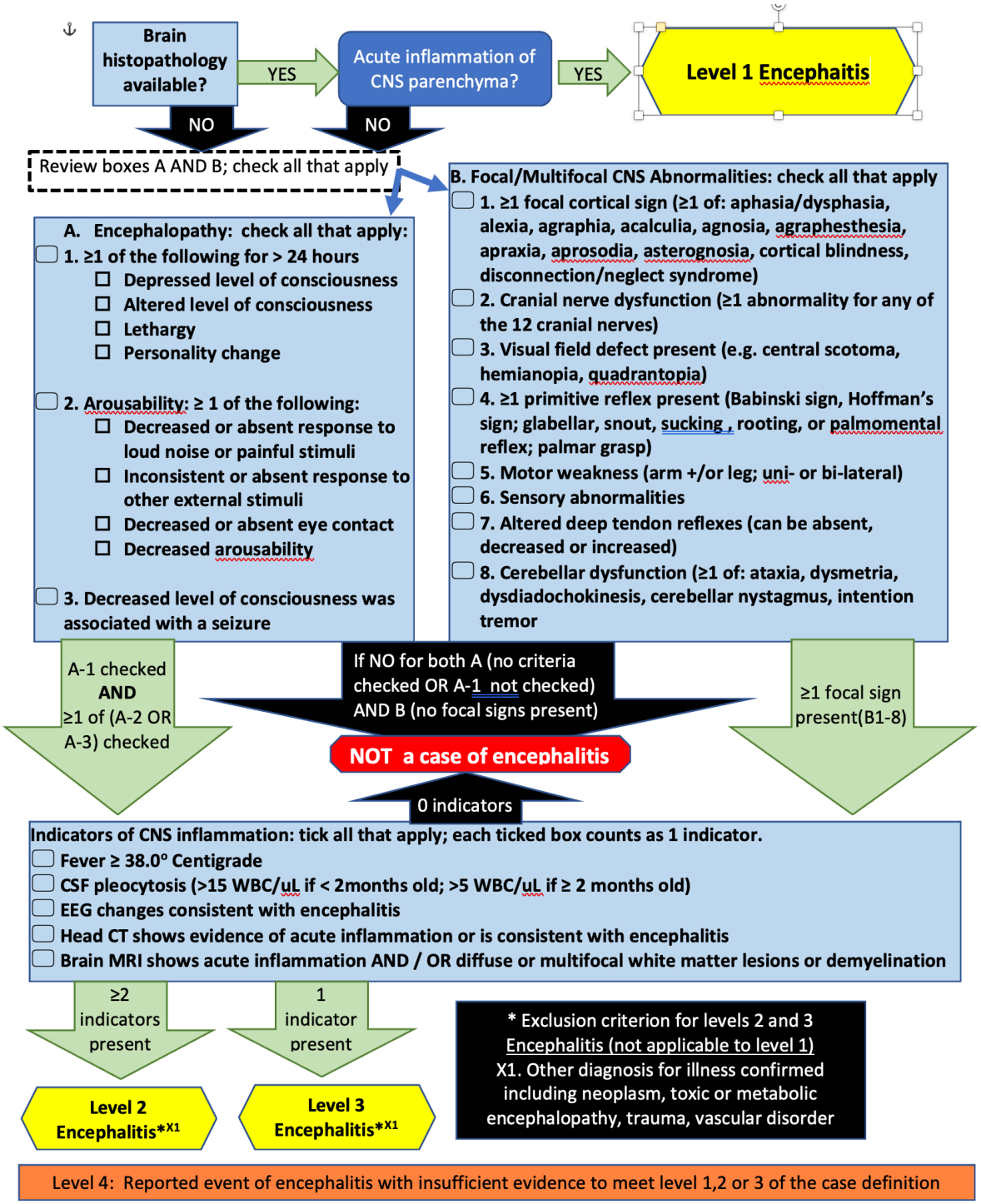
- Data Collection Guidelines
  - Document all encephalitis case definition criteria that are met by each case. As an aid, the SPEAC data abstraction form can be used to record the data (in the SPEAC toolbox for AESI in the AESI Data Abstraction & Interpretation Forms sub-folder) including:
    - Neurologic symptoms/signs plus all relevant (to the case definition criteria) laboratory results including neuroimaging and/or histopathologic features (include test dates). Relevant results include all brain biopsy if done, CSF test results, brain CT and MRIs, EEG, EMG & Nerve Conduction studies, relevant autopsy findings if applicable, and all tests done for etiology of encephalitis or exclusionary criteria for alternate causes.
    - Identify the initial neurologic findings that enabled the first fulfilment of case definition criteria including start and end dates.
    - Characterize the temporal nature of the onset of encephalopathy as either acute (evolving over minutes-hours to hours-days) or subacute (evolving over hours-days to days-weeks).
    - Identify the level of consciousness at the clinical nadir.
  - Document any concurrent signs, symptoms and diseases other than the event described
  - Document the neurologic/functional outcome and disposition at last observation as detailed in the general Data Collection Guidelines for all AESI (Section 6.1)

- Data Analysis Guidelines
  - When there is one or a few cases, individual case summaries or case reports represent the ideal method of assessment for each case of encephalitis. Include specification of the following intervals:
    - Days from immunization to onset of prodromal symptoms
    - Days from immunization to onset of neurologic signs
    - Days from onset of neurologic signs to clinical nadir

- Days with a Glasgow Coma Scale score <10.
- Days between onset of neurologic signs and each collection of CSF.

- The published case definition [10] provides much more detail on recommended analysis when many cases are being analyzed and should be consulted in the event of summarizing multiple cases.

ENCEPHALITIS FIGURE 1. KEY LABORATORY AND CLINICAL DATA AND ALGORITHM FOR ASSESSING LEVEL OF CERTAINTY



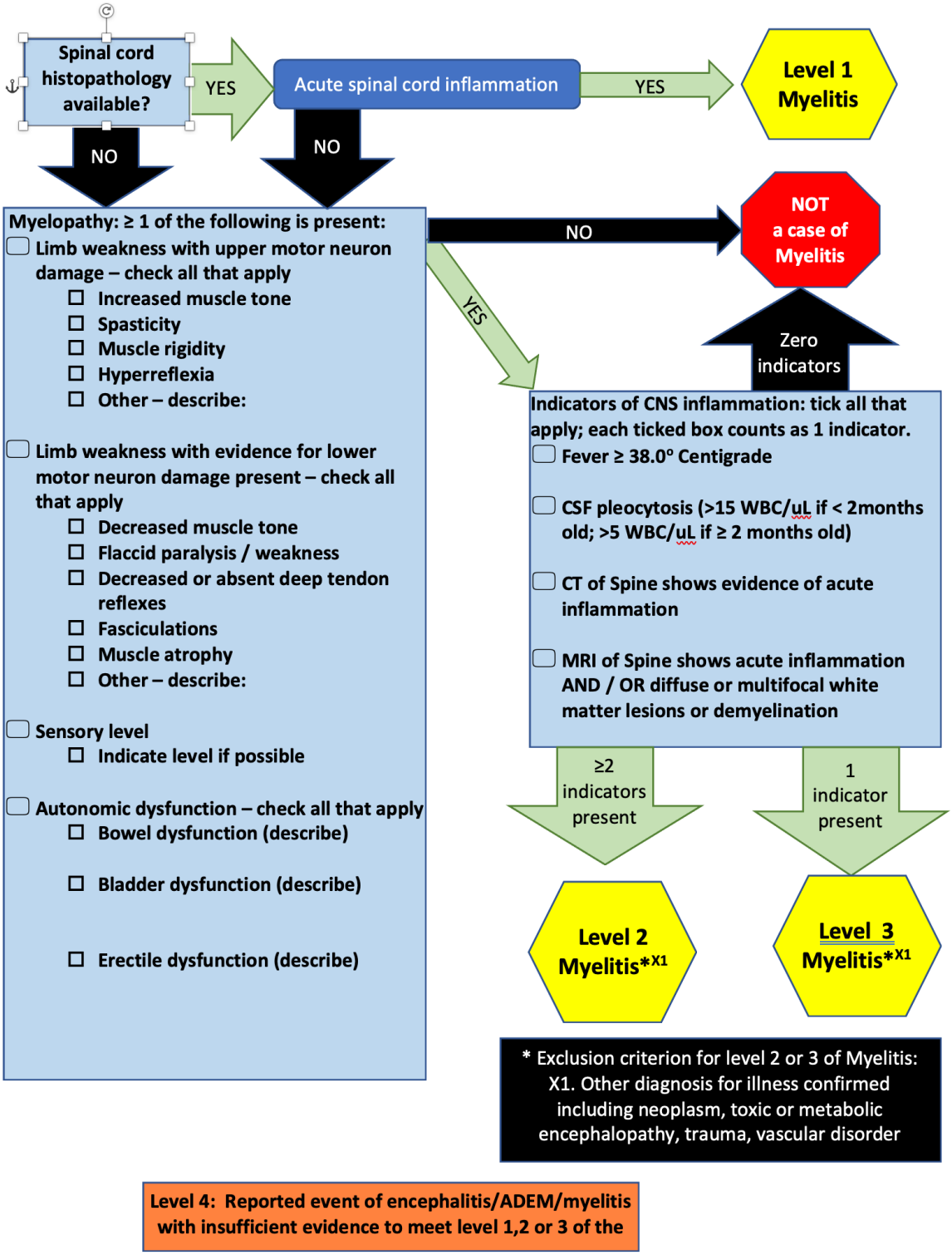
6.2.7 Myelitis (including Transverse myelitis)

- Key elements of Case Definition (CD)
  - There are 3 levels of certainty based on clinical and laboratory features (see figure 1)
  - Characteristic spinal cord biopsy findings of myelitis are all that are needed to meet level 1 but it is recognized this will rarely be obtained. Of critical importance to meet level 2 or 3 is documentation of at least one feature of myelopathy plus evidence of spinal cord inflammation (fever, CSF pleocytosis, characteristic CT/MRI findings in myelitis) and absence of alternative diagnoses.
  - Myelitis may present in combination with encephalitis (see 6.2.6 encephalitis). If so and both reach the same level of certainty the case is one of encephalomyelitis. If so but both reach different levels of certainty specify separately for each.
  - It also may present as part of acute disseminated encephalomyelitis. (see 6.2.7 ADEM). A level 3A of certainty can be used to specify cases where there are insufficient data to allow distinction between Level 3 myelitis and Level 3 ADEM. However, if one of the two entities achieve a higher level of certainty that should be the basis for categorization: e.g. level 2 myelitis and level 3 ADEM should be reported as level 2 myelitis.
- Recommendations for real time assessment
  - Neurologic consultation should be obtained when possible, as early as possible in the illness course.
  - Fever is one criterion for inflammation and should be documented following the Brighton case definition of temperature ≥38.0 C by any measurement.
  - Other criteria for inflammation require CSF examination for pleocytosis and spinal cord imaging with CT and/or MRI.
  - Recommended frequency of neurologic assessment is at initial presentation to medical care, at the clinical nadir (defined as when clinical status is at the worst), at all subsequent points of significant change in neurologic status until the end of the clinical course (recovery, death or end of follow-up).

- Data Collection Guidelines
  - Document all myelitis CD criteria that are met by each case. As an aid, the SPEAC data abstraction form can be used to record the data (in the SPEAC toolbox for AESI in the AESI Data Abstraction & Interpretation Forms sub-folder).

- Data Analysis Guidelines
  - If few cases are reported in the trial the concrete time course should be analyzed for each including interval from immunization to onset

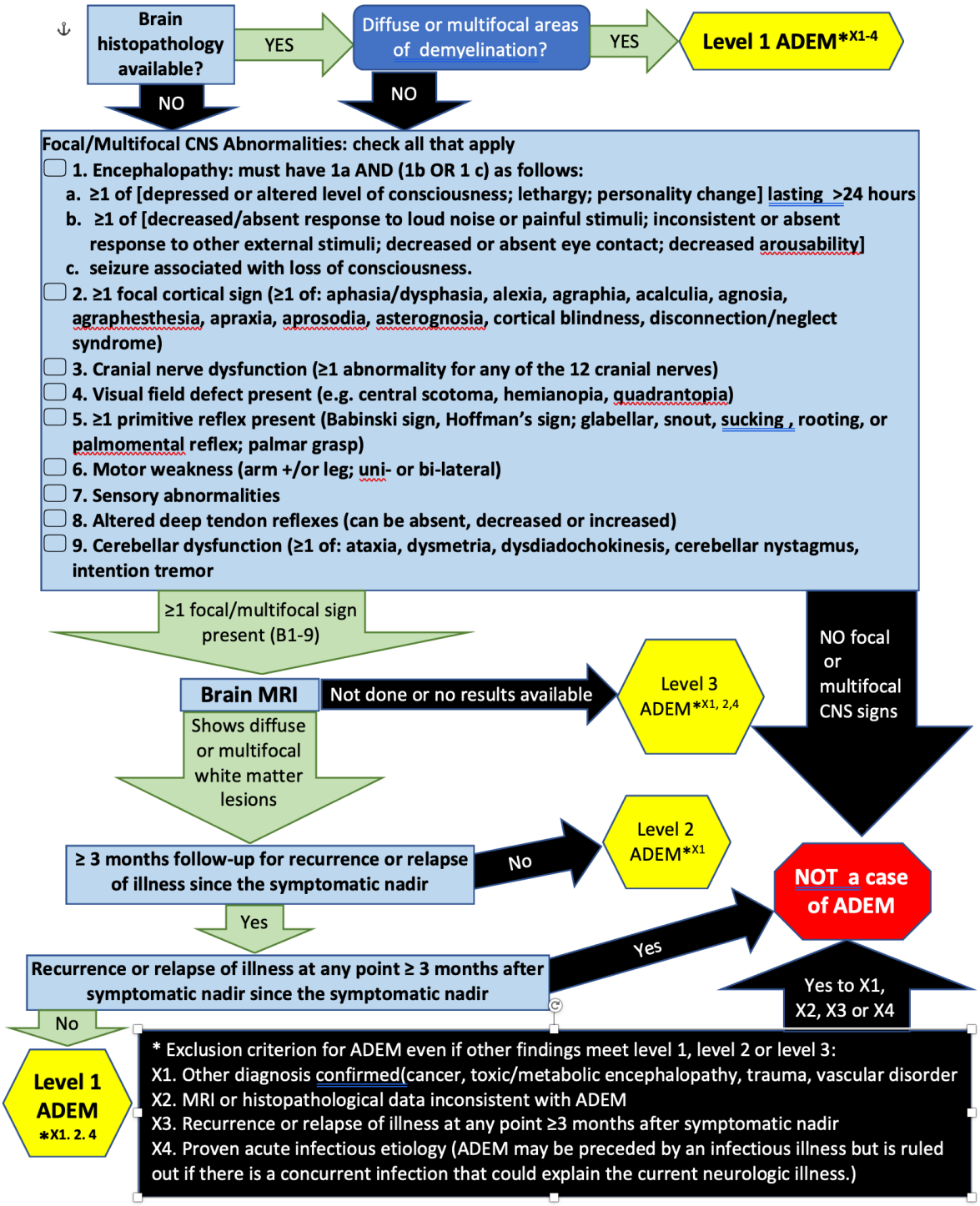
MYELITIS FIGURE 1. KEY LABORATORY AND CLINICAL DATA AND ALGORITHM FOR ASSESSING LEVEL OF CERTAINTY.



6.2.8 Acute Disseminated Encephalomyelitis (ADEM)

- Key elements of Case Definition (CD)
  - Figure 1 details the key criteria needed to meet the ADEM CD. There are 3 levels of certainty based on clinical signs, brain imaging with MRI and duration of follow-up for recurrence or relapse.
  - ADEM may be accompanied by evidence of myelitis. See section 6.2.7.
  - There is a great deal of overlap between ADEM and encephalitis (section 6.2.6). A level 3A of certainty can be used to specify cases where there are insufficient data to allow distinction between Level 3 encephalitis and Level 3 ADEM. However, if one of the two entities achieve a higher level of certainty that should be the basis for categorization: e.g. level 2 ADEM and level 3 encephalitis should be reported as level 2 ADEM.
  - Given the immunopathogenesis of ADEM frequently there may be a known prior infection. However, any proof of concurrent acute infection that could explain the neurologic illness rules out the diagnosis of ADEM.
- Recommendations for real time assessment
  - Neurologic consultation should be obtained when possible, as early as possible in the illness course.
    In addition to notes summarizing the neurologic exam findings, neurologic status should be measured using Glasgow Coma Scale/Pediatric Coma Score, Mini-Mental State Examination, Barthel Index, Modified Rankin Functional Score. (All can be found in the Brighton published CD[10] and are reproduced in the SPEAC encephalitis/myelitis/ADEM data abstraction and interpretation form to be found in the Developer's toolbox for AESI)
  - Follow-up should be for a minimum of 3 months from the time of clinical nadir, but a longer duration is recommended since it may enable identification of alternate illnesses, primarily multiple sclerosis, or neuromyelitis optica, should there be a recurrence or relapse of illness after 3 months.
  - Recommended frequency of neurologic assessment is at initial presentation to medical care, at the clinical nadir (defined as when clinical status is at the worst), at all subsequent points of significant change in neurologic status until the end of the clinical course (recovery, death or end of follow-up).
- Data Collection Guidelines
  - Document all ADEM case definition criteria that are met by each case. As an aid, the SPEAC data abstraction form can be used to record the data (in the SPEAC toolbox for AESI in the AESI Data Abstraction & Interpretation Forms sub-folder) including:
    - Neurologic symptoms/signs plus all relevant (to the case definition criteria) laboratory results including neuroimaging and/or histopathologic features (include test dates). Relevant results include all brain biopsy if done, brain CT and MRIs, EEG, EMG & Nerve Conduction studies, relevant autopsy findings if applicable, and all tests done for illness etiology or exclusionary criteria for alternate causes.
    - Identify the initial neurologic findings that enabled the first fulfilment of case definition criteria including start and end dates.
    - Characterize the temporal nature of the onset of encephalopathy as either acute (evolving over minutes-hours to hours-days) or subacute (evolving over hours-days to days-weeks).
    - Identify the level of consciousness at the clinical nadir.
  - Document any concurrent signs, symptoms and diseases other than the event described
  - Document the neurologic/functional outcome and disposition at last observation as detailed in the general Data Collection Guidelines for all AESI (Section 6.1)
- Data Analysis Guidelines
  - When there is one or a few cases, individual case summaries or case reports represent the ideal method of assessment for each case of encephalitis. Include specification of the following intervals:
    - Days from immunization to onset of prodromal symptoms
    - Days from immunization to onset of neurologic signs
    - Days from onset of neurologic signs to clinical nadir
    - Days with a Glasgow Coma Scale score <10.
    - Days between onset of neurologic signs and each collection of CSF.
  - The published case definition [10] provides much more detail on recommended analysis when many cases are being analyzed and should be consulted in the event of summarizing multiple cases.

ADEM FIGURE 1. KEY LABORATORY AND CLINICAL DATA AND ALGORITHM FOR ASSESSING LEVEL OF CERTAINTY

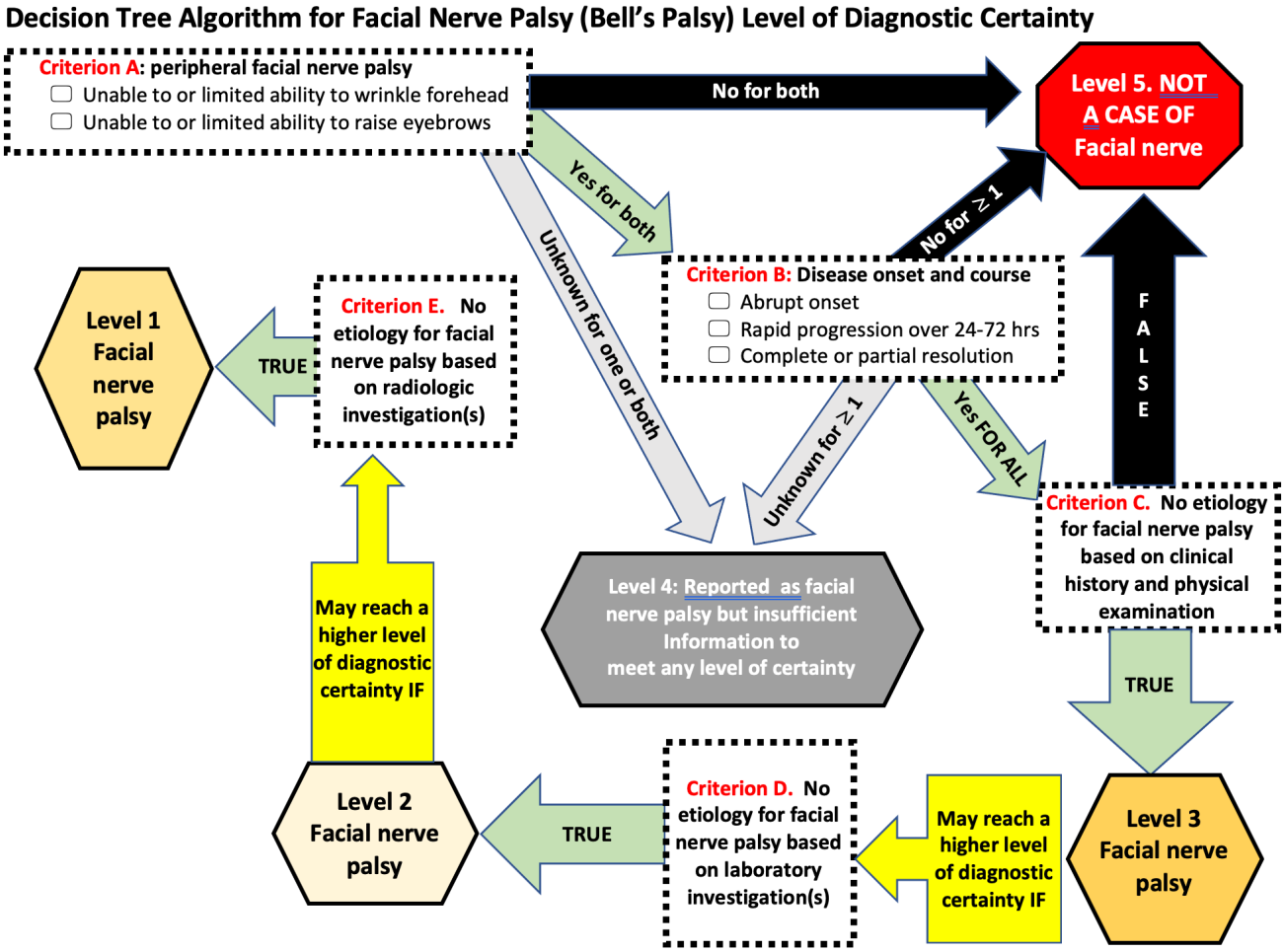


6.2.9 Idiopathic Peripheral Facial Nerve Palsy

- Key elements of Case Definition (CD)
  - Figure 1 details the key criteria needed to meet the facial palsy CD. There are 3 levels of certainty. Idiopathic facial nerve palsy is a diagnosis of exclusion. Level 3 is based solely on clinical history and physical examination. If alternate diagnoses are found based on clinical findings the diagnosis is ruled out, however, for level 3 there need not be evidence that alternate causes were looked for. However, to reach level 2 there needs to be some laboratory testing to rule out alternate causes and to reach level 1 there needs to be some radiologic assessment to rule out alternate causes.
  - Idiopathic bilateral (as opposed to unilateral) peripheral facial nerve palsy may occur but is rare. It is recommended that reports of bilateral facial palsy only be included if reported by a professional healthcare provider.
- Recommendations for real time assessment
  - Neurologic consultation should be obtained when possible, as early as possible in the illness course.
  - Required clinical evidence for facial nerve palsy is a documented decreased ability or complete inability to wrinkle the forehead or to raise the eyebrows on the affected side. There may be other findings but without these it cannot meet the case definition.
  - Laboratory and radiologic testing, to the extent possible at the study site, is recommended to assess the many possible causes of facial nerve palsy including acute infections, tumours, neurologic and autoimmune disorders, trauma and iatrogenic factors. A full list of causes is presented in the published CD[12] and the SPEAC data abstraction and interpretation form in the SPEAC toolbox for AESI (in the AESI Data Abstraction & Interpretation Forms sub-folder).
  - Severity of disease expression should be graded using a recognised international grading scale. The Housee-Brackmann Facial Nerve Grading System is commonly used and is provided in the published CD[11] as well as the SPEAC data abstraction and interpretation form in the SPEAC toolbox.
    - Levels peak between 15 and 120 minutes from onset
- Data Collection Guidelines
  - There should be a detailed clinical description of the adverse event including all the symptoms/signs upon which the case definition criteria were based.
  - Document all concurrent symptoms, signs and diseases.
  - Document any re-occurrence of facial palsy after resolution of the initial illness.
  - Provide all laboratory, radiologic and electrophysiologic tests that were done including dates.
  - Document treatment administered for facial palsy.
  - Document the clinical outcome at the last observation including:
    - (Complete / incomplete) resolution in the absence of treatment
    - (Complete / incomplete) resolution with treatment
    - No improvement (uni / bi- laterally)
    - Sequelae (specify)
    - Other outcome (describe)
    - Unknown clinical outcome

- Data Analysis Guidelines
  - If there are many cases they should be analyzed as the number and percentage following into each interval following immunization as follows: day of immunization to <2 weeks; then in successive 2-week intervals to <12 weeks, 12 - <16 weeks, 16-<20 weeks and >20 weeks.

FACIAL PALSY FIGURE 1. KEY LABORATORY AND CLINICAL DATA AND ALGORITHM FOR ASSESSING LEVEL OF CERTAINTY.



6.2.10 Neurologic AESI Glossary of Terms

Includes terms for the following Brighton Collaboration Case Definitions:

- Encephalitis, myelitis, acute disseminated encephalomyelitis
- Guillain Barré and Miller Fisher Syndromes
- Peripheral Facial Nerve Palsy (Bell's palsy)
- Aseptic meningitis
- Generalized convulsion

Acalculia: inability to perform simple mathematical tasks (addition, subtraction, multiplication)

Agnosia: inability to recognize objects or persons

Agraphesthesia: difficulty recognizing a written number or letter traced on the palm of the hand

Agraphia: impairment in the ability to write

AIDP: acute inflammatory demyelinating polyneuropathy (most common form of GBS)

Alexia: impairment of ability to read

AMAN: acute motor axonal neuropathy (a less common form of GBS)

AMSAN: acute motor and sensory axonal neuropathy (a less common form of GBS)

Aphasia / Dysphasia: impairment of spoken language abilities that affect production and/or comprehension of speech.

Apraxia: inability to execute purposeful movements

Aprosodia: decreased ability to generate or comprehend emotion as conveyed in spoken language

Asterognosia: inability to identify an object by active touch of the hands without other sensory input (e.g. visual)

Ataxia: loss of coordination in voluntary movements; can present in many ways including: lack of coordination, slurred speech, gait abnormalities, inability to balance, trouble eating and swallowing, loss of fine motor skills, tremors;

Atonic motor manifestations: sudden loss in tone of postural muscles; may be preceded by a myoclonic jerk; can be precipitated by hyperventilation in setting of syncope; may reflect a seizure but not in conjunction with a hypotonic hyporesponsive episode, myoclonic jerk or syncope.

Babinski sign (also see primitive reflexes): when sole of foot is stroked the toes fan out and upwards (instead of curling inwards which is normal); also referred to 'upgoing toe' or 'extensor response'

Brudzinski's sign: With Kernig's sign, evidence of meningeal irritation/inflammation; with individual lying supine (on back), passive flexion of the neck results in spontaneous hip flexion. Specificity 90%, sensitivity 5-14% (Putz K, Hayani K, Zar FA. Meningitis Primary care Clin Office Pract 2013; 40:707-736).

Bulbar palsy: dysfunction of one or more lower motor neuron centers in the brain stem. May involve cranial nerves IX to X11 (see table on cranial nerves) with loss or decreased ability to swallow, loss of sense of taste, weakness or loss of ability to move head side to side or up and down, heart rate abnormalities

Central scotoma: loss of central vision

Clinical nadir: the point at which clinical symptoms are felt to be at the clinical worst. This needs to be defined and identified by the health practitioner on a case by case basis.

Clonic movements: sudden, brief (<100 milliseconds) involuntary contractions of the same muscle groups, regularly repetitive at a frequency of about 2-3 contractions / second

Cortical blindness: total or partial loss of vision in a normal-appearing eye that is caused by damage to the brain's occipital cortex.

Corticospinal tract signs: evidence of upper motor neuron damage (as opposed to lower motor neuron damage seen in GBS). Paralysis with spasticity, increased muscle tone, hyperreflexia and presence of primitive reflexes (defined in glossary)

Cranial nerves: Normal function and evidence of dysfunction.

Cranial nerve (sensory/motor)	Function	Dysfunction
I Olfactory	Sensory: Smell	Hyposmia – decreased ability to smell Anosmia – absence of ability to smell
II Optic	Sensory: Vision	Partial or complete loss of vision
III Oculomotor	Motor: Eye movements	Ophthalmoparesis/plegia: decreased ability/inability to move the eye Double vision, Ptosis: loss of pupillary constriction to light
IV Trochlear	Motor: Eye movements	Decreased or loss of ability to look up
V Trigeminal	Motor: chewing; clenching teeth.	Decreased strength or loss of ability to bite
	Sensory: Ophthalmic branch: sensation to forehead, eyes and eyelid, skin on nose, nasal mucosa	Loss of sensation to forehead, eyelid, nasal mucosa; Loss of corneal reflex: involuntary blinking in response to anything touching the cornea
	Maxillary: sensation to middle third of face	Loss of sensation in middle third of face including side of nose, upper teeth, lower eyelid
	Mandibular: sensation to lower third of face	Loss of sensation in lower third of face, tongue, oral mucosa, lower teeth
VI Abducens	Motor: Eye movements	Decreased ability to look away from the nose (abduction). May have double vision; eye tends to turn inward towards nose
VII Facial	Motor: facial expression muscles	Inability to smile or frown
	Sensory: external ear, taste	Unable to detect sweet or salty on anterior 2/3 of tongue
VIII Vestibulo-cochlear	Sensory: hearing as well as positional changes of head with respect to gravity	Partial or complete loss of hearing; Loss of balance
IX Glosso-pharyngeal	Motor: some swallowing muscles	Loss of swallowing reflex;
	Sensory: taste back 1/3 of tongue	Unable to detect sweet/salty posterior tongue
X Vagus	Motor: throat/soft palate	Swallowing abnormalities; loss of gag reflex

	Sensory: to outer ear, throat, heart and abdominal organs	
	Autonomic: heart rhythm, smooth muscles in airway, lungs, GI tract	Bradycardia, decreased vascular tone, lowered blood pressure
XI Accessory	Motor: neck muscles	Decreased ability to rotate, extend or flex neck and shoulders
XII Hypoglossal	Motor: tongue muscles	Inability to stick out tongue or move it from side to side

Disconnection syndrome: term for various neurologic disorders in which there is an interruption of association pathways located either in one cerebral hemisphere or linking cerebral hemispheres. Symptoms and signs are variable depending on which pathways are affected.

Dysdiadochokinesis: impairment of the ability to perform rapidly alternating movements such as

Dysmetria: impairment in the ability to control the distance, power and speed of an act; one of the impairments observed in cerebellar ataxia. The finger – nose test is often used to assess (individual is asked to touch the clinician's finger and then his/her own nose repeatedly as quickly as possible).

Electromyogram (EMG): used to measure the electrical activity of muscles when at rest and when being used

Encephalitis: inflammation of the brain

Encephalomyelitis: inflammation of both the brain and spinal cord

Encephalopathy: state of being in which consciousness or mental status is altered

Epiphora: excess tearing, spilling over of tears outside of context of crying

Fasciculations: involuntary muscle twitching; often visible under the skin;

Flaccid weakness/paralysis: muscular weakness/total loss of function accompanied by decreased muscle tone.

GBS Overlap syndrome: disease presentation with features of both GBS and Miller Fisher Syndrome

Generalized Motor Manifestations as part of Seizure: bilateral and more than minimal muscle involvement (also see tonic, clonic, tonic-clonic, atonic seizure manifestations/movements)

Glabellar reflex (primitive reflex): Tapping on the forehead just above the bridge of the nose causes blinking of the eye.

Glasgow Coma Score: a scoring system for evaluating the severity of central nervous system involvement after a head injury or other brain injury that can alter the level of consciousness. Assesses motor, verbal and eye-opening responses to commands. Separate scoring systems are available for both adults and children. Test

Hemianopia: loss of one of half of the visual field on one or both side

Hoffman's sign (primitive reflex): an involuntary flexion movement of the thumb or index finger which occurs when the examiner flicks the middle fingernail while keeping the joint nearest the fingernail immobile. It is indicative of an upper motor neuron lesion.

Intention tremor: a coarse hand tremor that is aggravated by goal-directed movements (e.g. reaching to touch an object). Typically indicates cerebellar dysfunction.

Kernig sign: with Brudzinski's sign, indicator of meningeal irritation/inflammation; with hip flexed to 90° (right angle), inability or reluctance to allow full extension of knee (Putz K, Hayani K, Zar FA. Meningitis Primary care Clin Office Pract 2013; 40:707-736).

Meningismus: state of irritation of the membranes (meninges) that surround the brain and spinal code. The signs and symptoms produced by the irritation include neck stiffness, headache, (nuchal rigidity)

Meningitis: inflammation of the membranes (meninges) that surround the brain and spinal cord.

Meningoencephalitis: inflammation of the brain and the membranes (meninges) that surround the brain and spinal cord.

Meningoencephalomyelitis: inflammation of the membranes (meninges) that surround the brain and spinal cord plus inflammation of the brain ('encephal') and the spinal cord ('myelitis')

Monophasic illness pattern: a key criterion for selected BCCD case definitions but which may have nuances as follows:

- for Acute disseminated encephalomyelitis (ADEM): absence of recurrence of symptoms 3 months or more after the worst point of disease (symptomatic nadir) in the absence of treatment or while on appropriate treatment. Multiple sclerosis (MS) is characterized by relapses and recurrences. The first episode may meet the criteria for ADEM but will be diagnosed as MS (Not ADEM) if there is a recurrence 3 months or more after symptomatic nadir. However, if therapy for ADEM is being tapered there may be a recurrence/relapse of symptoms and this is compatible with an ADEM diagnosis.
- for Guillain Barré / Miller Fisher syndromes: from disease onset a steady progression to a symptomatic nadir followed by either a plateau (no worsening, no improvement), fatal outcome or gradual improvement. From the case definition footnote 10: "Fluctuations in level of weakness, before reaching nadir, or during the plateau or improvement phases, occur in some cases, usually associated with the use of disease-modifying therapies. Such fluctuations usually occur within the first 9 weeks after onset and are followed by eventual improvement.

Myoclonus: quick involuntary muscle contractions that results in visible movement; can involve a single muscle group or several; also, can present as hiccups.

Nadir: lowest point, used to refer to the worst state of clinical symptoms related to GBS, Miller Fisher syndrome, encephalitis, myelitis or acute disseminated encephalomyelitis (ADEM)

Nerve Conduction Studies: measure how well and how fast nerves can send electrical signals.

Nuchal rigidity: the inability to flex the neck forward due to rigidity of the neck muscles caused by meningismus.

Nystagmus: rhythmic, oscillating motions of the eyes

Ophthalmoparesis/plegia – weakness/paralysis of one or more extraocular muscles responsible for eye movements.

Cranial nerve	Innervated muscle(s)	Effect of dysfunction
III – Oculomotor	Superior, inferior and medial rectus muscles and inferior oblique muscle Pupillary constriction	• Eyeball displaced laterally and inferiorly – so gaze is down and out; inability to look up or towards the nose (adduction). • diplopia - double vision • ptosis - drooping of the eyelid • loss of pupillary light reflex
IV Trochlear	Superior oblique	Decreased or loss of ability to look up

VI – Abducens	Lateral rectus	Decreased ability to look away from the nose (abduction). May have double vision; eye tends to turn inward towards nose

Palmar grasp (primitive reflex): when an object is placed in a person's hand and their palm is stroked, the fingers close reflexively 'grasping' the object. This is normal in infancy but when present in older children and adults it indicates frontal lobe damage.

Palmomental reflex (primitive reflex): a twitch of the chin muscle is elicited by stroking the palm of the hand. When present it indicates frontal lobe damage.

Primitive reflexes: Indicate damage to the central nervous system; includes the following all of which are defined separately: Babinski sign, Hoffman's sign; glabellar, snout, rooting, sucking and palmomental reflexes; palmar grasp; (see each definition separately)

Ptosis: drooping of the eyelid(s)

Quantrantopia: loss of one quarter of the visual field on one or both sides

Rooting reflex (primitive reflex): when someone's cheek or lip is touched, the person automatically turns his or her face toward the stimulus and makes sucking motions with the mouth. This is normal in newborn babies but abnormal and indicative of central nervous system damage when it occurs beyond infancy.

Scotoma: an area of partial alteration in the field of vision that is surrounded by a field of normal or relatively well-preserved vision. The alteration may be partially diminished or entirely degenerated visual acuity.

Sensory level: associated with spinal cord disease where a defined level in the spinal cord can be determined below which sensation is decreased or absent

Snout reflex (primitive reflex): Pouting or pursing of the lips that is elicited by light tapping of the closed lips near the midline. It results from abnormal contraction of the orbicularis oris muscle around the mouth. When present the reflex indicates damage to the frontal lobe of the brain.

Sucking reflex (primitive reflex): instinctive sucking movements in response to anything that touches the roof of the mouth. It is normal in infancy but abnormal in older children and adults indicating brain damage.

Symptomatic nadir: point (date) at which clinical symptoms are felt to be at their worst. Should be defined and identified by the health practitioner on a case-by-case basis.

Synkinesis: Involuntary response in a muscle as a result of voluntary contraction of a distant muscle. Occurs due to aberrant reinnervation to a previously denervated muscle from collateral sprouting of a nerve supplying a different muscle. Examples in facial nerve palsy include eyelid closure that occurs when patient smiles; 'crocodile tears' (Bogorad's syndrome): unilateral lacrimation (tearing) while eating;

Tonic movements: sustained increase in muscle contraction lasting seconds to minutes

Tonic-clonic movements: sequence of tonic movement followed by clonic phase

ANNEX VII

Tabular Checklists for GAIA Guidelines on Safety Data Collection in Vaccine Trials in Pregnancy

Tabular Checklist: GAIA guideline for safety data collection in vaccine trials in pregnancy

Tables 1-5 Detail Essential and Complementary Data to gather relative to five key aspects of pregnancy vaccine trials as recommended in the GAIA guidelines [s,t]

Tables 6 and 7 provide key Brighton guidelines for analyzing and presenting safety data. These were part of the 2009 guidelines for pre- and post-licensure clinical vaccine safety trials [x] and were endorsed by the 2016 GAIA guidelines [s,t]

TABLE 1. CLINICAL TRIAL SITE BACKGROUND DATA COLLECTION. NOTE WHETHER BACKGROUND RATES ARE AVAILABLE FOR KEY CONDITIONS IN THE POPULATION FROM WHICH TRIAL PARTICIPANTS ARE SELECTED. CHECK ALL THAT ARE KNOWN AND IDENTIFY THE SOURCE AS FOLLOWS: 1=MINISTRY OF HEALTH DATA; 2=DISTRICT/PROVINCIAL EPIDEMIOLOGIC DATA; 3=PREVIOUS STUDIES IN COMPARABLE STUDY SETTINGS; 4=OBSERVATIONAL DATA FROM STUDY LOCALITY IN PREPARATION FOR CLINICAL TRIAL; 5=OTHER WHICH SHOULD BE DESCRIBED.

Maternal Outcome	Fetal Outcome	Neonatal Outcome
☐ Death ☐ Caesarian section(C/S) ☐ Preterm delivery ☐ Eclampsia/Preeclampsia	☐ Spontaneous abortion ☐ Miscarriage ☐ Stillbirth	☐ Congenital anomalies ☐ Small for gestation age ☐ Low birth weight ☐ Prematurity ☐ Death

TABLE 2. PRE-VACCINATION SCREENING DATA. ALL DATA CONSIDERED ESSENTIAL PRIORITY UNLESS OTHERWISE INDICATED.

In addition to Maternal/Fetal data the following should be collected:

☐ Essential priority - Inclusion/exclusion criteria; date/time of informed consent; withdrawal of mother / infant; date/reason for withdrawal; loss to follow up including date/reason;

☐ Complementary priority: person giving consent (maternal participant, partner/spouse, or both)

Maternal Data			
Demographics	Medical/Obstetric history (Hx)	Physical exam/Labs	Fetal data
Essential Priority ☐ Study participant identifiers ☐ Date of birth ☐ Age at time of screening (completed years) ☐ Race ☐ Ethnicity ☐ Household geographic location **Complementary Priority** ☐ Household environment	**Essential Priority** ☐ Pre-existing medical conditions Include: Diagnosis (diagnosis date & stop date if relevant); Continuing medical condition(s) ☐ Previous hospitalizations including inpatient surgical procedures Provide admission/discharge dates for all ☐ Obstetric Hx Include: Order of current pregnancy; Gravity & Parity; Previous pregnancy complications (e.g. antepartum or post-partum hemorrhage, incompetent cervix); Previous deliveries Including: date, singleton or multiple births, Gestational age(GA) at delivery, Delivery type (vaginal, elective or unplanned C-section), Outcome (live birth, still birth, abortion), neonatal death. ☐ Concomitant medications Name of drug; Route; Start/stop date; Indication ☐ Medication Hx (from 1 month pre pregnancy)	☐ Height & Weight ☐ Body Mass Index (BMI); or other validated nutritional indicator. Minimum: at enrollment If possible: prior to/ during pregnancy ☐ Vital signs (Resting heart rate [beats/min], Systolic + diastolic BP (mmHg), breaths/min, temperature) ☐ Abnormalities on general physical exam: General appearance,	☐ Fetal growth restriction (IUGR) ☐ Fetal anomaly noted before maternal vaccination (e.g. by U/S or any other screening test) ☐ Exposure to any other teratogens not yet noted

urban, suburban or rural ☐ Consanguinity Second cousins or closer (Yes or No) ☐ Highest attained education (1-9)[1] ☐ Local socioeconomic status indicators[2] Include: type of housing; # home occupants; size of home; household income; maternal occupation; household assets	Prescription/non-prescription drugs, herbals, homeopathic preparations, nutritional supplements. Note Hx of drug abuse. ☐ Hx of allergy & adverse drug reactions Include allergen/description of reaction ☐ Maternal HIV infection – if present[3] Include WHO clinical HIV staging; CD4 test date/result (% + absolute count); Viral load test date/result ☐ Vaccination Hx (from 1 year prior to enrollment including date(s) of administration) ☐ Current pregnancy Include: Date of last normal menstrual period(LMP); Estimated due date (EDD); Method of EDD estimation (LMP, ultrasound, symphysis-fundal height or combination); Dates of antenatal care visits; Infections: routine antenatal test[see Supp table A] ; Acute non-infectious conditions (Hematologic, metabolic, endocrine, gynecologic, renal, rheumatologic, cardiovascular, pulmonary, neurologic, any other related to vaccine safety/immunogencity; pregnancy complication(s), relevant lab results); Routine screening to assess pregnancy and fetus (U/S, amniocentesis); Tobacco use[4] (daily, less than daily, never); Alcohol consumption[5] (daily, several times a week or month, never) **Complementary Priority** ☐ Current pregnancy ○ Date of LMP: not known, unsure, sure ○ Tobacco consumption (average number per day or week or not available) ○ At high risk for serious obstetric complications (Yes or No)[see Supp table B]	dermatologic, cardio-vascular, respiratory, hematologic, urogenital, gastrointestinal, ocular / visual, musculoskeletal, endocrine/metabolic ☐ Abnormalities on obstetric exam: Scars from prior deliveries, Fundal height, Fetal heart tones, Fetal movement Dates & Results for: ☐ General Lab investigations Full CBC & diff, Urea / creatinine, AST, ALT, GGT Bilirubin, Na, K, Cl, Glucose ☐ Baseline lab for infections[see table 2] ☐ Investigations relevant to vaccine target infection ☐ Urine tests (protein, glucose, bacterial culture)	☐ GA[6] at time of vaccination of mother

[1] *Education level: classify as follows: 1-primary; 2-lower secondary; 3-upper secondary; 4-post-secondary non-tertiary education (e.g. vocational training); 5-short cycle tertiary education (e.g. diploma of higher education); 6-Bachelor's degree; 7-Master's degree; 8-Doctorate (for 6, 7 & 8: or equivalent level); 9-not elsewhere classified*
More information can be found at: http://www.uis.unesco.org/Education/Documents/isced-2011-en.pdf .
[2] *More information on socio-economic status can be found at: http://unstats.un.org/unsd/demographic/products/socind/*
[3] *For WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. ISBN: 978 92 41595562 9, Aug 7th 2006: http://www.who.ing/hiv/;pub/vct/hivstaging/en/*
[4] *For more information on tobacco use: http://www.who.int/tobacco/surveillance/en/*
[5] *For more information on alcohol consumption: http://www.niaaa.nih.gov/research/guidelines-and-resources/recommended-alcohol-questions*
[6] *For gestational age (GA) assessment: see GAIA case definition on pathways to preterm birth: 10.1016/j.vaccine.2016.03.054*

TABLE 3. STUDY VACCINE ADMINISTRATION AND RELATED DATA

Priority	Pre-vaccination: measure & only proceed if normal	Investigational vaccine and immunization procedures	Post Vaccination
Essential	☐ Baseline vital signs (Resting heart rate [beats/min], Systolic + diastolic BP (mmHg), breaths/min, temperature)	☐ Vaccine allocation ☐ Date & Time of administration ☐ Anatomical location of vaccine application ☐ Administration route (e.g. oral, intranasal, intramuscular, subcutaneous, intradermal) ☐ Actual dose volume administered ☐ Vaccine lot number and expiry date ☐ Any Diluent lot number & expiry date ☐ Name of person administering vaccine ☐ Accountability of vaccine (documenting stocks) ☐ Concomitant vaccines include indication (e.g. routine, mass campaign)	☐ Vital signs (Resting heart rate [beats/min], Systolic + diastolic BP (mmHg), breaths/min, temperature) ☐ Post-vaccination local reaction assessment ☐ Subject symptom diary kept for minimum of 7-14 days after each dose; for solicited & unsolicited acute local and systemic AEFI including: ○ Daily temperature including anatomical site of temperature monitoring ○ Systemic symptoms: chills, fatigue, malaise, myalgia, headache, arthralgia, nausea, rash (rated as none, mild, moderate or severe) ○ Local vaccination site reactions including: ▪ Pain, itching (rated as none, mild, moderate or severe) ▪ Erythema, induration, swelling or bruising (measured in mm)
Comple-mentary	☐ Baseline symptoms assessment temperature, headache, malaise, myalgia (none, mild, moderate, severe)	☐ Type of healthcare provider administering vaccine (MD, RN, other) ☐ Geographic location of vaccine administration ☐ Temperature monitoring of vaccine (e.g. in storage, during transport)	☐ Post-vaccination symptoms assessment temperature, headache, malaise, myalgia ☐ Need for analgesia or antipyretic

TABLE 4A. ESSENTIAL AND COMPLEMENTARY DATA TO CAPTURE, POST STUDY VACCINE ADMINISTRATION FOR PREGNANCY, DELIVERY AND NEONATAL OUTCOME.

☐ 4. Pregnancy Follow-up monitoring data.

Maternal Data	Fetal Data	Birth data	Neonatal data
1. Essential ☐ Date/GA for each visit ☐ New onset medical conditions, surgery, hospitalizations ☐ Any symptoms/signs of infection vaccinated against in study ☐ Details for any changes to previously reported AEFI ☐ Details of any additional pregnancy monitoring (e.g. ultrasound, amniocentesis) ☐ Any additional antenatal infection screening Suppl table A ☐ Any additional lab testing ☐ Any new or change to existing medication(s) Include name of drug, route, start and stop date, reason for medication. ☐ Any further vaccines + date given ☐ Any protocol deviations (with details) ☐ Vital signs (Resting heart rate [beats/min], Systolic + diastolic BP (mmHg), breaths/min, temperature)	1. **Essential** ☐ IUGR ☐ Any congenital anomaly noted (by U/S or other tests – which should be specified)	**1. Essential** ☐ Delivery location (city, country) ☐ Delivery setting (home, clinic, hospital) ☐ Mode of delivery Normal spontaneous vaginal delivery; elective or emergency C/S. ☐ Date/time of any antibiotic given in labor ☐ Date/time of delivery (for each infant if multiple) ☐ Results of any perinatal lab tests to assess maternal safety (as needed) ☐ Post-partum complications (e.g. fever, endometritis[1], wound infection, retained placenta, post-partum haemorrhage[2]) **1. Complementary** ☐ Date + dose of betamethasone given during pregnancy ☐ Start/end date of any antibiotics (specify) given in last week ☐ Delivery center admission + discharge dates ☐ Maximum temperature recorded during labor ☐ Presence/type of health care assistant at delivery (None/MD/midwife/other) ☐ Length of labor ○ 1st stage ○ 2nd stage ☐ Date/time of rupture of membranes ☐ Evidence of non-reassuring fetal status[3] (Yes/No, specify evidence) ☐ Details of decreased level of amniotic fluid	**1. Essential** ☐ Singleton or multiple birth (total number of infants born) ☐ Birth-related vitality status of each infant Live birth, stillbirth[6], neonatal death[7] ☐ Need for resuscitation (details) ☐ APGAR (1, 5 and 10 minutes) ☐ Birth: weight, length and head circumference ☐ Any abnormalities ☐ Sex (male, female or indeterminate) ☐ Gestational age[8] including method of assessment (e.g. by EDD, exam of external physical characteristics) ☐ Infant ethnicity / race ☐ Abnormal findings on exam General appearance (syndromic or normal), dermatologic, cardiovascular, respiratory, hematologic, GI, urogenital, musculoskeletal, neurologic (including audiologic tests results), neurodevelopmental, urogenital, ocular/visual, endocrine/metabolic ☐ Congenital malformations[9] ☐ Birth injuries ☐ Congenital or acute infection[10] ☐ Admission to neonatal unit None/transitional care/special care/intensive care ☐ Neonatal unit admission/discharge dates ☐ Respiratory abnormalities ☐ Respiratory support required Yes/No, provide details ☐ Nutrition – feed type and respective start/stop times by age in months Breast milk (maternal/donor), formula, parenteral nutrition, mixed feeding ☐ Medical or surgical treatment E.g. antibiotics, exchange transfusion, IV fluids, steroids, other immunosuppressive therapies, herbal remedies ☐ Protocol directed Lab tests

☐ General physical exam Including general appearance, dermatological, cardiovascular, respiratory, hematological, gastrointestinal, urogenital, musculoskeletal, neurological, ocular/visual and endocrine/metabolic signs. ☐ Obstetric examination ○ Fundal height ○ Fetal heart tones ○ Fetal movement ☐ Nutritional status (BMI)		☐ Meconium staining of amniotic fluid ☐ Suspicion of chorioamnionitis[4] Yes/No specifying parameters used to assess (maternal fever, tachycardia, uterine tenderness, fetal tachycardia) ☐ Details of any new antenatal complication (e.g. pre-eclampsia[5], eclampsia, antenatal bleeding) ☐ Details of any delivery complications (e.g. induction/convulsions/lacerations or episiotomy) ☐ Requirement for general anesthetic during delivery ☐ Medical treatment given to mother during delivery	Minimum of full blood count, differential, transaminases, bilirubin, glucose, blood urea nitrogen, creatinine ☐ Vaccinations including dates given during follow-up period ☐ Neonatal death (Yes/No, details) ☐ Autopsy/Verbal autopsy details where relevant ☐ Details of any medical/surgical treatment received ☐ Date/time of infant hospital discharge where relevant **2. Complementary** ☐ Infant feeding: breast milk (mother or donor), formula feeding, parenteral nutrition, mixed feeding, other (specify nutrient given), with start dates

[1] *Link to GAIA Brighton Case Definition for Postpartum endometritis* 10.1016/j.vaccine.2019.09.101
[2] *Link to GAIA Brighton Case Definition for Post-partum haemorrhage* 10.1016/j.vaccine.2019.09.101
[3] *Link to GAIA Brighton Case Definition for Non-reassuring fetal status* 10.1016/j.vaccine.2016.03.043
[4] *Link to GAIA Brighton Case Definition for Chorioamnionitis* 10.1016/j.vaccine.2019.05.030
[5] *Link to GAIA Brighton Case Definition for Hyptertensive disorders of pregnancy* 10.1016/j.vaccine.2016.03.038
[6] *Link to GAIA Brighton Case Definition for Stillbirth* 10.1016/j.vaccine.2016.03.044
[7] *Link to GAIA Brighton Case Definition for Neonatal death* 10.1016/j.vaccine.2016.03.040
[8] *Link to GAIA Brighton Case Definition for Pathways to preterm birth* 10.1016/j.vaccine.2016.03.054
[9] *Link to GAIA Brighton Case Definition for Congenital anomalies* 10.1016/j.vaccine.2016.03.047 *and Congenital microcephaly* 10.1016/j.vaccine.2017.01.044
[10] *Link to GAIA Brighton Case Definition for Neonatal infections* 10.1016/j.vaccine.2016.03.046

TABLE 4B. ESSENTIAL AND COMPLEMENTARY DATA TO CAPTURE, POST STUDY VACCINE ADMINISTRATION AND POST DELIVERY OR EARLY TERMINATION OF PREGNANCY.

Priority	Maternal Follow-up	Infant Follow-up	Maternal or Infant Hospital Admission during follow-up
Minimum length	☐ ≥ 6 months after delivery or early termination of pregnancy	☐ ≥ 1 year after birth	
Essential for each visit	☐ Date ☐ Time interval since delivery ☐ Location (phone, clinic, home) ☐ Date/reason for any missed visit(s) ☐ Details of any new medical conditions/surgical procedures ☐ Any symptoms/signs of target infection vaccinated against in study ☐ Dates/results of lab tests ☐ Any change to previously reported AEFI ☐ Any new medications or changes to existing medications Including name of drug, route, start/stop date, reason for medication. ☐ Any vaccines given since study vaccine including date of administration ☐ Any protocol deviations ☐ BMI	☐ Date ☐ Age at visit ☐ Location (phone, clinic, home visit) ☐ Source of information (mother, father, other family member, other caregiver, medical records) ☐ Reason for any missed visit ☐ Details of new medical conditions (diagnosis/date of diagnosis) ☐ Surgical procedures with dates ☐ Medical reviews with dates ☐ New medical diagnoses with date of diagnosis ☐ Any new symptoms/signs related to target infection that vaccine intended to prevent ☐ Any changes to previously reported AEFI, ☐ Any new medications (prescribed and non-prescribed) or changes to existing medications Include: name of drug, route, start/stop date, reason for medication ☐ Weight, length, head circumference ☐ Medical examination results ☐ Developmental assessment ☐ If HIV exposed – PCR test result and date.	☐ Admission/discharge dates, ☐ Admission location ☐ Intensity of care (ward/high dependency/intensive care) ☐ Onset date/detail of symptoms ☐ Antibiotics received prior to admission ☐ If infant, admission weight ☐ Admission due to obstetric complication (Yes or No) ☐ Dates/results of lab tests ☐ Dates/results of radiology tests ☐ Diagnosis ☐ Treatment received ☐ Discharge outcome Specify if: discharged without sequelae, discharged with sequelae, still in hospital, death, specify AEFI identification number relating to hospitalization
Comple-mentary for each visit	☐ Vital signs (Resting heart rate [beats/min], Systolic + diastolic BP (mmHg), breaths/min, temperature) ☐ General physical exam including general appearance, dermatological, cardiovascular, respiratory, hematological, gastrointestinal, urogenital, musculoskeletal,	☐ Infant feeding modality Specify: breasted/replacement/mixed specifying nutrient given and start/stop dates), w	☐ Admission medical observations

	neurological, ocular/visual and endocrine/metabolic signs		

TABLE 5. AEFI DATA COLLECTION AND MONITORING. THIS SHOULD BE IN LINE WITH EXISTING GUIDANCE INCLUDING: BRIGHTON COLLABORATION FOR CLINICAL TRIALS 2009[1], 2013[3]; GENERAL DRUG SAFETY GUIDELINES SPECIFIED BY ICH (HTTP://WWW.ICH.ORG); ETHICAL STANDARDS IN RESEARCH & REPORTING REQUIREMENTS FOR DRUG ADVERSE EVENTS BY COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS, HTTP://WWW.CIOMS.CH); INTERNATIONALLY STANDARDIZED TERMINOLOGY AND AEFI CASE DEFINITIONS FOR CASE VERIFICATION AND FOLLOW-UP.

Essential Data collection for AEFI in vaccinated mother or fetus/neonate/infant of vaccinated mother

- ☐ Criteria fulfilled to meet a case definition
- ☐ Other signs/symptoms indicative of solicited and/or unsolicited AEFI
- ☐ Detailed clinical description of the event, including the quality of symptoms
- ☐ Date and time of:
  - Onset
  - First observation
  - Diagnosis
  - End of an episode
  - Final outcome
- ☐ Concurrent signs, symptoms and diseases other than the event described
- ☐ Recurrence of event after initial AEFI [only relevant for maternal AEFI]
- ☐ Onset or occurrence of similar event prior to immunization [only relevant for maternal AEFI]
- ☐ Values and units of routinely measured parameters
- ☐ Method of measurement
- ☐ Results of laboratory examinations, surgical and/or pathologic findings and diagnoses
- ☐ Treatment given for the AEFI (i.e. systemic and/or local site treatment)
- ☐ Outcome at last observation of each AEFI should be clearly described
  - Recovery to pre-immunization health status
  - Spontaneous resolution
  - Therapeutic intervention
  - Persistence of the event
  - Sequelae
  - Death
  - Other outcome (describe)
- ☐ Medical review of the event (if seen by physician)
- ☐ Presence or absence of concurrent local disease outbreaks or environmental exposures pertinent to the AEFI
- ☐ Further doses given and the outcome (i.e. re-vaccination) [only relevant for maternal AEFI]

TABLE 6. 2009 BRIGHTON RECOMMENDATIONS FOR SAFETY DATA ANALYSIS[1]

Check all that are being utilized.
☐ Classify AEFI with Brighton Collaboration case definitions as: ○ Level 1 of diagnostic certainty ○ Level 2 of diagnostic certainty ○ Level 3 of diagnostic certainty ○ Level 4 – reported case of [specified AEFI] with insufficient evidence to meet the case definition ○ Level 5 – not an event of [specified AEFI]
☐ Specify interval between immunization and AEFI based on date / time of immunization and either date/time of AEFI [onset or first observation or diagnosis as appropriate]. Whichever AEFI date is used should be used consistently for all study groups.
☐ Specify duration of AEFI as interval from date/time of [onset or first observation or diagnosis] and end of episode or final outcome. Same caveat applies to using consistent AEFI start date across all subjects
☐ For any AEFI which occur intermittently categorize based on the event that corresponds to the greatest magnitude. Also analyze frequency and pattern of re-occurrence.
☐ If >1 measurement of a particular parameter is taken and recorded, categorize based on the value corresponding to the greatest AEFI magnitude (e.g. highest body temperature during AEFI). Analysis may include other characteristics like qualitative patterns of criteria defining the event – e.g. periodicity, frequency, fever-days.
☐ Use predefined increments to analyze distribution of data where applicable. If there are too few cases for stratification, describe the respective values or time course for each case.
☐ AEFI should be analyzed by study arm and dose.
☐ Ideally, results in vaccinated subjects should be compared to appropriate selected and documented control group.

TABLE 7. 2009 BRIGHTON RECOMMENDATIONS FOR PRE- AND POST-LICENSURE VACCINE TRIAL SAFETY DATA PRESENTATION[1]

Safety Data Presentation – recommended to follow the 2009 Brighton Guideline for clinical trials
☐ Avoid subjective terms to describe AEFI (e.g. 'low-grade', 'mild', 'moderate', 'high', 'severe', 'significant') unless validated or clearly defined ☐ Present safety data using numerator and denominator numbers (as opposed to only percentages and/or graphical illustrations). ☐ Present safety data by lot or vaccine if applicable ☐ If median and range are appropriate statistical descriptors but distribution of data is skewed, provide the mean and standard deviation as well to enable meta-analysis ☐ Present the incidence of events meeting the case definition ☐ For any publication of AEFI data, there should be a description of the methods used for data collection & analysis including specification of: o Study design o Study group(s) and comparison group(s) o Instrument of data collection (e.g. standardized questionnaire, diary card, other) o Data analysis plan per protocol, statistical plan and any amendments added during study o Trial profile, indicating participant flow during study, including drop-outs and withdrawals to indicate size and nature of respective groups under investigation o Reference of the AEFI case definition used

SUPPLEMENTAL TABLE A. GAIA PRIORITY 1 RECOMMENDATIONS[4] FOR TESTING RELATED TO INFECTIONS THAT MAY HAVE IMPACT ON THE IMMUNOGENICITY, EFFICACY AND/OR SAFETY OF PREGNANCY VACCINES OR AID INTERPRETATION OF EVENTS THAT OCCUR IN THE MOTHER, FETUS, NEONATE OR INFANT. FOR EACH LISTED INFECTION INDICATE IF DATA GATHERED (Y FOR YES), NOT GATHERED (N FOR NO) OR IF IT IS NOT RELEVANT TO GEOGRAPHIC LOCALE (E.G. FOR MALARIA, TB, ZIKA)

Infection	Check which infection(s) were documented or screened for relative to each specified time period before, at entry and follow-up		
	Pre-trial entry Antenatal history	Screening at Trial Entry	Post Immunization Follow-up
HIV-1			
HIV-2			
If maternal HIV infection	☐ WHO clinical staging ☐ CD4 result (%/absolute) & date of test ☐ Viral load test & date		
Malaria			
Syphilis			
Tuberculosis			
Zika virus			
Hepatitis B			
Hepatitis C			
Rubella			
Group B streptococcus			
Toxoplasmosis			
Genital HSV			
Other STD: Chlamydia			
Other STD: gonococcus			
Other STD: specify			
Study vaccine target disease			
Other: specify			

SUPPLEMENTAL TABLE B. TYPE OF DATA TO COLLECT TO INFORM OBSTETRICAL RISK ASSESSMENT[5]

Priority	Maternal medical history	Yes or No
Essential	Diabetes mellitus, requiring medication[1]	
	Hypertension, requiring drug therapy[2]	
	Heart disease	
	Autoimmune disorder	
	Kidney disease	
	Neurologic disease	
	Psychiatric disorder requiring drug therapy	
	Hepatitis / liver disease	
	Varicosities / phlebitis of deep veins	
	Thyroid dysfunction	
	Pulmonary disease	
	Substance abuse	
	D (Rh) sensitized	
	Three or more spontaneous abortions[3]	
	Previous stillbirth[4] or neonatal death[5]	
	Six or more previous deliveries	
	Previous infant with known genetic disorder	
	Previous infant with a major congenital anomaly[6]	
Complementary	Malaria in previous pregnancy	
Priority	History of current pregnancy	Yes or No
Essential	Expected to deliver an infant at <37 weeks gestation	
	Expected to deliver multiple infants	
	Expected to deliver an infant with a major congenital anomaly	
	Incompetent cervix	
	Polyhydramnios or oligohydramnios	
	Intrauterine growth retardation or fetal growth restriction[7]	

[1] *Link to GAIA Brighton Case Definition for Gestational diabetes* 10.1016/j.vaccine.2017.01.043
[2] *Link to GAIA Brighton Case Definition for Hypertensive disorders in pregnancy* 10.1016/j.vaccine.2016.03.038
[3] *Link to GAIA Brighton Case Definition for Spontaneous abortion and ectopic pregnancy* 10.1016/j.vaccine.2017.01.047
[4] *Link to GAIA Brighton Case Definition for Stillbirth* 10.1016/j.vaccine.2016.03.044
[5] *Link to GAIA Brighton Case Definition for Neonatal death* 10.1016/j.vaccine.2016.03.040
[6] *Link to GAIA Brighton Case Definition for Congenital anomalies* 10.1016/j.vaccine.2016.03.047 *and Congenital microcephaly* 10.1016/j.vaccine.2017.01.044
[7] *Link to GAIA Brighton Case Definition for Fetal growth restriction*