



Immunization site pain: Case definition and guidelines for collection, analysis, and presentation of immunization safety data[☆]

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1. Preamble

1.1. Need for developing a case definition and guidelines for immunization site pain as an adverse event following immunization [AEFI]

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (International Association for the Study of Pain, IASP) [1]. Pain is the most frequent local adverse event following immunization (AEFI) [2–5]. It results from the stimulation of nociceptive sensory neurons at the time of vaccine administration or inflammatory process in the damaged tissue afterward.

To date, there has not been a commonly accepted, standardized definition and related assessment of immunization site pain

as an AEFI [6–15]. This hinders comparability and uniform reporting of pain across study settings or surveillance systems. Establishing criteria for assessing immunization site pain during and following immunization is important for individuals collecting, analyzing, presenting and/or communicating data on immunization pain as AEFIs.

A previous Brighton working group identified a list of local reactions from coding terminologies [16–18] for injection site AEFIs that included a general term to describe “a local reaction” as well as more specific local reactions, including pain. Some definitions for local reactions have been defined and are published [19–24]. In this manuscript, we describe the case definition and guidelines for the assessment of pain as a specific local reaction. The case definitions for published local reactions can be accessed at the Brighton Website through a free online e-mail subscription process <https://brightoncollaboration.org/public/resources.htm>.

Sections 2 and 3 of this paper provide the case definition and guidelines for data collection, analysis, and presentation that the Brighton Collaboration *Local Reactions Working Group* has developed for the standardized collection and assessment of information about immunization site pain. Widespread use of this definition with its guidelines will improve data comparability and allow for a better understanding of immunization pain. The case definition and guidelines are intended to be applicable in diverse geographic, administrative, and cultural settings, regardless of differences in the availability of health care resources.

1.2. Methods for the development of the case definition and guidelines for immunization site pain as an AEFI

Following the process described previously [25], a Brighton Collaboration *Local Reactions Working Group* was formed in December 2008 with 19 inter-disciplinary members with public health, regulatory, clinical, academic, industry backgrounds, as well as expertise in pain. In January 2009, the working group began to develop the current definition of “immunization site pain” together with guidelines for data collection, analysis, and presentation of vaccine safety data.

To guide the decision-making for the case definition and guidelines, a literature search was conducted using English and non-English citations of immunization site pain in the context of immunization. The literature search was performed within Medline, the Cochrane library, and Embase from 1966 to April 2001 with the following search terms: pain, local reaction, local inflammation, injection site reaction, nociception, injection pain, needle pain, vaccines/complications, vaccines/contraindications, vaccines/toxicity, immunization/adverse effects, vaccines/adverse effects, immunization/complications, immunization/toxicity, immunization/contraindications, and humans. The search resulted in the identification of 1620 references including review articles. An additional updated search (Medline 2001 May–February 2009) obtained an additional 980 references using the same search terms. Relevant citations from the articles above were also obtained and included in this paper. The abstracts for all articles were reviewed and relevant articles were considered as necessary. Our literature review was limited to the English language due to practicability; the working group recognizes this as a possible limitation.

Additionally, the working group also queried the more than 1900 professionals enrolled in the Brighton Collaboration e-mail list at the time about use or development of any standardized definition of pain and grading scales for severity of pain. Responses were received from different groups involved with pre-and post-marketing surveillance or vaccine safety clinical trials, including regulatory agencies, universities, and vaccine manufacturers; however, they did not yield a standardized definition.

1.3. Rationale for selected decisions about the case definition for immunization site pain as an AEFI

It was the consensus of the Working Group (WG) to define immunization site pain as an adverse event from an epidemiological or clinical stand point for use in both clinical trials and post marketing surveillance systems. To achieve this objective, the WG agreed to use the IASP definition of pain, as specified in Section 1.1. The case definition was subsequently categorized into three levels of diagnostic certainty according to the methods of pain assessment used (Section 2).

1.3.1. Scope of definition and components of pain

The scope of the case definition was originally proposed to include pain that develops in the minutes to hours following vaccination (delayed pain). However, the WG expanded the case definition to include pain that develops in response to vaccine administration (acute pain) as well. As a result of the change in the original scope of the case definition, the WG agreed to broaden the original title of this AEFI from “Pain at or near injection site” to “Immunization site Pain.”

It was acknowledged that acute pain in response to vaccine administration is the synergistic effect of anxiety and nociception and in practice it is difficult to separate the two. The subjective experience of pain and distress may or may not be directly linked to a behavioral manifestation and for children, child–parent interactions and/or clinician biases may affect judgments about a child’s pain. The WG agreed to develop a definition that focuses on immunization pain, but recognized that pain and distress cannot be easily separated. The WG agreed to include both needle injection pain and needle-free injection pain in the case definition; noting that pain may be experienced from a variety of administration techniques, not just needle puncture through the skin.

The working group acknowledges that (1) technique, (2) methods of immunization administration and (3) immunization site identification (see Appendix C) are important in the assessment of pain. Studies have shown some associations with these 3 aspects to pain experience [26,27,13,28]. However, these aspects are outside the scope of this document. Capturing this information could be considered depending on the study question and if deemed of value in specific studies or field investigations.

The working group recognizes that the field of pain is evolving and over time new approaches of pain assessment may emerge. Similarly, other methods of delivering vaccines are evolving with increasingly lesser emphasis on the use of “needles” in delivering vaccines.

The working group considered muscular (myalgia) and joint (arthralgia) pain; however, it was decided not to address these aspects in the definition of immunization site pain.

1.3.2. Subjective nature of pain

Of all the local reactions, pain is probably the most challenging and difficult to describe, quantify and standardize. Pain is by its very nature a personal experience whose measurement depends upon the subjective response of the person experiencing the pain. As is the case with so many developmental phenomena, reactions to minor invasive procedures are determined by genetic bases that interact with environmental events. The basic elements of nociception and pain response are fairly predictable. However, pain responses combine intra- and inter-personal elements, contextual factors, and nociceptive stimulation [29]. The experience of pain is a blend of many factors, including physiological responses to tissue damage, general pain responsiveness (related to genetic endowment or temperament), emotional overlay associated with the cause of the pain, cultural factors, and prior pain experience.

Thus, there is no simple linear relationship between the amount of pain reported and the amount of tissue damage [30]. Similarly, anticipatory anxiety and stress response including coping factors may depend on broader environmental factors as well as values placed on the disease in question and its related context. Other elements, for example, include how subjects respond to painful stimulation during vaccinations and the role of coping with distress. The situation becomes more complicated as “pain responses” may include subjective experience, pain behaviors, or physiological changes associated with nociception and stress.

In children, the child–parent interaction factor may influence the parents’ interpretation of their child’s pain. The situation is further complicated in preverbal children because their pain is being assessed and reported by an adult observer, usually the parent of the child or a clinician. Thus, pain assessment depends on the adults’ subjective interpretation of the child’s behavioral response [31].

Since pain is a subjective experience, the working group agreed with the recommendations of pain researchers that self-report should be considered the primary method of pain assessment for immunization site pain [32–35]. When self-report is not possible, then assessments with validated and reliable instruments made by adult observers (either parents or clinicians) may be used.

1.3.3. Additional considerations

Historically, pain has received little attention. Pain-control measures are adopted infrequently because of unresolved scientific issues and lack of appreciation for the need to control pain and its long term sequelae [36]. Today, it is clear that even very premature neonates experience pain, and the “lower limit” of the age at which pain systems are intact continues to be revised downward, even into the fetal period [36,37]. There is mounting evidence to show that untreated or poorly treated pain, especially during critical or sensitive periods in development, leads to irreversible deleterious effects on pain processing [34,36]. In addition, negative experiences with needles may trigger needle phobias, known to be associated with subsequent non-compliance with immunization and other preventive healthcare measures [38–40].

The working group recommends the accurate assessment and documentation of immunization pain (including needle pain) in order to improve its management. Attending to immunization pain supports immunization. This is because it: (1) reduces suffering, which improves the immunization experience, and (2) reduces subsequent non-compliance as a result of minimizing injection-induced anxiety and pain. It also maintains the ethical principle to ‘do no harm’ [41].

1.3.4. Pain management during immunization

While the WG’s scope does not include the prevention, management and treatment of pain, this section is included as informational to health care providers. The WG recommends that future studies should incorporate acute pain as part of vaccine trial outcomes and the use of pain management strategies should become a standard of care. There is substantive scientific literature addressing the prevention and management of acute pain associated with immunization injections. Readers are referred to a recently published clinical practice guideline on evidence-based methods for managing vaccine injection pain for specific guidance on effective modalities from 3 different domains of pain management: pharmacological interventions, psychological interventions and physical interventions [42].

Evidence-based pain management strategies for delayed pain, on the other hand, are less well studied. Moreover, a recent study suggests that prophylactic use of paracetamol (acetaminophen) as an analgesic strategy for delayed onset pain and other AEFI may interfere with antibody responses to some antigens [43]. While the

working group recognizes the underutilization of analgesics in prevention of pain, it does not endorse the prophylactic use of oral analgesics [44–46].

1.3.5. Pain assessment

Pain assessment is a difficult yet imperative challenge facing health professionals and researchers who work with children and adults. Accurate assessment is necessary to ensure the proper management of pain and to facilitate the scientific investigation of pain. Self-report by verbal children and adults is considered the optimal method of pain assessment. The WG recognized the fact that pain assessment is a growing field and more tools may be available in the future. See [Appendix A](#) for additional details on the tools for both acute and delayed pain assessment.

Since the manner in which pain is expressed and communicated varies for individuals of different ages, developmentally appropriate rating scales are needed for assessing pain. The working group determined that specific tools should be identified in order to facilitate pain assessment in individuals undergoing immunization. The WG selected tools identified in evidence-based reviews and clinical practice guidelines [47,48]. Using a consensus process, the panel applied additional criteria related to feasibility and practicality of use of age-specific tools within the context of immunization pain. The working group determined that specific tools should be identified (see guideline 23) in order to facilitate pain assessment in individuals undergoing immunization. Several tools are recommended, based on whether pain is acute and proximal to vaccine administration (occurring within 5 min) or delayed (occurring after 5 min) [26,49].

(a) Acute pain

The working group recommends tools outlined in [Appendix A \(Table A.1\)](#) for the assessment of acute pain in individuals of different ages from infancy to adulthood. These tools have been selected based on the best currently available evidence. It is acknowledged that there are differences in pain assessment related to whether the assessment is conducted by a trained healthcare provider or parent (or care giver).

(b) Delayed pain

The working group recommends tools outlined in [Appendix A \(Table A.2\)](#) for the assessment of delayed pain in individuals of different ages from infancy to adulthood. Individual assessments are recommended for three distinct but potentially related aspects of delayed pain (not completely independent) when reporting pain: (1) persistent pain (including at rest), (2) pain associated with movement or touch, and (3) impact of pain on functioning. There is a lack of well validated tools that encompass all of these constructs. These tools have been selected based on the best currently available evidence in individuals of all ages. The WG felt that while pain assessment tools for delayed pain have limited validation specifically in the context of post-immunization pain, based on similar applications and validation, they would still be useful in this setting. Parents (or care givers) are primarily responsible for assessing pain in settings where subjects cannot provide self-report. See [Appendix A](#) for additional details on the tools for delayed pain assessment.

In order to discern among the various aspects of delayed pain [i.e., persistent pain (including at rest) *versus* pain associated with movement or touch *versus* impact of pain on functioning], it is recommended that instructions be provided that orient the individual performing the assessment before obtaining the score.

1.3.6. Grading the severity of pain

Several scoring scales have been used in studies to grade the severity of pain [50–64,48,65–74]. In vaccine studies, examples of grading systems include: no pain, pain when touched, pain on movement, and pain all the time. Other studies have graded pain as none, minimal effect on activity, moderate effect on activity, or precludes activity. Should an investigator decide to grade the severity of pain, the WG recommends the use of 3 grades for severity of pain based on symptoms: grade 1 or mild, grade 2, or moderate and grade 3 or severe (see guideline 36, Section 3)

1.3.7. Case definition of pain

The case definition is structured according to 3 levels of diagnostic certainty. It should be stressed that although potentially applicable in a clinical setting, the levels of diagnostic certainty are intended for epidemiologic purposes and not as criteria for treatment. Similar to other Brighton Collaboration definitions, the aim is to systematically describe a clinical entity without inference of a causal relation to a given exposure.

The guidelines are structured according to the steps of conducting a study, i.e., data collection, analysis, and presentation. The guideline section of this local reaction document includes the desirable information necessary to assess any local reaction.

Finally, similar to all Brighton Collaboration case definitions and guidelines, review of the definition with its guidelines is planned on a regular basis (i.e., every 3–5 years), or more often, if needed.

2. The case definition of “immunization site pain”

Level 1 of diagnostic certainty

Presence of

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage^{3,4,5,6,7} [1]

AND

- occurring at the immunization site with or without involvement of surrounding tissue
- **AND**
- at the time of vaccine administration or following such a procedure
- **AND**
- Self-report of pain or distress as assessed by a subject (self-report) using validated or verified instruments⁸;
- For pre- or non-verbal subjects, observer report using validated tools (specific method depends on age)^{9,10} [see guideline 23 and Appendix A]

³ Immunization site pain is limited to the immunization site and surrounding tissue.

⁴ For level 1 the subject assesses the pain themselves using a validated or verified instrument. If a subject is unable to provide self-report (e.g., due to age or some other reason), other reporter (parent/care giver or health care provider) may use a validated and reliable instrument to assess the pain. It may be a different instrument used.

⁵ The inability to communicate verbally does not negate the possibility that an individual is experiencing pain.

⁶ Definition includes distress which is a combination of nociception and anticipatory anxiety.

⁷ Pain is subjective, not standardized across individuals, and therefore not directly measurable. Although a subjective perception, psychometrically sound methods enable evaluation of pain with reliability, validity, and clinical sensitivity in individuals of all ages.

⁸ Pain is fundamentally a private, internal subjective experience and is best described by the person experiencing it [75].

⁹ There are various methods available to assess pain, including: self-report based on a person's experience, behavioral observation and physiological responses (guideline 23 and Appendix A).

¹⁰ Grading the severity of pain is further described in (guideline 36).

Level 2 of diagnostic certainty¹⁰

Presence of

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage^{3–7} [1]

AND

- occurring at the immunization site with or without involvement of surrounding tissue
- **AND**
- at the time of vaccine administration or following such a procedure
- **AND**
- Other observer or reporter of pain or distress in a subject capable of self-report, whereby pain is assessed by an observer using a validated or verified instrument on behalf of the subject.¹¹

Level 3 of diagnostic certainty

Presence of

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage^{3–7} [1]

AND

- occurring at the immunization site with or without surrounding tissue
- **AND**
- at the time of vaccine administration or following such a procedure
- **WITHOUT**
- Additional description of pain and distress or assessment with a validated method

3. Guidelines for data collection, analysis, and presentation

It was the consensus of the working group to recommend the following guidelines to enable meaningful and standardized data collection, analysis, and presentation of data about immunization site pain. However, implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographic region, and whether the source of information is a prospectively designed clinical trial, a post-marketing surveillance or epidemiologic study, or an individual report of immunization pain. Also, as explained in more detail in an overview paper for all Brighton Collaboration case definitions and guidelines [25], these guidelines are not considered a mandatory requirement for data collection, analysis, or presentation.

3.1. Data collection

These guidelines represent a desirable standard for the collection of data on pain cases to allow for comparability of data, and are recommended as a supplement to data collected for the specific study question and setting. These guidelines are not intended to replace local legal reporting requirements, but rather to serve as a guide towards harmonization of vaccine safety reporting of pain as an AEFI to a surveillance system or study monitor. Investigators developing a data collection tool based on these data collection guidelines also need to refer to the criteria in the case definition in Section 2, which are not repeated in this section. Appendix B provides an example of how the case definition and guidelines could be applied in a data collection form.

¹¹ In level 2 the pain or distress is assessed by an observer. This may be a parent/care giver or a health care provider on behalf of the subject. An example is when an adult assesses the pain on behalf of the child who is verbal but was not asked to self-assess pain.

Guidelines 2, 4, 5, 10, 19–26 below have been developed to address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use [76], and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences (CIOMS) [77]. These data elements include an identifiable reporter and patient, one or more prior immunizations, and a detailed description of pain as an AEFI.

3.1.1. Source of information/reporter

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

- (1) Date of report.
- (2) Name and contact information of person reporting¹² and/or assessing or diagnosing pain in accordance with country specific data protection law.
- (3) Relationship to the patient (e.g., immunizer [clinician, nurse], family member [indicate relationship], other).
- (4) Location of subject within study area including country, if a multi-country study, as appropriate

Vaccinee/control

For all cases and/or all study participants, as appropriate, the following information should be recorded.

3.1.2. Demographics

- (5) Case/study participant identifiers (first name initial followed by last name initial), or code, or as otherwise specified in country-specific data protection laws.
- (6) Date of birth (specify calendar used if not the commonly used Julian calendar),¹³ age, sex, ethnicity (if appropriate).
- (7) For infants (<12 months of age): gestational age, birth weight, and weight at the time of assessment and length, as applicable.

3.1.3. Clinical and immunization history

- (8) Medical history including hospitalizations, underlying diseases/disorders, pre-immunization signs and symptoms that may affect the evaluation of pain such as prior history of pain and anxiety.
- (9) Any medication history prior to, during, and after vaccination 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 transfusions, immunosuppressants) and analgesics that could affect the evaluation of pain, but other than treatment given for the pain.
- (10) Immunization history, including exact dates of administration and vaccines given including their number in series; indicate the history for previous immunizations and any occurrence of immunization site pain after previous immunizations if documented or verbal.

3.1.4. Details of the immunization

- (11) Date and time of immunization, specify if a 12 or 24-h clock was used. The 24-h clock is preferred as it avoids potential confusion about a.m. and p.m. times.
- (12) Description of vaccine(s): trade name and generic name of vaccine, lot number, expiration date, manufacturer, dose, multi- or mono-dose vial, pre-filled syringe, volume (e.g., 0.5 mL) and number of dose (if part of a series of immunizations against the same disease), diluent lot number (if used), adjuvants, preservatives, buffer preparation, expiration date, preparation of vaccine e.g., for multi-dose vials of lyophilized vaccines, whether reconstituted vaccine was used within the recommended period and condition.
- (13) Detailed description on combination vaccines: if used, provide the trade name and generic names if present. Specify the antigen components if the vaccine was a combined one (single shot) or was administered at separate injection sites concomitantly, as appropriate.
- (14) Anatomical sites of all immunizations (e.g., deltoid, or other site), details of administration techniques (e.g., needle length and gauge) (see Appendix C).
- (15) Storage conditions of the vaccine: vaccines should be stored at temperatures according to the manufacturer's recommendations. If possible, temperature logs, type of refrigerator, power outages, and vaccine storage conditions should be reviewed and noted, especially in prospective studies [78–80].
- (16) Type of professional who immunized the subject (e.g., physician, nurse, other health care provider).
- (17) Route and method of administration (e.g., intranasal, intramuscular, intradermal, subcutaneous, needle-free such as transcutaneous patch [including type and size of needle] or other injection devices).

3.1.5. The adverse event

- (18) Criteria fulfilled to meet a case definition and other signs or symptoms indicative of immunization site pain.
- (19) Detailed clinical description of the event including the quality of symptoms (e.g., type of pain).
- (20) Date and time of: onset,¹⁴ first observation,¹⁴ diagnosis,¹⁵ end of an episode¹⁶, and final outcome¹⁷.
- (21) Concurrent signs, symptoms, and diseases other than the event described.
- (22) Recurrence of pain to earlier immunizations.
- (23) Method of measurement of pain: the tools used depend on whether pain is acute and proximal to vaccine administration (occurring within 5 min) or delayed (occurring after 5 min).¹⁸ The working group determined that specific tools should be identified in this guideline in order to facilitate pain assessment in individuals undergoing immunization. The specific tools were selected based on the best currently available evidence in verbal and pre-verbal children and adults.

(c) Acute pain

¹⁴ The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative for pain is observed. This may only be possible to determine in retrospect.

¹⁵ The date of diagnosis of an episode is the day the event met the case definition.

¹⁶ The end of an episode is defined as the time the event no longer meets the case definition.

¹⁷ Pain not resolved at the time of reporting or evaluation may be followed up as clinically necessary and additional reporting should be encouraged in order to describe progress until the final outcome. "Persistence of pain" refers to pain continuing to meet the case definition at the last time of follow-up. "Sequelae are long term clinical consequences resulting from the event."

¹⁸ The 5-min cut-off time for acute pain was based on common research practices [26,49].

¹² If the reporting center is different from the vaccinating center, appropriate and timely communication of the adverse event should occur.

¹³ The Julian Calendar is the common calendar widely used. The average length of a year in the Julian calendar is 365.25 days (one additional 'leap' day being added every four years) http://www.hermetic.ch/cal.stud/cal.art.html#Julian_Calendar.

The working group recommends tools outlined in Table A.1.

(d) *Delayed pain*

The working group recommends tools outlined in Table A.2 after the aspect of delayed pain is identified.

- (24) Treatment (e.g., analgesics, physical methods or other interventions¹⁹) given for the pain.
- (25) Recurrence of pain episodes after resolution of initial reaction²⁰ e.g., as a biphasic illness. Record the frequency of pain episodes patterns or re-occurrence, include dates whenever possible.
- (26) The outcome¹⁷ at last follow-up, as well as the timing relative to immunization and the time course of the evolution of the pain (including date of final outcome or observation). The following terms can be used:
- Resolved without treatment;
 - Resolved with treatment (e.g., use on analgesics);
 - Pain still present;
 - Sequelae, please specify
 - Outcome unknown/not reported;
 - Description of any other outcome: please specify.

If pain has not resolved at the time of reporting or the end of a pre-defined study period, follow-up may be done as clinically necessary and additional reporting should be encouraged in order to describe progress until the final outcome is reached.

3.1.6. Miscellaneous/general recommendations

- (27) The duration of surveillance for pain is to some extent arbitrary, should be predefined, and depends on:
- Biologic characteristics of the vaccine, e.g., live attenuated versus inactivated component vaccines; Composition of the vaccine (including adjuvant, if present);
 - Biologic characteristics of the vaccine-targeted disease;
 - Biologic characteristics of the local injection pain including patterns identified in previous trials (e.g., early-phase trials); and
 - Biologic characteristics of the vaccinee [e.g., underlying disease like immunosuppressing illness and immune reactivation syndrome [96–99]].
- (28) Methods of data collection should be consistent within and between study groups, if applicable.
- Reports of pain should be collected/included in the database regardless of the time elapsed between immunizations and the adverse event. If not feasible, the study period during which safety data are being collected and/or included in the database should be clearly defined.
- (29) Follow-up of reported events should attempt to verify and complete the collection of information as outlined in the data collection guidelines 1–26.

3.2. Data analysis

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

- (30) Reported events should be classified into one of the following five categories. When events meet the case definition, it should be classified according to the three levels of diagnostic

certainty as specified in the case definition. Events that do not meet the case definition of pain should be classified according to the additional two categories for analysis.

Event classification in five categories

Event meets case definition

Main categories

- (1) Level 1: as specified in the case definition for pain
- (2) Level 2: as specified in the case definition for pain
- (3) Level 3: as specified in the case definition for pain

Event does not meet case definition

Additional categories

- (4) Insufficient evidence to meet the case definition for pain²¹
 - (5) Not a case of pain²²
- (31) The interval between immunization and pain could be defined as the date/time of immunizations to the date/time of onset¹⁴ or diagnosis,¹⁵ whichever is available and most appropriate in the given study setting. Whatever dates are used, they should be used consistently within and across study subjects and described. The working group recommends the use of date/time of onset.

The time interval could be analyzed in the following increments where n = the number of subjects with pain newly present at, and N = the number of all subjects with pain in the study population or all study subjects (specify which was used).

<5 min	n/N _____ (%)
5 min to ≤24 h	n/N _____ (%)
25 h to ≤48 h	n/N _____ (%)
49 h to ≤72 h	n/N _____ (%)
73 h to ≤7 days	n/N _____ (%)
>7 days to ≤14 days	n/N _____ (%)
>14 to ≤28 days	n/N _____ (%)
>28 days	n/N _____ (%)

- (32) The duration of pain, if applicable, could be analyzed as the interval between date/time of onset¹⁴ or diagnosis¹⁵ and the end of episode¹⁶ or final outcome.¹⁷ Whatever start and ending dates are used, they should be used consistently within and across subjects and described. The duration could be analyzed in predefined time increments listed in guideline 31.

If detailed analysis is not available (e.g., in surveillance systems), acute pain (i.e., episode of pain that has an onset of ≤5 min from the time of vaccine administration); delayed pain (i.e., episode of pain that has an onset of >5 min from the time of vaccine administration) should be analyzed.¹⁸

- (33) If the pain occurs intermittently, the event corresponding to the greatest magnitude (e.g., the number of days or hours) could be used as the basis for analysis. Also the frequency and pattern of re-occurrence (i.e., periodicity) can be analyzed.
- (34) If more than one measurement of a particular parameter is obtained and recorded, the value corresponding to the greatest magnitude of the adverse event should be used as the basis for categorization. Analysis may also include other characteristics or qualitative patterns of criteria defining the event (e.g., periodicity, frequency, pain-days, etc.).
- (35) Data on pain in subjects receiving a vaccine should be compared with those obtained from appropriately selected and documented comparison group(s), and should be analyzed by study arm and dose, where possible, e.g., in prospective clinical trials.

²¹ If information about necessary criteria to classify an event as level 1, 2 or 3 is missing, the case should be classified as category 4, capturing reported event of pain with insufficient evidence to meet the case definition.

²² If criteria necessary to classify an event as level 1, 2 or 3 are known to be absent, the event should be classified as category 5 capturing reported events which are not pain.

¹⁹ Many of these interventions are not evidence-based.

²⁰ For recurrence of pain, there needs to have been at least two intervening pain-free days.

- (36) Terms to describe pain as “mild”, “moderate”, or “severe”, are highly subjective and prone to wide interpretation. However the working group suggests a following arbitrary grading based on WG expertise and consensus using an 11-point scoring scale.
- Mild or Grade 1 or score of 1 to 3
 - Moderate or Grade 2 or score between 4 and 6
 - Severe or Grade 3 score of 7 or above.
- (37) If a report includes multiple signs and symptoms, which could be considered part of a single diagnosis (e.g., swelling + induration + pain = cellulitis), duplicate counting of signs/symptoms separately and as part of the overriding diagnosis should be avoided. Each event should be reported with respective start and ending dates. The basis for analysis is preferably the overriding diagnosis encompassing those signs/symptoms.²³

3.3. Data presentation

These guidelines represent a desirable standard for presentation or publication of data on pain in order to allow comparability of data, and are recommended as an addition to data presented for the specific study question and setting. Additionally, it is recommended to refer to existing general guidelines for the presentation and publication of randomized controlled trials, systematic reviews, and meta-analyses of observational studies in epidemiology (e.g., statements of Consolidated Standards of Reporting Trials [CONSORT], of Improving the Quality of Reports of Meta-analyses of Randomized Controlled Trials [QUORUM], Meta-analysis Of Observational Studies in Epidemiology [MOOSE], the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND, and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) respectively) [81–85].

- (38) All reported events on pain should be presented according to the categories listed in guideline 30.
- (39) Data on pain should be presented in accordance with data collection guidelines 1–29 and data analysis guidelines 30–37.
- (40) Data should be presented with numerator and denominator (n/N) and not only in percentages, where possible.
- Although in immunization safety surveillance systems, denominators are usually not readily available; attempts should be made to identify approximate denominators. The source of the denominator data should be reported and calculations of estimates described (e.g., obtained from manufacturer, Ministry of Health and coverage/population-based data doses distributed). Describe the numerator and denominator used in detail including any limitations.
- (41) The distribution of data (as numerator and denominator data) should be presented in the predefined time increments as listed in the analysis guideline 31. If the number of cases is small, the exact time course could be presented for each case.
- (42) The incidence and prevalence of events meeting the case definition should be presented and clearly identified as such.²⁴
- (43) If the distribution of data is skewed, the median and range are more appropriate statistical descriptors than a mean (with appropriate confidence intervals).

- (44) Any publication of data on pain as an AEFI should include a detailed description of the methods used for data collection and analysis. It is essential to specify:
- The study design;
 - For surveillance systems
 - The type of surveillance (e.g., passive or active surveillance);
 - The characteristics of the surveillance system (e.g., population served, mode of report solicitation); and
 - The search strategy used to query surveillance databases;
 - Comparison group(s), if used for analysis;
 - Whether the day of immunization was considered “day one” or “day zero” in the analysis;
 - Whether the date of onset,¹⁴ and/or the date of diagnosis,¹⁵ end of episode¹⁶ or final outcome¹⁷ were used for analysis. Whatever dates are used, they should be used consistently within and across subjects and described; and
 - Reference of the case definition(s) used (Brighton Collaboration²⁵ or other) in the abstract or methods section of a publication.

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Appendix A. Pain assessment tools

Since the manner in which pain is expressed and communicated is different for individuals of different ages, developmentally appropriate rating scales are needed for assessing pain. The working group panel determined that specific tools should be identified in this guideline in order to facilitate pain assessment in individuals undergoing immunization. The tools were selected from a range of tools identified in evidence-based reviews and clinical practice guidelines. Using a consensus process, the panel applied additional criteria related to feasibility and practicality of use of age-specific tools within the context of immunization injections. Self-report by verbal children and adults is considered the optimal method of pain assessment.

(1) Acute pain

The specific tools recommended for assessment of acute pain following immunization in individuals of different ages are displayed in Table A.1 (below). In pre-verbal children, clinicians and/or parents are required to assess pain. Clinicians may use one of two observational tools: the Modified Behavioral Pain Scale (MBPS) in Table A.3 below [90] or the Face Legs Activity Crying Consolability (FLACC) scale in Table A.4 below [91]. Parents performing assessments of pain in their children are advised to use the Numerical Rating Scale (NRS) [92–94]. Parents can be instructed to consider the presence of spontaneous behavioral indicators of acute pain, such as: crying, grimacing, guarding, compensatory posturing, body

²³ At the analysis stage, one has to be careful not to count pain twice if it is part of an overriding diagnosis like cellulitis. Databases can be programmed so that a code for pain could be automatically linked to a code of cellulitis, if this pain was part of the cellulitis; the corresponding level of diagnostic certainty for pain and e.g., cellulitis can be viewed and a decision made according to the study question. An overriding diagnosis is preferred.

²⁴ E.g., total of 10 cases of pain in 2000 study participants or 1 case per million during 5 days; use as appropriate.

²⁵ Use of this document should be referenced by referring to the link on the Brighton Collaboration website <https://brightoncollaboration.org/public/resources/case-definitions.html>.

Table A.1
Assessment methods for acute pain following immunization^a.

Age	Assessor and tool	Validity	Reliability	Ease of use ^b
Pre-verbal child				
≤18 months	Clinician: MBPS Parent: NRS	Good Good	Good Good	Fair Good
>18 months	Clinician: FLACC Parent: NRS	Good Good	Good Good	Fair Good
Verbal child				
≥3–6 years ^c	Child: Poker Chip	Good	Good	Good
≥4 years	Child: FPS-R	Good	Good	Good
≥9 years	Child: NRS	Good	Good	Good
Adult				
≥18 years	Adult: NRS	Good	Good	Good

^a The criteria was based on WG expert opinion consensus and review of literature.

^b Ease of use considers: burden to user (time to complete, need for special equipment, training, language/culture barriers), scaling properties/interpretability (e.g., out of 10 or 100).

^c If child unable to reliably self-report pain, clinicians and parents can assess pain using the assessment tools recommended for children > 18 months [42,86,87].

writhing movements or rigidity, when assessing their child's pain. Verbal children who are able to provide self-report are advised to self-report pain using the Poker Chip tool [95], Faces Pain Scale–Revised (FPS-R) [62] (<http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/FacesPainScaleRevised/default.htm>) or Numerical Rating Scale (NRS), as appropriate. Adults can self-report pain using the NRS.

(2) Delayed pain

The specific tools recommended for assessment of delayed pain following immunization in individuals of different ages are displayed in Table A.2 (below). In pre-verbal children, parents are required to assess pain. Parents performing assessments of delayed pain in their children are advised to use the Numerical Rating Scale (NRS). Verbal children who are able to provide self-report, which is considered the optimal method of pain assessment, are advised to self-report pain using the Poker Chip tool, Faces Pain Scale – Revised (FPS-R) or Numerical Rating Scale (NRS), as appropriate. Adults can self-report pain using the NRS [100].

All of the recommended scales have demonstrated validity and reliability for various pain states in children, including post-operative pain and pain associated with specific medical conditions. The WG felt that while pain assessment tools for delayed pain have limited validity specifically in the context of post-immunization pain, based on similar applications and validation, they would still be useful in this setting.

Table A.2
Assessment methods for delayed pain following immunization^a.

Age	Assessor and tool	Validity	Reliability	Ease of use ^b
Pre-verbal child				
≤3 years	Parent: NRS	Good	Good	Good
Verbal child				
≥3–6 years ^c	Child: Poker Chip	Good	Good	Good
≥4 years	Child: FPS-R	Good	Good	Good
≥9 years	Child: NRS	Good	Good	Good
Adult				
≥18 years	Adult: NRS	Good	Good	Good

^a The criteria was based on WG expert opinion consensus and review of literature.

^b Ease of use considers: burden to user (time to complete, need for special equipment, training, language/culture barriers), scaling properties/interpretability (e.g., out of 10 or 100).

^c If child unable to reliably self-report pain, parents can assess pain using the assessment tools recommended for children ≤ 3 years.

Table A.3
Modified Behavioral Pain Scale [90].

Modified Behavioral Pain Scale (MBPS)		Score
Facial expression		
0	Definite positive expression: i.e., smiling	
1	Neutral expression	
2	Negative expression: i.e., grimace	
3	Definitive negative expression: i.e., Furrowed brows. Eyes closed tightly	
Crying		
0	Laughing or giggling	
1	Not crying	
2	Moaning, quietly vocalizing, or gentle or whimpering cry	
3	Full lunged cry or sobbing	
4	Full lunged cry, more than baseline cry	
Body movements		
0	Usual movements and activity	
1	Resting and relaxed	
2	Partial movement or attempt to avoid pain by withdrawing the limb where the puncture is done	
3	Agitation with complex movements involving the head, torso or other limbs, or rigidity	
Total		

In order to discern among the three distinct but potentially related aspects of delayed pain [i.e., persistent pain (including at rest) *versus* pain associated with movement or touch *versus* impact of pain on functioning], it is recommended that instructions be provided that orient the individual performing the assessment to the aspect of pain being measured before obtaining the score. For persistent pain, individuals can be asked to consider the presence of spontaneous behavioral indicators of persistent pain, such as: crying, grimacing, guarding, compensatory posturing, and immobilization. Similar behavioral indicators may be considered to assess pain associated with movement or touching, with the addition of body writhing movements. For assessment of the impact of pain on functioning, individuals can consider the disruption to normal activities.

Poker Chip [95]

English Instructions:

Say to the child: “I want to talk with you about the hurt you may be having right now.”

Align the chips horizontally in front of the child on the bedside table, a clipboard, or other firm surface.

Tell the child, “These are pieces of hurt.” Beginning at the chip nearest the child’s left side and ending at the one nearest the right side, point to the chips and say, “This (first chip) is a little bit of hurt and this (fourth chip) is the most hurt you could ever have.” For a young child or for any child who may not fully comprehend the instructions, clarify by saying, “That means this (one) is just a little hurt, this (two) is a little more hurt, this (three) is more yet, and this (four) is the most hurt you could ever have.”

Do not give children an option for zero hurt. Research with the Poker Chip Tool has verified that children without pain will so indicate by responses such as, “I don’t have any.”

Ask the child, “How many pieces of hurt do you have right now?”

After initial use of the Poker Chip Tool, some children internalize the concept “pieces of hurt”. If a child gives a response such as “I have one right now”, before you ask or before you lay out the poker chips, proceed with instruction # 5.

Record the number of chips on the Pain Flow Sheet.

Table A.4
FLACC Scale [91].

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractable	Difficult to console or comfort

Each of the five categories (F) face; (L) legs; (A) activity; (C) cry; (C) consolability is scored from 0 to 2, which results in a total score between 0 and 10.

Clarify the child’s answer by words such as, “Oh, you have a little hurt? Tell me about the hurt.”

Faces Pain Scale – Revised (for children aged 4–12 years) [62]
In the following instructions, say “hurt” or “pain,” whichever seems right for a particular child.

“These faces show how much something can hurt. This face [point to left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face] – it shows very much pain. Point to the face that shows how much you hurt [right now].”

Score the chosen face 0, 2, 4, 6, 8, or 10, counting left to right, so ‘0’= ‘no pain’ and ‘10’= ‘very much pain.’ Do not use words like ‘happy’ and ‘sad’. This scale is intended to measure how children feel inside, not how their face looks.

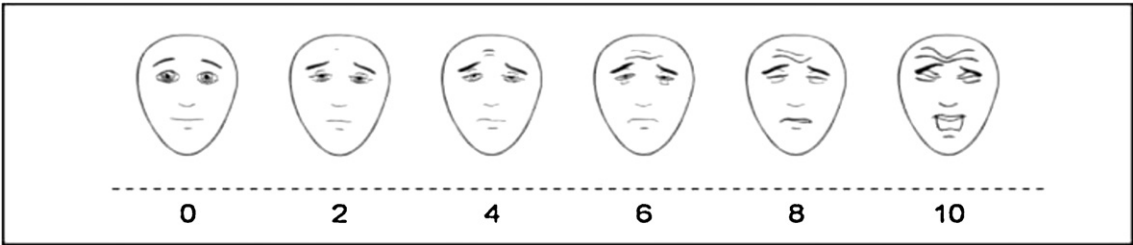
Available in 35 languages

Appendix B. Data collection checklist

This checklist is derived from the criteria listed in the case definition and guidelines for data collection. It is intended as a data collection template for use in study protocols and for active follow up in surveillance systems. Additional information or a different format depending on the study question and setting may be required.

B.1. Source of information/reported by

	Assessing	Reporting
a. Medical provider including professional status		
b. Parent/care giver		
c. Self		
d. Other (describe)		



NRS [92–94]

“Tell me how much pain you have from 0 to 10, where 0 is no pain, and 10 is worst possible pain”.

B.2. Vaccinee/control subject

1. Demographics			
a. Patient's initials (first name initial followed by last name initial) or code or as specified in country-specific data protection laws or study protocol.			
b. Date of birth	____/____/____ (mm / dd / yyyy) ^a	Unknown	
^a All dates, specify type of calendar used, the common Julian calendar is preferred			
c. Age	----- years-----months	Unknown	
d. Sex	M [] F []	Unknown []	
If female, pregnancy status	Non-pregnant []	Unknown []	
	Pregnant []		
e. Race/Ethnicity (if appropriate)		Unknown []	
f. Infants (≤12 months of age)	Gestational age -----Years	Unknown []	
	Birth weight		
	-----kg/or -----ounces	Unknown []	
	Weight at assessment		
	-----kg/or-----ounces	Unknown []	
	Length of infant		
	-----cm/ or -----inches	Unknown []	
2. Clinical / immunization history			
a. Relevant past medical conditions including hospitalizations, underlying disease, immunological disorders that may affect the evaluation of pain as an AEFI?	Yes []	No []	Unknown
If YES, please describe condition			
b. Any medication prior to, during, and after vaccination including prescription and non-prescription medication, and treatment with long half-life (e.g., immunoglobulins, blood transfusion, immunosuppressants) but excluding any treatment given for pain.	Yes []	No []	Unknown
If YES, please specify (including the dates/and or times of their administration if available)			
c. Immunization history: indicate if history is: verbal [] or documented [] Unknown []			

B.3. Details of the immunization

1. Timing				
a. Date of immunization	____/____/____ (mm / dd / yyyy)			Unknown
b. Time of immunization ^	_____ am / pm(check which)			Unknown
^ Specify if 12 or 24 hour clock was used. The 24 hour clock is preferred since it eliminates the am and pm differences.				
2.Vaccine details				
If >1 vaccine was given				
Vaccine	1	2	3	4
a. Trade name				
b. Manufacturer				
c. Lot number and expiration date expiration date [if used]				
e. Vaccine presentation	Single dose vial [] Multidose-vial []	Single dose vial [] Multidose-vial []	Single dose vial [] Multidose-vial []	Single dose vial [] Multidose-vial []
	Liquid []		Lyophilized []	Unknown
f. Vaccine reconstitution	Used within 6 hours Yes [] No [] Unknown []			
If other presentation, specify-----				
g. Volume (mL)				
h Dose number				
i. If combined vaccine, specify :				
<ul style="list-style-type: none"> antigen components ----- 				
<ul style="list-style-type: none"> was vaccine was administered as separate injection sites concomitantly? Yes[] No [] 				

j. Route of administration	Injectable [] Site: Deltoid [] Buttock [] Thigh [] Other route of administration (specify)----- ----- Unknown []	Injectable [] Site: Deltoid [] Buttock [] Thigh [] Other route of administration (specify)----- ----- Unknown []	Injectable [] Site: Deltoid [] Buttock [] Thigh [] Other route of administration (specify)----- ----- Unknown []	Injectable [] Site: Deltoid [] Buttock [] Thigh [] Other route of administration (specify) ----- ----- Unknown []
k. Needle gauge -----				

l. Person who immunized the subject	Nurse [] Other health care provider (specify) Unknown []	Nurse [] Other health care provider (specify) Unknown []	Nurse [] Other health care provider (specify) Unknown []	Nurse [] Other health care provider (specify) Unknown []
m. Describe any information the reporter finds relevant to the evaluation of the pain.				

B.4. The adverse event [88,89]

1. Immunization site pain associated characteristics			
a. Description of immunization site pain	Yes	No	Insufficient evidence
b. Occurring at immunization site?	Yes	No	Unknown
c. Is the patient verbal ?	Yes	No	Unknown
d. Assessed by:			
<input type="checkbox"/> Self <input type="checkbox"/> Healthcare Provider <input type="checkbox"/> Parent/ care giver			
e. Pain assessment validated tools used	Yes	No	
f. If yes, select tool used			
<input type="checkbox"/> MBPS <input type="checkbox"/> NRS , specify adult----- child <input type="checkbox"/> FLACC <input type="checkbox"/> Poker Chip <input type="checkbox"/> FPS-R <input type="checkbox"/> Other tool, specify			
g. Describe severity of pain	Grade 1	Grade 2	Grade 3
h. Duration of Pain	-----Hours -----days		Unknown
Please check the following if present.			
i Presence of fever(90)?	Yes	No	Unknown
If yes, record highest temperature	----- °C ----- °F		
j. Presence of injection site swelling (24) ^a ?	Yes	No	Unknown
Presence of local injection site warmth			
Presence of local injection site cellulitis ^a (21)			
k. Presence of persistent crying (91) ^a			
l. Other description (specify)			
^a Refer to the specific Brighton document for a more comprehensive description of the adverse event. Specific documents can be downloaded freely at: https://brightoncollaboration.org/public/resources/case-definitions.html			
2. Timing of pain	Date	Time (check am or pm)	
a. Onset of pain:	____/____/____ (mm/dd/yyyy)	____ am/pm	Unknown
b. 1st Observation:	____/____/____ (mm/dd/yyyy)	____ am/pm	Unknown
c. Diagnosis	____/____/____ (mm/dd/yyyy)	____ am/pm	Unknown
*Please review guideline 31 on suggested time intervals in section 3 of this document.			

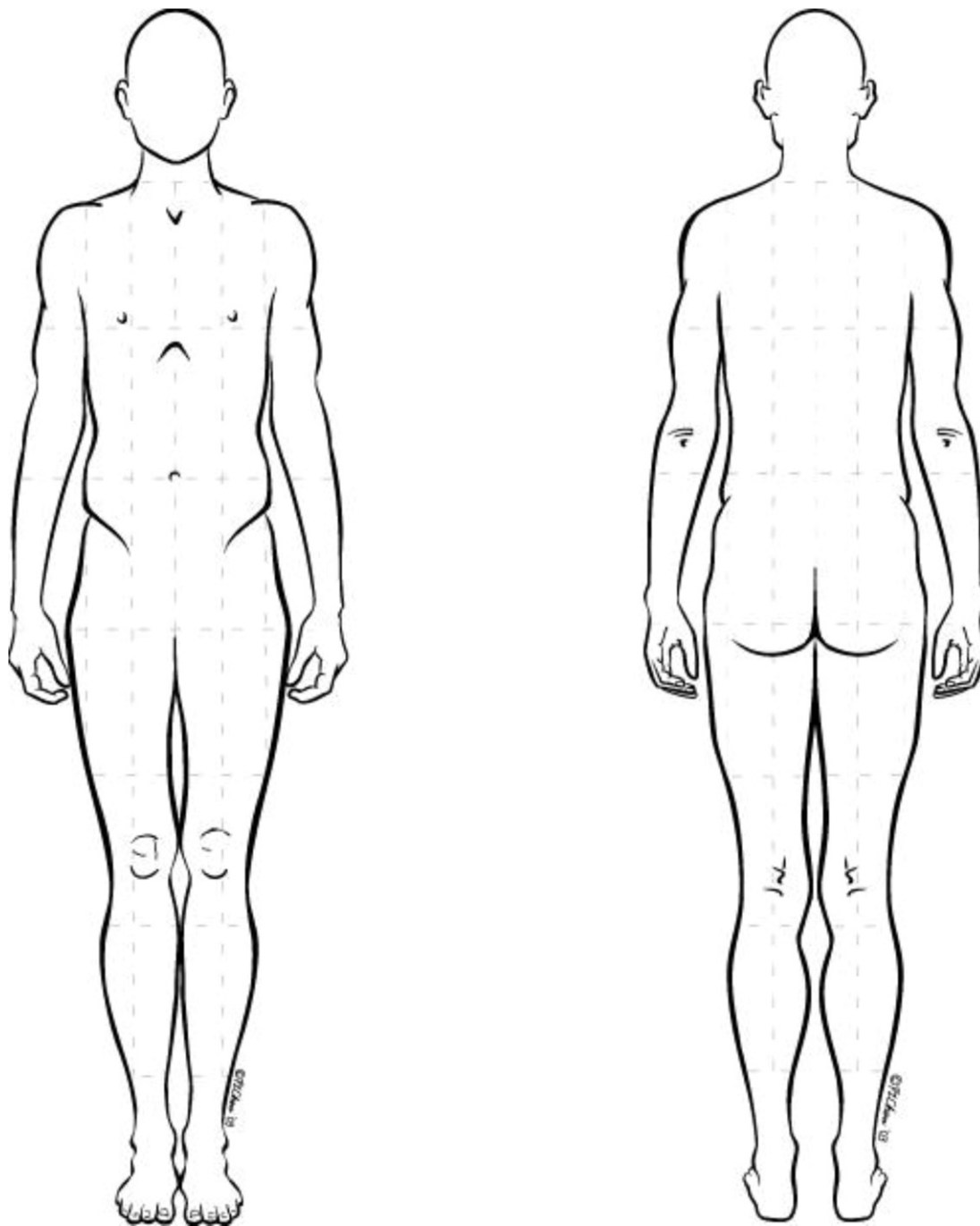
3.Outcome at last follow-up			
a. Date of outcome at last follow-up	____/____/____ ____ (mm/dd/yyyy)		Unknown
b. What was the outcome at final follow-up?	Yes	No	Unknown
Resolved without treatment			
Resolved with treatment			
Pain still present			
Sequelae, please specify-----			
Outcome unknown []			
Any other outcome, (specify)			
8. Outcome at last follow-up			
E. Miscellaneous			
Please add any other comments or a clinical narrative if you think it will add to the understanding of the clinical course or pathophysiology of this adverse event. Copy of medical record relating to the event may be attached			

Contact the Brighton Collaboration secretariat for comments about this checklist at: secretariat@brightoncollaboration.org.

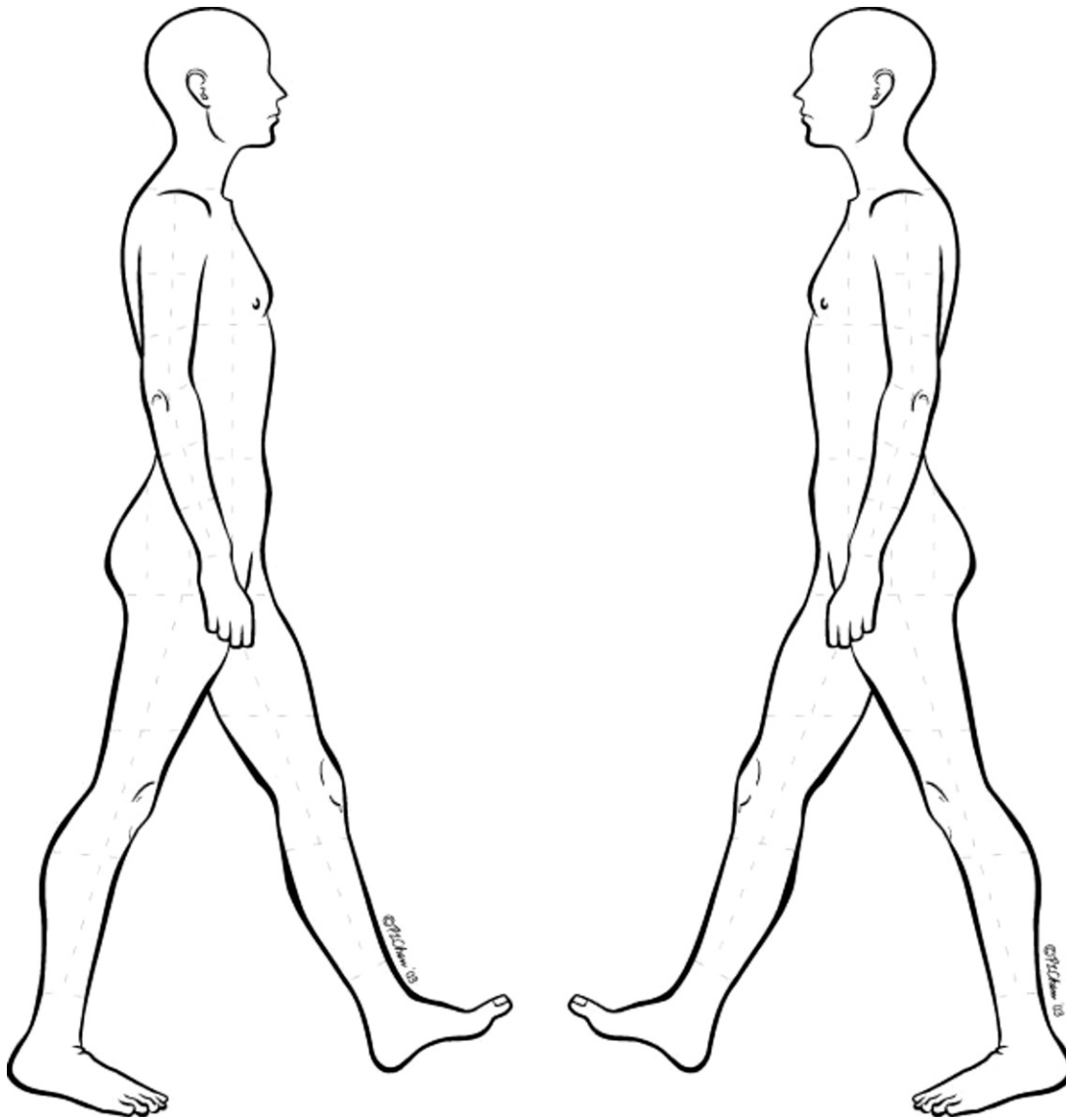
Appendix C. Medical illustrations

N.B: These drawings are used as a guide to record Immunization site pain

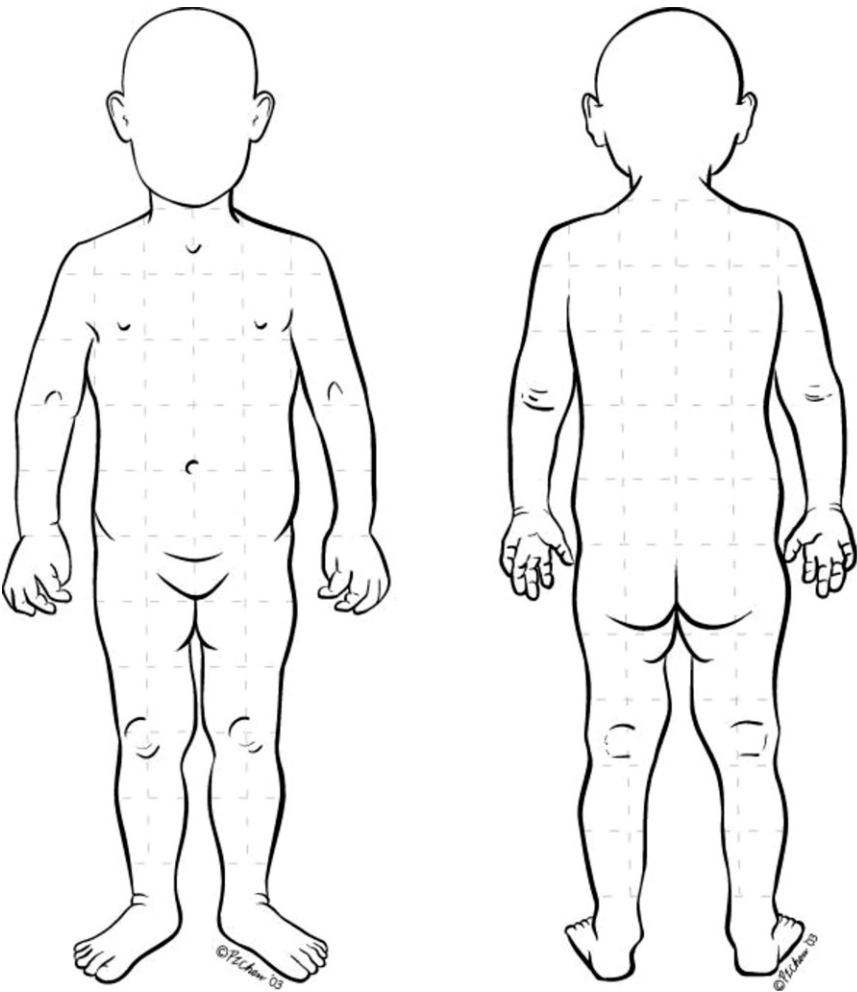
C.1. Drawing of front and back of adult to mark injection site(s) with respective vaccines and immunization site pain



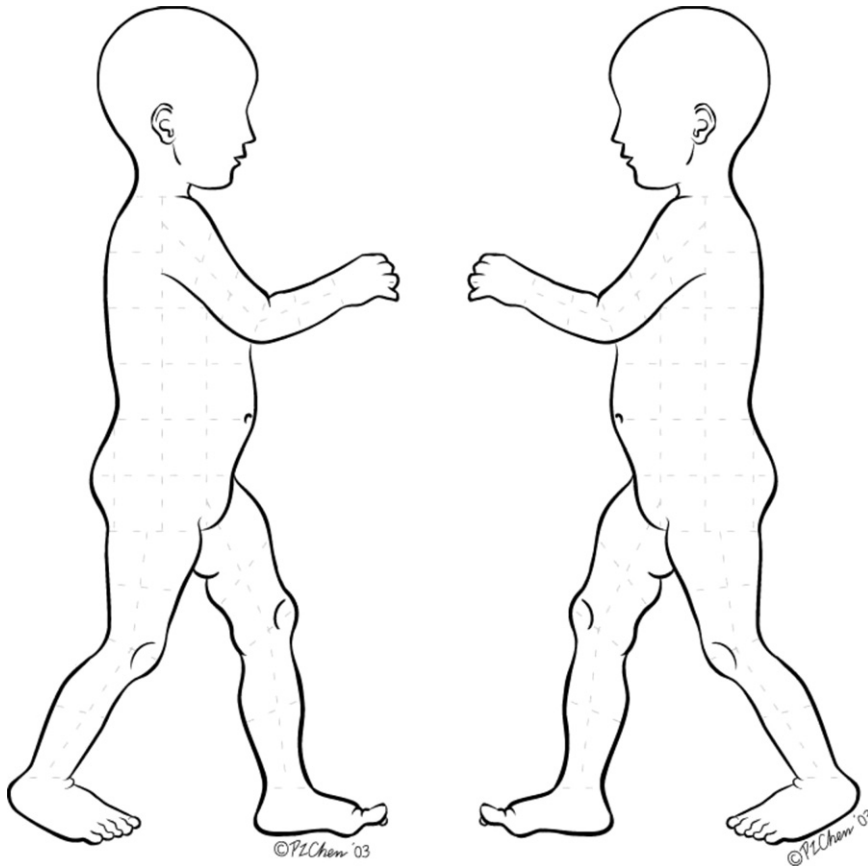
C.2. Drawings of left and right side of adult to mark injection site(s) with respective vaccines and location of immunization site pain



C.3. Drawings of front and back of infant to mark injection site(s) with respective vaccines and location of the immunization site pain



C.4. Drawings of left and right side of infant to mark injection site(s) with respective vaccines and location of the immunization site pain



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