Safety Platform for Emergency vACcines

SO2- D2.5.2.1 - AESI Case Definition Companion Guide for 1st Tier AESI

Facial Nerve Palsy

Work Package: WP2 Standards and tools

V1.0 – February 11th, 2021

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Nature: Report | Diss. level: Public

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DEFINITIONS & ACRONYMS

ADEM	Acute Disseminated Encephalomyelitis
AESI	Adverse Events of Special Interest
BC	Brighton Collaboration
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CM	Clinical Modification (Relates to numbered versions of ICD codes)
CMV	Cytomegalovirus
CT	Commuted Tomography (Radiologic Scan)
CUI	Concept Unique Identifier
EBV	Epstein Barr Virus
EMG	Electromyogram
ENT	Ear Nose Throat (consultant expertise)
GBS	Guillain Barré Syndrome
HHV6	Human Herpesvirus 6
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Medical Resonance Imaging (Radiologic Scan)
PCR	Polymerase Chain Reaction
SLE	Systemic Lupus Erythematosus
SPEAC	Safety Platform for Emergency Vaccines
UMLS	Unified Medical Language System
VZV	Varicella Zoster Virus

INTRODUCTION

1. Background

CEPI has contracted 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 aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

SPEAC Work Package 2 is creating resources and tools for the AESI including:

1. Tabular summaries of risk factors and background rates for each AESI.
2. Guidance on AESI real time investigation, data collection, analysis and presentation.
3. Spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.
4. Tools to facilitate capturing the specific clinical data needed to meet AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
    a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
    b. Tabular checklists that are a stand-alone tool useful for summarizing key clinical data needed to determine the level of diagnostic certainty for a given case definition.
    c. Tabular logic and pictorial decision tree algorithms, also stand-alone tools, to facilitate correct application of key clinical data to determine the level of diagnostic certainty for each AESI.
    d. Glossary of terms relevant to anaphylaxis and the neurologic AESI.

To guide timelines for the activities above, the AESIs have been prioritized into 4 tiers as shown in the Table below (process described in SO1-D2.0 Addendum to SO1-D2.2 & 2.3 Landscape Analyses Priority Tiers for All CEPI Vaccine Development AESI). This is available in the Developers Toolbox and on the Brighton Collaboration website.

TABLE 1. AESI PRIORITIZED BY TIER

Tier 1	Tier 2	Tier 3	Tier 4
Anaphylaxis	Vaccine associated enhanced disease	Sensorineural hearing loss	Acute/Chronic inflammatory rheumatism
Thrombocytopenia	Acute respiratory distress syndrome	Anosmia/ageusia	Total/partial loss of vision
Generalized convulsion	Acute cardiovascular injury	Chilblain like lesions	Optic neuritis
Aseptic meningitis	Coagulation disorder	Erythema multiforme	Alopecia
Encephalitis	Acute kidney injury	Acute aseptic arthritis	Neonatal sepsis
Myelitis	Acute liver injury	Single organ cutaneous vasculitis	Neonatal encephalopathy
Acute disseminated encephalomyelitis	Stillbirth	Maternal death	Neonatal neuro-developmental delay
Guillain Barré & Miller Fisher Syndromes	Spontaneous abortion and ectopic pregnancy	Neonatal death	
Peripheral facial nerve palsy	Pathways to Preterm birth & Preterm birth		

To simplify access to AESI specific tools and resources, companion guides to the Brighton AESI case definition are being prepared for each AESI.
This deliverable, focuses on idiopathic peripheral facial nerve palsy, hereinafter referred to as Facial Nerve Palsy (also known as 'Bell's Palsy').

2. Objective of this deliverable

To collate SPEAC & BC tools, resources and guidance that have been developed for Facial Nerve Palsy.

3. Methods

The methods for developing each of the tools included in this guide were detailed in previously completed SPEAC deliverables as follows:

- Facial Nerve Palsy risk factors and background rates: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Facial Nerve Palsy Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- Facial Nerve Palsy Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Facial Nerve Palsy Data Abstraction, Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation

The methods are briefly described in Appendix 8 of this Guide along with links to source documents which have more detailed methodology.

4. Results

The outputs are provided as separate appendices to simplify printing as needed. These are provided as shown below.

1. Facial Nerve Palsy Risk Factors
2. Facial Nerve Palsy Background Rates
3. Facial Nerve Palsy Case Definition key caveats for diagnosis, data analysis and presentation
4. Facial Nerve Palsy Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA
5. Facial Nerve Palsy Data Abstraction and Interpretation Form for Medical Chart Review
6. Facial Nerve Palsy Tabular checklist for key case definition criteria and level of certainty algorithm
7. Facial Nerve Palsy Pictorial level of certainty algorithm
8. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together many resources and tools related to the AESI of Facial Nerve Palsy including risk factors, background rates, guidance for real time investigation, ICD-9/10-CM and MedDRA codes for data entry or database searching and provides tools for collecting and interpreting clinical data to apply the Brighton Facial Nerve Palsy case definition and determine the level of diagnostic certainty. The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used in order to assign level of certainty for all identified AEFI with features of Facial Nerve Palsy. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

6. References

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APPENDIX 1.
Facial Nerve Palsy Risk Factors

1.1. Idiopathic Facial Nerve Palsy Risk Factors

TABLE 1. IDIOPATHIC FACIAL NERVE PALSY RISK FACTORS [1-26]

Note: *about half of all cases of acute peripheral facial nerve palsy are idiopathic, with no specific cause found. The risk factors in the table below are specifically for such cases. Annex 5 – table 6 provides a list of the many entities included in the other half of cases where a specific cause may be found including: infection (viral, bacterial, mycoplasma, mycobacteria, spirochetal, tick borne zoonoses), cancer, neurologic/neuromuscular junction/ autoimmune/endocrine disorders, trauma, drug toxicity, inherited disorders.*

Age [1-5]	The incidence is higher among adults than children. Some evidence for peak prevalence at age 15-45 years but some population-based incidence studies suggest a steadily increasing incidence from young to older age (Israel & Laredo studies)
Pregnancy[6-9]	Increased incidence among pregnant women especially 3rd trimester and 1st 2 weeks postpartum[6-8] but this is controversial[9]
Geography [10,11]	Cold weather season[10]; extremes in wind chill positively correlated with case frequency[11]
Comorbidity [3-5, 12-18]	Diabetes [12-14], pre-diabetes [15;] hypertension[16]; migraine[17] ; psychologic factors[18]
History of previous episode[19]	Mean (range) of recurrence was 6.5% (0.8%-19.4%) based on a systematic review of 27 studies involving 1041 adult patients from 13 countries (4 USA, 5 England, 1 Sweden, 2 Norway, 1 Denmark, 2 Netherlands, 1 Austria, 1 Czechoslovakia, 1 Italy, c1 Egypt, 1 India, 4 China, 1 Korea, 2 Japan)
Vaccine[20-26]	The proven association between an intranasally administered influenza vaccine adjuvanted with *E. coli* heat labile toxin (Nasalflu®, Berna Biotech) and Bell's Palsy is the only one demonstrated to date. The evidence is briefly summarized below. • Berna Biotech Nasalflu ®: inactivated, virosome-formulated intranasally administered influenza vaccine adjuvanted with *E. coli* heat labile toxin; 9 cases noted in a phase II/III trial with 2700 subjects[2]; Licensed in Switzerland in October 2000 with 36 cases reported up to May 2001 when taken off market; Case control study estimated 13 excess cases / 100,000 doses [20] The attributable risk was for the interval from 1 to 91 days following immunization. The Relative Incidence (95% Confidence Interval) was determined for 3 separate intervals with results as follows: 1-30 days: 14.0(5.2-37.9); 31-60 days: 35.6(14.1-89.8); 61-91 days: 11.8(4.3-32.3). • A background paper preceded the 2017 Brighton case definition and included a systematic review of the literature published up to December 2006.[2] in addition to the link to the inactivated nasally administered vaccine (see above), it was noted that Bell's Palsy had been reported in temporal association following several vaccines including: HBV, Rabies, polio, Lyme disease, DTP, acellular pertussis, meningococcal C conjugate, measles alone and in combination with mumps/rubella, smallpox, pneumococcal conjugate and HIV. The cited literature dated from 1967 to 2006 but none involved a proven association. • In 2011 the Institute of Medicine reviewed vaccine safety for MMR, Hepatitis A and B, HPV, meningococcal and pneumococcal conjugate, influenza and D-T-aP containing vaccines.[21] Existing evidence regarding an association with Bell's Palsy was examined and found inconclusive for Hepatitis A and D-T-aP containing vaccines. For inactivated influenza vaccine the evidence was sufficient to reject an association with Bell's Palsy based on two

	epidemiologic studies. The first was a self-controlled case series using UK – GPRD administrative data that involved 2263 episodes of Bell's Palsy among 2128 individuals aged 2–95-year-olds who had received at least 1 inactivated influenza vaccine from July 1992 to June 2005.[22] the relative risk for Bell's palsy occurring within 1-91 days following vaccination was 0.92(95% Confidence Interval 0.78-1.02). Similar results were found for secondary analyses that examined each of three successive risk intervals (1-30, 31-60, 61-91days) following immunization as well as by separate age groups (0-44 years, 45-64 years and ≥65 years). The second was done by the US Vaccine Safety Datalink (VSDL) project over three successive influenza seasons (2005-2006; 2006-2007; 2007-2008) using a risk period of 1-42 days following vaccination and a control period from 15 to 74 days before vaccination.[23] The relative risks for the 3 seasons were 0.67, 1.81 and 1.27 for children and 1.06, 1.07 and 0.99 for adults. No data were presented for the other vaccines. • A systematic search for evidence published after the IOM study through July 2018 did not find any evidence for an association between vaccines used to immunize children in the USA and Bell's Palsy. [24] • A self-controlled case series study done using UK primary health care electronic data (The Health Improvement Network 'THIN' database) found no evidence for an increased occurrence of Bell's palsy after either seasonal influenza vaccines or monovalent 2009 pandemic influenza vaccines which included both AS03 adjuvanted and non-adjuvanted inactivated vaccines.[25] They did note an association between acute respiratory infection and Bell's palsy. • Risk window for Bell's Palsy as a vaccine product related reaction[20,22,23,25,26] o Intranasal adjuvanted vaccine: elevated risk from 1-91 days, with the highest risk falling into the 31-60 days period following immunization[20]. o Inactivated or subunit vaccines: Theoretically the same risk period as used for ADEM[26], might apply, i.e. 2-42 days for individual risk and for epidemiologic studies 5-28 days for primary analysis, and 2-42 days for secondary analysis ▪ The UK GPRD study[22] used the same risk intervals as the Swiss case control study[20] ▪ The US-VSD proof of concept study [23] and the UK-THIN study[25] used a 1–42-day risk interval • Live attenuated vaccines: similar to inactivated vaccines but adjusted for the known incubation period for the vaccine strain, adding as above, 5-28 days for primary analysis and 2-42 days for secondary analysis following the end of the incubation period.

APPENDIX 2.
Facial Nerve Palsy Background Rates

2.1 Facial Nerve Palsy Background Rates

TABLE 1. FACIAL NERVE PALSY BACKGROUND RATES [12, 25, 27-35]

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 patient years [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs					
USA (Laredo, Texas; Predominantly Hispanic)[12]	1974 to 1982	0-9		4.6 [0.1-9.1] (4)	7.1 [1.4-12.8] (6)
		10-19		10.5 [3.6-17.4] (9)	19.7 [10.3-29.0] (17)
		20-29		11.0 [2.8-19.1] (7)	32.3 [18.8-45.9] (22)
		30-39		32.2 [14.7-49.7] (13)	43.6 [24.5-62.7] (20)
		40-49		39.2 [17.0-61.3] (12)	52.6 [29.5-75.7] (20)
		50-59		52.4 [25.0-79.9] (14)	49.1 [25.8-72.4] (17)
		60-69		97.6 [53.7-141.5] (19)	61.5 [31.4-91.7] (16)
		≥ 70		51.3 [17.8-84.8] (9)	60.4 [30.8-90.1] (16)
		All ages		**23.5 [not stated] (87)**	**32.7[not stated](134)**
USA (Rochester, Minnesota) [27]	1968 to 1982	0-9	4.2 (6)	2.1 (2)	5.7 (4)
		10-19	15.3 (22)	10.1 (7)	20.3 (15)
		20-29	24.0 (39)	25.8 (17)	22.8 (22)
		30-39	30.9 (35)	28.4 (16)	33.5 (19)
		40-49	35.2 (29)	35.6 (14)	34.9 (15)
		50-59	35.8 (25)	34.7 (11)	36.8 (14)
		60-69	37.1 (20)	36.5 (8)	37.5 (12)
		≥ 70	52.7 (32)	58.2 (11)	50.2 (21)
		All ages	**25.2 (208)**	**24.2[18.9-29.4](86)**	**26.4[21.6-31.3](122)**
USA (Minnesota)[28]	1955-1967	0-9	6.4 (8)	4.7 (3)	8.1 (5)
		10-19	15.0 (13)	5.4 (2)	22.2 (11)
		20-29	23.7 (19)	22.3 (7)	24.1 (12)
		30-39	42.2 (29)	38.2 (13)	46.2 (16)
		40-49	33.9 (19)	30.7 (8)	36.7 (11)
		50-59	21.4 (10)	14.9 (3)	26.4 (7)
		60-69	27.4 (10)	33.9 (5)	23.4 (5)
		≥ 70	42.8 (13)	64.2 (7)	30.8 (6)
		All ages	**22.8 (121)**	**20.1 (48)**	**25.0 (73)**
ASIA					
Japan [29]	1984	All ages	32.4 (486)	32.6 (234)	32.1 (252)
	1985	All age	31.1 (473)	31.0 (224)	31.2 (249)
	1986	All ages	28.3 (433)	28.3 (206)	28.3 (227)
	1984-86	**All ages**	**30.6 (1392)**	**30.6 (664)**	**30.4 (728)**
EUROPE and EASTERN MEDITERRANEAN REGION					
Israel[30]	2003	0-1	6.39 (6)	4.24 (2)	8.57 (4)
	To	1-4	18.9 (66)	18.97 (34)	18.82 (32)

	2012	5-14 15-24 25-34 35-44 45-54 55-64 65-74 75-84 ≥85 **All ages**	30.92 (233) 47.65 (409) 72.33 (564) 91.08 (477) 118.37 (685) 154.51 (819) 190.89 (641) 190.74 (463) 125.39 (100) **87.0 (4463)**	25.54 (98) 41.87 (186) 62.24 (256) 88.3 (232) 108.3 (301) 170.79 (440) 183.0 (283) 210.6 (209) 161.66 (49) **82.0(2090)**	36.5 (135) 53.84 (223) 83.6 (308) 93.87 (245) 127.67 (384) 139.11 (379) 197.63 (358) 177.0 (254) 103.16 (51) **92.0 (2373)**
Denmark[31]	1976 to 2000	All ages	32 (1701)		
Norway(north) [32]	1969-1971	0-9 10-19 20-29 30-39 40-49 50-59 60-69 70+ **All ages**	4.7 (5) 9.5 (9) 25.8 (22) 26.1 (15) 17.0 (10) 32.2 (18) 24.7 (10) 35.0 (11) **18.8(100)**	1.8 6.2 26.2 32.5 19.1 31.3 29.5 41.7 **19.3**	7.6 13.1 25.4 18.0 14.5 33.2 19.9 29.3 **18.4**
UK[25]	2009-2013	All ages	38.7 (6288)		
Spain [33]	1980 to 1996	All ages	24.1 (1906)		
Italy (Rome) [34]	2006-2008	All ages	53.32 (381)		
European ADVANCE (Accelerated Development of Vaccine benefit-risk Collaboration in Europe) Project[35]					
All country data combined	2003-2014	0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	6.76 [6.08-7.52] 7.05 [6.45-7.69] 11.83 [11.41-12.28] 19.06 [18.55-19.59] 24.90 [24.51-25.30] 28.83 [28.39-29.28] 31.13 [23.64-24.05] 23.84 [23.64-24.05]		
Denmark (Aarhus University Hospital and Staten Serum Institute)	2003-2014 for all	0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	22.3 [20.08-24.6] 14.9 [13.47-16.51] 5.3 [4.85-5.80] 4.9 [4.58-5.44] 7..9 [7.49-8.28] 15.9 [15.37-16.54] 35.7 [34.63-36.8] **13.9[13.66-14.20](14,087)**		
Italy		0-1 2-4	4.7 [3.34-6.60] 5.5 [4.20-7.09]		

(Agenzia regionale di sanità)		5-14 15-24 25-44 45-64 ≥65 **All ages**	6.5 [5.66-7.37] 3.2 [2.67-3.87] 4.9 [4.48-5.29] 6.9 [6.4.1-7.37] 10.5 [9.82-11.13] **6.7 [6.47-6.97] (2,758)**		
Italy (Val Padana)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	5.7 [2.15-15.27] 3.9 [1.45-10.27] 6.4 [4.26-9.65] 1.5 [0.62-3.58] 2.1 [1.37-3.16] 2.8 [1.99-4.01] 4.6 [3.36-6.20] **3.3 [2.79-3.94] (130)**		
Italy (Pedianet)		0-1 2-4 5-14 **All 0-14**	3.7 [1.19-11.47] 3.9 [1.45-10.30] 8.2 [5.11-13.22] **6.1 [4.11-9.15](24)**		
Spain (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	14.8 [12.2-17.95] 8.9 [7.14-11.09] 19.3 [17.68-20.98] 35.2 [33.53-36.84] 42.3 [40.97-43.61] 51.3 [49.66-53.07] 62.9 [60.52-65.3] **42.4[41.62-43.1](12,542)**		
UK (Royal College of General Practitioners Research and Surveillance Centre)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	3.2 [1.79-5.57] 7.6 [5.47-10.43] 12.3 [10.74-14.14] 22.9 [20.69-25.28] 29.7 [28.02-31.40] 36.7 [34.88-38.72] 39.0 [36.58-41.49] **28.9[28.08-29.83](4,194)**		
UK (The Health Improvement Network)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	5.8 [4.86-7.03] 13.8 [12.94-14.75] 26.5 [25.25-27.80] 33.7 [32.84-34.65] 40.1 [39.16-41.16] 41.8 [40.59-43.15] 32.1 [31.65-32.58] **32.1[31.65-32.58](18,398)**		

APPENDIX 3

Facial Nerve Palsy Case Definition Key Caveats for Diagnosis, Data Analysis and Presentation

3.1. Facial Nerve Palsy Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

- Key elements of Case Definition (CD)
  - Idiopathic facial nerve palsy is a peripheral neuropathy (lower motor neuron); this is why the CD requires impairment of the ability to wrinkle the forehead OR to raise the eyebrow on the affected side – both of these are spared in upper motor neuron 'central' lesions. Ideally information on both should be gathered, but the CD allows for one or the other abnormality to be documented, increasing the sensitivity of the CD.
  - Idiopathic facial nerve palsy is a diagnosis of exclusion. There are 3 levels of certainty (LOC). Level 3 is based solely on clinical history/physical examination. If alternate diagnoses are found based on clinical findings the diagnosis is ruled out, but it is not a requirement that alternate causes be looked for. On the other hand, to reach higher LOCs some testing must be done to rule out alternate causes: lab tests for level 2, and lab + radiology for level 1.
  - The CD requires that onset be sudden (i.e., occurred unexpectedly and without warning leading to a marked change in the subject's previously stable condition), with rapid progression (worsening over a short period of time) and partial/complete resolution (with or without treatment). Specific time courses are not defined but in a review paper that preceded the CD[2] it is noted that usually there is rapid evolution with maximal weakness within 24-72 hours but may be as long as 10 days. Any evolution over >2 weeks should suggest tumor or cholesteatoma.
  - The vast majority of Idiopathic peripheral facial nerve palsy cases are unilateral; bilateral cases are so rare that the working group set a requirement that such cases must be 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.
  - The facial palsy must be peripheral, based on documented decreased ability or complete inability to wrinkle the forehead or to raise the eyebrow on the affected side.
  - 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, tumors, neurologic or autoimmune disorders, trauma and iatrogenic factors. A full list of causes is presented in the published CD[1] and in table 6 of the data abstraction and interpretation form (see Annex 5).
  - The review of Bell's Palsy by Reich[4] provides several pictures showing key physical exam findings as well as a guide to 'red flags' that point to non-idiopathic causes:
    - History: concomitant vertigo or hearing loss, constitutional symptoms, cancer, HIV or risk factors for HIV, endemic area for Lyme disease and/or features suggesting Lyme disease (known tick bite, rash), chronic otitis media / cholesteatoma.
    - Physical exam: bilateral facial palsy; other cranial nerve involvement; limb or bulbar weakness; parotid gland enlargement; vesicles in external auditory canal, tympanic membrane or oropharynx; cervical adenopathy; facial swelling with fissured tongue.
    - Course of facial palsy: gradual onset over weeks to months; no improvement within 3 months
  - Severity of disease expression should be graded using a recognized international grading scale. The House-Brackmann Facial Nerve Grading System is commonly used and is provided in the published CD[1] as well as in table 5 of the data abstraction and interpretation form (See Annex 5).

- 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 (Annex 5 has a data abstraction form; Annex 6 a tabular check list for the key criteria needed to meet case definition). Where possible document date and time of onset, first observation, diagnosis, end of episode (defined as the time the event no longer meets the Brighton case definition).
  - Document all concurrent symptoms, signs and diseases.
  - Document, including date, 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 as one of: a. Complete/ incomplete resolution in the absence of treatment; b. Complete / incomplete resolution with treatment; c. No improvement (unilateral/bilateral); d. Sequelae (specify); e. Another outcome (describe); or f. Unknown clinical outcome

- Data Analysis Guidelines
  - Classify each reported event into one of five possible categories: Event meets case definition criteria at 1. Level 1; 2. Level 2 or 3. Level 3; 4. Event reported as facial nerve palsy but information insufficient to meet any level of the case definition; and 5. Not a case of facial nerve palsy.
  - If there are many cases they should be analyzed as the number(percentage) distributed into each of the following intervals after immunization: day of immunization to <2 weeks; then in successive 2-week intervals to <12 weeks, 12 - <16 weeks, 16-<20 weeks and >20 weeks.

APPENDIX 4
Facial Nerve Palsy Diagnostic Codes: ICD-9/10-CM and MedDRA

4.1 Facial Nerve Palsy Diagnostic Codes: ICD-9/10-CM and MedDRA

TABLE 1. NARROW SEARCH TERMS FOR PERIPHERAL FACIAL NERVE PALSY

UMLS Concept		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0376175	Bell Palsy	Bell's palsy	10004223	351.0	G51.0
		Palsy Bells	10033559		
C0015469	Facial paralysis	Facial palsy	10016060		G51.0
		Facial paralysis	10016062		
		Paralysis facial	10033808		

APPENDIX 5
Facial Nerve Palsy Data Abstraction and Interpretation Form for Medical Chart Review

5.1. Facial Nerve Palsy Data Abstraction and Interpretation Form for Medical Chart Review

Instructions are provided with each table. The focus is on the specific data needed to meet and/or exclude Facial Nerve Palsy based on the Brighton case definition.[1] This form will be most applicable to situations where a hospital/other institutional chart is available and used retrospectively to gather the information needed to validate that a case coded as Facial Nerve Palsy meets or does not meet the Brighton case definition. It may also serve as a guide for the type of data to be collected and investigations to be done at the time a possible case is identified or reported during a clinical trial or active surveillance for cases as part of pharmacovigilance. A neurologic glossary of terms is available as well.

Six tables are included in the form.

- Table 1 is a guide to likely sources of information for the key case definition clinical and laboratory criteria.
- Table 2 is the main data abstraction form. Use it to record data from the chart and based on the evidence to assign a value to each case definition criterion. Space is limited and additional paper can be used as appropriate to capture key clinical and laboratory data.
- Table 3 should be used to summarize the criterion values as determined once table 2 is completed.
- Table 4 is the key to determine the level of certainty based on the summary data in Table 3. It follows the logic of the Brighton case definition.
- Table 5 presents the House-Brackmann Facial Nerve Grading System (part of the case definition appendices)
- Table 6 lists the major differential diagnoses for Idiopathic facial nerve palsy with space to summarize positive investigations (6A) and record all laboratory investigations that were done (reproduced from the published case definition appendices).

TABLE 1. FACIAL NERVE PALSY KEY CASE DEFINITION CRITERIA, LIKELY AND ACTUAL SOURCES OF INFORMATION

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Peripheral facial nerve palsy	Outpatient clinic/emergency room record(s) Neurology/ENT/other consultation(s) Hospital admitting history & physical; discharge summary; Follow-up clinic records	
B	Disease onset and course		
C	Alternative diagnosis based on history and physical examination		
D	Alternative diagnosis based on lab investigations	Outpatient / inpatient laboratory results	
E	Alternative diagnosis based on radiology studies	Outpatient / inpatient radiology reports	`
Not a criterion	Electrophysiologic investigations	Outpatient / inpatient electrophysiology (EMG, nerve conduction) tests.	

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TABLE 2. ACUTE FACIAL NERVE PALSY DATA ABSTRACTION FORM: NOTE: GLOSSARY OF TERMS AVAILABLE AS A SEPARATE DOCUMENT

1. Record specific information, to the extent possible, for all column 1 criteria in the results column 2 below.
2. Use recorded results to circle most appropriate BC CD criterion value based on the formulae in column 3.

1. **Data Category**	2. **Results *NOTE: glossary of neurologic terms available as a separate document***	3. **BCCD Criteria Value Determination**
Onset of neurologic illness	a) Date of first symptom(s) onset: (dd/mon/yy): __ / ___ /__ b) Hospital admission? ___Yes ___No ___Uncertain If yes date of admission: (dd/mon/yy): __ / ___ /__	Not Applicable
Diagnosis. *Caveat: Idiopathic facial nerve palsy is usually unilateral. Given rarity of bilateral peripheral facial nerve palsy, the working group recommends all attempts to exclude an alternative cause should be made. The case definition allows for bilateral facial nerve palsy ONLY IF reported by a professional healthcare provider.*	Admitting diagnosis: Discharge diagnosis(If different from above): Who made the final diagnosis? __Neurologist __MD, other* __other* __not stated *Describe: Is diagnosis Bell's palsy/idiopathic facial nerve palsy? __Yes __No* __not stated *if no what is the diagnosis?	If insufficient data to meet any level of the peripheral facial nerve palsy case definition, the data on diagnosis and who made it may help to establish a level 4 of certainty – i.e. reported as idiopathic facial nerve palsy
Criterion A **Peripheral facial nerve palsy** ***Caveat: For children and infants with limited ability to follow***	**1. Wrinkling of the forehead:** __impossible __limited __normal __not described	**A = 'Yes'** IF **1 = impossible or limited** **OR** **2 = impossible or barely possible** **A = 'No'** IF (**1 AND 2) = normal**
	2. Raise eyebrows: **Right:** __impossible __barely possible __normal __not described	

instructions, an observation period to look for spontaneous/ provoked movement of affected muscles should be used	**Left:** __impossible __barely possible __normal __not described	**A = 'Unknown'** IF **(1 AND 2) = not described** *NOTE: criteria 3-11 are not essential to define peripheral facial nerve palsy, but may be helpful if 1 and/or 2 not clear. Seek expert help to interpret.*
	3. Facial symmetry at rest: __very symmetric ___moderately symmetric __barely noticeable asymmetry ___not described	
	4. Eye closure: **Right:** __incomplete __barely possible __minor limitation __normal __not described **Left:** __incomplete __barely possible __minor limitation __normal __not described	
	5. Laughing: __obvious asymmetry __discretely possible __barely possible __normal __not described	
	6. Whistling: _impossible _barely possible _minor limitation _normal _not described	
	7. Completeness of Palsy: ___complete paralysis (all facial nerve motor branches involved + asymmetry at rest) ___incomplete paresis ___not described	
	8. Taste abnormalities: __Present (describe) __Absent __not described	
	9. Epiphora (excess tearing): __Present __Absent __not described	
	10. Facial / neck pain: __Present(describe) __Absent __not described	
	11. Dry eyes __Present (describe) __Absent __not described	
Criterion B **Disease onset, progression, and resolution** ***Caveat: the working group decided against defining a specific interval for 'rapid progression'. Acute timeframes are defined as minutes to days, and it is noted that most cases would progress within 7 days.***	**1. Symptom onset suddenly -** i.e. occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition: __Yes __No __not described **2. Speed of progression from first onset to maximal facial paralysis/paresis?** __Rapid* (24-72 hrs usual) __Slow* __not described * For either Rapid or Slow – describe timeframe: **3. Resolution of symptoms/signs at last documented assessment** Date: __/____/__ (dd/ mon/ yy) __a. Complete (i.e. back to baseline) __b. partial __c. None __d. not described or uncertain **4. Residual abnormalities**: __Yes*(check/describe below) __No __Not described __motor residuals (voice, mouth, tone at rest, eye) __sensory residuals (taste, dysesthesia, pain) __Synkinesia (non-voluntary locomotion)	**Criterion B = 'Yes'** IF: **1 = 'Yes' AND** **2 = 'Rapid' AND** **3 = (a.complete OR b.partial)** **Criterion B = 'No'** IF **1 = No OR** **2 = Slow OR** **3 = None** **Else Criterion B = 'Unknown'**

	5. Was facial nerve function assessed? __Yes* __No __Not described * Describe system used (e.g. see appendix 1), date and score for each (can record in Appendix 2 table 2B)	
Alternative etiology for peripheral facial nerve palsy: (See Appendix 2) Only definitive proof of alternate etiologies excludes from being a case.		
Criterion C: clinical history + physical examination failed to identify alternative etiology for facial nerve palsy	Alternative Diagnosis: __Yes* __No __Unknown * Use Appendix 2, Tables 1 and 2 to record findings. Record alternative etiology here:	**C = 'True'** IF No OR unknown checked **C** = '**False'** IF Yes checked
Criterion D: laboratory investigations failed to identify an alternative etiology for facial nerve palsy	**Category** / **Complete Appendix 2, Tables A & B, and then summarize below**	**D = 'True'** IF some laboratory testing done and no alternative etiology found based on results **D= 'False'** IF any laboratory testing revealed an alternative etiology **D= 'Unknown'** IF no laboratory testing done or no information available
	Infection — __Positive (describe below) __Negative __no tests/unknown	
	Head/neck tumor — __Positive (describe below) __Negative __no tests/unknown	
	Neurologic disorder — __Positive (describe below) __Negative __no tests/unknown	
	Autoimmune disorder — __Positive (describe below) __Negative __no tests/unknown	
	Trauma — __Positive (describe below) __Negative __no tests/unknown	
	Endocrine disorder — __Positive (describe below) __Negative __no tests/unknown	
	Drug toxicity — __Positive (describe below) __Negative __no tests/unknown	
	Inherited disorder — __Positive (describe below) __Negative __no tests/unknown	
	Congenital disorder — __Positive (describe below) __Negative __no tests/unknown	

Criterion E Radiology investigations failed to identify an alternative etiology for facial nerve palsy	**a. CT head:** __Done* __Not done __Unknown if done or no results *if done use Appendix 2, Table 2B to record test date(s) and result(s). Record alternative etiology, if any found here:	**E = 'True'** IF head CT +/or MRI done and failed to identify an alternate etiology **E = 'False'** IF alternative etiology found on head CT and/or MRI **E = 'unknown'** IF head CT/MRI not done or status/result unknown
	b. MRI head: __Done* __Not done __Unknown if done or no results *if done use Appendix 2, Table 2B to record test date(s) and result(s). Record alternative etiology, if any found here:	
Electro-physiologic tests	Facial muscle electrophysiology: __done* __Not done __Unknown if done or no results *if done use Appendix 2, Table 2B to record test date(s) and result(s). Summarize here:	Not a criterion – but may contribute to facial nerve palsy diagnosis

TABLE 3. Based on the information recorded in Table 2 above, record the status for each of the listed criteria (A-E)

Clinical Criteria	Criterion Value		
A. Peripheral facial nerve palsy	__Yes	__No	__Unknown
B. Disease onset abrupt, course rapidly progressive and some or complete resolution	__Yes	__No	__Unknown
C. Disease unexplained after review of clinical history and physical examination	__True	__False	
D. Disease unexplained after review of laboratory investigation(s)	__True	__False	__Unknown
E. Disease unexplained after review of radiologic investigation(s)	__True	__False	__Unknown

TABLE 4. Based on the values for the Criteria in table 3 above, circle the corresponding value in the table below to determine the highest achievable level of certainty (LOC) for peripheral facial nerve palsy (Level 1 > Level 2 > Level 3)

LOC	
Level 1	A = YES AND B = YES AND (C + D + E) = True
Level 2	A = YES AND B = YES AND (C + D) = True AND E = Unknown
Level 3	A = YES AND B = YES AND C = True AND [D + E] = Unknown
Level 4	Event reported as facial nerve or Bell's palsy but insufficient evidence to meet level 1, 2 or 3[1]
Level 5	A = NO AND/OR B = NO AND/OR (C +/or D +/or E) = False

[1] *Caveat: If there is bilateral facial palsy, the case must have been reported by a healthcare professional*

TABLE 5. House-Brackmann Facial Nerve Grading System (standard of Am Acad of Otolyaryngology – Head&Neck Surgery)
House JW, Brackmann DE. Facial nerve grading system. Otolaryngol Head Neck Surg 1985; 93(2): 146-147.

Grade	% function	General description	Appearance at rest	Appearance in motion	Synkinesis	Contracture or hemifacial spasm
1	100%	Normal	Normal	Normal	None	None
2	76-99%	Mild dysfunction; slight weakness noticeable only on close inspection	Normal forehead symmetry	Able to close eye with minimal effort	None	None
3	51-75%	Moderate dysfunction; obvious but not disfiguring difference between 2 sides; no functional impairment noticeable	Normal symmetry & tone	Forehead: slight to no movement Eye closure/corners of mouth: able to close eye/move mouth corners with maximal effort & obvious asymmetry	No disfiguring synkinesis	None
4	26-50%	Moderately severe dysfunction; obvious weakness and/or disfiguring asymmetry	Normal symmetry and tone	Forehead: no movement Eye closure: unable to close completely, with maximal effort	If present meets grade 4 regardless of other findings	Meets grade 4 If hemifacial spasm interfering with function regardless of other findings
5	1-25%	Severe dysfunction; barely perceptible motion	Possible asymmetry with droop of corner of mouth and decreased or absent nasal labial fold	Forehead: no movement Eye closure: incomplete and only slight movement of lid with maximal effort Corner of mouth: slight movement	Usually absent	Usually absent
6	0%	Total paralysis	Asymmetry	None	Absent	None

Other grading systems include: Facial Nerve Grading Scale 2.0, Yanagihara (unweighted), Burres-Fisch (weighted), Nottingham (objective), Sunnybrook (weighted), Adour-Swanson, Computer analysis, Moire topography, Facial reanimation measurement system and Electroneurography (yielding prognostic information). See the Facial Nerve Palsy case definition, Box 2 and references if more detail needed on any of these.

TABLE 6. (From published case definition – see publication guidelines, section 3.1.2.2 for referenced lists of alternate diagnoses)
TABLE 6A. Differential Diagnoses for Facial nerve palsy (* use table 6B for each specific test & date done; only record positive results in table 6A)

Category	Etiologies	Investigation	Results
Infection	Viral (Enterovirus, Herpes simplex, HHV6, EBV, CMV, HIV, Influenza, Mumps, Polio, Rubella, VZV / Ramsay Hunt Syndrome)	Culture: __done* __not done __unknown PCR: __done* __not done __unknown Serology: __done* __not done __unknown Clinical features of Ramsay Hunt Syndrome: __vesicular rash around ears __hearing loss __vertigo	
	Bacterial (meningitis; acute/chronic otitis media, cholesteatoma , mastoiditis, tetanus	Culture: __done* __not done __unknown ENT exam: __done* __not done __unknown	
	Mycoplasma spp.	Serology: __done* __not done __unknown	
	Mycobacteria: Tuberculosis, Leprosy	Culture: __done* __not done __unknown Other test: __done* __not done __unknown	
	Spirochete: syphilis	Culture: __done* __not done __unknown Serology: __done* __not done __unknown Other test: __done* __not done __unknown	
	Tick-borne diseases Bacteria: Ehrlichiosis, Spirochete: Lyme disease	Culture: __done* __not done __unknown Serology: __done* __not done __unknown Tick identification: __done* __not done __unknown	
Tumour	Head / neck melanoma, Glomus tumor, Neuroma/Schwannoma, Parotid tumor(primary), other benign tumors; malignant/metastatic tumors; paraneoplastic process; rhomboencephalitis, leukemia	__Present(describe) __Absent __Unknown	
Neurologic	GBS, polyneuritis cranialis, ADEM, small pontine infarcts, trigeminal neuropathy, psudobulbar palsy	__Present(describe) __Absent __Unknown	
Autoimmune	Sjogren's, SLE, Sarcoidosis, Kawasaki disease, other	__Present(describe) __Absent __Unknown	
Trauma	Birth trauma, barotrauma, petrous bone fracture, pontine lesions, cold exposure, Post Traumatic Stress Disorder	__Present(describe) __Absent __Unknown	
Iatrogenic	Dental treatment, surgery	__Present(describe) __Absent __Unknown	
Endocrine	Diabetes mellitus, Paget's disease of bone	__Present(describe) __Absent __Unknown	

Drug toxicity	INH, tetanus serotherapy	__Present(describe) __Absent __Unknown	
Inherited disorders	Hemophilia, hereditary neuropathy, Melkersson-Rosenthal / Mobius / Cayler syndromes	__Present(describe) __Absent __Unknown	
Other	Hypertension, perineural edema, pregnancy, exposure to cold temperature	__Present(describe) __Absent __Unknown	

TABLE 6B. Investigations to rule out other causes of facial nerve palsy (Record any positive results in Table 6A above)

Test	Date sample obtained or test done (dd/mon/yy)	Result

APPENDIX 6

Facial Nerve Palsy Tabular Checklist for Key Case Definition Criteria and Level of Certainty Algorithm

6.1 Facial Nerve Palsy Tabular Checklist for Key Case Definition Criteria and Level of Certainty Algorithm*

STEP 1. Use available clinical data to assign values for criteria A-E. 'Yes' means criterion as described is documented to be present; 'No' means it is documented to be absent; 'unknown' means there was no documentation of clinical findings OR test not done OR unknown if test done OR test results are unavailable.

Criterion	Clinical Criteria	Criterion Value
A. Peripheral Facial Nerve Palsy For A1+A2 choose most appropriate answer	A1. Ability to wrinkle forehead[1]: __impossible*__limited* __normal __not described A2. Ability to raise eyebrow(s)[1]: __impossible* __limited*__normal __notdescribed * Location if abnormal: __Unilateral (__Right__Left __side unknown) __Bilateral[2] [2]If bilateral was it reported by a health care professional? __Yes __No __ Unknown	__A=YES IF A1 OR A2=impossible or limited __A=NO IF A1 AND A2 = normal __A=UNKNOWN IF A1 AND A2 = not described
B. Disease onset: For B1, B2 + B3 check YES, NO or UNKNOWN	B1 onset was sudden[3] __YES __NO __UNKNOWN B2 Disease progressed rapidly[4] __YES __NO __UNKNOWN B3 Disease resolved completely or partially with or without therapy __YES __NO __UNKNOWN	__B=YES IF B1+B2+B3 = YES __B=NO IF B1 or B2 or B3 = NO __B=UNKNOWN IF B1 or B2 or B3 = unknown
No alternative etiology found for peripheral nerve palsy after careful review of (check TRUE if no other etiology; if there was an alternate etiology found check False and provide detail in the appropriate row):		
C. Clinical history + physical exam	* What alternative etiology was found on clinical history and/or physical exam?	__C = TRUE[5] __C = FALSE*
D. Laboratory investigations	* What alternative etiology was found on laboratory investigation(s)?	__D = TRUE[6] __D = FALSE*
E. Radiologic investigations	* What alternative etiology was found on radiologic investigation(s)?	__E = TRUE[6] __E = FALSE*

[1] For children/infants with limited ability to follow instructions, observe for spontaneous or provoked movement of affected muscles

[2] Bilateral idiopathic (Bell's) facial nerve palsy may occur but is very rare. Such cases must be reported by a health care professional to be included as a case.

[3] Defined as an event that occurred unexpectedly and without warning and led to a marked change in a subject's previously stable condition

[4] Speed of progression not absolutely defined in case definition; usually progression occurs over 1-7 days before resolving or reaching a plateau.

[5] If absence of clinical detail/information re alternate etiologies Criterion C can be considered TRUE. This is not the case for Criteria D and E – see footnote 6.

[6] For D+E, to be TRUE, some testing must have been done to exclude alternate causes of peripheral nerve palsy; otherwise, neither criterion can be met.

STEP 2. Apply Criterion values from checklist above to formulae below to determine level of certainty (LOC)

LOC	
Level 1	A = YES AND B = YES AND (C + D + E) = TRUE
Level 2	A = YES AND B = YES AND (C + D) = TRUE AND radiologic studies not done or unknown
Level 3	A = YES AND B = YES AND C = TRUE AND radiologic and laboratory studies not done or unknown
Level 4	Event reported as facial nerve or Bell's palsy but insufficient evidence to meet level 1, 2 or 3
Level 5 (Not a case)	A = UNKNOWN AND/OR B = UNKNOWN AND/OR (C, D or E) = FALSE

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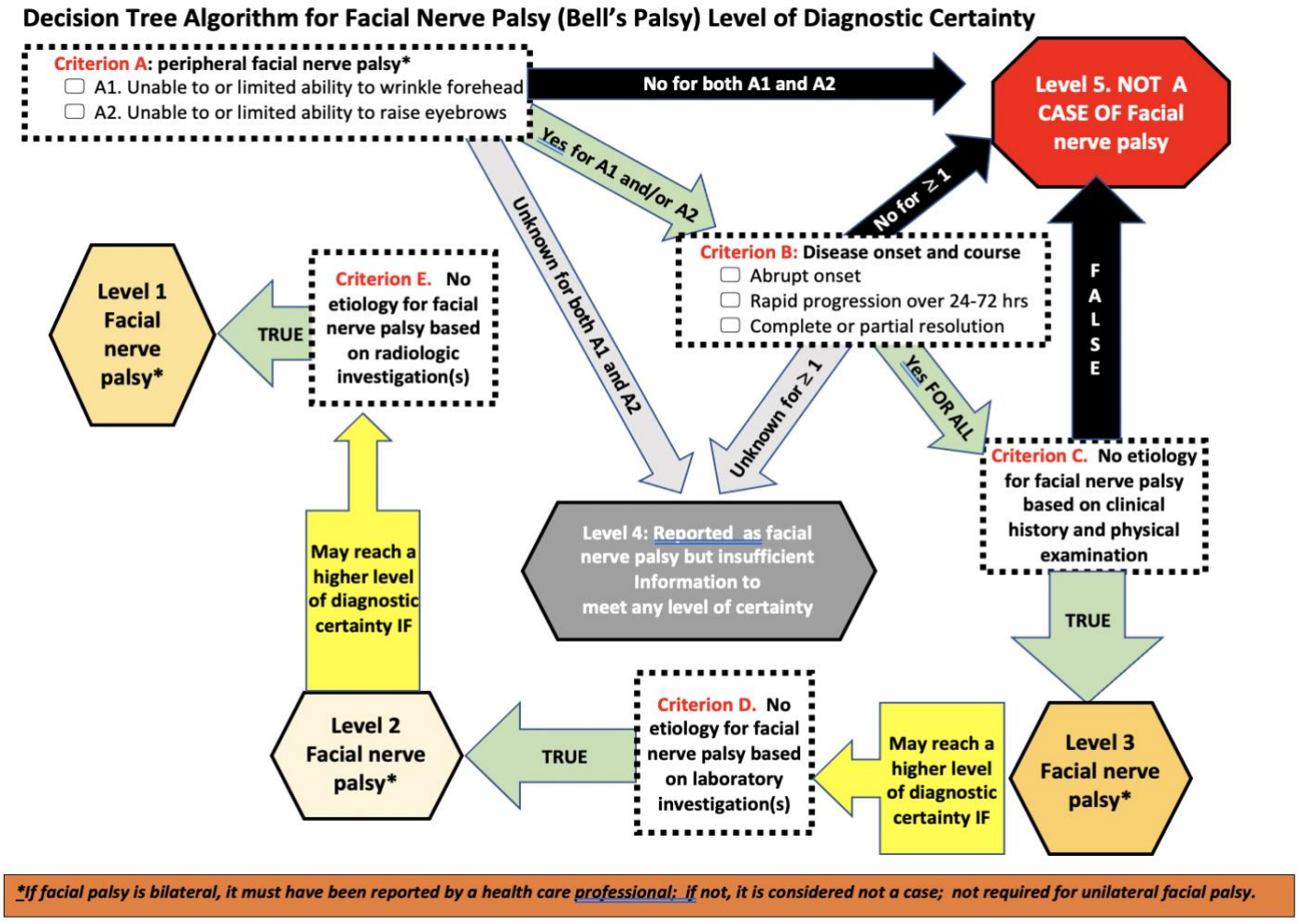
APPENDIX 7

Facial Nerve Palsy Pictorial Level of Certainty Algorithm

7.1 Facial Nerve Palsy Pictorial level of certainty algorithm

Use available clinical history, examination and laboratory investigation results to determine level of diagnostic certainty for Facial Nerve Palsy



If facial palsy is bilateral, it must have been reported by a health care professional; if not, it is considered not a case; not required for unilateral facial palsy.

APPENDIX 8.

Methodology: Brief Summary

8.1. Facial Nerve Palsy Risk Factors [1-26]

A risk factor is "an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor". According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:
1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attribute includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published Brighton Case definition[1] for Facial Nerve Palsywas reviewed for evidence related to associated risk factors. In addition, review articles published after the Brighton case definition were retrieved and reviewed in depth regarding known risk factors for Facial Nerve Palsy.[2-25]

8.2. Facial Nerve Palsy Background Incidence [12, 25, 27-35]

A systematic literature search to estimate the incidence of Facial Nerve Palsy in the population was conducted using the following search strategy:
("Bell Palsy"[Mesh:noexp] OR "facial palsy"[ti] OR "idiopathic facial palsy"[ti] OR "idiopathic peripheral facial nerve palsy"[ti] OR "facial nerve palsy"[ti] OR "Bell palsy"[ti] OR "Bell's palsy"[ti] OR "Bell's palsy"[ti]) AND ("Incidence"[Mesh:noexp] OR "incidence"[tiab]) AND English[lang] AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT]) AND ("Meta-Analysis"[Publication Type] NOT ("animals"[Mesh:noexp] NOT "humans"[Mesh:noexp]) NOT ("Coronavirus"[Mesh:noexp] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti]) NOT ("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR trial[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti]).

Articles had to meet the following criteria:
1. Original research/meta-analysis
2. Population-based study (selecting the entire population or using probability-based sampling methods)
3. Reported an incidence estimate (or raw numbers that allowed the calculation of an estimate).

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all nonoverlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for Facial Nerve Palsy were extracted. Facial Nerve Palsy incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a single medical reviewer (BL). Screened in articles were then reviewed and relevant data abstracted for inclusion in the background rate table. Additional articles were found based on citations in the screened in articles as well as articles reviewed for risk factors. The spreadsheet with all extracted background incidence data is available on the Brighton Collaboration website.

8.3. Facial Nerve Palsy Case Definition[1] key caveats for diagnosis, data analysis and presentation

The published Brighton case definition for Facial Nerve Palsy was reviewed and key aspects identified with particular relevance to real time assessment of Facial Nerve Palsy in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published Facial Nerve Palsy case definition was reviewed, and key recommendations identified for data collection, analysis and presentation.

For a more detailed description of methodology see SO1-D2.7 Guidance for CEPI Developers which is available in the CEPI Developers' Toolbox.

8.4. Facial Nerve Palsy ICD-9/10-CM and MedDRA Codes [36-40]

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper[36] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[37] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[38,39] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[40] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMED-CT, MeSH, ICPC-2 and Read-CTv3.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the

targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.

3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the Codemapper concepts was reviewed by a medical expert (BL) familiar with the Facial Nerve Palsy Brighton case definitions for all Tier 1 AESI. The concepts identified for Facial Nerve Palsy were considered relevant for background incidence rate determination as well as to study hypotheses related to Facial Nerve Palsy as a vaccine-product related reaction.

For a more detailed description of methodology see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available in the CEPI Developers' Toolbox and at the Brighton Collaboration website.

8.5. Data Abstraction & Interpretation Form, Tabular Checklist and Algorithms for Level of Certainty Determination

The Brighton Collaboration case definition for Facial Nerve Palsy[1] was thoroughly and repeatedly reviewed by one individual (BL) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each and every case definition level of certainty.
The Facial Nerve Palsy criteria were displayed in a tabular format to enable recording of all relevant clinical data (based on history, physical examination, laboratory investigation and temporal criteria as relevant to each case definition) needed to meet each criterion. A guide was developed for each criterion in the data abstraction table to ensure a standard approach to assigning a value to the criterion. For most criteria the following terms were used with the meaning as noted below:

- Yes: criterion was documented to be present (for some the term 'True' or 'Met' was used instead of 'Yes').
- No: criterion was documented to be absent (for some the term 'Not True' or 'Not met' was used instead of 'No').
- Unknown: criterion was not assessed, or not mentioned, or no results were available, so it was not possible to document it as either present or absent.

In some cases, lettered or numbered values were assigned to a given criterion. Rules to assign these values to the criterion were embedded within the data abstraction table or the tabular checklist depending on the specific tool, further described in results below.
Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition. Two types of algorithm were developed for each case definition. For one, formulae based on the logic in the case definition were put into tables with each row representing a level of certainty. For the second a more visual decision tree algorithm was developed. Both however, were based on the logic inherent in the published case definition.

For a more detailed description of methodology see Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation which is available in the CEPI Developers' Toolbox.