Narcolepsy as an adverse event following immunization: Case definition and guidelines for data collection, analysis and presentation

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1. Preamble

1.1. The need for developing a case definition for narcolepsy as an adverse event following immunization (AEFI)

1.1.1. General introduction

Narcolepsy is a sleep disorder primarily characterized by excessive daytime sleepiness and cataplexy – episodes of muscle weakness brought on by emotions [1]. Additional symptoms may comprise hypnagogic hallucinations (vivid dream-like experiences occurring during the transition between wakefulness and sleep), sleep paralysis (episodes of inability to move during the onset of sleep or upon awakening, lasting for a few seconds or minutes),fragmented nocturnal sleep, as well as impaired ability for sustained attention and non-sleep symptoms such as obesity, anxiety, cognitive and emotional disturbances, and behavioral problems and precocious puberty in children [2–7]. Excessive daytime sleepiness can occur in other disorders [8], but most patients suffering from narcolepsy experience their unwanted sleep episodes as short and refreshing [3,4]. Cataplexy consists of brief episodes of muscle weakness without altered consciousness, usually triggered by emotions. Cataplexy constitutes a virtually pathognomonic symptom for narcolepsy [1], although it must be separated from a specific feeling of muscle weakness with emotions in normal subjects [4]. Cataplexy may rarely occur in some other disorders which are easily distinguished from narcolepsy, such as Niemann-Pick type C, Coffin-Lowry syndrome, and Norrie Disease [10–19]. Given its specificity, determining of cataplexy is of paramount importance, although an objective test is not available [9] as of yet.

1.1.2. Diagnosis of narcolepsy

Formally, the diagnosis of narcolepsy can be made on clinical grounds [1]. However, particularly when cataplexy is absent, the diagnosis must be supported by additional polysomnographic testing and/or by the measurement of the neuropeptide hypocretin-1 (also called orexin A) in the cerebrospinal fluid (CSF) obtained by lumbar puncture [1]. A very low or undetectable hypocretin-1 level (<110 pg/ml) is the most specific finding in narcolepsy in general. For narcolepsy with cataplexy it also is highly sensitive: more than 90% of unambiguous cases are hypocretin deficient, making this neuropeptide a valuable diagnostic biomarker [20,21]. For narcolepsy without cataplexy it is much less sensitive, with up to 20% of cases hypocretin-1 deficient [21–24]. Intermediate levels of CSF hypocretin-1 (between 110 and 200 pg/ml) may not always suggest a diagnosis of narcolepsy, as they may also be observed in other neurologic conditions, tumors, infections, acute traumatic brain injury, and syndromic/genetic cases [25–36]. Importantly, however, these conditions are unlikely to lead to diagnostic confusion, since they have substantially different symptoms compared to narcolepsy. CSF hypocretin-1 measurement is the most precise diagnostic tool available in narcolepsy with cataplexy [1,21,37], and will be incorporated in the upcoming 3rd edition of the International Classification of Sleep Disorders (ICSD) as preferential and not only alternative criterion [1].

The main polysomnographic test is the Multiple Sleep Latency Test (MSLT), typically showing a short mean sleep latency (SL, <8 min) and ≥2 Sleep Onset Rapid Eye Movement Periods (SOREMPs) [1]. With such cut-offs, the MSLT sensitivity is 94.5% but the specificity is only 73.3% [38,39].

1.1.3. Demographics and diagnostic rate

Narcolepsy with cataplexy has an estimated prevalence of 2–5/10,000 [40] and an average incidence of 7.4 per million person-years [41]. More than 50% of cases appear to have disease onset before 18 years of age [42]. Onset as late as 70 years of age is rare but has been described [4,43]. Bimodal peaks have been reported, with one around 15 years of age (range 10–19 years) and the other around 35 years [44]. Onset of the disease can be insidious (over years) or acute (within weeks or even days). Acute onset is most often reported in children, especially for narcolepsy with cataplexy associated with a large BMI increase close to the onset of narcoleptic symptoms. Cataplexy develops in 5–8% of patients as an initial symptom but usually either together with excessive daytime sleepiness or within on average 6 years after the onset of sleepiness [4,45–47]. Significant sex differences are not observed, although a slight male predominance was reported, while females showed a slightly earlier manifestation of symptoms in one German study [47]. As with many other rare diseases, narcolepsy is often overlooked or misdiagnosed, leading to an estimated mean diagnostic delay of 8 years, ranging from a few weeks to 60 years after the onset of clinical symptoms [48]. The delay between excessive daytime sleepiness and cataplexy onset may contribute to diagnostic delay [47]. In clinical practice, recognition of childhood cases is increasing, perhaps because of better awareness of the disease in the general population and in medical community [5,48–51]. Recognition of the disease in children is particularly challenging, since a wide range of daytime sleep requirements is often considered normal, cataplexy in children presents with atypical features [51], and there is a lack of objective pediatric diagnostic criteria [1].

1.1.4. Pathophysiology

Sporadic narcolepsy with cataplexy is associated with a loss of hypocretin-producing neurons in the hypothalamus (which is not always the case in secondary or familial forms of narcolepsy) as demonstrated in post-mortem studies on sporadic cases [52–54], but the exact pathological mechanism still remains to be elucidated. Abnormalities in genes coding for hypocretin peptides or their receptors could only be identified in a single patient with a point mutation in the prepro-hypocretin gene [53]. An autoimmune etiology is hypothesized on the basis of a strong association with the Human Leukocyte Antigen (HLA) DRB1*06:02, with 85–98% of patients carrying this allele [55]. So far studies have not identified hypocretin neuron specific antibodies [56–60]. More recently, the hypothesis of an autoimmune etiology was supported by association with a polymorphism in the T cell receptor alpha locus, involved in the HLA-peptide presentation, and with a polymorphism of the T cell and natural killer 2R1Y1 receptor, involved in the regulation of immune-cell survival [61,62]. Moreover, patients with recent onset narcolepsy showed elevated anti-streptolysin-O titers, suggesting recent streptococcal infections [63], and increased titers of antibodies against Tribbles homolog 2, an intracellular and membrane protein enriched in hypocretin neurons, were detected in a small but significant proportion of recent onset narcolepsy patients [64]. The relation between these findings and hypocretin cell loss has yet to be explained.

In contrast to narcolepsy with cataplexy, narcolepsy without cataplexy is probably not a single disease. Only some individuals in this heterogeneous group will develop cataplexy later, but most will not [65–68]. For this latter group there is evidence that narcolepsy without cataplexy may be caused by a partial localized loss of hypocretin cells when compared to narcolepsy with cataplexy, which may explain why hypocretin-1 levels are normal/intermediate rather than undetectable [20,37,67–71]. A pathophysiological mechanism similar to narcolepsy with cataplexy is presumed in these patients. However, there is also evidence that a clinical picture resembling narcolepsy without cataplexy can occur with behaviorally induced insufficient sleep, sleep related breathing disorders, periodic limb movement disease, or environmental sleep disorder [1,72–75]. The differential diagnosis should consider these conditions, which can however be co-morbid with
a diagnosis of narcolepsy without cataplexy if daytime sleepiness and REM abnormalities are not resolved after adequate treatment.

1.1.5. Possible relation between narcolepsy and H1N1 vaccination

In 2010, clustering of new narcolepsy cases was reported in Sweden (34 cases), Finland (30), France (10), Norway (6) and Portugal (1) among children and adolescents, after immunization with Pandemrix®, the brand of monovalent pandemic 2009 H1N1 influenza vaccine used in these countries [74]. In response to this signal, several epidemiologic studies were conducted and initial results were published in case reports from the Swedish and Finnish national authorities [76–78]. The Finnish National Institute for Health and Welfare immediately recommended discontinuing vaccination with Pandemrix® as a precautionary measure [79]. A first letter reporting post-H1N1 vaccine/infection cases diagnosed in Montpellier (France), Stanford (CA, USA), Montreal (Canada), and Rochester (MN, USA) was published [80], followed by reports from Finland and Sweden, regulatory, and public health agencies (see also National Institute for Health and Welfare documents available online: http://www.thl.fi/thl-client/pdfs/dce182fb-651e-48a1-b018-3f774d6d1875 and http://www.thl.fi/en_US/web/en/pressrelease?id=26352). Reports of narcolepsy after H1N1 vaccination or H1N1 infection also began to emerge [81–84]. For a summary of events, see also Table 1.

1.1.6. Need to develop a narcolepsy case definition

In response to these developments, in September 2010 at the 20th Meeting of the European Sleep Research Society in Lisbon, the European Narcolepsy Network Group discussed the need for a coordinated action to elucidate the observed increased frequency of narcolepsy following vaccination. During the fall of 2010, sleep medicine experts, epidemiologists, and public health officials rapidly set out to further assess the safety signal for narcolepsy. Researchers agreed that there was a critical need to develop a generally accepted definition of narcolepsy with a special focus on pediatric narcolepsy. In November 2010, a small group of European sleep medicine specialists developed a working case definition for data collection and study protocols including the concerted European effort to investigate the signal as part of the vaccine adverse event surveillance and communication (VAESCO) project (http://vaesco.net). Building on this initial document, a formal Brighton Collaboration Narcolepsy Working Group was created to develop a standardized narcolepsy case definition according to the well-established Brighton Collaboration process (http://brightoncollaboration.org).

This paper presents the case definition and guidelines for data collection, analysis, and presentation that the Narcolepsy Working Group developed for the standardized assessment of narcolepsy. Note that this is not intended as a clinical diagnostic classification, but primarily as a research tool. Widespread use of this definition and guidelines in studies focused on narcolepsy as an adverse event following immunization (AEFI) will enable data comparability and lead to a better understanding of narcolepsy in the context of immunization.

1.2. Methods for the development of the case definition for narcolepsy as an AEFI

Following previously established procedures [85] (see http://www.brightoncollaboration.org/internet/en/index/process.html), the Brighton Collaboration Narcolepsy Working Group was initiated in October 2010, with 22 inter-disciplinary members from 4 continents with clinical, academic, public health and industry backgrounds, as well as expertise in narcolepsy. Based on the preliminary case definition used in the VAESCO consortium studies, the Narcolepsy Working Group began to develop the current definition of narcolepsy together with guidelines for data collection, analysis, and presentation of vaccine safety data. A systematic literature search to guide decision-making for the case definition and guidelines was conducted. The search focused on three topics: the relation between narcolepsy and vaccinations, existing narcolepsy case definitions or diagnostic classification systems, and diagnostic tools for narcolepsy used in clinical practice. The literature search included the following terms: vaccination, immunization (or terms beginning with vaccin-, immun-, inoculat-), classification, definition, nosology, diagnostic criteria (or terms beginning with classific-, definitio-, criter-, diagnos-), HLA, orexin-, hypocretin-, maintenance of wakefulness test, polysomnography, multiple sleep latency test, objective measurements, subjective measurements, and narcolepsy. The search was limited to articles on human narcolepsy, published from 1950 through December 2011, written in English, French, Italian, Dutch, German, Spanish, and Portuguese. The search resulted in initial identification of 1649 references. All abstracts were screened for possible reports of narcolepsy following immunization and diagnostic markers for narcolepsy. We reviewed 501 articles with potentially relevant material in more detail to identify studies that used case definitions or provided clinical descriptions of case material. This review resulted in a detailed summary of 235 articles, including information on study type, vaccine, diagnostic criteria or case definition proposals, onset interval, and any other symptoms. General medical, pediatric and sleep disease textbooks were also searched. An inventory that comprised the final selection of these 235 references was made available to working group members.

1.3. Rationale for selected decisions about the case definition of narcolepsy

1.3.1. Definition of narcolepsy: current classification, what is there, what is missing?

The first descriptions of the term “narcolepsy” date back to the late 19th century [86]. Narcolepsy was proposed as a specific disease entity by Adie in 1926 [87], characterized by the combined presence of excessive daytime sleepiness and cataplexy as the core features [88,89]. In later years, a broader definition of narcolepsy emerged that included the combination of sleepiness with “abnormal” manifestations of rapid eye movement (REM) sleep [89,90], mainly identified in clinical practice by the presence of sleep-onset REM sleep periods during the (MSLT) [38,39,74,75,91–102]. The current 2nd edition of the ICSD distinguishes “narcolepsy with cataplexy” based on the presence of a definite history of cataplexy, from “narcolepsy without cataplexy,” which may include questionable or atypical cataplexy-like episodes [1]. Moreover, a spectrum of different entities, sometimes called “narcolepsy’s borderland” encompasses presentations suggestive of narcolepsy without cataplexy and not fulfilling the MSLT criteria [4,97,103,104]. This notion is supported by data indicating that up to 90% of narcolepsy patients with cataplexy are hypocretin-1 deficient, compared to approximately 15% of narcolepsy patients without cataplexy [4,21,37,99,105].

Although cataplexy is central to the current clinical classification, its presence can only be assessed on the basis of clinical history. Indeed, the ICSD-2 definition of cataplexy is descriptive [1] and may result in misclassification of non-specific episodes of muscle weakness as cataplexy attacks or vice versa [4,106,112]. This is further complicated by variations in cataplexy ranging from infrequent partial attacks to frequent complete episodes, characterized by different durations and atypical features observed in children [9,50,51,113–119]. The potential for an imprecise diagnosis of narcolepsy with cataplexy is recognized as a likely limitation for research studies [68,120,121]. To address this issue, graded
Table 1

Narcolepsy and H1N1 pandemia: event summary.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Cases</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 2009–March 2010</td>
<td>H1N1 flu vaccination campaign in several European countries</td>
<td>Mass vaccination in Sweden (vaccine coverage of about 60%) and Finland. Risk group vaccination in other countries.</td>
<td></td>
</tr>
<tr>
<td>March–August 2010</td>
<td>First cases of narcolepsy after H1N1 vaccination with Pandemrix® are reported in Sweden and Finland to the Swedish Authority Medical Product Agency (MPA) and to the Finnish National Institute for Health and Welfare (THL) respectively</td>
<td>6 cases of narcolepsy after H1N1 vaccination in Sweden and 6 cases in Finland</td>
<td>Children and adolescents appear to be the most involved. Short delay (2 weeks) between vaccine and narcolepsy symptoms. Abrupt symptom onset.</td>
</tr>
<tr>
<td>August 2010</td>
<td>Finland: THL recommends that vaccination with Pandemrix® vaccine is discontinued until an explanation is found [79]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>November 2010</td>
<td>Europe–USA–Canada–China cases [80]</td>
<td>16 cases of narcolepsy with cataplexy after H1N1 vaccination or flu</td>
<td>Abrupt symptom onset Unusual symptom severity. Low hypocretin-1, pathological MSLT1 [1], DQB1*06:02 allele presence.</td>
</tr>
<tr>
<td>March 2011</td>
<td>MPA publishes a case inventory study of Swedish cases from clinical departments and sleep laboratories (retrospective cohort January 1st 2009–December 31st 2010) [77,78]</td>
<td>81 narcolepsy cases ascertained, 69 (85%) vaccinated before symptom onset, aged 19 years and younger</td>
<td>Incidence rate vaccinated versus unvaccinated: 4.2 versus 0.64 per 100,000 person-years. Relative risk: 6.6 (95% CI 3.1–14.5). Absolute risk of 3.6 (95% CI 2.5–4.7) per 100,000 vaccinated cases.</td>
</tr>
<tr>
<td>August 2011</td>
<td>Switzerland: case reports [82]</td>
<td>2 narcolepsy with cataplexy cases after H1N1 vaccination</td>
<td>Abrupt onset of severe sleepiness and cataplexy. Low hypocretin-1, pathological MSLT1 [1], DQB1*06:02 allele presence.</td>
</tr>
<tr>
<td>September 2011</td>
<td>China: retrospective study of narcolepsy onset in Beijing (1998–2010) [83]</td>
<td>629 narcolepsy with cataplexy cases (86% children), 5.6% had H1N1 vaccination</td>
<td>3-Fold increase of narcolepsy incidence after 2009 H1N1 pandemic (year-to-year variation). Abrupt symptom onset. Onset at an early age. The increase is explained with seasonal/annual patterns of upper airway infections, including H1N1 influenza.</td>
</tr>
<tr>
<td>March 2012</td>
<td>Systematic analysis of narcolepsy incidence in Finland in 2002–2010 [154]</td>
<td>335 cases, 93% had Pandemrix® vaccination</td>
<td>17-Fold increase of narcolepsy incidence in 2010 compared to the preceding years in patients under 17 years old. Abrupt symptom onset. Low hypocretin-1, pathological MSLT1 [1], DQB1*06:02 allele presence.</td>
</tr>
<tr>
<td>March 2012</td>
<td>Retrospective study on a Finnish cohort (January 1st 2009–December 31st 2010) [153]</td>
<td>67 ascertained cases of narcolepsy in 4–19 years old subjects, 85% had Pandemrix® vaccination</td>
<td>Incidence rate vaccinated versus unvaccinated: 9.0 versus 0.7 per 100,000 person-years. Relative risk: 12.7 (95% CI 6.1–30.8). Pandemrix® vaccine seems to represent a risk for developing narcolepsy.</td>
</tr>
</tbody>
</table>

classification systems based on categories of increasing diagnostic certainty, but not yet including hypocretin-1 measurements, were proposed [9,120].

1.3.2. Selected decisions on case definition structure and criteria

The case definition for narcolepsy proposed by the Narcolepsy Working Group is structured in 3 levels of diagnostic certainty (from highest to lowest). The main purpose is to provide a classification with high specificity, preferably on the basis of reproducible measurements and biomarkers, aiming at a homogenous patient population to be used in scientific research studies.

As recent-onset narcolepsy in children may have a different clinical presentation compared to adults, especially regarding cataplexy [5,50,51], the Narcolepsy Working Group chose to describe clinical features separately for adults and children (see Section 2).

1.3.2.1. Hypocretin-1. Hypocretin-1 deficiency in the CSF is strongly associated with narcolepsy with cataplexy, and very
low levels of hypocretin-1 are rarely found in other diseases [21,27,37,104,105,122–127]. In patients with unambiguous cataplexy, hypocretin-1 deficiency is present in more than 90% of cases; exceptions are mainly familial cases and/or HLA DQB1*06:02 negative cases [21,27,37,105]. In patients without cataplexy, a much smaller proportion, up to 20%, is hypocretin-1 deficient [21,98,102,122]. The highest level of diagnostic certainty therefore requires a CSF hypocretin-1 measurement.

Hypocretin-1 levels in CSF are usually measured using a commercially available radioimmunoassay with polyclonal antibodies against hypocretin-1 [20,128]. When the assay is standardized using the Stanford reference sample, a cut-off of 110 pg/ml defines abnormally low levels. Alternatively, if a laboratory wishes to include its own control sample, the cut-off is defined either as a level less than one-third the mean of normal healthy controls, or two or more standard deviations from the mean [129]. Using the Stanford cut-off, hypocretin-1 assay levels lower than 110 pg/ml showed a sensitivity between 88 and 94% in narcolepsy with cataplexy [37,105] and a specificity of 99% [21]. Higher hypocretin-1 levels must therefore raise suspicion of other diseases, including secondary forms of narcolepsy with or without cataplexy. Despite costs and inconveniences related to lumbar puncture, the assay of hypocretin-1 is intrinsic to achieve the maximal diagnostic certainty. Further reasons for assessing CSF hypocretin-1 are that its validity is not affected by age, ethnicity, medications, sleep deprivation, or time of day, thus making it useful when patients are taking medications (and unwilling/unable to interrupt treatment), or habitually sleeping at unusual times. Hypocretin measurement also has value in children younger than 8 years of age, who may be unable to follow MSLT instructions, and in patients with other co-morbid sleep disorders in whom MSLT is difficult to interpret [68]. Even in recent onset cases (within 3 years), CSF hypocretin-1 is very low or undetectable [21,63,130].

1.3.2.2. Cataplexy. In the absence of hypocretin-1 measurement, the second level of the case definition strongly relies on the presence of unambiguous cataplexy, evaluated on the basis of unequivocal clinical features, to minimize the likelihood of misclassification [4,9,121,131,132]. Cataplexy can be challenging to correctly identify and even more so to objectively quantify. The large number of published questionnaires evaluating cataplexy and used in different centers as well as the large number of requirements for unambiguous cataplexy listed in the present case definition, reflect this difficulty. However, cataplexy is a highly specific symptom in the presence of excessive daytime sleepiness and in the absence of other disorders [97].

Cataplexy usually develops within the first years of disease onset in adults (50% of cases within one year, 85% within 3 years) [107]. Nevertheless, appearance many years or even decades after the first symptoms are also possible [65–67]. Cataplexy is often most severe around onset and decreases with age [51,68]. This apparent improvement with age may be due to a natural evolution in cataplexy, a decrease in “emotionality” with age [133], development of strategies to prevent progression of attacks, such as learning to avoid situations in which attacks may occur, response to effective therapies, or any combination of these factors. Because non-specific feelings of muscle weakness associated with emotions have been reported in the general population which may not represent cataplexy [131], the Narcolepsy Working Group applied a stringent definition to diagnose ‘unambiguous cataplexy’ requiring the presence of four key features: (1) episodes of partial or generalized muscle weakness, (2) preserved consciousness during these episodes, (3) at least two attacks with clear emotional triggers (usually positive emotions, such as laughing and joking, but also other forms of intense emotions; at least 2 attacks, rather than one, are required to minimize possible misdiagnosis due to inaccurate terms used to describe the symptoms), and (4) most attacks, partial or complete (usually bilateral) lasting less than 30 s (arbitrary cut-off based on clinical evidence that attacks are typically short). These features should be reported in the clinical history or directly observed by an experienced clinician documenting reversible areflexia [4,9,109,121].

In children, cataplexy usually develops within the first years after narcolepsy onset, although initially (during the first weeks or few months) its clinical manifestation may be atypical [42,50,51,134–136]. These atypical cataplexy events in children often include prominent facial involvement with a droopy expression, eyelid ptosis, paroxysmal episodes of mouth opening and tongue protrusion (described as “cataplectic facies”) [50]. Frequently there are superimposed active motor phenomena that can be confused with tics or dystonia, along with a generalized reduction in muscle tone with an unsteady gait also present in baseline conditions (i.e. inter-ictal) [51]. These initial episodes of cataplexy often lack clear emotional triggers and may persist across the day, but as the disease progresses the typical pattern of muscle weakness triggered by laughter or emotion emerges [51]. Cataplexy in children may also occur spontaneously, without any kind of identified trigger and may be increased by sleepiness or excessive fatigue.

1.3.2.3. Excessive daytime sleepiness. Excessive daytime sleepiness is the initial symptom in 90% of adult cases. Initially sleepiness can manifest as an increased need for sleep across the 24 h [4,137,138]. As the disease progresses, expression of sleepiness changes into constant difficulty staying awake during the day, and many patients find it difficult to maintain continuous sleep at night [4,139]. In addition, sleepiness often reduces vigilance. Attentiveness is unstable during wakefulness, which leads to impaired performance at school and work and complaints of poor concentration and memory [7].

In children, sleepiness often makes it difficult to maintain alertness and vigilance [140]. Impairment of cognitive capacities may occur, which leads to more errors, difficulty in academic settings, and unintentionally falling asleep during inappropriate situations, i.e., in class, while reading or studying, doing homework, watching television, and even while eating [7,68,135,141–150]. Sleepy children may also be irritable, inattentive, or, paradoxically may display hyperactive behaviors, probably because they try to resist excessive daytime sleepiness [4,7,68,135,151,152].

In the ICD-2 definition of narcolepsy, sleepiness must be present for at least 3 months to exclude possible temporary, non-specific causes and other sleep disorders, such as recurrent hypersomnias [1]. However, as narcolepsy may be suspected even when the disease course is shorter than 3 months [80–84,153,154], we reduced the minimum time for symptoms to one month. We considered this to be sufficient, given that it is unlikely that an episode of recurrent hypersomnia would last more than one month, the clinical picture of recurrent hypersomnias is usually clearly different from narcolepsy, and these conditions are not associated with hypocretin deficiency. In addition, other causes for somatic sleepiness attributable to infections, intoxications, or loss of sleep have to be excluded in our narcolepsy case definition. And finally, according to our definition the presence of other ICD-2 defined sleep disorders is not allowed or they must clearly be comorbidities.

1.3.2.4. Multiple sleep latency test. The vast majority of patients are currently diagnosed using the MSLT, the only internationally accepted diagnostic test of excessive daytime sleepiness and REM sleep abnormalities [101]. During the MSLT, subjects attempt to fall asleep in a quiet and dimly lit setting, while avoiding alcohol and caffeine throughout the day. During 4 or 5 20-min test episodes over a day, the time it takes for the patient to fall asleep is...
measured. A prerequisite for valid interpretation of the MSLT results is that the subject slept for ≥6h during the night before the test [155]. According to ICSD-2, MSLT is defined as pathological for narcolepsy when SL is ≤8 min and there are ≥2 SOREMPs, showing a sensitivity of 94.5% and a specificity of 73.3% [38,39].

SOREMPs, although more specific for narcolepsy, appear with relatively high frequencies (up to 27%) in randomly selected populations or presenting disorders different from narcolepsy, which may also exist as a co-morbid condition in narcolepsy [38,73,91,156]. To diagnose narcolepsy, the additional occurrence of REM sleep in at least 2 naps is required [1,101]. SOREMPs are indicative of REM sleep abnormalities in narcolepsy. Previous and ongoing studies indicate that the presence of SOREMPs during nocturnal polysomnography (PSG, i.e., REM latency ≤15 min) has a high specificity in identifying cases of narcolepsy with cataplexy, both in adults and children, representing therefore a potentially valid marker [74,75,120,157]. Further validation studies will be needed, particularly in populations including patients suffering from other conditions known to facilitate the occurrence of REM sleep e.g., depression, when PSG is performed without control for sleep habits immediately before the start of registration e.g., a nap before entering the laboratory, or in subjects who recently withdrew from antidepressants.

Despite wide use and acceptance of these MSLT criteria for the diagnosis of narcolepsy with cataplexy, the sensitivity and specificity are suboptimal [38,72,73,93,156]. The level 2 diagnostic classification hinges on the presence of cataplexy, and, given the suboptimal sensitivity of the full MSLT criteria, less stringent MSLT criteria were applied, by allowing either a mean sleep latency ≤8 min, or ≥2 SOREMPs. The less stringent MSLT criteria provide objective confirmation without sacrificing sensitivity; while the presence of unambiguous cataplexy already provides the required specificity. Although the adjusted MSLT criteria are not formally validated, the Narcolepsy Working Group deemed it unlikely that a case with unambiguous cataplexy and either a mean sleep latency ≤8 min, or ≥2 SOREMPs would not be correctly identified. The adjusted MSLT criteria have not yet been formally validated and need appropriate validation studies to confirm that this change will maintain the diagnostic validity.

Data are lacking to support the diagnostic value of the MSLT in narcoleptic children [151]. Most children with narcolepsy with cataplexy fulfill the above criteria adopted for adult patients, as mirrored by the pediatric section for narcolepsy in ICSD-2 [1]. However, the validity of adult criteria for children was questioned [158]. Some pediatric patients have sleep latencies ≥8 min and ≤12 min [50,151]. In normal adolescents, an increase in the ability to fall asleep was noted during MSLT naps around pubertal maturation (Tanner stage scale 3). In contrast, children at lower Tanner stages, as well as adolescents, show a significantly longer sleep latency during MSLT [159,160]. Moreover, no published data describe baseline MSLT values in children younger than 8 years old, when children are thought to be unable to follow the MSLT instructions to try to fall asleep [161]. Serial PSG and MSLT recordings were proposed to aid in the diagnosis of narcoleptic children [162]. Based on this information, the Narcolepsy Working Group proposed to adopt the cut-off of ≤12 min for pathological sleepiness in childhood cases, together with a detailed clinical history [163].

1.3.2.5. Human leukocyte antigen typing. More than 90% of patients with typical sporadic narcolepsy with cataplexy are positive for the HLA subtype DQB1*06:02 compared to around 25% in control groups [164]. The low specificity of this finding implies that HLA typing is of limited value in the diagnosis of narcolepsy. Furthermore, in clinically difficult cases (e.g., absence of unambiguous cataplexy, onset at very young age, or a positive family history), HLA positivity is considerably less common [164]. For these reasons, HLA typing was not included in the diagnostic classification. It remains possible – given the continued research on genetic determinants of narcolepsy in humans – that genetic characterization will evolve as a diagnostic tool with a high sensitivity and specificity in the future. HLA typing is also crucial in pathophysiologic studies, including ones examining possible post-immunization narcolepsy sporadic cases [153,154]. Recently, the HLA DRB1*13:01-DQB1*06:03 haplotype proved to be protective against sporadic narcolepsy [165,166].

1.3.3. Formulating a case definition that reflects diagnostic certainty: sensitivity and specificity, the importance of laboratory tests and objective measures

The levels of diagnostic certainty are intended to reflect the likelihood that a patient with sporadic narcolepsy will be hypocretin-1 deficient: the pathophysiologic hallmark of the disease. The highest level of diagnostic certainty requires a CSF hypocretin-1 measurement. In the absence of hypocretin-1 measurement, the second level of the definition strongly relies on the presence of unambiguous cataplexy, evaluated on the basis of unequivocal clinical features, to minimize the likelihood of misclassification [9,121].

The presence of unambiguous cataplexy strongly suggests of narcolepsy with cataplexy even when hypocretin-1 measurement is lacking (Level 2), while the presence of doubtful cataplexy would reflect a lower level of diagnostic certainty (Level 3). Level 3 then includes cases of narcolepsy without cataplexy, at least until unambiguous cataplexy may appear [65–67].

When the hypocretin-1 level is unknown, and there is no history of unambiguous cataplexy, the third level of diagnostic classification relies on the MSLT. The physiopathology of narcolepsy without cataplexy is probably different than that of narcolepsy with cataplexy [71], and the clinical significance of SOREMPs in non-cataplectic patients still need further studies [65]. Since there are other causes for excessive daytime sleepiness besides narcolepsy, it is of paramount importance to have an objective criterion that is as specific as possible. The present case definition has therefore proposed more flexible MSLT criteria for narcolepsy with cataplexy, maintaining however a strong reference to the ICSD-2 [1], in order to not exclude patients on the basis of cut-offs that appear to be too restrictive. Consistently with ICSD-2 criteria, the Narcolepsy Working Group applied the traditional set of MSLT criteria for level 3, those without cataplexy. By doing so, false positive diagnoses are avoided to the extent possible and misclassification of real narcoleptic cases as non-narcoleptic is minimized. In this circumstance, the researcher must exclude other conditions that are associated with daytime sleepiness and can have comparable MSLT outcomes. Besides sleep related breathing disorders, periodic limb movement disease, habitual sleep deprivation (‘behaviorally induced insufficient sleep’ in ICSD-2 [1]), environmental sleep disorder, and the impacts of psychotropic drugs especially selective serotonin reuptake inhibitors are important to be considered [65,72,73,97,101,156].

In rare cases, a suspected narcolepsy case may not be classifiable according to the levels above (e.g. when there is cataplexy, no objective sleepiness, and CSF hypocretin-1 level is unavailable). In these instances, the case will be classified in the 4th level (see below).

1.4. Narcolepsy as a possible AEfi

It should be emphasized to patients, parents, health care providers, and others concerned with immunization safety, that narcolepsy – or any other adverse event – that follows administration of a vaccine may be temporally associated with, but is not necessarily the result of, the vaccination. Any occurrence of narcolepsy in vaccine recipients should be compared to an
adequate control group and/or against a background rate. The definition by itself addresses a clinical outcome without inference of a causal relationship to a given exposure. Therefore the time interval between immunization and onset is not part of the definition, but rather should be assessed independently as described in the guidelines. Also, the definition of time from exposure to onset varies from one setting or study to another depending which data are available. The guidelines in Section 3 have been developed to complement the case definition in order to improve data quality and comparability and to lead to a better understanding of the possibility that narcolepsy may occur as an AE. The guidelines are structured to be consistent with steps of conducting a scientific study, i.e., description of the signal, forming a case definition, data collection, analysis, and presentation. 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. Case definition of narcolepsy

**Level 1**
In the presence of:
- Excessive daytime sleepiness* OR
- Unambiguous cataplexy
AND
- CSF hypocretin-1 deficiency

**Level 2**
In the presence of:
- Excessive daytime sleepiness*
AND
- Unambiguous cataplexy
AND
- MSLT* mean sleep latency ≤8 min in adults OR
- MSLT* mean sleep latency ≤12 min in children and adolescents OR
- MSLT* SOREM ≥ 2

**Level 3**
In the presence of:
- Excessive daytime sleepiness*
AND
- MSLT* mean sleep latency ≤8 min in adults OR
- MSLT* mean sleep latency ≤12 min in children and adolescents
AND
- MSLT* SOREM ≥ 2

**All levels**
AND in the absence of other mimicking disorders, see†

*Excessive daytime sleepiness*
In adults (≥16 years):
- Unintended sleep episodes during the day
AND
- present almost daily for at least one month
In children and adolescents (<16 years):
- an increase in daytime sleep episodes
AND
- present almost daily for at least one month

Note: usually in combination with feelings of subjective sleepiness and impaired concentration. Sleepiness may also be manifested as irritability or hyperactivity.

*CSF hypocretin-1 deficiency*
- hypocretin-1 concentration below 110 pg/ml in crude, unextracted CSF.
AND
- measured by the Phoenix radioimmunoassay
AND
- performed in a laboratory according to published guidelines and by using the Stanford reference sample [31,128]

*Unambiguous cataplexy*
In adults (≥16 years):
- sudden AND unexpected onset of episodes
AND
- presence of all of the following criteria during episodes (before initiation of treatment):
  - partial or generalized muscle weakness
  - preserved consciousness
  - clear emotional trigger in ≥ 2 episodes
  - duration of <30 s
OR
  - episodes with documented, reversible areflexia AND
  - duration of <30 s
NOT
  - partial or generalized seizure OR
  - neuromuscular disorders

In children and adolescents (<16 years):
- episodes of cataplexy that fulfill the criteria for adult cataplexy
OR
- the following criteria of pediatric cataplexy:

**Pediatric Cataplexy**
- sudden AND unexpected onset of episodes
AND
- loss of muscle tone, e.g., falling during routine activity (i.e., while walking or running), wide-based gait, head droops, prominent facial involvement resulting in “cataplectic facies,” eyelid plosis, mouth opening, tongue protrusion, facial weakness, facial grimacing, abnormal postures, swaying of the head and trunk, stereotypic movements or chorea-like patterns.

Hypotonia and wide-based gait may also be disclosed at neurological examination
AND
- preserved consciousness
AND
- duration of episodes is a few seconds to several minutes (sometimes present in protracted clusters if emotional triggers continue)

Note: cataplexy in children may or may not be triggered by ‘emotional’ circumstances (e.g., watching funny cartoons, eating certain foods, playing games or video-games)

NOT
- partial or generalized seizure OR
- neuromuscular disorders
- any other known explanation

† 4 or 5 nap MSLT performed according to the American Academy of Sleep Medicine (AASM) protocol [101]

*Exclusion of other conditions*
The following conditions must be clinically/instrumentally assessed, since they could either mimic one or more narcolepsy symptoms (mainly excessive daytime sleepiness) or constitute co-morbidities with narcolepsy:
- other sleep disorders, according to ICSD-2 criteria:
  - sleep related disorder breathing
  - behaviorally induced insufficient sleep
  - circadian rhythm disorders
  - recurrent hypersomnias secondary to medical or psychiatric conditions
  - use of sedating medication and antidepresants
  - focal cerebral lesions, indicated by neurological examination and/or brain imaging

Note: Clinical assessment should be performed after adequate treatment of the co-morbid conditions, to show that they are not the primary cause of the symptoms.

3. Guidelines for data collection, analysis and presentation of narcolepsy

The Brighton Collaboration Narcolepsy Working Group recommends the following guidelines to facilitate standardized collection, analysis, and presentation of information about narcolepsy. Full implementation of the guidelines might not be possible in all settings. Availability of information may vary depending on resources, geographical region, and whether the source of information is a prospective clinical trial, post-marketing surveillance, an epidemiologic study, or an individual report of narcolepsy.

The guidelines represent a minimum standard and are not intended to establish criteria for management of ill infants, children or adults. Additional data may be collected, analyzed and presented by investigators.
3.1. Data collection

The data collection guidelines provide a standardized method for collection of data on narcolepsy following immunization to allow comparability of data. They can supplement data collected for a specific study question and setting. They are not intended to guide primary reporting of narcolepsy to a surveillance system or study monitor. Investigators developing a data collection tool based on these guidelines should refer to criteria in the case definition, which are not restated in these guidelines. The guidelines below have been developed to address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [167] and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences (CIOMS) [168]. These data elements include an identifiable reporter and patient, who received one or more immunizations before event onset and a detailed description of the adverse event.

The guidelines below have also been developed for the collection of additional information to allow for a more comprehensive understanding of narcolepsy following immunization and comparability of data. As appropriate, and to the extent possible, for all reports and/or all study participants the following information should be recorded.

3.1.1. Source of information/reporter
(1) Date of report.
(2) Name and contact information of person reporting and/or diagnosing narcolepsy as specified by country-specific data protection laws.
(3) Name and contact information of the investigator responsible for the patient.
(4) Relation to the patient (e.g., immunizer [clinician, nurse], treating health professional, family member [indicate relationship], other).

3.1.2. Vaccine/control
3.1.2.1. Demographics.
(5) Case/study participant identifiers (e.g., 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 the calendar used if not the commonly used Gregorian calendar), age, sex, and race/ethnicity (as appropriate).
(7) For infants (<12 months): Gestational age, birth weight, and weight at the time of assessment and length.

3.1.2.2. Clinical and immunization history.
(8) Past medical history including hospitalizations and surgery, underlying diseases/disorders, pre-immunization signs and symptoms that may affect the evaluation of narcolepsy. In particular, pre-existing neurological illness should be recorded.
(9) Any drug/toxin or medication history (other than treatment for the adverse event described) prior to, during, and after immunization by any route, including prescription and non-prescription medication as well as medication or treatment with long half-life or long-term effect (e.g., immunoglobulins, blood transfusion, and immunosuppressants).

3.1.3. Details of the immunization
(10) Immunization history (i.e., previous or other immunizations in addition to the immunization in question and any adverse event following these immunizations) and occurrence of narcolepsy or similar symptoms after a previous immunization or any other adverse event.

3.1.3.1. Details of the immunization
(11) Date and time and geographic location of immunization(s), specify if a 12 or a 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) (name of vaccine, manufacturer, lot number, expiration date, dose [e.g., 0.25 mL, 0.5 mL, etc.] and dose number if part of a series of immunizations against the same disease).
(13) The anatomical site(s) (including left or right side) of all immunizations (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid).
(14) Route(s) and method of administration (e.g., intramuscular, intradermal, subcutaneous [including needle size and gauge] and needle-free [including type and size], other injection devices).
(15) Storage conditions of the vaccine(s): temperature logs, storage conditions according to manufacturer, especially in prospective studies.

3.1.4. The adverse event
For all cases at any level of diagnostic certainty and/or all other study participants including reported events with insufficient evidence, the following information should be recorded.

(16) Criteria fulfilled to meet the case definition, and other signs or symptoms indicative of narcolepsy.
(17) Clinical description of signs and symptoms of narcolepsy and medical confirmation of the event (i.e., if the patient was seen by a physician). All individual aspects of the case definition should be recorded. This is especially important for the individual criteria for identifying unambiguous cataplexy.
(18) Date of the following events: first observation, referral to specialist, diagnosis, and final outcome or outcome at the last observation.
(19) Concurrent signs, symptoms, and diseases other than the event described.
(20) Measurement/testing
The following measurements/tests should be recorded, including the date of specimen collection and/or measurement and the normal ranges for each parameter measured:
- Values and units of routinely measured parameters (e.g., temperature, blood pressure) – in particular those indicating the severity of the event.
- Results of laboratory examinations, surgical and/or pathological findings and diagnoses if present.
- Individual results of additional procedures and tests to diagnose narcolepsy, such as outcomes of polysomnographic studies.
(21) Treatments given for narcolepsy, including stimulants, antidepressants, sodium oxybate, intravenous immunoglobulins and

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

4 The date and/or time of first symptom of narcolepsy.

5 Referral to specialist is a useful date as it is a surrogate for clinical suspicion of the primary care provider, objectively assessable and comparable.

6 The date of diagnosis is the day post immunization when the event met the case definition at Level 1, 2, or 3, or at the time of physician diagnosis of Level 4.

7 The date of last observation is the date of the last clinical evaluation of the patient with narcolepsy. “Persistence of the event” refers to events continuing to meet the case definition beyond the follow-up period.
others. Record dosing, number of sessions, timing after disease onset, timing after vaccination. Record the names and contact information of treating physicians and/or institutions.

(22) Outcome at last observation should be clearly described including date, such as:
- ongoing therapeutic intervention
- persistence of the event
- significant complications of treatment
- death
- description of any other outcome

(23) Objective clinical evidence supporting classification of the event as "serious".

(24) Exposures other than the immunization within 6 months before and after immunization (e.g., infections, medication) considered potentially relevant to the reported event.

3.1.5. Miscellaneous/general

(25) The duration of surveillance for narcolepsy should be predefined based on:
- Biologic characteristics of the vaccine e.g., live attenuated versus inactivated component vaccines;
- Biologic characteristics of the vaccine-targeted disease; and
- Biologic characteristics of the vaccine (e.g., nutrition, underlying disease like autoimmune disease or immune system disorders).

(26) The duration of follow-up reported during the surveillance period should be predefined. Reports of narcolepsy should be collected throughout the study period regardless of the time elapsed between immunization and the adverse event. If this is not feasible due to the study design, the study periods during which safety data are being collected should be clearly defined.

(27) Methods of data collection should be consistent within and between study groups.

(28) Follow-up of cases should attempt to verify existing information, if indicated, and address incomplete information and data deficiencies/inconsistencies as outlined in data collection guidelines 1–24.

(29) Investigators of patients with narcolepsy should provide guidance to reporters to optimize the quality and completeness of information provided.

3.2. Data analysis

The data analysis guidelines provide a standardized method for analysis of data on narcolepsy following immunization to allow comparability of data, and can supplement data analyzed for a specific study question and setting.

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

3.2.1. Event classification in 5 categories

In Tables 2 and 3, the various levels of diagnostic certainty are schematically represented for adults and children, respectively.

Event meets case definition

Main categories
- Level 1: Criteria as specified in the narcolepsy case definition
- Level 2: Criteria as specified in the narcolepsy case definition
- Level 3: Criteria as specified in the narcolepsy case definition

Event does not meet case definition

Additional categories for analysis
- Level 4: Reported narcolepsy with insufficient evidence to meet the case definition:
  4a: Diagnosed by sleep specialist but not meeting the case definition
  4b: Any other case with insufficient evidence to meet the case definition
- Level 5: Reported narcolepsy with sufficient evidence to rule out narcolepsy.

(31) The interval between immunization and symptom onset is ideally defined from the date/time of immunization until first observation of narcolepsy symptoms. However, this may be difficult to obtain retrospectively, because narcolepsy symptoms may occur consecutively over a long time span and because it is difficult to identify the time elapsed between the immunization and symptom appearance. Alternatively, consistently documented dates may be used as a surrogate for epidemiologic studies: first presentation to health care provider, or the date of first referral to specialist, or the date of diagnosis. Start date/time and end date/time definitions should be applied consistently within and across study groups. If few cases are reported, the detailed time course should be analyzed for each. In instances with large numbers of reported cases, data may be analyzed in following increments represented in Table 4.

(32) If more than 1 measurement of a particular criterion is taken and recorded, the greatest value for that particular criterion may be used in the analysis. Analysis may also include other characteristics like qualitative patterns of criteria defining the event.

(33) The distribution of data (numerator and denominator data) may be analyzed in predefined increments (e.g., measured values, times), where applicable. Increments specified above should be used. When only a small number of cases are analyzed, their respective values or time courses can be presented individually.

(34) Data on narcolepsy obtained from subjects receiving a vaccine should be compared with data obtained from an appropriately selected and documented control group(s) to assess background rates of narcolepsy in non-exposed populations. The data should be analyzed by study arm and dose, where possible, e.g., in prospective clinical trials. If a control group is not available, consideration should be given to using a background rate from an appropriate source population. These comparisons may not be possible when analyzing post-marketing surveillance reports due to the numerous factors that influence passive reporting.

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

9 To select the appropriate category, the user should first establish whether a reported event meets the criteria for the lowest applicable level of diagnostic certainty, e.g., Level 3. If the lowest applicable level of diagnostic certainty of the definition is met and there is evidence that the criteria of the next higher level of diagnostic certainty is met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event is identified. Major criteria may be used to satisfy the requirements of minor criteria. If the lowest level of the case definition is not met, the user should rule out that any higher levels of diagnostic certainty are met and the event should then be classified in additional categories 4 or 5.

10 If the evidence available for an event is insufficient because information is missing, such an event should be classified as "Reported narcolepsy with insufficient evidence to meet the case definition".

11 An event does not meet the case definition if investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as "Not a case of narcolepsy".
Table 2
Schematic narcolepsy classification for adults.ª

<table>
<thead>
<tr>
<th>EDS</th>
<th>Unambiguous cataplexy</th>
<th>Hcrt 1 deficiency</th>
<th>MSLT msl ≤8 min</th>
<th>MSLT SOREMPs ≥2</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>n.n.</td>
<td>n.n.</td>
<td>Level 1</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>+</td>
<td>n.n.</td>
<td>n.n.</td>
<td>Level 1</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>+</td>
<td>n.n.</td>
<td>n.n.</td>
<td>Level 1</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>n.a.</td>
<td>+</td>
<td>+</td>
<td>Level 2</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>n.a.</td>
<td>−</td>
<td>+</td>
<td>Level 2</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>n.a.</td>
<td>+</td>
<td>−</td>
<td>Level 2</td>
</tr>
<tr>
<td>+</td>
<td>n.a./absent</td>
<td>n.a.</td>
<td>+</td>
<td>+</td>
<td>Level 3</td>
</tr>
</tbody>
</table>

EDS, excessive daytime sleepiness; Hcrt 1, hypocretin-1; MSLT, multiple sleep latency test; msl, mean sleep latency; SOREMPs, sleep onset REM periods; n.n., not necessary; n.a., not available.

ª All other possible combinations either are classifiable as Level 4 (i.e., “Reported narcolepsy with insufficient evidence to meet the case definition”) or do not represent a case of narcolepsy.

Table 3
Schematic narcolepsy classification for children.ª

<table>
<thead>
<tr>
<th>EDS</th>
<th>Unambiguous cataplexy</th>
<th>Hcrt 1 deficiency</th>
<th>MSLT msl ≤12 min</th>
<th>MSLT SOREMPs ≥2</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>n.n.</td>
<td>n.n.</td>
<td>Level 1</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>+</td>
<td>n.n.</td>
<td>n.n.</td>
<td>Level 1</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>+</td>
<td>n.n.</td>
<td>n.n.</td>
<td>Level 1</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>n.a.</td>
<td>+</td>
<td>+</td>
<td>Level 2</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>n.a.</td>
<td>−</td>
<td>+</td>
<td>Level 2</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>n.a.</td>
<td>+</td>
<td>−</td>
<td>Level 2</td>
</tr>
<tr>
<td>+</td>
<td>n.a./absent</td>
<td>n.a.</td>
<td>+</td>
<td>+</td>
<td>Level 3</td>
</tr>
</tbody>
</table>

EDS, excessive daytime sleepiness; Hcrt 1, hypocretin-1; MSLT, multiple sleep latency test; msl, mean sleep latency; SOREMPs, sleep onset REM periods; n.n., not necessary; n.a., not available.

ª All other possible combinations either are classifiable as Level 4 (i.e., “Reported narcolepsy with insufficient evidence to meet the case definition”) or do not represent a case of narcolepsy.

3.3. Data presentation

The data presentation guidelines provide a standardized method for presentation and publication of data on narcolepsy following immunization to allow comparability of data and can supplement data presented for a specific study question and setting. General guidelines for presentation and publication of randomized controlled trials, systematic reviews, and meta-analyses of observational studies in epidemiology include Consolidated Standards of Reporting Trials [CONSORT], Improving the quality of reports of meta-analyses of randomized controlled trials [QUORUM], Meta-analysis Of Observational Studies in Epidemiology [MOOSE], Transparent Reporting of Evaluations with Nonrandomized Designs (TREND), and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [169–173].

(35) All reported events of narcolepsy should be presented according to the categories listed in guideline 31.

(36) Data on narcolepsy should be presented according to data collection guidelines 1–29 and data analysis guidelines 30–35.

(37) Terms to describe narcolepsy such as “low-grade”, “mild”, “moderate”, “high”, “severe” or “significant” are highly subjective, prone to wide interpretation, and should be avoided.

(38) Data should be presented with numerator and denominator (n/N) along with percentages. Confidence intervals around estimates should be presented if possible. Although immunization safety surveillance systems denominator data are usually not readily available, attempts should be made to estimate denominators. The source of denominator data should be reported, and calculations of estimates should be described (e.g., manufacturer data such as total doses distributed, reporting through Ministry of Health, population-based coverage data, etc.). Caution should be exercised in these circumstances, due to uncertainty surrounding denominator estimates and variability in adverse event reporting due to various factors. Limitations should be clearly described.

Table 4
Suggested-to-be-reported time intervals to onset.

<table>
<thead>
<tr>
<th>Interval</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with narcolepsy by interval to onset</td>
<td>..</td>
<td>..%</td>
</tr>
<tr>
<td>0–6 days (&lt;1 week after immunization)</td>
<td>...</td>
<td>..%</td>
</tr>
<tr>
<td>7–27 days (1–3 weeks after immunization)</td>
<td>...</td>
<td>..%</td>
</tr>
<tr>
<td>28–55 days (4–7 weeks after immunization)</td>
<td>...</td>
<td>..%</td>
</tr>
<tr>
<td>56–83 days (8 to &lt;12 weeks after immunization)</td>
<td>...</td>
<td>..%</td>
</tr>
<tr>
<td>Monthly increments thereafter</td>
<td>...</td>
<td>..%</td>
</tr>
<tr>
<td>Total</td>
<td>...</td>
<td>..%</td>
</tr>
</tbody>
</table>

(39) The incidence12 of cases in the study population should be clearly described in the text when appropriate. For data comparability the format n/million/year is recommended.

(40) If the distribution of data is skewed, median and range are usually the more appropriate statistical descriptors than a mean. However, the mean and standard deviation should also be provided.

(41) Publication of data on narcolepsy should include a detailed description of methods used for data collection and analysis. It is essential to specify:

- Study design;
- Method, frequency, and duration of monitoring for narcolepsy;
- Trial profile, indicating participant flow during a study including drop-outs and withdrawals to indicate the size and nature of the respective groups under investigation.
- For surveillance system:
  - Type of surveillance (e.g., passive or active surveillance)
  - Characteristics of the surveillance system (e.g., population served, mode of report solicitation)
  - Search strategy in surveillance databases;

12 E.g., total of 10 cases of narcolepsy in 2000 study participants or 1 case per million during 5 days; use as appropriate.
• Comparison group(s), if used for analysis;
• Instrument(s) of data collection (e.g., standardized questionnaire, diary card, report form)
• Whether the day of immunization was considered “day one” or “day zero” in the analysis;
• Whether the date of onset and/or the date of first observation and/or the date of diagnosis was used for analysis; and
• Reference of the Brighton Collaboration case definition for narcolepsy, in the abstract or methods section of a publication.  

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Appendix A.

The working group was formed in close collaboration with the European Narcolepsy Network and includes the following additional members: Wan-Ting Huang, Taiwan Centers for Disease Control, Taiwan; Jukka Jokinen, National Institute for Health and Welfare, Finland; Jacques Montplaisir, Université de Montréal, Montreal, Canada; Isabelle Rouleau, Centre Hospitalier de l’Université Laval, Canada; Leonardo Triggiani, Food and Agriculture Organization of the United Nations, Rome, Italy.

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13 Use of this document should be referenced according to guidance available on the Brighton Collaboration website (http://www.brightoncollaboration.org).


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